

Investigating risk factors for postpartum psychosis in bipolar disorder

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Thesis summary

Risk of postpartum psychosis (PP) is high in bipolar disorder (BD), however, factors influencing this risk are poorly understood. In particular, whether adverse childhood experiences (ACEs), anxiety disorders and a range of within-pregnancy factors increase risk of PP in BD is yet to be examined. Of within-pregnancy factors that have been investigated, most have been assessed retrospectively. Prospective studies examining risk of PP in BD are scarce. The main aims of this thesis were to a) examine the relationship between ACEs, anxiety disorders and the lifetime occurrence of PP in BD and b) investigate potential within-pregnancy risk factors for PP in BD using a prospective follow-up design.

ACEs, anxiety disorders and lifetime occurrence of PP were assessed via semi-structured interview and self-report questionnaires in 504 parous women with DSM-IV BD-I. Within-pregnancy potential risk factors (including medication, sleep, obstetric and psychosocial factors) were assessed prospectively in 103 pregnant women with DSM-5 BD (n=84 BD-I/SA-BD; n=19 BD-II/BD-NOS) via semi-structured interview in late pregnancy (baseline); perinatal psychopathology was assessed via interview at 12-weeks postpartum. All data were supplemented by clinician questionnaires and/or psychiatric case-notes.

Neither history of ACEs (p-values of 0.06-0.95) nor anxiety disorders (of any type; p=0.47, phobias; p=0.23, panic; p=0.53) were significantly associated with the lifetime occurrence of PP. 21% women in the prospective sample experienced PP within 6 weeks of delivery. In unadjusted analyses, an episode of mania/affective psychosis during pregnancy (p=0.001; OR 11.67, 95% CI 2.61-52.21) and loss of at least one complete night of sleep across labour/delivery (p=<0.01; OR 5.35, 95% CI 1.50-19.11) significantly increased risk of PP. After adjusting for known lifetime correlates of PP, mania/affective psychosis in pregnancy remained a significant predictor of PP (p=<0.01; OR 16.49, 95% CI 2.76-98.48). Further adjustment revealed prophylactic mood stabilising medication in the postpartum period had little influence in moderating risk of PP (p=0.61; OR 0.67 95% CI 0.14-3.16). No significant associations were found between within-pregnancy psychosocial or psychological factors and PP.

This prospective study demonstrated that risk of PP is high in women with BD, despite use of prophylactic mood stabilising medication. History of ACEs or anxiety disorders did not influence lifetime risk of PP. Mania/affective psychosis with onset during pregnancy significantly increased risk of PP, over and above associations with known lifetime risk factors. Sleep loss associated with labour may act as a final common pathway in the triggering of PP. If replicated, these findings have clinical implications for managing risk of PP in women with BD. The role of neurobiological and medication related factors in the pathophysiology of PP requires further investigation in larger samples.

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Formal statement of contribution

The work presented in this thesis was conducted as part of Bipolar Disorder Research Network (BDRN); a large, ongoing programme of research that aims to investigate genetic and non-genetic determinants of bipolar disorder and related mood disorders. BDRN is a collaboration between the Mood Disorders Research Groups at the University of Worcester (led by Professor Lisa Jones) and at Cardiff University (led by Professor Ian Jones and previously, Professor Nick Craddock).

I have been a member of the BDRN research team since February 2011. During this time, I have been involved in the recruitment of participants and collection of data, having conducted >600 interviews with individuals with mood disorders. It is through my work with BDRN that I became particularly interested in researching the causes of PP. A striking proportion of women interviewed had experienced severe mood episodes in relation to childbirth, yet data to explain this phenomenon were surprisingly lacking. My keen interest to learn more about the pathophysiology of PP in this high-risk group led me to commence this PhD.

All investigations subsequently presented in this thesis were conducted by myself. This included the selection of variables, data cleaning, statistical analysis and interpretation of results. The BDRN Pregnancy Study (Chapters 4-7) was initially designed and conducted by BDRN as a pilot study in 2010. However, during the course of this PhD, I revised and amended the study design and was responsible for the selection and inclusion of additional measures and assessments. I recruited all participants to the BDRN Pregnancy Study following the initial pilot phase, which was achieved by identifying and establishing links with clinical collaborators and setting up new recruiting sites within seven additional NHS Trusts and Health Boards nationwide.

Following the pilot phase, I conducted all baseline assessments with participants during pregnancy and all follow-up telephone interviews. I was also responsible for the distribution of clinician follow-up questionnaires and for reviewing psychiatric case-notes. I collated assessment data to produce detailed, clinical vignettes for all women in the BDRN Pregnancy Study (including those who participated in the pilot phase) and alongside Christine Fraser (for the purposes of consensus), independently rated all cases. I was responsible for electronically scanning and validating all raw data.

Papers resulting from work within this thesis

Perry, A. Gordon-Smith, K. Di Florio, A. Forty, L., Craddock, N. Jones, L. Jones, I. (2016) Adverse childhood life events and postpartum psychosis in bipolar disorder. *Journal of Affective Disorders*, 205, 69-72

Perry, A. Gordon-Smith, K. Jones, L. Jones, I. (2017) A visual timeline tool for tracking mood and medication perinatally in affective disorders. *Archives of Women's Mental Health*, 20 (5), 709-710

List of abbreviations

ACE: Adverse childhood experience

APP: Action on Postpartum Psychosis

BD: Bipolar disorder

BD-I: Bipolar I disorder

BD-II: Bipolar II disorder

BD-NOS: Bipolar disorder not otherwise specified

BDRN: Bipolar Disorder Research Network

BLEQ: Brief Life Events Questionnaire

CLEQ: Childhood Life Events Questionnaire

CSO: Clinical Studies Officer

DSM: Diagnostic and Statistical Manual of Mental Disorders

ICD: International Classification of Diseases

ISCO: International Standard Classification of Occupations

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

No PME: No perinatal mood episode

PND: Postnatal non-psychotic depression

PP: Postpartum psychosis

PRQ: Pregnancy Risk Questionnaire

PSQI: Pittsburgh Sleep Quality Index

RDC: Research Diagnostic Criteria

SA-BD: Schizoaffective disorder bipolar type

SCAN: Schedules for Clinical Assessment in Neuropsychiatry

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Chapter 1

Overview of thesis

The relationship between childbirth and mood disorders has long been recognised. Episodes of depression are common among new mothers, affecting 10-15% of women in the general population. More rarely, postpartum psychoses occur, affecting 1-2 in every 1000 deliveries. Postpartum psychosis (PP) is a life-threatening psychiatric emergency, typically presenting as acute mania or affective psychosis within the first few weeks of childbirth. The consequences of these episodes can be especially devastating for the mother, her baby and wider family. Though the nosological status of PP remains controversial, evidence indicates these episodes to be manifestations of bipolar disorder (BD) triggered by childbirth. Longitudinal studies demonstrate that in a high proportion of cases, PP marks the onset of BD. Moreover, women with BD are also at particularly high risk of PP. Nevertheless, the factors that influence risk of PP within this diagnostic group are poorly understood.

Research in this area is important for the development of National Health Services within the UK (National Institute for Health and Clinical Excellence 2014; NHS England 2019b). Additional funding of £239 million pounds is being invested in perinatal psychiatric services over the next five years (NHS England 2019a, 2019b), ensuring more women with moderate to severe mental illness will have access to the specialist care they urgently need. High quality research data that contributes to risk prediction in PP is required to inform evidence-based practices within these services (National Institute for Health and Clinical Excellence 2014).

Accordingly, the aim of this thesis was to identify factors involved in the aetiology and triggering of PP in women with BD. This work was conducted in the context of Bipolar Disorder Research Network (BDRN); a large ongoing programme of research to investigate genetic and non-genetic determinants of BD and related mood disorders. For many years, a key focus of BDRN has been to examine the pathogenesis of PP. Investigations were conducted in two samples of women recruited to BDRN:

Retrospective sample: Using retrospective data collected as part of BDRN, I examined whether lifetime anxiety disorders and adverse childhood experiences

(ACEs) were associated with the lifetime occurrence of PP in a large sample of parous women with BD.

Prospective sample: To further build on knowledge from previous literature (and also findings obtained from investigations conducted within the retrospective sample), I aimed to investigate the role that within-pregnancy factors play in the occurrence of PP, over and above that of known lifetime correlates of PP. These investigations were conducted using a prospective follow-up design in a sample of pregnant women with BD (The BDRN Pregnancy Study).

An overview of the layout of this thesis is provided below:

- **Chapter 2** reviews the existing literature on PP to date, providing further context for this thesis and identifying areas of further research. In this chapter, I discuss the relationship of childbirth to mood disorders and explore issues regarding the nosology of the postpartum period, postpartum mood disorders and PP. The specificity of PP to BD will be discussed, followed by a review of the literature examining aetiological and triggering factors of PP. This chapter concludes with a detailed description of the aims of this thesis.
- **Chapter 3** describes the BDRN retrospective dataset in which the association between ACEs, lifetime comorbid anxiety disorders and the lifetime occurrence of PP was examined. Methods of recruitment, assessment and analysis are detailed, following which the results of these investigations are presented and discussed (Aim 1).
- **Chapter 4** provides an introduction to the second part of this thesis, reviewing literature that has reported on risk of perinatal recurrence of BD using a prospective follow-up methodology. This chapter concludes with a summary of the specific aims of The BDRN Pregnancy Study (discussed further in Chapters 5-7).

- **Chapter 5** describes the design and methods used in the recruitment and assessment of women with BD in The BDRN Pregnancy Study.
- **Chapter 6** presents the first set of results of The BDRN Pregnancy Study in which I describe and discuss psychotropic medication use and psychiatric outcomes across the perinatal period in the sample of women recruited to this study (Aim 2).
- **Chapter 7** describes and discusses results of investigations examining the influence of a range of within-pregnancy factors on risk of PP in women recruited to the BDRN Pregnancy Study (Aim 3).
- **Chapter 8** summarises the main findings of this thesis. The limitations and potential implications for clinical practice will be discussed, concluding with suggestions for further research.

Chapter 2

Introduction to bipolar disorder
and postpartum psychosis

2.1 Overview of chapter

This chapter establishes the context for this thesis by providing a review of literature that has examined potential aetiological and triggering factors of PP. While the primary aim of this review was to identify areas for further research, I also aimed to gain a thorough understanding of key issues that have methodological implications for future studies of PP. These issues concerned the nosological status of PP, presenting questions such as i) which populations of women should be included in future studies of this disorder? and ii) how should the concept of PP be defined? This review therefore discusses a broad range of related research areas and for this reason, a systematic review was not conducted. Nevertheless, a systematic approach was adopted for the literature search which is described further in **Table 2.1**.

Table 2.1: Methods of literature search

Process adopted for literature search	
1: Identify relevant databases	Relevant databases were identified for the search: PubMed, Ovid, Web of Science, Science Direct, Scopus, PsychINFO and Google Scholar
2: Establish key search terms	Databases were searched using the following search terms: <ul style="list-style-type: none"> • Postpartum psychosis/psychoses OR puerperal psychosis/psychoses OR postnatal psychosis/psychoses • Postpartum psychosis/psychoses OR puerperal psychosis/psychoses OR postnatal psychosis/psychoses AND aetiology OR etiology OR risk/trigger factors OR genetic factors • Postpartum psychosis/psychoses OR puerperal psychosis/psychoses OR postnatal psychosis/psychoses OR postpartum recurrence/relapse OR childbirth OR childbearing OR postpartum mood disorder(s) OR perinatal mood disorder(s) AND bipolar disorder OR manic depression • Postpartum psychosis/psychoses OR puerperal psychosis/psychoses OR postnatal psychosis/psychoses OR postpartum recurrence/relapse OR childbirth OR childbearing OR postpartum mood disorder(s) OR perinatal mood disorder(s) AND bipolar disorder OR manic depression AND aetiology OR etiology OR risk/trigger factors OR genetic factors
3: Review abstract of articles	The abstracts of articles were read to establish relevance. Only articles published in English language (from any country) were read further.
4: Review bibliography and related articles of relevant articles	The bibliography of each relevant article was reviewed to identify any further literature that had not been located in the initial search. Online links to 'related articles' and 'citing articles' were also searched.
5: Journal search alerts	Database search alerts were established to identify newly published literature meeting the search terms outlined in step 2.

Relevant literature identified in the search was subsequently collated and summarised within this chapter. First, to define the concept of PP, I describe the relationship between childbirth and affective disorders and provide an overview of postpartum mood disorders. The nosological status of PP and its relationship to BD will be

discussed, followed by a review of the literature that has investigated aetiological and triggering factors of PP. The final section of this chapter will describe the aims of this thesis.

2.2 Childbirth as a trigger of affective illness

The postpartum period has long been recognised as a time of high risk for affective illness in new mothers, with cases being described as early as 400 BC by the ancient Greeks (Klompener 1992). As cited by Klompener (1992), Hippocrates was the first to document the onset of severe affective illness in a woman during the first postpartum week, characterised by symptoms of restlessness, severe insomnia and delirium. Esquirol and Marcé were the first to conduct systematic studies of women with postpartum psychiatric illness, finding that although symptoms of depression occurred frequently, psychotic symptoms, extreme mood lability (periods of elation and dysphoria) and perplexity were especially common features of illness in women admitted for psychiatric treatment soon following delivery (Jansson 1964; Klompener 1992).

The temporal relationship between childbirth and affective illness has since been confirmed in epidemiological studies. Compared with pregnancy, or any other time in a woman's life, incidence rates of affective episodes are found to be significantly elevated in the postpartum period (Kendell, Chalmers and Platz 1987; Kendell et al. 1976; Langan Martin et al. 2016; Munk-Olsen et al. 2006; Terp et al. 1999). This level of risk remains elevated for up to 2 years following childbirth (Kendell, Chalmers and Platz 1987; Langan Martin et al. 2016), with the first 3 postpartum months being a time of peak incidence (Kendell et al. 1976; Langan Martin et al. 2016; Munk-Olsen et al. 2006; Nott 1982; Terp and Mortensen 1998). Episodes of non-psychotic depression represent a high proportion of postpartum psychiatric cases (Kendell, Chalmers and Platz 1987; Langan Martin et al. 2016), however, the relative risk of admission is particularly increased for psychotic illnesses compared to prior to or during pregnancy (Kendell et

al. 1976; Langan Martin et al. 2016; Munk-Olsen et al. 2006; Nott 1982; Terp and Mortensen 1998). In a UK population study, admissions (per week) for psychotic illnesses were up to 11 times more frequent within the first two postpartum weeks compared to the two-year period prior to pregnancy, and more than 17 times more frequent postpartum compared to during pregnancy (Langan Martin et al. 2016).

This striking vulnerability is particularly observed among women who present with affective psychoses (Bågedahl-Strindlund 1986; Kendell, Chalmers and Platz 1987; Kendell et al. 1976; Terp and Mortensen 1998). In a general population sample, Kendell et al. (1987) found the risk of admission for an affective psychotic illness to be 13 times higher within the first 3 postpartum months compared to before pregnancy. When only the first postpartum month was considered, the relative risk is dramatically increased further, with women being approximately 22 times more likely to be admitted than before pregnancy. Based on these observations, mood disorders that have onset following childbirth are typically classified according to a spectrum, described further in the following section.

2.3 Spectrum of postpartum mood disorders

Affective disturbances with postpartum onset are traditionally classified into three main categories: postpartum 'baby' blues, postnatal (non-psychotic) depression (PND) and PP. While not typically classified within this spectrum, postpartum 'highs' are also common among new mothers. The incidence and phenomenology of each is described in **Table 2.2**. Postpartum 'baby blues' and 'highs' are the mildest and most common forms of affective disturbances in new mothers, both of which are self-limiting in duration and do not require treatment. Consequently, neither forms of mood disturbance are considered clinically impairing episodes of mood disorder and as such are not classified within the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, American Psychiatric Association 2013a) or the International Classification of Diseases (ICD-11; World Health Organization, 2019). For this reason, the remainder of

this section will focus on describing PND and PP, which are traditionally classified as mood disorders.

Table 2.2: Incidence and phenomenology of postpartum mood disturbances

	Baby 'blues'	Postpartum H highs	Postnatal depression	Postpartum psychosis
Prevalence	20-75%	10-44%	10-15%	1-2/1000
Clinical features	Tearfulness Affective lability Irritability Poor concentration Fatigue	Euphoria Irritability	Dysphoria Tearfulness Anhedonia Fatigue Suicidal ideation Disturbed sleep/appetite	Mania/mixed affective state Mood lability/kaleidoscopic presentation Psychotic features Perplexity
Timing of postpartum onset	Day 4-5	Day 1-3	Week 1-6 months	Day 1-2 weeks
Duration	1-2 weeks (self limiting)	1-3 days	2 weeks - years	Weeks-months

2.3.1 Postnatal non-psychotic depression

Episodes of PND are estimated to occur in between 10-15% of women in the general population (Gavin et al. 2005; O'Hara and Wisner 2014; Le Strat, Dubertret and Le Foll 2011; Watson et al. 1984). These episodes may be the first of affective illness experienced or can occur within the context of an existing mood disorder. Women with a history of affective illness are at increased risk of depression following childbirth, with PND occurring in up to 37% of all deliveries (Di Florio et al. 2013).

Whether childbirth acts as a specific trigger for depression occurring in the postpartum period remains unclear. A number of large population register studies (Dean and Kendell 1981; Kendell et al. 1976; Munk-Olsen et al. 2006), and a controlled prospective study (Cooper et al. 1988) have found the relative risk of a depressive episode to be significantly increased in the postpartum period compared to pregnancy, while others have found no such difference (Heron et al. 2009; Nott 1982; Le Strat, Dubertret and Le

Foll 2011). Compared to non-postpartum control groups, episodes of depression have been shown to be more frequent in women who have recently given birth in some studies (Eberhard-Gran et al. 2002; Vesga-Lopez et al. 2008) but not in all (O'Hara et al. 1990). It is likely that the incidence of PND has been overestimated in some cases, potentially including episodes with onset during pregnancy. In their large register study of psychiatric postpartum admissions, Dean and Kendell (1981) found that over 50% of episodes of PND in their sample had onset in pregnancy. Similarly, Wisner et al. (2013) also found that of women who screened positive for depression within 6 weeks of childbirth, 60% of episodes either had onset before or during pregnancy.

If childbirth was a specific causal factor in the onset of depression, then episodes of depression which do have onset in the postpartum period would be expected to show a close temporal relationship to childbirth. Several studies have reported a peak in onset of depressive symptoms within the first four weeks following delivery (Cooper et al. 1988; Dean and Kendell 1981; Kendell et al. 1976; Munk-Olsen et al. 2006). However, compared to non-parent samples or during pregnancy, the relative risk of depressive illness remains particularly elevated for up to 6 months postpartum (Kendell et al. 1976; Langan Martin et al. 2016; Munk-Olsen et al. 2006), with onset of episodes being widely distributed throughout this period (Dean and Kendell 1981; Di Florio et al. 2013; Kendell et al. 1976; Langan Martin et al. 2016; Meltzer and Kumar 1985; Munk-Olsen et al. 2006). As will be discussed in section 2.3.4, no consensus exists on what time criterion should be used to define the postpartum period, yet it is reasonable to assume that episodes occurring more distally from the time of delivery are less likely to have a specific relationship with childbirth. Thus, whether childbirth plays a specific role in the pathophysiology of depression with onset in the postpartum period remains unclear.

2.3.2 Postpartum psychosis

In contrast to episodes of PND, there is clear and consistent evidence to suggest a specific relationship between childbirth and PP. These episodes are described further within this section.

2.3.2.1 Phenomenology

As noted previously, affective symptoms are prominent features in the clinical presentation of PP episodes (Brockington et al. 1981; Kamperman et al. 2017; Katona 1982; Kendell, Chalmers and Platz 1987; Klompenhouwer and van Hulst 1991; Kumar et al. 1995; McNeil 1986; Singh, Kaur and Mohan 1999; Videbech and Gouliaev 1995). Mania or hypomania (described further in section 2.4) frequently marks the onset of PP (Heron et al. 2008, 2007) while depressive symptoms, lability of mood and anxiety are also common features within these episodes (Davidson, Samspon and Davidson 2017; Ganjekar et al. 2013; Hays and Douglass 1984). Despite the presence of manic features, the prevailing mood state has been frequently observed as one of dysphoria (Klompenhouwer et al. 1995), contrasting with symptoms of expansive and elevated mood predominantly experienced in episodes of mania unrelated to childbirth. Similar to psychiatric illness occurring secondary to general medical conditions, women with PP typically present with marked confusion and perplexity (Brockington 1996; Brockington et al. 1981; Ganjekar et al. 2013; Klompenhouwer et al. 1995; McNeil 1986; Videbech and Gouliaev 1995), suggesting this symptom may be a defining feature of severe affective episodes related to childbirth.

As the name would suggest, psychotic symptoms frequently co-occur within the context of affective symptoms, and are especially prevalent in cases with early onset in the postpartum period (McNeil 1986; Vladimirova, Stoyanova and Milanova 2016). Almost every psychotic symptom has been observed to occur (Brockington 1996), though Schneiderian first rank symptoms (such as passivity phenomena and auditory hallucinations) and delusions of misrepresentation are particularly common (Hays and

Douglass 1984; Kadrmas, Winokur and Crowe 1979; Klompenhouwer et al. 1995; O’Sullivan and Dean 1991; Oosthuizen, Russouw and Roberts 1995; Pfuhmann et al. 1998). In episodes in which delusional ideas are present, the content typically relates to the child (Chandra et al. 2006; McNeil 1986). Overall, the classic presentation of PP is one of a ‘kaleidoscopic’ picture in which rapid changes in mood and psychotic symptoms may also be interspersed with brief, symptom free periods of lucidity (Di Florio, Smith and Jones 2013; Klompenhouwer et al. 1995; Sit, Rothschild and Wisner 2006).

PP is considered a psychiatric emergency, usually necessitating urgent treatment by hospital admission and pharmacological therapy. However, with treatment, recovery from an initial episode of PP is excellent in most women (Benvenuti et al. 1992; Davidson and Robertson 1985; Dean, Williams and Brockington 1989; Pfuhmann et al. 1999; Protheroe 1969). In contrast to psychoses unrelated to childbirth, the long term prognosis of PP is more favourable (Bell et al. 1994; Dean, Williams and Brockington 1989; Katona 1982; Pfuhmann, Stoeber and Beckmann 2002), particularly if the postpartum episode is the first of psychiatric illness experienced (Davidson and Robertson 1985; Dean, Williams and Brockington 1989; Nager et al. 2013; Polachek, Fung and Vigod 2016; Serretti, Olgiati and Colombo 2006; Terp et al. 1999).

2.3.2.2 Prevalence

PP is rare in the general population, estimated to affect between 1-2 in every 1000 deliveries (Kendell, Chalmers and Platz 1987; Munk-Olsen et al. 2006; Valdimarsdóttir et al. 2009; Videbech and Gouliaev 1995). Notably, not only are incidence rates of PP reliably consistent across cultures (Kumar 1994) but episodes can also present as phenotypically similar (Cox 1979), further implicating the physiology of childbirth in the triggering of PP.

2.3.2.3 Timing of onset

The onset of symptoms of PP is extremely rapid. Psychosis presents in the majority of cases within the first two weeks following delivery (Dean and Kendell 1981; Heron et al. 2007, 2008; Kendell, Chalmers and Platz 1987; Klompenhouwer et al. 1995; Kumar et al. 1995; Munk-Olsen et al. 2006; Videbech and Gouliaev 1995). While it has previously been assumed that a symptom free 'latent period' was a unique characteristic of psychoses in the immediate postpartum (Robinson and Stewart 1986), this view has since been challenged (Heron et al. 2008, 2007; Kendell, Chalmers and Platz 1987). In a study of 101 episodes of PP, onset of clinically significant symptoms was retrospectively identified to be present on days 1-3 in over 50% of episodes and on the first postpartum day in 22% of cases (Heron et al. 2007). Subjective recall of initial symptoms suggest hypomania is particularly prevalent in the first few days following childbirth, with feelings of elation, reduced need for sleep, excessive energy and pressured speech being most commonly reported (Heron et al. 2008). In some cases, symptoms of PP have also been noted to have onset during labour (Brockington 1996).

2.3.3 Adverse consequences of postpartum mood disorders

The consequences of postpartum mood episodes, but particularly of PP can be devastating for the mother, her baby and wider family. In the short-term, the relationship between the mother and her new baby is often disrupted, particularly when feelings of depersonalisation or delusional ideas relating to the child are present (Klompenhouwer et al. 1995; Mowry and Lennon 1998). The cognitive, behavioural and social development of infants of mothers with severe postnatal illness may also be impaired longer-term (Hoffman, Dunn and Njoroge 2017; Stein et al. 2014). During acute phases of illness, mothers often lack insight into their condition, reducing their ability to care for the infant appropriately and increasing the likelihood of neglect or accidental injury (Kumar et al. 1995; Rohde and Marneros 1993). Delusional ideation may provoke increased affection or protective behaviours from the mother, yet they can also lead to a higher prevalence of abusive behaviour, such as shouting, hitting or

smothering the infant (Chandra et al. 2006). While homicidal ideation is more frequently reported in PP compared with non-psychotic postpartum episodes (Kumar et al. 1995; Wisner, Peindl and Hanusa 1994), infanticide is extremely rare, estimated to occur in only 4% of all cases (Hatters Friedman and Sorrentino 2012). Conversely, the risk of self-harm is high. Compared with women outside the postpartum period, new mothers are up to 70 times more likely to die by suicide (Appleby, Mortensen and Faragher 1998), identifying suicide as a leading cause of maternal death in the UK (Knight 2018).

2.3.3.1 Recurrence of PP

While a small proportion of women with PP (10-15%) do not experience further episodes (Bell et al. 1994; Pfuhmann et al. 1999), the majority are at high risk of subsequent psychiatric episodes, both related and unrelated to childbirth. Of women who do have further children, recurrence of psychiatric illness is estimated to follow between 25-60% of subsequent deliveries (Benvenuti et al. 1992; Dean, Williams and Brockington 1989; Pfuhmann et al. 1999; Protheroe 1969; Robertson et al. 2005; Robling et al. 2000). Seemingly, some women may be particularly vulnerable to psychiatric illness triggered by childbirth, given that they only ever experience psychotic episodes in the postpartum period (Bell et al. 1994; Bergink et al. 2012; Brockington 1996; Pfuhmann et al. 1999). However, longitudinal studies reveal that as many as 40-75% of PP episodes are followed by episodes of psychiatric illness unrelated to childbirth (Pfuhmann et al. 1999; Robertson et al. 2005; Robling et al. 2000; Terp et al. 1999; Videbech and Gouliaev 1995), with the index episode often marking the onset of a recurrent affective or psychotic disorder.

2.3.4 Nosology of postpartum mood disorders

The nosological status of postpartum mood disorders and of PP in particular remains controversial. As discussed, the specificity of childbirth as a trigger for non-psychotic

depression is ambiguous, while PP is difficult to classify given that psychotic and affective symptoms are both prominent features of illness. Considering these difficulties, the following key theories have been proposed to explain the nosological context of postpartum mood disorders:

- **Distinct entities:** Postpartum mood episodes are unique illnesses, distinct from other functional psychiatric illnesses in terms of aetiology, phenomenology and prognosis.
- **Non-distinct entities:** Postpartum mood episodes are non-distinct occurrences of psychiatric illnesses, initiated by a non-specific trigger in the postpartum period.
- **Diathesis-trigger model:** Childbirth is a potent, specific trigger for psychiatric illness in individuals with a genetic predisposition, while the threshold for this triggering also differs between individuals who are susceptible. Vulnerability to the childbirth trigger is likely to depend on a complex interaction between social, psychological and biological factors.

Despite continued debate, current classification systems reject the notion that postpartum mood episodes are distinct entities, instead recognising them as episodes occurring in the context of other psychiatric disorders, exacerbated by the childbirth trigger. Affective illnesses with postpartum onset can be coded according to the DSM-5 using a peripartum specifier, though episodes with onset in pregnancy are not distinguished from those developing following childbirth. Furthermore, only episodes with onset within 4 weeks of delivery can be acknowledged using this specifier, a time period which may be too narrow for depressive episodes (Dean and Kendell 1981; Di Florio et al. 2013; Kendell et al. 1976; Langan Martin et al. 2016; Meltzer and Kumar 1985; Munk-Olsen et al. 2006).

In contrast, the ICD-11 includes a distinct category for psychiatric episodes occurring within 6 weeks of delivery ('Mental or behavioural disorders associated with pregnancy,

childbirth or the puerperium'), however this should only be used when presenting episodes are unable to be classified within the context of other disorders. Alternatively, psychotic or affective episodes occurring within 6 weeks of childbirth are encouraged to be denoted by a postpartum specifier, indicating the presence or absence of psychotic features. While current practice recognises episodes of PND and PP to be manifestations of major psychotic or affective disorders, temporal definitions of the postpartum period are considered arbitrary, with a timeframe of up to one year following childbirth being frequently used to define the postpartum period.

2.3.4.1 Nosology of postpartum psychosis

PP is not typically recognised as a distinct disorder in current diagnostic criteria, but has been included in previous editions of the DSM and ICD (see **Table 2.3**), reflecting diagnostic uncertainty as to whether these episodes are most appropriately categorised as a psychotic disorder, affective illness or distinct entity (McGorry and Connell 1990). This debate is ongoing and is not discussed in detail here (see **Figure 2.1** for an overview of relevant literature). However, the vast majority of literature provides compelling and consistent evidence to indicate that most episodes of PP are manifestations of BD triggered by childbirth (BD is described further below in section 2.4). As shown in **Figure 2.1**, frequently cited evidence in support of this theory is that:

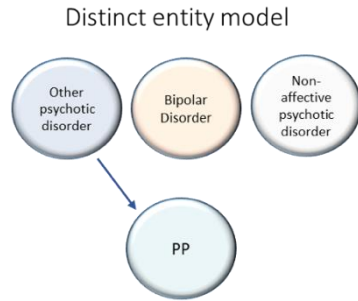
- **Affective symptoms, particularly manic features that also define BD are key characteristics of PP** (Brockington et al. 1981; Kamperman et al. 2017; Katona 1982; Kendell, Chalmers and Platz 1987; Klompenhouwer and van Hulst 1991; Klompenhouwer et al. 1995; Kumar et al. 1995; McNeil 1986; Singh, Kaur and Mohan 1999; Videbech and Gouliaev 1995).

Table 2.3: Clinical classification of PP according to standard diagnostic criteria

Diagnostic criteria	Category	Definition	Notes
ICD-8 (1967)	294.4	'Psychosis associated with childbirth' occurring within 6 weeks of delivery	<ul style="list-style-type: none"> Only to be used when episodes are unable to be classified elsewhere
DSM-II (1968)	294.4	'Psychosis associated with childbirth' No temporal specifier	<ul style="list-style-type: none"> Only to be used when episodes are unable to be classified elsewhere No postpartum specifier for other categories of psychotic disorders
ICD-9 (1975)	648.8	'Mental disorders complicating pregnancy, childbirth or the puerperium' occurring within 6 weeks of delivery	<ul style="list-style-type: none"> Included within a general obstetric category (codes 630-679 'complications of pregnancy, childbirth and the puerperium'). Code only to be used when episodes of psychosis are unable to be classified elsewhere
DSM-III (1980)	298.90	'Psychotic disorders not classified elsewhere' No temporal specifier	<ul style="list-style-type: none"> Code only to be used when episodes of psychosis are unable to be classified elsewhere No postpartum specifier for other categories of psychotic disorders
ICD-10 (1992)	F53	'Mental and behavioural disorders associated with the puerperium, not elsewhere classified' within 6 weeks of delivery	<ul style="list-style-type: none"> Code only to be used when episodes of psychosis are unable to be classified elsewhere
DSM-IV (1994)	No distinct category	-	<ul style="list-style-type: none"> No distinct category but postpartum specifier 'with postpartum onset' within 4 weeks of delivery can be applied to any episode of mood disorder or brief psychotic disorder only
DSM-5 (2013)	No distinct category	-	<ul style="list-style-type: none"> Postpartum specifier expanded to peripartum onset. The specifier 'with peripartum onset' can be applied to any episode of mood disorder or brief psychotic disorder occurring during pregnancy or within 4 weeks of delivery.
ICD-11 (2018)	SE21	'Mental or behavioural disorders associated with pregnancy, childbirth or the puerperium, with psychotic symptoms'	<ul style="list-style-type: none"> Code only to be used when episodes of psychosis are unable to be classified elsewhere

- Women who experience PP as the first episode of psychiatric illness frequently have a family history of affective disorders (Benvenuti et al. 1992; Platz and Kendell 1988; Vladimirova, Stoyanova and Milanova 2016).
- The long-term clinical course of PP is episodic rather than chronic, sharing greater similarities with affective disorders than schizophrenia like illnesses (Platz and Kendell 1988).
- Over time, diagnostic conversion from PP to BD occurs in a high proportion of cases. This is discussed in further detail in section 2.5.1 (Benvenuti et al. 1992; Blackmore et al. 2013; Munk-olsen et al. 2012; Protheroe 1969; Robling et al. 2000; Schöpf and Rust 1994a; Videbech and Gouliaev 1995).

Figure 2.1: Nosological models of postpartum psychosis



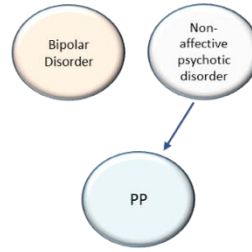
Evidence for distinct entity model

- Distinct phenomenology of PP episodes compared to episodes unrelated to childbirth (Agrawal, Bhatia and Malik 1997; Ganjekar et al. 2018; Kamperman et al. 2017; Katona 1982; Klompenhouwer and van Hulst 1991; Klompenhouwer et al. 1995; McNeil 1986; Nager et al. 2013; Polachek, Fung and Vigod 2016; Terp and Mortensen 1998)
- Non-puerperal recurrences following the index PP episode are diagnostically heterogeneous (Benvenuti et al. 1992; Munk-olsen et al. 2012; Protheroe 1969)
- Evidence of a 'pure postpartum group' of women who only experience psychiatric illness in relation to childbirth (Bergink et al. 2012; Brockington 1996, 1993; Wesseloo et al. 2016)

Evidence against distinct entity model

- No evidence of familiarity of a 'pure postpartum' disorder (Dean and Kendell 1981; Platz and Kendell 1988)
- Frequent diagnostic conversion to BD following the index PP episode (Benvenuti et al. 1992; Munk-olsen et al. 2012)
- Presence of affective symptoms in PP (Brockington et al. 1981; Kamperman et al. 2017; Katona 1982; Kendell, Chalmers and Platz 1987; Klompenhouwer and van Hulst 1991; Kumar et al. 1995; McNeil 1986; Singh, Kaur and Mohan 1999; Videbech and Gouliaev 1995).

PP as a psychotic spectrum disorder



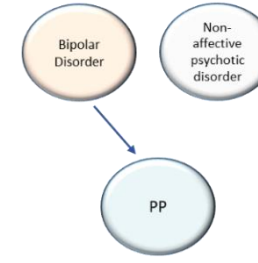
Evidence for PP as a psychotic spectrum disorder

- Distinct phenomenology of PP episodes compared to episodes unrelated to childbirth (see left for references), including presence of Schneiderian first rank symptoms (Brockington 1996; Kadmas, Winokur and Crowe 1979; Oosthuizen, Russouw and Roberts 1995)
- Increased risk of recurrence of schizophrenia in the postpartum period (Langan Martin et al. 2016; Munk-Olsen et al. 2009, 2006)

Evidence against PP as a psychotic spectrum disorder

- Few index PP episodes diagnosed in the context of schizophrenia (Bågedahl-Strindlund 1986; Benvenuti et al. 1992; Dean and Kendell 1981; Katona 1982; Kendell, Chalmers and Platz 1987; Klompenhouwer and van Hulst 1991; Nager et al. 2013; Schöpf and Rust 1994c; Videbech and Gouliaev 1996)
- High proportion of postpartum episodes of schizophrenia have onset in pregnancy or later in the postpartum period (Kumar et al. 1995; McNeil 1986; Schöpf and Rust 1994b; Terp and Mortensen 1998; Videbech and Gouliaev 1995)
- Risk of postpartum episodes of schizophrenia comparable with other non-affective or non-psychotic disorders, but lower than in BD (Munk-Olsen et al. 2009, 2006)
- Presence of affective symptoms (see left for references)

PP as a bipolar spectrum disorder



Evidence for PP as a bipolar spectrum disorder

- Distinct phenomenology of PP episodes compared to episodes unrelated to childbirth (Agrawal, Bhatia and Malik 1997; Ganjekar et al. 2018; Kamperman et al. 2017; Katona 1982; Klompenhouwer and van Hulst 1991; Klompenhouwer et al. 1995; McNeil 1986; Nager et al. 2013; Polachek, Fung and Vigod 2016; Terp and Mortensen 1998)
- Non-puerperal recurrences following the index PP episode are diagnostically heterogeneous (Benvenuti et al. 1992; Munk-olsen et al. 2012; Protheroe 1969)
- Evidence of a 'pure postpartum group' of women who only experience psychiatric illness in relation to childbirth (Bergink et al. 2012; Brockington 1996, 1993; Wesseloo et al. 2016)

Evidence against PP as a bipolar spectrum disorder

- No evidence of familiarity of a 'pure postpartum' disorder (Dean and Kendell 1981; Platz and Kendell 1988)
- Frequent diagnostic conversion to BD following the index PP episode (Benvenuti et al. 1992; Munk-olsen et al. 2012)
- Presence of affective symptoms in PP (Brockington et al. 1981; Kamperman et al. 2017; Katona 1982; Kendell, Chalmers and Platz 1987; Klompenhouwer and van Hulst 1991; Kumar et al. 1995; McNeil 1986; Singh, Kaur and Mohan 1999; Videbech and Gouliaev 1995).

- The risk of PP is highest among women with BD compared to any other psychiatric illness and the general population. This is discussed in further detail in section 2.5.2 (Kendell, Chalmers and Platz 1987; Langan Martin et al. 2016; Munk-Olsen et al. 2009; Viguera et al. 2011).

Thus, in light of the evidence indicating PP to be a form of BD, the concept of PP is used within this thesis to describe episodes of mania or mixed affective states (with or without psychotic features) that have onset following childbirth. The relationship between childbirth and BD is discussed in further detail in section 2.5. First however, I provide a brief overview of BD.

2.4 Bipolar disorder

BD, previously known as ‘manic depression’, is a severe and episodic psychiatric illness characterised by periods of impairing fluctuations in mood. Episodes of depression are a common occurrence in BD; however, the presence of mania is the defining feature of this illness. Episodes of mania are typically characterised by abnormally elated or expansive mood, feelings of irritability, racing thoughts, a reduced need for sleep, reckless or disinhibited behaviour and excessive energy and activity. While these symptoms are also present in hypomania, they are less severe and impairing than mania. Psychotic features are also common within BD, with more than 50% of individuals estimated to experience at least one psychotic symptom throughout the course of their illness (Goodwin and Jamison 2007; Perälä et al. 2007). Delusions of a religious or grandiose nature are particularly prevalent, being most likely to occur during severe episodes of mania (Canuso et al. 2008; Dunayevich and Keck 2000; Goodwin and Jamison 2007).

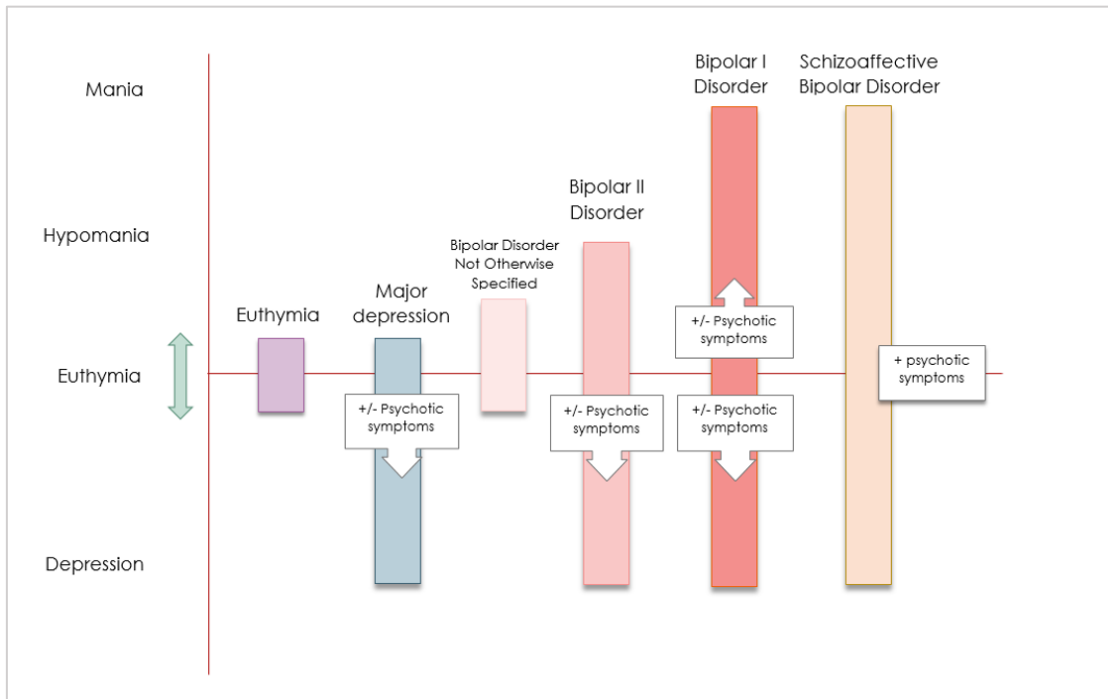
2.4.1 Spectrum of bipolar disorders

The phenotype of BD varies considerably between individuals (Judd et al. 2003; Mantere et al. 2004; Merikangas and Jin 2011) supporting the notion of a ‘mood disorder spectrum’ (see **Figure 2.2**). Distinct subtypes of BD are recognised in clinical practice, being categorised according to level of impairment in standardised diagnostic criteria. Episodes of mania are most impairing in Bipolar I disorder (BD-I), which is defined in DSM-5 criteria by the presence of a single manic episode lasting at least one week in duration, with or without psychotic features. Bipolar II (BD-II) is defined by the presence of at least one episode of hypomania lasting at least four days in the absence of psychotic features. Despite BD-I being widely considered as more impairing than BD-II, evidence suggests that depressive episodes are more frequent in BD-II, resulting in a more chronic course of illness within this subtype (Choi et al. 2011; Judd et al. 2003; Saunders and Goodwin 2010). Presentations of impairing high mood that do not meet clinical criteria for BD are also recognised within the DSM-5 as those ‘not otherwise specified’ (BD-NOS).

2.4.1.1 Schizoaffective disorder bipolar type

Historically, BD has been considered distinct from non-affective psychoses, a paradigm which is still adopted in clinical practice today. The Kraepelin Dichotomy, proposed by Emil Kraepelin in the early 20th century, differentiated between ‘Dementia Praecox’ (later termed schizophrenia) and BD. This approach assumed that distinctions in the phenotypic characteristics of schizophrenia and BD are also likely to reflect the aetiological heterogeneity underlying affective and non-affective psychoses. As discussed in section 2.3.4.1, this view has had important implications for the classification and nosology of PP (Brockington 1996). This traditional method of classifying psychiatric illness is however being challenged, with findings from genetic studies providing evidence for shared genetic susceptibility to schizophrenia and BD (Craddock and Owen 2010; Cross-Disorder Group of the Psychiatric Genomics Consortium 2013).

Figure 2.2 Spectrum of mood disorders



Schizoaffective disorders demonstrate the overlap between affective and psychotic illnesses. These disorders fully meet diagnostic criteria for schizophrenia, yet clinically impairing mood episodes are also a prominent feature of illness. Episodes of mania are a defining feature of schizoaffective disorder bipolar type (SA-BD), further suggesting shared aetiological factors with other bipolar spectrum disorders. For this reason, SA-BD is defined as a sub-type of BD within this thesis.

2.4.2 Epidemiology and illness course of bipolar disorder

BD is relatively common in the general population, affecting men and women equally (Bauer and Pfennig 2005; Di Florio and Jones 2010). Lifetime prevalence rates are estimated to be between 0.3 -1.5% for BD-I (Bauer and Pfennig 2005; Merikangas and Jin 2011; Weissman et al. 1996), 0.3-1.1% for SA-BD (Perälä et al. 2007; Scully et al. 2004) and between 0.4-3% for BD-II disorder (Bauer and Pfennig 2005; Merikangas and Jin 2011). These findings are however likely to underestimate the true prevalence of BD, given that milder manifestations of the illness may go undetected or untreated

(Mantere et al. 2004). Studies assessing a wider range of bipolar spectrum disorders, including those of subthreshold severity have estimated that BD is more likely to affect between 2.4 and 6.5% of the general population (Bauer and Pfennig 2005; Merikangas and Jin 2011).

Overall, evidence indicates few epidemiological differences in the prevalence, age at onset and course of BD between men and women (Azorin et al. 2012; Erol et al. 2015; Di Florio and Jones 2010; Nivoli et al. 2011). However, the most striking sex difference is observed during the perinatal period. The impact of childbirth is profoundly unique among women with BD, with little evidence to suggest this event acts as a course modifier of BD among new fathers (Kendell et al. 1976; Munk-Olsen et al. 2006).

2.5 Specificity of the childbirth trigger to bipolar disorder

As discussed in section 2.3.4.1, episodes of PP are most frequently defined as a subtype of BD. In this section, I discuss the literature examining the specific relationship between childbirth and BD.

2.5.1 Childbirth as a trigger of new onset bipolar disorder

Approximately 50-70% of women admitted for a psychotic episode following childbirth have no previous history of psychiatric illness (Blackmore et al. 2013; Davidson and Robertson 1985; Kendell, Chalmers and Platz 1987; Polachek, Fung and Vigod 2016; Robertson et al. 2005; Robling et al. 2000; Terp and Mortensen 1998; Valdimarsdóttir et al. 2009). However as shown previously, following the index episode, these women are at high risk of psychiatric illness unrelated to childbirth. Longitudinal follow-up studies of women admitted with a first episode of PP show that a considerable proportion subsequently develop BD (Benvenuti et al. 1992; Blackmore et al. 2013; Munk-olsen et al. 2012; Schöpf and Rust 1994a; Videbech and Gouliaev 1995), particularly if the index PP episode presented with a manic or mixed affective clinical picture (Benvenuti et al.

1992; Protheroe 1969; Robling et al. 2000). In a sample of 50 women who experienced PP as their first episode of psychiatric illness, more than 50% had a diagnosis of BD at follow-up after a median duration of 11 years (Videbech and Gouliaev 1995). In a similar study, Schöpf and Rust (1994a) reported a lower but substantial proportion of 31% of women (n=119) to be diagnosed with BD over a follow-up period of 22 years following an initial PP episode.

Several studies have also suggested that first onset of depression in the postpartum period may be an indicator of underlying BD. Women presenting with severe depression in the postpartum period have been found to more frequently experience atypical features such as mixed affective and psychotic symptoms (Azorin et al. 2012), thus being more consistent with a bipolar diathesis. Diagnostic conversion from psychotic unipolar depression to BD is estimated to occur in 11-29% of cases (Benvenuti et al. 1992; Bratfos and Haug 1966; Robling et al. 2000).

Onset of a psychiatric illness in the postpartum period that does not meet diagnostic criteria for an affective or psychotic disorder may also be an early indicator of underlying bipolarity (Benvenuti et al. 1992). In a study of 120,378 women with a first-time psychiatric contact for a non-bipolar related illness in the postpartum period, 3062 later had an admission or contact with psychiatric services for BD. Those whose first episode of illness occurred within a month of childbirth were significantly more likely to convert to BD (Munk-olsen et al. 2012), particularly if the episode required admission to hospital or occurred within the first two postpartum weeks. Overall, approximately 14% of women with postpartum onset of psychiatric symptoms in the first month converted to BD within 15 years of initial psychiatric contact, increasing to almost 19% within 22 years. This compared to 6.5% of women whose initial episode occurred later in the postpartum period and 5.4% of women for whom the index episode of psychiatric illness was unrelated to childbirth.

2.5.2 Childbirth and risk of recurrence of bipolar disorder

While a high proportion of women with BD experience their first impairing episode of mood illness following childbirth, consistent evidence also indicates that women with pre-existing BD are especially vulnerable to recurrence in the postpartum period. Thus, further implicating childbirth as a unique and specific trigger of affective illness within this group. This is in contrast to pregnancy, for which there is little indication that vulnerability to recurrence of BD is increased during this period (Di Florio and Jones 2010; Viguera et al. 2000). Viguera et al. (2000) compared risk of recurrence over time in pregnant and non-pregnant women with BD who had discontinued mood stabilising medication. Over a period of 40 weeks (consistent with the average gestation period of most pregnancies), women who were pregnant were no more likely to experience a mood episode compared to a sample of non-pregnant women, suggesting pregnancy itself has little influence on the course of BD. Conversely, it has been suggested that pregnancy may be protective for women with BD (Brockington 1996), resulting in a decrease in psychopathology compared to the period prior to pregnancy (Grof et al. 2000) and a decrease in the relative risk of psychiatric admission compared to non-mothers with BD (Munk-Olsen et al. 2006).

By comparison, the risk of psychiatric admission in women with BD is significantly greater following childbirth compared to any other time in their lives (Munk-Olsen et al. 2006). Though non-psychotic depression is a common form of postpartum mood disturbance in women with BD (Maina et al. 2014; Viguera et al. 2011), the risk of a psychotic episode following childbirth is strikingly elevated, compared not only to the general population (Jones and Craddock 2001) but also to women with a history of other non-psychotic or affective psychiatric illnesses (Kendell, Chalmers and Platz 1987; Langan Martin et al. 2016; Munk-Olsen et al. 2009; Viguera et al. 2011). In a Danish registry study, the influence of childbirth on risk of admission for psychotic episodes was examined across a range of psychiatric disorders (Munk-Olsen et al. 2009). Admission rates within the first postpartum month were compared with those in samples of non-mothers matched for psychiatric diagnosis. Compared to non-mothers,

admissions for a psychotic episode were 37 times more likely in the first postpartum month in women with BD. Comparatively, the relative risk of admission was considerably lower at 4.6 for schizophrenia and 3.0 for other psychiatric disorders. Moreover, of disorders specified, Langan Martin et al. (2016) found the majority of psychiatric admissions during the first six weeks following childbirth to be for BD related episodes (14.4%), being considerably more common than admissions for any other psychiatric disorder (1.4%-7.2%).

Studies which have assessed postpartum recurrence in samples of women with BD are described in **Table 2.4**. A recent meta-analysis of 25 studies (including both retrospective and prospective studies) sought to examine postpartum recurrence in 5105 deliveries from 3495 women with BD (Wesseloo et al. 2016). Wesseloo and colleagues found that 37% of all women experienced a broadly defined mood episode (i.e. at least one mood episode of any type) within 12 months of childbirth and 17% an episode of PP, with no evidence to suggest significant differences in risk between women with BD-I and BD-II. Notably however, few studies included in this meta-analysis assessed postpartum recurrence of BD using a prospective follow-up design. Of those that did, risk of broadly defined recurrence occurred following childbirth in 25-70% cases, and affective psychotic recurrence in 25-40%, though sample sizes of these studies were small (n=11-37).

Importantly however, the findings of this meta-analysis were based on estimates of postpartum recurrence that varied widely across individual studies, ranging from 13% (Bilszta, Meyer and Buist 2010) to 75% (Maina et al. 2014). Methodological differences between studies are likely to account for this variation, such as differences in the temporal cut-off used to define the postpartum period (between 1 and 12 months), the diagnostic inclusion criteria used, the definition of postpartum recurrence (i.e. type and polarity of episode) and the design of the study (i.e. retrospective or prospective).

Table 2.4: Studies assessing postpartum recurrence in women with bipolar disorder

Author	Sample	Method of assessment	Definition of recurrence	Recurrence rates in the postpartum period
Bratfos and Haug (1964)	n=82 (251 deliveries)	Case-note review and clinical interview Follow-up period of 10 years	No diagnostic criteria specified Postpartum period defined as 3 months	<ul style="list-style-type: none"> • 33.5% of women experienced a postpartum recurrence • 20.7% of all deliveries affected
Reich and Winokur (1970)	n=20	Structured interview Case note review	No diagnostic criteria specified Postpartum period defined as 6 months	8/20 (40%) of women experienced postpartum recurrence
Kendell et al. (1987)	n=47,000 women from the general population (54,087 deliveries) n=33 ICD-9 BD	Psychiatric case-register Admissions assessed over 12 years	RDC episode requiring psychiatric admission Postpartum period defined as 3 months	21.4% of women with history of BD
Dean, Williams and Brockington (1989)	n=103 women ICD-8/9 defined postpartum psychosis or BD <ul style="list-style-type: none"> • n=51 women (PP only <2 weeks) • n=33 (childbirth and non-childbirth related episodes) • n=19 (non-childbirth related episodes only) 	Structured interview Case-note review	RDC affective or psychotic episode. Postpartum period defined as 6 months	29/80 (36%) of subsequent deliveries to women with BD who have a history of previous postpartum episode
Marks et al. (1992)	n=26 (RDC BD-I, BD-II and SA-BD)	Structured interview Case-note review	RDC affective or psychotic episode Postpartum period defined as 6 months	65% of women (sample included schizoaffective disorder)
Cohen et al. (1995)	n=27 (DSM-III BD)	Case-note review Follow-up telephone interview	No diagnostic criteria specified Postpartum period defined as 3 months	9/27 (33%) of women experienced postpartum recurrence
Hunt and Silverstone (1995)	n=23 (RDC BD)	Case-note review Structured interview	RDC affective episode Postpartum period defined as 3 months	<ul style="list-style-type: none"> • 4/10 (40%) deliveries to 13 women with postpartum onset BD • 5/16 (31%) deliveries to 10 women for whom the onset of BD occurred prior to having children • 1/4 (25%) of deliveries assessed prospectively resulted in recurrence
Blehar et al. (1998)	n=186 (DSM-III BD-I)	Structured clinical interview Case-note review	No diagnostic criteria specified Affective episode within 4 weeks of delivery	<ul style="list-style-type: none"> • 69/139 (45.3%) of women experienced at least one perinatal episode • 25/51 (49%) women experienced postpartum recurrence
Grof et al (2000)	n=28 (RDC BD-I)	Semi-structured interview Case-note review	No diagnostic criteria specified Affective episode within 9 months of delivery	7/28 (25%) women experienced postpartum recurrence

BD: Bipolar disorder, **BD-I:** Bipolar I disorder, **BD-II:** Bipolar II disorder, **SA-BD:** Schizoaffective disorder bipolar type, **PP:** Postpartum psychosis, **ICD:** International Statistical Classification of Diseases and Related Health Problems; **DSM:** Diagnostic and Statistical Manual of Mental Disorders; **RDC:** Research diagnostic criteria

Table 2.4: Studies assessing postpartum recurrence in women with bipolar disorder

Author	Sample	Method of assessment	Definition of recurrence	Recurrence rates in the postpartum period
Jones and Cradock (2001)	n=152 (DSM-IV BD-I, BD-II, SA-BD, BD-NOS)	Semi-structured interview Case-note review	DSM-IV affective episode within 6 weeks of delivery	<ul style="list-style-type: none"> • 81/313 (26%) deliveries to 152 women were followed by postpartum psychosis • 28/152 (18%) women experienced other postpartum episodes within six months of delivery
Freeman et al. (2002)	n=30 (DSM-IV BD-I, BD-II, BD-NOS)	Structured interview	No diagnostic criteria specified Affective episode within 4 weeks of delivery	20/30 (67%) of women experienced postpartum recurrence
Akdeniz et al. (2003)	n=72 (DSM-IV BD)	Semi-structured interview Case-note review	No diagnostic criteria specified Affective episode within 4 weeks of delivery	26/160 (16.3%) deliveries affected 9/160 (5.3%) deliveries followed by mania
Wisner et al. (2004)	n=26 (DSM-IV BD)	Structured interview	DSM-IV affective episode Postpartum period defined as 5 months	18/26 (69%) women at least one recurrence; <ul style="list-style-type: none"> • 5/26 (19%) mania, hypomania or mixed affective state • 13/26 (50%) major depressive episode
Robertson et al. (2005)	n=103 (DSM-IV BD or SA-BD, all of whom had a history of PP)	Semi-structured interview Case-note review	DSM-IV affective or psychotic episode Postpartum period defined as 4 weeks	<ul style="list-style-type: none"> • 31/54 (57%) women mania/affective psychosis < 6 weeks of delivery • 5/54 (9%) women mania/affective psychosis between 6 weeks and 6 months postpartum
Munk-Olsen et al. (2006)	Subset of women with ICD-8/ICD-9 BD (n not reported), selected from 630,373 women in general population .	Psychiatric case-register	ICD-8 and ICD-10 affective episode requiring admission Postpartum period defined as 12 months	<ul style="list-style-type: none"> • 0.5/1000 deliveries within 4 weeks • 0.14/1000 deliveries within 8 weeks • 0.02/1000 deliveries within 5 months (months 6-12 not analysed due to limited power)
Sharma, Smith and Mazmanian (2006)	n=25 (DSM-IV BD-I and BD-II)	Structured interview	DSM-IV affective psychosis Postpartum period defined as 4 weeks	10/25 (40%) women at least one recurrence <ul style="list-style-type: none"> • 3/25 (12%) women mania or mixed episode
Harlow et al. (2007)	n=786 (ICD-8/9/10 BD)	Psychiatric case-register	Admission for psychotic or affective episode Postpartum period defined as 3 months	8.5% of women readmitted following delivery
Munk-Olsen et al. (2009)	n=208 (ICD-8/ICD-10 BD)	Psychiatric case-register	Admission for any psychiatric illness Postpartum period defined as 12 months	22% of women within 3 months postpartum 26.9% of women within 12 months postpartum

BD: Bipolar disorder, **BD-I:** Bipolar I disorder, **BD-II:** Bipolar II disorder, **SA-BD:** Schizoaffective disorder bipolar type, **PP:** Postpartum psychosis, **ICD:** International Statistical Classification of Diseases and Related Health Problems; **DSM:** Diagnostic and Statistical Manual of Mental Disorders; **RDC:** Research diagnostic criteria

Table 2.4: Studies assessing postpartum recurrence in women with bipolar disorder

Author	Sample	Method of assessment	Definition of recurrence	Recurrence rates in the postpartum period
Colom et al. (2010)	n=200 (DSM-IV BD-I and BD-II)	Structured interview Case-note review	DSM-IV affective episode within 4 weeks of delivery	43/180 (24%) women with lifetime postpartum recurrence, of which: <ul style="list-style-type: none"> • 74.4% (32/43) major depression • 20.9% (9/43) mania • 2.3% (1/43) mixed affective state • 2.3% (1/43) hypomania and depression
Bilszta et al. (2010)	n=23 (DSM-IV BD-I and BD-II)	Structured interview Case-note review	Any change in mood symptoms requiring inpatient or outpatient intervention within 6 months of delivery	3/23 (13%) women experienced postpartum recurrence
Viguera et al. (2011)	n=621 (DSM-IV BD-I and BD-II)	Case-note review	DSM-III and IV affective episode within 6 months of delivery	51.5% of women experienced at least one lifetime postpartum recurrence 16% of BD-I women had postpartum psychotic episode
Abdel-Hay et al. (2010)	n=83 (DSM-IV BD-I)	Structured interview	No diagnostic criteria specified Affective episode within 4 weeks of delivery	26/83 (31%) women experienced postpartum recurrence
Bergink et al. (2012)	n=41 (DSM-IV BD-I and BD-II)	Structured interview Case-note review	DSM-IV affective episode within 4 weeks of delivery	10/41 (24.4%) women experienced postpartum recurrence
Doyle et al. (2012)	n=78 (DSM-IV BD-I, BD-II, SA-BD, Mania; single episode)	Case-note review	DSM-IV affective or psychotic episode within 6 weeks of delivery	20/43 (46.5%) women had a recurrence postpartum • 14/43 (33%) had an episode of mania/affective psychosis
Di Florio et al. (2013)	n=1212 (DSM-IV BD-I and BD-II)	Semi-structured interview Case-note review	a) DSM-IV lifetime affective mania, hypomania, mixed affective state or affective psychosis within 6 weeks of delivery b) DSM-IV lifetime non-psychotic depression within 6 weeks of delivery, plus episodes meeting narrow definition c) DSM-IV lifetime affective psychotic or non-psychotic episode during pregnancy or within 6 months of delivery	Lifetime recurrence rates according to definition: a) 326/980 (33.3%) women BD-I and 21/232 (9.1%) women BD-II b) 544/980 (55.5%) women BD-I and 93/232 (40.1%) women BD-II c) 681/980 (69.5%) women BD-I and 160/232 (69%) women BD-II
Maina et al. (2014)	n=276 (DSM-IV BD-I and BD-II)	Case-note review	No diagnostic criteria specified Affective episode within 4 weeks of delivery	207/276 (75%) women experienced at least one recurrence, of which: <ul style="list-style-type: none"> • 79.7% major depression • 17.4% mania/mixed • 2.9% hypomania 23% of all episodes affective psychosis

BD: Bipolar disorder, **BD-I:** Bipolar I disorder, **BD-II:** Bipolar II disorder, **SA-BD:** Schizoaffective disorder bipolar type, **PP:** Postpartum psychosis, **ICD:** International Statistical Classification of Diseases and Related Health Problems; **DSM:** Diagnostic and Statistical Manual of Mental Disorders; **RDC:** Research Diagnostic Criteria

2.5.3 History of postpartum psychosis and risk of subsequent recurrence

As in the general population, recurrence of PP after the index PP episode is high among women with BD, with 50-87% of women experiencing affective psychosis following a subsequent delivery (Bergink et al. 2012; Blackmore et al. 2013; Maina et al. 2014; Pfuhmann et al. 1999; Robertson et al. 2005). Using a narrow temporal definition of the postpartum period (restricted to the first 2 weeks following delivery), a history of both BD and PP places women at significantly greater risk of PP compared to those who have only ever experienced mood episodes unrelated to childbirth (Dean, Williams and Brockington 1989). Seemingly, risk is increased even further among women who only ever experience affective psychosis in relation to childbirth (i.e. a pure postpartum group), with PP occurring significantly more frequently compared to women with a more classical bipolar illness in which episodes related and unrelated to childbirth occur (Bergink et al. 2012). To date, it remains unclear whether a postpartum onset of BD predisposes women to further postpartum episodes. Though some studies indicate recurrence of PP to be more frequent among women with postpartum onset BD (Dean, Williams and Brockington 1989; Hunt and Silverstone 1995) others have reported little influence on subsequent risk of PP (Robertson et al. 2005).

In summary, research to date suggests that most episodes of PP are manifestations of BD, indicating childbirth to be a potent trigger for the onset or recurrence of BD. Nevertheless, findings show that despite vulnerability to mania (and psychosis in some cases), not all women with BD experience PP (McNeil 1988d). This would indicate that over and above vulnerability for BD, susceptibility to the childbirth trigger also varies between individuals within this disorder (consistent with the diathesis stress model described in section 2.3.4.). Risk of PP is therefore likely to depend on a complex interaction between a range of aetiological and triggering factors. The literature that has examined factors influencing risk of PP will be reviewed in the remainder of this chapter.

2.6 Factors influencing risk for postpartum psychosis in bipolar disorder

A history of BD is consistently identified as the strongest risk factor for PP. However, little is known regarding the aetiological and triggering factors that may predispose some women within this high-risk group to be especially vulnerable to postpartum relapse. Limited evidence has implicated neurobiological factors related to endocrine, immunological and circadian functions in the mechanism of onset of PP. Nonetheless, findings to date are inconclusive, suggesting that other factors may also play a role in the pathogenesis of PP. Here, the research examining neurobiological factors of PP will first be discussed, followed by a review of literature investigating other potential triggers and protective factors of these episodes.

2.6.1 Neurobiological factors

2.6.1.1 Genetic factors

The familial clustering of affective disorders and of childbirth related episodes in women with PP strongly implies a degree of shared heritability of genetic factors in the onset of these disorders. PP is associated with higher rates of psychiatric illness among first or second degree relatives than is observed in the general population (Benvenuti et al. 1992; Robertson et al. 2005; Schöpf and Rust 1994a; Da Silva and Johnstone 1981). Family history of affective disorders is especially common, being present in between 40-50% of women with PP (Benvenuti et al. 1992; McNeil 1988d; Da Silva and Johnstone 1981). A positive family history of BD is also frequently observed in women whose initial PP episode met criteria for mania (Oosthuizen, Russouw and Roberts 1995; Protheroe 1969; Schöpf and Rust 1994a). Studies examining the familial clustering of PP in BD are scarce, however, episodes of PP have been observed to occur in 74% of women with BD with a positive family history of PP in a first degree relative (20/27 cases), compared

with only 30% of women with BD without this family history (38/125 cases) (Jones and Craddock 2001).

Though evidence from family history studies indicate that genetic factors are likely to play an important role in susceptibility to PP, specific genes are yet to be identified. Findings to date are limited to genetic linkage and candidate studies. In a genome wide scan of 54 sibling pairs with BD and at least one family member with a history of PP, significant linkage found was at chromosomal location 16p13 and suggestive linkage at 8q24 (Jones et al. 2007). These locations were not identified in the genome wide scan of a BD sample, suggesting a specific relationship between these locations and the postpartum triggering of episodes of BD.

The close temporal relationship of PP to childbirth strongly suggests a role for sex hormones in the triggering of these episodes (discussed further in the following section). Genes implicated in oestrogen and neurotransmitter function have therefore been identified as plausible targets for candidate studies. Methyl transferase like 13 gene (METTL13) is suspected to be involved in gene transcription associated with oestrogen receptor sites, thus making it an ideal candidate for an association with postpartum mood disorders. In a sample of 759 women with broadly defined affective disorders, METTL13 was associated with the occurrence of severe postpartum mood symptoms (Mahon et al. 2009). Importantly, this gene has also been associated specifically with PP among a diagnostically heterogeneous sample (Thippeswamy et al. 2017). While the relationship of the oestrogen receptor alpha gene (ESR 1) to PP has also been examined, no associations have been reported between polymorphisms of ESR 1 and broadly defined PP (Thippeswamy et al. 2017) or with PP in women with BD (Middle et al. 2003).

Genes which interact with neurotransmitter function, particularly in cases where expression of the gene is likely influenced by oestrogen have also been a focus of research. The 5-HTTT serotonin transporter gene is one such gene whose expression is

known to be influenced by hormones. Coyle et al. (2000) found variations in the 5-HTTT gene to be significantly associated with PP in women with BD. In particular, the presence of the STin2.12 allele was associated with a four times increased risk of postpartum relapse. This effect size was further increased when analysis was restricted to multiparous women with a recurrent history of PP only. These findings have since been replicated, with associations between a number of polymorphisms of serotonergic genes (including 5-HTT) and PP being found in an independent sample of women with BD (Kumar et al. 2007). While several additional genetic locations of interest related to hormonal and neurotransmitter functioning have been investigated, these have not been associated with the occurrence of PP (Mahon et al. 2009; Pfuhlmann, Stoeber and Beckmann 2002; Thippeswamy et al. 2017). Genes with a known influence on immunological function (Weigelt et al. 2013) and regulation of circadian rhythms have also been indicated as potentially important in the pathogenesis of PP (Dallaspezia et al. 2011), yet remain to be examined further.

The influence of genetic factors on susceptibility to PP remains a key focus of future research. International collaborative efforts to conduct genome wide association studies (GWAS) of postpartum mood disorders and specifically of PP, are currently underway (<https://www.momgenesfightppd.org/> and <https://www.mghp3.org/>). To achieve sufficient power, samples of up to 100,000 individuals will be required to detect genetic biomarkers of PP (Davies 2017). As only 1 per every 1000 deliveries in the general population are affected, accruing the sample size needed has thus far been challenging. For this reason, genetic factors will not be examined within this thesis and as such, are not discussed further. Nevertheless, among women who are genetically susceptible, the postpartum triggering of severe mood disorders is also likely to depend on a complex interaction with other biological and psychosocial factors (Jones and Craddock 2007). The influence that these other factors may have in determining risk of PP will be discussed in subsequent chapters of this thesis.

2.6.1.2 Sex hormones

Reproductive hormones fluctuate significantly across the perinatal period, with progesterone and oestrogen rising steadily during pregnancy and falling abruptly following delivery (Vannuccini et al. 2016). The rapid withdrawal of oestrogen following childbirth (between a 100-1000 times below that of late pregnancy) coincides with the period of greatest risk for onset of affective psychosis, implicating oestrogen pathways in the aetiology of PP (Kumar et al. 1997; Meakin et al. 1995; Wieck et al. 1991).

Support for this theory has been provided by several case-studies, in which levels of oestrogen plasma have been found to be lower than expected among women with PP (Ahokas, Aito and Turtiainen 2000). In a limited number of cases, episodes of PP have also been effectively treated with oestradiol (Sichel et al, 1995). Nonetheless differences in absolute hormone levels are not observed among all women with postpartum mood disorders (Gale and Harlow 2003; Klier et al. 2007; Skalkidou et al. 2012), leading to the revised hypothesis that some women may be particularly sensitive to the fluctuations of hormones that occur in relation to childbirth (Bloch et al. 2000; Elder Schiller, Meltzer-Brody and Rubinow 2015). Consistent with this theory, it has been demonstrated that some women experience mood episodes in relation to a range of reproductive cycle events. Associations have been found between mood episodes triggered by childbirth, the premenstrual phase of the menstrual cycle and/or menopause in women with BD (Brockington et al. 1988; Fornaro and Perugi 2010; Perich et al. 2016; Robertson Blackmore et al. 2008; Slyepchenko et al. 2017).

2.6.1.3 Immunological factors

Emerging research also suggests that immune dysfunction may play a key role in the pathogenesis of PP. This hypothesis is plausible for several reasons. Firstly, immunological factors have been implicated in the aetiology of psychosis more generally (Bergink, Gibney and Drexhage 2014) and in BD (Piccoli de Melo et al. 2017). Prevalence of comorbid immune disorders are high in BD (SayuriYamagata et al. 2017),

while the risk of BD is also increased among individuals with autoimmune disorders (Benros et al. 2013). Inflammatory cytokines (responsible for cell signalling and promotion of systemic inflammatory response) are found to be significantly elevated during acute phases of bipolar related mood episodes, most consistently during episodes of mania (Brietzke et al. 2009; Sayana et al. 2017). Secondly, immune disorders such as postpartum thyroiditis, rheumatoid arthritis and multiple sclerosis are typically exacerbated in the postpartum period, sharing similarities with the clinical course of PP (Bergink et al., 2013, 2015). In some cases, PP and immune disorders have been known to co-occur (Ganjekar et al. 2018).

Other studies which have investigated the immunological hypothesis of PP have provided further support for this theory. Generalised immune dysregulation has been observed in women with PP (Kumar et al. 2017). Furthermore, PP has been associated with significantly increased rates of autoimmune thyroid dysfunction, which progresses significantly faster to clinical thyroid disease in women admitted for PP compared to a postpartum control group (Bergink et al. 2011b). In this study, rates of thyroid dysfunction and of clinical thyroid disease remained significantly elevated at 9 months postpartum and were found to be independent of the effect of lithium treatment, which has been demonstrated to adversely affect thyroid function. More recently, monocyte levels and upregulation of inflammatory monocyte genes have also been reported in women admitted for first-onset PP compared to postpartum and non-postpartum control groups who did not have PP (Bergink et al. 2013).

2.6.2 Other triggering and protective factors

Compared to neurobiological factors, comparatively less is known regarding other factors that may influence risk of PP. Identifying triggering and protective factors of PP (especially those that are modifiable) are important for the management of BD during the perinatal period, and in particular, the prevention of these episodes. Here, I review

the literature examining the relationship between other, non-neurobiological factors and PP.

2.6.2.1 Sleep disruption

Sleep loss and the disruption of circadian rhythms has long been proposed as a final common pathway in the aetiology of PP (Jones et al. 2014). This hypothesis is proposed for several reasons. First, sleep loss is both a symptom and frequently cited precipitant of mania unrelated to childbirth (Benedetti and Colombo 2011; Lewis et al. 2017; Lewis, Foster and Jones 2016). Second, reproductive hormones and neurotransmitters play a role in the regulation of the circadian sleep/wake cycle (Rosenwasser and Turek 2015), both of which are also implicated in the aetiology of mood disorders more generally and of PP. Third, the period from late pregnancy through the immediate postpartum is associated with acute sleep loss in new mothers, a time which typically coincides with the onset of PP. Strouse, Szuba and Baxter (1992) reported on the cases of three women in which mania was induced following partial sleep deprivation therapy for first onset of postpartum psychotic and mood symptoms. Symptoms remitted in all women after a period of recovery sleep, though all women required further treatment with mood stabilisers.

Only three studies have since investigated the potential triggering of PP associated with sleep disruption. In the first, duration of labour and time of delivery were compared as proxy measures of sleep disruption during labour between 21 women admitted with PP and a comparison group of 21 parous women without PP recruited from the same hospital. These women were also matched for age, parity and year of delivery. The PP group comprised women meeting DSM-IV diagnostic criteria for BD, schizoaffective disorder (both bipolar and depressed type) and major recurrent depression (with psychotic features). Compared to the control group, women with PP were found to have experienced significantly longer labours and were more likely to give birth during the night time, suggesting acute sleep loss during labour may precipitate the onset of

PP (Sharma, Smith and Khan 2004). It is however difficult to relate these findings to PP within BD, given that women with major psychotic depression and schizoaffective disorder depressed type were also included in the PP group. Furthermore, the control group consisted of healthy parous women without a personal or family history of mood disorders, thus it is possible that differences in the length of labour and time of delivery reflect factors associated with the presence or absence of psychiatric disorder. Furthermore, sample sizes in this study were small (n=21 in each group) and no information was obtained regarding sleep patterns in late pregnancy. This may be important given that changes in sleep in late pregnancy may be indicators of more chronic sleep disruption prior to childbirth.

Bilszta, Meyer and Buist (2010) aimed to prospectively compare sleep patterns throughout pregnancy and the postpartum period between women at high-risk of PP (defined as women with a diagnosis of BD-I or BD-II or a history of PP, n=23) and a control group of 15 pregnant women without any psychiatric history. Assessments included sleep diaries that were completed daily and self-report questionnaires administered at baseline, in the last two weeks of pregnancy and at weeks one, four and eight postpartum. The authors found no significant differences between the two groups in any sleep related factors across the perinatal period (such as time in bed, time available for sleep, time awake during the night and subjective sleep). However, given that so few women experienced a severe recurrence of mood disorder following delivery (n=3, defined as any recurrence causing impairment that required inpatient or outpatient clinical intervention), it was not possible to perform comparisons of sleep factors between women who did and did not experience a severe postpartum mood episode.

Finally, in a large sample of women with well-defined BD-I (n=870), our research group (BDRN) examined whether overall vulnerability to mania triggered by sleep loss (indicated by a self-reported history of manic episodes triggered by sleep loss) was also associated with the lifetime occurrence of PP (Lewis et al. 2018). In this study, we

compared the lifetime occurrence of PP between women who self-reported at least three episodes of mania triggered by sleep loss and women who did not report this. PP episodes were significantly more frequent among women who report sleep loss as a frequent trigger of mania (36.8%), compared to women who did not (21.8%). Conversely, we found no association between self-reported history of depressive episodes triggered by sleep loss and the occurrence of PP or of PND, indicating specificity of the sleep loss trigger to episodes of mania and of PP. However, due to the retrospective nature of this study, we were not able to directly assess the role of sleep loss within the same perinatal period in which the episode of PP occurred. Furthermore, whether sleep loss was a causal factor in the triggering of mania as opposed to the onset of early prodromal symptoms could not be determined.

Thus, based on literature to date, the role of sleep disruption occurring *within* the perinatal period (for example during late pregnancy or associated with labour) in the occurrence of PP remains unclear. Furthermore, these relationships are yet to be investigated in women with BD using a prospective methodology.

2.6.2.2 Mood stabilising medication during the perinatal period

Women who have BD face difficult decisions regarding medication use during the perinatal period, often in the absence of an established evidence base (Dolman, Jones and Howard 2016; Jones and Jones 2017). Careful consideration must be given to the risks and benefits of psychotropic medication use not only for the mother, but also for her baby and wider family. This decision-making process is influenced by a range of factors, such as the woman's illness history and previous response to treatment, efficacy and teratogenicity of psychotropic medications, intention to breastfeed and crucially, risk of recurrence during the perinatal period (Dolman, Jones and Howard 2016; National Institute for Health and Clinical Excellence 2014; Stevenson et al. 2016). Subsequently, many women withdraw pharmacotherapy during pregnancy, particularly when there are concerns of teratogenic effects on the foetus (Dolman, Jones and

Howard 2016; Stevenson et al. 2016). Nevertheless, few studies have examined the effects of medication withdrawal on course of BD during pregnancy. Available evidence indicates that compared to women who continue prophylactic mood stabilisers during pregnancy, the risk of antenatal recurrence of BD is significantly higher among women who discontinue medication (Stevens et al. 2019; Viguera et al. 2007). Furthermore, latency to illness recurrence has been found to be 11 times quicker in women with BD who discontinued lithium treatment rapidly during pregnancy (within two weeks) compared to those who withdrew lithium more gradually (over a period greater than two weeks; Viguera et al. 2007).

In contrast to pregnancy, there is limited evidence to suggest that prophylactic mood stabilisers during the perinatal period moderate risk for postpartum recurrence in BD. Based on data obtained from only eleven studies, a recent meta-analysis found women who continued prophylactic mood stabilisers throughout the perinatal period were significantly less likely to experience a mood episode following childbirth compared to those did not take any medication (Wesseloo et al. 2016). The authors reported 23% of women who had taken prophylactic mood stabilisers during pregnancy to experience a postpartum recurrence, compared to 66% of women who remained medication free. However, these findings are predominantly based on case-reports or small retrospective studies of lithium. Controlled studies examining the efficacy of prophylactic mood stabilisers in preventing postpartum relapse in women with BD are rare (Cohen et al. 1995; Viguera et al. 2000; Wisner et al. 2004).

Due to the focus of research on lithium, little is known regarding the prophylactic efficacy of antipsychotics and anticonvulsants for prevention of PP, despite these medications being frequently utilised for their mood stabilising properties (Galbally et al. 2019). Only one small study has examined prophylactic antipsychotic use during the perinatal period in a sample of 25 women with BD (Sharma, Smith and Mazmanian 2006). Of 11 women who were taking prophylactic olanzapine for at least one month following delivery, only two subsequently experienced psychotic relapse (18.2%). In

comparison, more than half of those who did not take prophylactic olanzapine (but remained on other psychotropic medications) experienced PP (8/14, 57.1%). However, the small sample size of this study did not allow for statistical comparison between the groups.

The efficacy of prophylactic lamotrigine for preventing postpartum relapse in BD has been compared to that of lithium in a Danish registry study (Wesseloo et al. 2017b). After controlling for potential confounders such as parity and other medication use, prophylactic lamotrigine during pregnancy was found to be no more effective at preventing postpartum relapse than lithium (7.3% versus 15.3%). However, the risk for PP was not specifically examined. Notably, postpartum recurrence was defined in this study as an episode of any mental disorder requiring hospitalisation within 3 months postpartum. It is therefore likely that episodes of illness that were managed in the community were not captured by this description. Also, in this study, medication use was defined on the basis of prescriptions only, as indicated by the register. Neither duration of use or adherence to prescribed medication across the perinatal period could be confirmed by this method. Finally, diagnosis of BD was based on case-note review only and not confirmed by clinical research interview.

More recently, among a sample of 196 women with a history of severe affective disorders (primarily of BD and PP), exposure to any type of prophylactic medication in the third trimester of pregnancy and/or the postpartum period did not significantly reduce risk of mood episodes that required admission to acute care within the first three months of delivery (Taylor et al. 2018). Importantly however, use of prophylactic mood stabilisers and antipsychotics were not distinguished from prophylactic antidepressant use. Use of antidepressant medications (particularly without a concomitant mood stabiliser) has been shown to increase risk of recurrence of BD during the perinatal period (Viguera et al. 2007). It is therefore possible that antidepressant use confounded the results of this study, inflating recurrence rates among women who were using psychotropic medication. Furthermore, findings of

Taylor et al.'s study (2018) were based on health records of women who were all under the care of secondary psychiatric services and in some cases, specialist perinatal psychiatric services. Thus, their findings may be subject to confounding by indication. That is, women recruited from secondary and tertiary psychiatric services may be more likely to have a more severe form of BD illness that is potentially associated with both medication use and postpartum recurrence. Consequently, severity of illness may be a moderating factor in the relationship between medication use and postpartum recurrence.

Considering findings to date, the efficacy of mood stabilising medications for prophylaxis of PP in women with BD remains ambiguous. It is however apparent that withdrawal of medication in the perinatal period cannot fully explain the particularly elevated rates of recurrence observed within this high-risk group. As discussed previously, Viguera et al., (2000) found that pregnant women with BD who withdraw mood stabilising medication are no more likely to relapse compared to a sample of non-pregnant women who also discontinued medication. However, of women who were euthymic at the 40-week follow-up, recurrence between weeks 41-64 was 2.9 times more frequent among parous women in the postpartum period compared to women in the non-postpartum equivalent period.

2.6.2.3 Obstetric factors

The close temporal relationship between childbirth and the onset of PP has led to the suggestion that obstetric factors may also influence susceptibility to PP. Several factors have previously been associated with PP, including mode of delivery (Kendell et al. 1981; McNeil 1988c; Nager et al. 2008), female sex of baby (Agrawal, Bhatia and Malik 1990), pre-term delivery (Nager et al. 2008; Paffenbarger et al. 1961; Videbech and Gouliaev 1995), reduced birth weight (Videbech and Gouliaev 1995), twin birth (Munk-Olsen and Agerbo 2015) and longer interval between pregnancies (Paffenbarger et al. 1961). Findings are however inconsistent or without replication in independent

samples. The role of obstetric complications has specifically been investigated, similarly being shown to be associated with PP in some studies (Blackmore et al. 2006; Hellerstedt et al. 2013; Kendell et al. 1981; Paffenbarger et al. 1961; Paffenbarger and McCabe 1966; Upadhyaya, Sharma and Raval 2014), but not all (Bergink et al. 2011a; Kumar et al. 1995; McNeil 1988c; Meltzer-Brody et al. 2017; Nott 1982; Videbech and Gouliaev 1995).

Thus far, primiparity is the only obstetric factor to be robustly related to the onset of PP, being reported in epidemiological studies (Kendell et al. 1981; Munk-Olsen, Jones and Laursen 2014; Nager et al. 2008), broadly defined clinical samples (Paffenbarger and McCabe 1966; Upadhyaya, Sharma and Raval 2014) and among women with BD (Blackmore et al. 2006; Di Florio et al. 2014). The effect of primiparity is strongest among women with BD (Munk-Olsen, Jones and Laursen 2014). Arguably, it is possible this association reflects a bias of women who experience PP following their first baby to be less likely to have further children (for fear of recurrence). However, as the relationship between primiparity and PP has also been demonstrated among samples of multiparous women, this is unlikely to explain such findings (Di Florio et al. 2014; Nager et al. 2008). Currently, the mechanism by which primiparity increases risk for PP is not well understood, given that in addition to the physiological changes that occur, first pregnancies may also cause greater disruption to sleep routines and require greater psychosocial adjustment (for example financially, changes in daily and occupational routine and social relationships) from subsequent pregnancies.

A small number of studies have also suggested an association between pre-eclampsia and PP (Annagur and Kerimoglu 2013; Bergink et al. 2015b). This association is of interest for further research, given that pre-eclampsia and PP can present as clinically similar. Case reports have shown that psychotic features, mood symptoms, mutism or catatonia and perplexity can be features of both illnesses, suggesting potential overlap in the underlying aetiological mechanisms of both disorders (Brockington 1996; Joseph, Shebak and Greenage 2016; Ranzini et al. 1996). Furthermore, much like PP, pre-

eclampsia has also been associated with first pregnancies (Hernández-Díaz, Toh and Cnattingius 2009) and immunological factors implicated in the pathophysiology of symptoms (Lokki, Heikkinen-Eloranta and Laivuori 2018). Nonetheless, no published studies, retrospective or otherwise have examined the relationship between pre-eclampsia and PP in women with BD.

In summary, based on the literature to date, it is unclear whether obstetric factors are associated with PP. Inconsistent findings are likely due to variation in definitions of both obstetric complications (e.g. severity, type and timing of occurrence) and the postpartum period. Findings are further limited by frequent use of retrospective methods of assessments, potentially leading to a detection bias of obstetric complications in women admitted with PP. Several studies also lacked an appropriate control group, comprised of 'healthy' parous women as opposed to women with BD who did not experience obstetric complications (Hellerstedt et al. 2013; Meltzer-Brody et al. 2017; Paffenbarger and McCabe 1966; Upadhyaya, Sharma and Raval 2014). Given that women with psychiatric disorders are more likely to use medications during pregnancy and are known to be at increased risk of obstetric complications compared to women without any psychiatric illness (Jablensky et al. 2005), it is possible that the effect of obstetric complications reflect differences between women with and without psychiatric disorders. Finally, despite being at greatest risk of PP, only two studies have specifically assessed obstetric factors in relation to postpartum recurrence in women with BD (Blackmore et al. 2006; Di Florio et al. 2014).

2.6.2.4 Comorbid anxiety disorders

Women are approximately twice more likely to experience anxiety disorders than men, with the onset of symptoms occurring in most cases before the age of 35 years (Remes et al. 2016). Consequently, many women are affected by anxiety disorders during their childbearing years, and commonly during the perinatal period (Dennis, Falah-Hassani and Shiri 2017). Evidence suggests that compared to pregnancy or outside the perinatal

period, risk of new onset or exacerbation of existing anxiety disorders may be greater in the postpartum period (Goodman, Watson and Stubbs 2016; Remes et al. 2016).

Several studies have also shown that the onset of panic disorder may be delayed and symptoms less severe among women who are breastfeeding, compared to parous women who were not breastfeeding (Goodman, Watson and Stubbs 2016).

The mechanism by which anxiety disorders are exacerbated or triggered by childbirth is not well understood, however findings suggest that similar to postpartum mood disorders, oestrogen and progesterone may also play an important role in the pathogenesis of anxiety disorders (Li and Graham 2017). In addition, the perinatal period is associated with unique psychological and psychosocial stressors which may also act to further provoke symptoms of anxiety (Huizink et al. 2017). Women experiencing pathological anxiety during the perinatal period are by definition likely to experience excessive, uncontrollable worrying and disturbances to sleep pattern, which may in turn have an adverse impact on mood. This may be especially the case during the postpartum period, when sleep is scarce and the developmental needs of the baby are considered a priority over the needs of the mother.

The link between anxiety disorders and postpartum mood disorders has been primarily been examined in relation to PND. History of lifetime anxiety disorders prior to pregnancy has been associated with the occurrence of PND (Guintivano et al. 2018). Moreover, antenatal anxiety has been identified as a strong predictor of PND (Austin, Tully and Parker 2007; Heron et al. 2004; Skouteris et al. 2009), independent of the effect of antenatal depression (Austin, Tully and Parker 2007; Heron et al. 2004). Anxiety disorders and PND also frequently co-occur within the same period (Falah-Hassani, Shiri and Dennis 2016; Merikangas and Jin 2011; Nakić Radoš, Tadinac and Herman 2018).

Despite focus of research on the association between anxiety and PPD, whether comorbid anxiety disorders also increase risk of PP, over and above the relationship

with BD is yet to be investigated. Only one previous study has reported on the association between anxiety during pregnancy and the occurrence of broadly defined PP (psychosis in the postpartum period that was affective or non-affective). In this prospective study, 88 women with a history of psychotic disorders were followed through pregnancy to six months postpartum (McNeil 1988a). The authors found that women who experienced the onset of PP within three weeks of delivery (which were predominantly affective or cycloid episodes) were significantly more anxious during pregnancy than women who remained well. Interestingly, the same association was not observed in relation to episodes of PP that occurred later in the postpartum period and were predominantly schizophrenic-like psychoses. Thus, suggesting an association between anxiety during pregnancy and postpartum affective psychoses in particular.

In addition to the findings of this study, a relationship between anxiety and PP within BD is also plausible for several other reasons. First, anxiety disorders are highly prevalent in individuals with BD (Vázquez, Baldessarini and Tondo 2014) and have also been demonstrated to adversely influence course of BD (Hawke et al. 2013; Hunt et al. 2016). Second, sleep disruption associated with anxiety during the perinatal period may increase risk of PP, given that sleep loss has also been identified as a common trigger of episodes of mania unrelated to childbirth. Third, symptoms of anxiety have been observed more frequently in postpartum manias compared to those unrelated to childbirth (Ganjekar et al. 2013). Fourth, hormonal factors have been implicated in both anxiety disorders and PP, suggesting these disorders may share underlying aetiological factors. For these reasons, studies further examining the role of anxiety disorders in the occurrence of PP within BD is required. Such findings may provide important clues to the pathogenesis of both disorders. Furthermore, if related, the presence of anxiety disorders prior to or during pregnancy can be easily screened for and treated in clinical practice, thus potentially reducing risk of subsequent PP.

2.6.2.5 Psychosocial factors

Much of the research to date suggests a lack of association between psychosocial factors and the occurrence of PP. In contrast to episodes of PND, there is little indication that level of social support, relationship or occupation difficulties influence risk of PP (Dowlatshahi and Paykel 1990). Several studies have reported being unmarried or single at the time of delivery as a potential risk factor for PP (Kendell, Chalmers and Platz 1987; Kendell et al. 1981; Nager, Johansson and Sundquist 2005; Terp and Mortensen 1998; Upadhyaya, Sharma and Raval 2014), though many others have not (Davidson and Robertson 1985; Dowlatshahi and Paykel 1990; McNeil 1987; Protheroe 1969; Wisner, Peindl and Hanusa 1994). Marital difficulties have been associated with the occurrence of PP in one study, however were indicated to most likely be a consequence of psychological vulnerability as opposed to being a precipitating factor of illness (Marks et al. 1992). Alternatively, these findings may reflect an increased likelihood of single mothers (or women lacking a supportive relationship) to be admitted with their baby during the postpartum period.

Adverse life experiences have been frequently identified as predictors of PND (Buist and Janson 2001; Dennis and Vigod 2013; Guintivano et al. 2018; Howard et al. 2014; Kettunen and Hintikka 2017; Meltzer-Brody et al. 2018; Plaza et al. 2012), but have rarely been studied in relation to PP (Brockington et al. 1990; Dowlatshahi and Paykel 1990; Marks et al. 1992; Meltzer-Brody et al. 2018). Brockington et al. (1990) examined the presence of adverse life events occurring prior to pregnancy in 33 women admitted to hospital with broadly defined PP (a diagnostically heterogeneous sample) and 25 women with PND. Adverse events, defined as those objectively causing moderate to severe psychological impact, were found to have occurred in only 15% of women with PP compared to 32% of women with PND. However, the specific time period during which these events occurred was not clear.

In a prospective study of 47 pregnant women with a history of broadly defined affective disorder, adverse life events occurring within the 12 months prior to childbirth were

found to significantly predict episodes of PND but not PP (Marks et al. 1992). Similarly, when compared with a control group of parous women who did not experience PP, adverse life events occurring within the 12 months prior to delivery or in the postpartum period (before the onset of PP) were no more prevalent among a sample of 33 women admitted for psychiatric treatment of PP within the first month of delivery (Dowlatshahi and Paykel 1990).

Adverse events occurring during childhood have also been shown to influence risk of PND, with exposure to an increased number of adverse childhood experiences (ACEs) seemingly having a cumulative effect on risk of PND (Guintivano et al. 2018; Meltzer-Brody et al. 2018). Childhood abuse in particular may be a strong risk factor for PND (Buist and Janson 2001; Guintivano et al. 2018; Kettunen and Hintikka 2017; Plaza et al. 2012). Prior to commencing this thesis, the relationship between ACEs and PP had only been investigated in one study, which is also described further above (Dowlatshahi and Paykel 1990). Dowlatshahi and Paykel (1990) compared a limited range of ACEs (specifically the death of a parent or sibling during childhood and separation from parents during childhood for two years or more) between the PP and control group. Compared to the control group, women with PP were not significantly more likely to report a history of ACEs. However, these factors were only assessed in combination with other aspects of personal history and other ACEs such as childhood abuse were not investigated. As discussed previously, the sample size of this study was small, including only 33 women with broadly defined PP.

More recently, using data obtained from Danish national health registers (from 129,439 childbirths), Meltzer-Brody et al. (2018) assessed whether a range of ACEs (including parental death, parental psychiatric illness, out of home care and parental criminality) experienced between the age of 0-15 years were associated with subsequent inpatient or outpatient contact for postpartum psychiatric illness within the first six months following childbirth. While the authors found out of home care during childhood and parental psychiatric illness to be associated with strongest risk of developing any

postpartum psychiatric disorder (and specifically non-psychotic PND and postpartum anxiety disorders), none of the ACEs assessed were independently associated with the occurrence of PP (broadly defined as any episode of mania, affective or non-affective psychosis). Again however, the relationship between childhood abuse and PP was not examined in this study. Overall, studies assessing psychosocial risk factors for PP in samples of high-risk women are limited. Furthermore, despite indications of a strong relationship between adverse life events (and in particular those occurring during childhood) and PND, the influence of these factors on risk of PP within BD is yet to be investigated.

2.7 Summary

In summary, a review of the literature indicates that the aetiology of PP within BD remains poorly understood. While neurobiological factors have been implicated in the pathogenesis of PP, emerging evidence suggests that a range of within-pregnancy factors may also be involved in the triggering of these episodes. Despite this, the literature thus far has been limited by substantial methodology heterogeneity between studies. Specifically, in regards to definitions used to define postpartum recurrence (both in the temporal cut off used to define the postpartum period and inclusion of diagnostically heterogeneous samples), the diagnostic criteria used and lack of an appropriate control group. Moreover, of potential risk factors that have been examined, findings between studies have been inconsistent (for example, those investigating the influence of obstetric complications or psychotropic medication use on risk of PP) or are based on retrospective methods of assessment. Importantly, prospective studies in this area are limited. Finally, many potential risk factors for PP, such as those occurring within pregnancy are either unstudied or remain to be investigated. The role that lifetime comorbid anxiety disorders or ACEs play in the occurrence of PP in BD is yet to be determined.

2.8 Thesis aims

To address the gaps identified within the literature and extend findings in this area, this thesis aims to investigate potential aetiological and triggering factors of PP in BD.

Specifically, the three main aims of this thesis are to:

1. Investigate potential relationships between history of ACEs, anxiety disorders and the lifetime occurrence of PP in a sample of parous women with BD (Chapter 3).
2. Describe psychotropic medication use and psychiatric outcomes across the perinatal period in a sample of pregnant women with BD using a prospective follow-up design (*further refining the phenotype of postpartum mood episodes for investigations of potential risk factors for PP within this sample; Chapter 6*)
3. Investigate a wide range of within-pregnancy potential risk factors for PP in a sample of pregnant women with BD using a prospective follow-up design (*Chapter 7*).

In the following chapter (Chapter 3), results of investigations examining the association between lifetime co-morbid anxiety disorders, ACEs and the lifetime occurrence of PP among women with BD will be presented and discussed. First, the methods used in the recruitment and assessment of the sample within which these investigations were conducted will be described.

Chapter 3

Adverse childhood experiences, anxiety disorders
and postpartum psychosis in bipolar disorder: a
retrospective study

3.1 Introduction

As discussed in Chapter 2 (section 2.7, page 47) the association between adverse childhood experiences (ACEs), lifetime comorbid anxiety disorders and PP remains to be investigated. The aim of this chapter is to examine these relationships among a large sample of parous women with BD recruited to BDRN. In this chapter, I first describe the BDRN programme of research, detailing inclusion criteria, approaches to recruitment and the process of screening and obtaining written, informed consent from those recruited. This is followed by a description of the neuropsychiatric assessment of participants including demographic characteristics, lifetime psychopathology and history of ACEs. Statistical approaches used to assess the relationship between potential risk factors and the occurrence of PP within this sample are summarised. Finally, the results of these analyses are presented, followed by a detailed discussion of these findings in relation to the literature.

3.2 Methods

3.2.1 Bipolar Disorder Research Network (BDRN)

BDRN is a long-standing research collaboration between the Mood Disorders Research Group at the University of Worcester (led by Professor Lisa Jones) and at Cardiff University (previously led for many years by Professor Nick Craddock and currently by Professor Ian Jones). While recruitment to BDRN is ongoing, more than 7000 individuals with BD have been recruited into the research programme. The broad aims of BDRN are to investigate genetic and non-genetic determinants (such as adverse life events and psychosocial factors) of BD and related mood disorders.

This research (and all subsequent substantial amendments to the initial protocol) has received a favourable opinion for conduct in the National Health Service (NHS) by the West Midlands Multi-Centre Research Ethics Committee (MREC/97/7/01) and has

received local Research and Development approval in all participating health boards and NHS trusts nationwide.

3.2.2 Recruitment: BDRN retrospective sample

A combination of systematic and non-systematic approaches has been used for recruiting eligible participants to BDRN. Individuals were eligible to take part in BDRN if they are at least 18 years of age and have a lifetime history of BD. Individuals were not eligible to participate if they do not have a lifetime history of BD or the onset of BD occurred over the age of 65 years. Detailed descriptions of methods used to recruit eligible participants to BDRN are summarised below.

3.2.2.1 Systematic Recruitment

Systematically recruited participants were identified by Clinical Studies Officers (CSOs; researchers employed by the NHS to facilitate the identification and recruitment of participants to studies) or members of their psychiatric clinical team via case load screening in 25 NHS community mental health teams and lithium clinics nationwide. Eligible individuals were provided with brief information about the research either in person or by an information pack and asked if they would be willing to participate. Each information pack contained a standard study invitation letter signed by the individual's lead clinician, a participant information sheet, an annual BDRN newsletter and a standard contact reply form. Individuals who expressed an interest in the research gave permission for their details to be passed on to the research team either directly by the CSO or clinical team, or by completing the reply form that was returned to the research team in a freepost envelope.

Further systematic recruitment of participants was achieved by displaying posters and study information leaflets that advertised the research in waiting rooms of community mental health services and lithium clinics.

3.2.2.2 Non-Systematic Recruitment

Participants have also been recruited to BDRN using a variety of non-systematic approaches. Non-systematic methods of recruitment predominantly involved the BDRN website, coverage of the study via national and local media (e.g. radio, television and newspapers) and national patient support charities. BDRN has worked closely with two charities in particular, Bipolar UK and Action on Postpartum Psychosis (APP). Specific methods of recruitment tailored to each charity are described below.

- ***Bipolar UK***

Bipolar UK (www.bipolaruk.org), previously called the Manic Depression Fellowship (MDF) is a national charity which provides support and advice to over 80,000 individuals and their families affected by BD. Subscribing members to Bipolar UK regularly receive charity updates via a biannually published magazine (Pendulum) and monthly e-newsletters. BDRN has been frequently advertised to members of Bipolar UK online, in Pendulum and at annual national conferences hosted by the charity. In 2010, the Bipolar UK annual conference was hosted by BDRN.

- ***Action on Postpartum Psychosis***

Action on Postpartum Psychosis (APP) is a national charity specifically targeted to providing support and advice to women with a history of PP. The charity, which was established in 1996, is a collaborative project run by women who have experienced PP, specialist healthcare professionals and academic experts. APP also aims to facilitate research into PP and has collaborated closely with BDRN for many years. BDRN has been advertised widely to over 700 members of APP, including online via the charity's website and discussion forums, in e-newsletters and charity publications.

Individuals who expressed interest in participating in BDRN were contacted via telephone and screened by members of the research team to confirm eligibility.

3.2.3 Assessments: BDRN retrospective sample

Participants were provided with a detailed participant information sheet and written consent obtained by a trained member of the BDRN study team. All participants completed a semi-structured interview lasting approximately one and a half hours and a battery of self-report questionnaires. Only those assessments that are relevant for the analysis presented in this chapter are described in detail below.

3.2.3.1 Semi-structured interview

The majority of interview assessments took place in participants' own homes and were conducted by myself (>600 interviews completed as of June 2019), or other members of the BDRN study team who were either research psychologists or psychiatrists trained in administering the assessments. If conducting an interview at a participant's home was not feasible, this was arranged at an alternative location convenient for the participant such as the home of a relative, their workplace or a room situated in a community mental health centre or GP clinic. The interview included the following assessments:

- *Schedules for Clinical Assessment in Neuropsychiatry (SCAN)*

The Schedules for Clinical Assessment in Neuropsychiatry (SCAN; Wing et al. 1990) is a widely used research psychiatric assessment tool used to determine the presence and severity of psychopathology associated with major psychiatric disorders. Relevant sections of the SCAN were used to assess lifetime history of anxiety disorders, affective symptomatology during episodes of depression and mania and to elicit the lifetime presence or absence of psychotic symptoms, including hallucinations, delusions and experiences of thought disorder and replacement of will.

- *Lifetime Perinatal Psychiatric History*

For all parous women, information was obtained at interview regarding lifetime psychopathology experienced during the perinatal period (during pregnancy up

to six months postpartum) for all pregnancies. Participants were asked about the occurrence and type of the most impairing mood episode with onset during each perinatal period, the timing of onset, the duration of each episode and whether psychotic features had been present during the episode.

- ***BDRN Childhood Life Events Questionnaire - CLEQ***

History of ACEs was assessed during the interview using a bespoke questionnaire developed by senior members of BDRN team for the purpose of this research (Childhood Life Events Questionnaire, CLEQ, see Appendix A). The CLEQ was administered verbally by the researcher to all participants following the SCAN interview once rapport had been established. Participants were asked if they had experienced one or more of a list of twelve ACEs before the age of 16 years. Due to the sensitive nature of such events, participants were not asked directly about experiences of childhood abuse. Instead, participants were given the opportunity to disclose additional events by being asked “Are there any other significant life events you experienced as a child?”

3.2.3.2 Self-report questionnaires

Following the interview, participants were provided with a battery of self-report questionnaires to be completed and returned in a freepost envelope within two weeks of the interview. If questionnaires were not returned within two weeks, a reminder letter and further questionnaire pack were sent to the participant. The questionnaires comprised measures assessing lifetime clinical diagnosis of a range of physical and psychiatric illnesses, current mood state, cognitive and personality factors and history of adverse life events. Only assessments included in the questionnaire pack that are relevant for analysis reported in this chapter are described further below:

- ***Lifetime doctor diagnosis of psychiatric illness***

Participants were asked to report whether they had ever received a doctor diagnosis of a range of psychiatric illnesses (including anxiety and specifically panic disorder) from a specified list by indicating yes, no or unsure (see Appendix B).

- *Adverse life events*

Adverse life events were assessed using a self-report questionnaire (Brief Life Events Questionnaire, BLEQ) which asked about the occurrence of severe adverse life events during a six-month timeframe (including the six-months prior to onset of impairing BD) based on a list proposed by Brugha et al. (1985). An open question was also added to the questionnaire that asked participants “Do you think there is anything that has happened to you during your life which has contributed to you becoming unwell (i.e. the onset of BD, see Appendix C)?”

3.2.3.3 Psychiatric Case-Note Screen

Where available, psychiatric case-notes for consenting participants were screened for further information (case-notes have been obtained for approximately 72% of all individuals with BD recruited into BDRN).

3.2.4 Lifetime consensus ratings

Psychiatric case note data were combined with information obtained at interview and from self-report questionnaires to produce a detailed vignette for each participant. Vignettes summarised participants’ lifetime and perinatal psychopathology, demographic and social information, lifetime substance use, obstetric history and family history of psychiatric illness. From these vignettes, ratings were made for all variables outlined in the following sections.

3.2.4.1 Demographic characteristics

Ratings were made of demographic variables including age at interview, ethnicity, relationship status, highest educational achievement, highest level of occupation and method of recruitment.

3.2.4.2 Adverse childhood experiences (ACEs)

Information about ACEs obtained at interview (via the CLEQ) and from responses to the open question of the BLEQ (included in the battery of self-report questionnaires, see section 3.2.3.2) were combined with information from psychiatric case notes to code the presence or absence of the following ACEs occurring before the age of 16 years: a) death of a parent, b) death of sibling, c) death of a close friend, d) divorce and/or separation of parents and e) serious illness that required hospitalisation.

The presence or absence of childhood abuse was rated according to the following categories a) any emotional abuse, b) any sexual abuse and c) any physical abuse. Individual abuse categories were combined to create an additional variable which coded the presence or absence of *any* childhood abuse (defined as any sexual and/or physical and/or emotional abuse).

3.2.4.3 Lifetime psychiatric history

- *Best-estimate main lifetime DSM-IV diagnoses*

Best-estimate main lifetime psychiatric diagnoses for all participants were made according to standard operationalised diagnostic criteria of the DSM-IV. In cases where more than one lifetime diagnosis was indicated, diagnoses were rated hierarchically according to level of functional impairment. The diagnosis causing the highest level of functional impairment was rated as the main lifetime diagnosis.

- *Key lifetime psychiatric features*

Ratings were made for key lifetime clinical features of psychiatric illness such as the age of onset of impairing BD, number of lifetime episodes of mania and depression and the lifetime occurrence of psychotic features.

- *Lifetime anxiety disorders*

Information obtained at interview (using the SCAN) and from the self-report questionnaire regarding lifetime history of anxiety disorders was combined to code the presence or absence of a lifetime history of any anxiety disorder and specifically of panic and generalised anxiety disorder.

3.2.4.4 Lifetime perinatal psychiatric history

- *Pregnancy by pregnancy*

For all parous women (i.e. women who had given birth to at least one live child), collated data were used to rate the presence and type of the most impairing mood episode with onset within each perinatal period (defined as during pregnancy or within 6 months postpartum). Episodes were rated hierarchically, with mania/affective psychoses being rated in favour of episodes of non-psychotic depression. In cases in which a participant had experienced episodes with onset during pregnancy *and* the postpartum period, only the postpartum episode was rated.

- *Lifetime most impairing perinatal mood episode*

To further refine ratings of perinatal mood episodes according to phenotype, pregnancy by pregnancy ratings were used to code the lifetime most impairing perinatal mood episode. Episodes were rated hierarchically as shown in **Figure 3.1**. This system ensured that only the most impairing, narrowly defined episode was rated. For multiparous women with a lifetime history of postpartum mania/affective psychosis and of any other mood episode (i.e. hypomania or

PND), the episode of mania/affective psychosis was rated as the lifetime most impairing perinatal mood episode.

Figure 3.1: Rating categories of the lifetime most impairing perinatal mood episode in parous women in the BDRN retrospective sample

Lifetime most impairing perinatal mood episode
Mania (with or without mixed features) within 6 weeks of delivery
Psychotic depression with onset within 6 weeks of delivery
Hypomania with onset within 6 weeks of delivery
Non-psychotic depression with onset within 6 weeks of delivery
Mania (with or without mixed features) with onset between 6 weeks and 3 months after delivery
Non-affective psychotic illness with onset within 3 months of delivery
Non-psychotic depression with onset between 6 weeks and 6 months after delivery
Mood episode not reaching impairment criteria with onset within 6 weeks of delivery
Onset of impairing mood episode during pregnancy
No perinatal episode of psychiatric illness (including baby blues) during pregnancy or within 6 months postpartum

- **Definition of perinatal psychiatric outcomes**

Ratings of the worst lifetime perinatal mood episode were used to define the outcome variable for analysis (PP/control group) by stratifying women to the following two groups (samples are described further in section 3.2.5):

Postpartum psychosis group (PP group): defined as parous women with a lifetime worst history of mania (with or without mixed features) or an episode of affective psychosis with onset within six weeks of delivery. To further refine this group, multiparous women with a lifetime history of PP who also had a lifetime history of PND were excluded from this analysis. As discussed in section 2.3.4 (page 14, Chapter 2), there is currently no consensus regarding the temporal

definition of the postpartum period, therefore a cut-off of six weeks was chosen to be consistent with both DSM-IV and ICD-11 definitions of the postpartum period.

No perinatal mood episode group (No PME group): defined as parous women with no lifetime history of any mood episode during pregnancy or within six months following delivery. A broader temporal definition of the perinatal period (to include both pregnancy and up to six months postpartum) was selected for this group to ensure that participants did not experience any episodes of affective illness that could be considered related to childbirth.

Parous women who did not meet criteria for inclusion in the PP or No PME groups according to the strict definitions above were excluded from analyses. This included women who experienced:

- a) Non-psychotic depression with onset within six weeks of delivery.
- b) Hypomania with onset within six weeks of delivery.
- c) Any other perinatal mood episode: including a mood episode with onset during pregnancy, any mood episode with onset between 6 weeks and six months of delivery and a mood episode with onset during the perinatal period that did not meet DSM criteria for impairment.

3.2.4.5 Inter-rater reliability

Senior members of the BDRN team who were trained in rating raw data according to clinical diagnostic criteria made all ratings. In cases of ambiguity, at least two members of the study team made ratings (blind to each other's ratings) and consensus reached via discussion if necessary.

Inter-rater reliability for consensus ratings was formally assessed for 20 cases using Cohen's Kappa Coefficient. Mean kappa statistics were 0.85 for DSM-IV diagnosis, 0.97

for the lifetime most impairing perinatal mood episode and between 0.81 and 0.99 for other key categorical clinical variables. Mean intra-class correlation coefficients were between 0.91 and 0.97 for key continuous clinical variables.

3.2.5 Sample

Participants were 1113 unrelated, parous women with a lifetime diagnosis of BD-I (for whom data were also collected on ACEs and/or anxiety disorders) recruited to BDRN. Analyses included women with BD-I only, given that no women with BD-II had experienced a postpartum episode of psychotic depression (consistent with the strict definition of PP detailed above in section 3.2.4.4). This step was taken to control for potential confounding effects of diagnosis by including all BD-II women in the No PME group.

As 98.2% (n=1093/1113) of women were of white ethnicity (due to the focus of BDRN on investigating genetic aetiological factors of BD), analyses were further restricted to this ethnic group only. This resulted in a sample of 1093 women who were eligible for inclusion in the current analysis.

As shown in **Figure 3.2**, the lifetime worst occurrence of perinatal mood episodes among the 1093 parous women was as follows:

- 601 (55%) experienced a lifetime worst postpartum recurrence of mood disorder with onset within six weeks of delivery; PP (n=297), non-psychotic depression (n=283) and hypomania (n=21)
- 200 (18%) had a lifetime history of other perinatal mood episodes; onset of a mood episode during pregnancy (n=70), onset of a mood episode between six weeks and six months postpartum (n=110), onset of a mood episode not meeting DSM criteria for impairment (n=20)

- 292 (27%) women had no lifetime history of any perinatal mood episode (during pregnancy or within six months postpartum, No PME group)

From this sample, women were selected for inclusion if they met the following criteria:

- a) had a lifetime history of No PME or PP
- b) the onset of impairing BD occurred at 45 years or younger (to ensure that only women who had experienced BD during their childbearing years were included)

After excluding multiparous women who had a lifetime history of both PP and PND (n=61) from the PP group and women with an age of onset of impairing BD \geq 45 years (n=24), the final groupings for each subset of analyses were as follows:

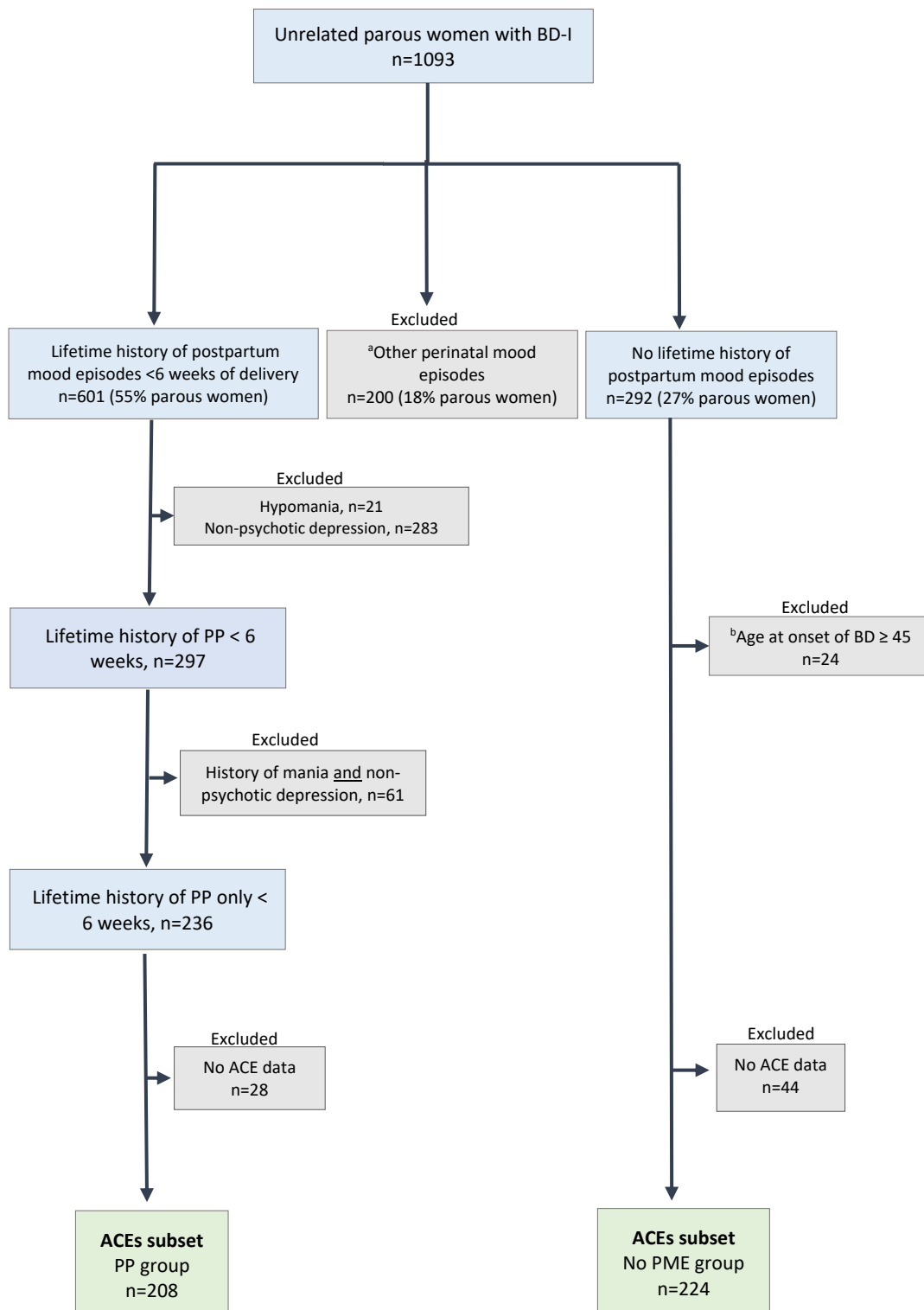
ACEs subset (see **Figure 3.2** for flow-chart of sample selection)

- PP group (n=208) and No PME group (n=224)

Anxiety subset (see **Figure 3.3** for flow-chart of sample selection)

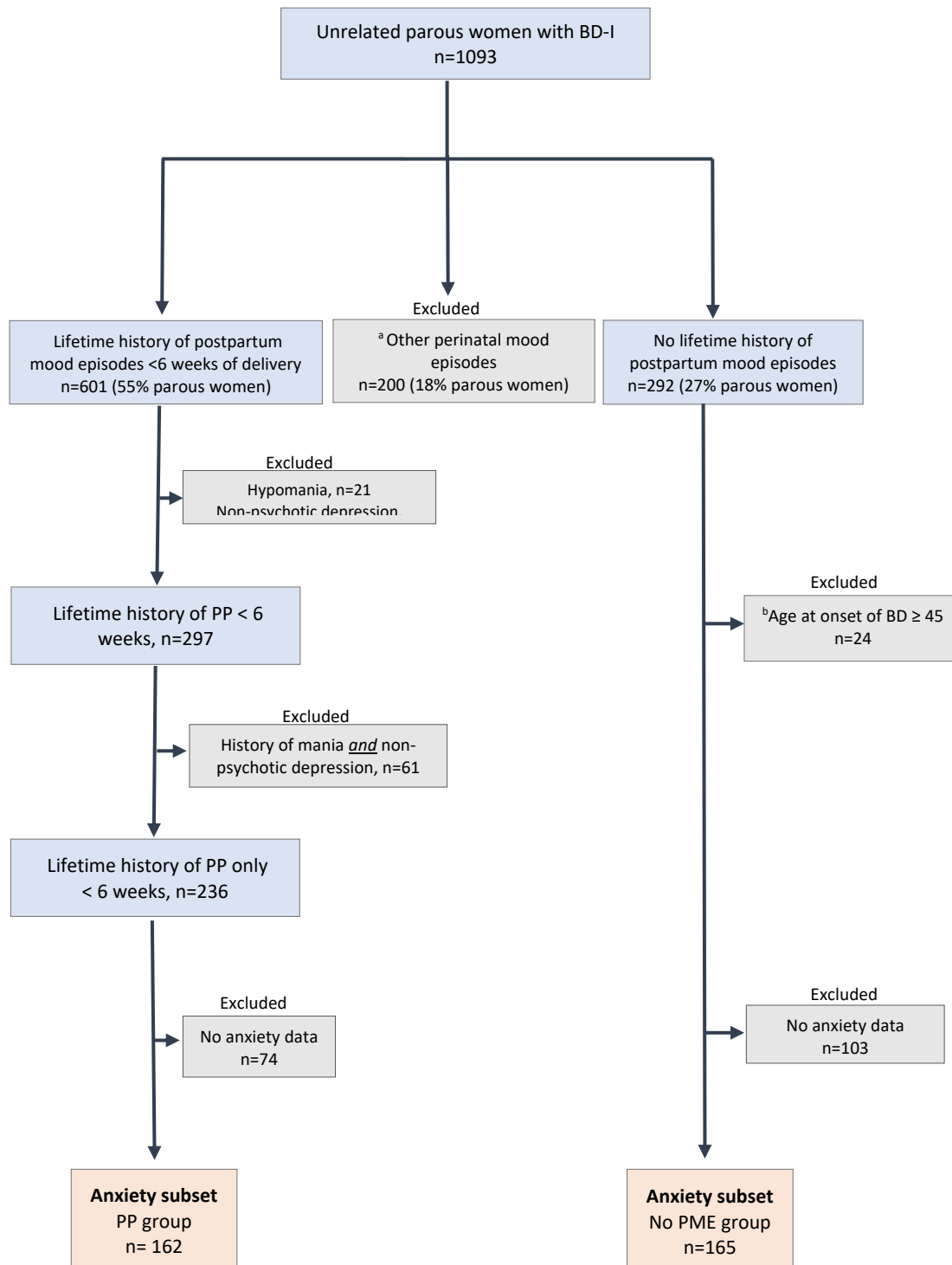
- PP group (n=162) and No PME group (n=165). Groups are smaller within this subset as information about lifetime history of anxiety disorders was not systematically collected for all women in the sample.

Figure 3.2: Flowchart of sample selection of the ACE subset from 1093 parous women with BD-I in BDRN retrospective dataset



BDRN: Bipolar Disorder Research Network; **ACEs:** Adverse childhood experiences; **BD-I:** Bipolar I disorder; **PP:** Postpartum psychosis (defined as an episode of mania, mixed affective state or affective psychosis within 6 weeks of delivery; **No PME:** No lifetime history of perinatal mood episodes during pregnancy or within 6 months postpartum. ^aThis group comprised episodes with onset during pregnancy, postpartum mood episodes with onset >6 weeks following delivery and episodes not meeting DSM impairment criteria ^bAge at onset defined as age at onset of impairing BD in years.

Figure 3.3: Flowchart of sample selection of the anxiety subset from 1093 parous women with BD-I in BDRN retrospective dataset



BDRN: Bipolar Disorder Research Network; **BD-I:** Bipolar I disorder; **PP:** Postpartum psychosis (defined as an episode of mania, mixed affective state or affective psychosis within 6 weeks of delivery; **No PME:** No lifetime history of perinatal mood episodes during pregnancy or within 6 months postpartum. ^aThis group comprised episodes with onset during pregnancy, postpartum mood episodes with onset >6 weeks following delivery and episodes not meeting DSM impairment criteria ^bAge at onset defined as age at onset of impairing BD in years.

3.2.6 Statistical Analysis

All data were analysed using the statistical package SPSS version 24. As continuous data were non-normally distributed (as indicated by the Kolmogorov–Smirnov test), non-parametric tests were used to compare differences between groups, as summarised below. All tests were deemed significant at a p-value of <0.05 (two-tailed).

3.2.6.1 Continuous Data

Due to being non-normally distributed, continuous data (including age at interview, age at onset of impairing BD illness, average lifetime number of episodes of mania and depression per illness year, age at first pregnancy and number of deliveries) were compared between the No PME and PP groups using Mann Whitney-U tests. For this reason, medians, range and inter-quartile ranges are reported for each continuous variable within each group.

3.2.6.2 Categorical Data

Categorical data (including level of education, method of recruitment, the presence/absence of ACEs and lifetime history of anxiety disorders) were compared between the No PME and PP groups using Pearson's Chi Square tests. For each variable, the number of cases and proportions within each group are reported.

3.2.6.3 Logistic regression analyses

Associations between potential risk factors and postpartum psychiatric outcome were further assessed in binary logistic regression models (using the enter method) with No PME/PP as the outcome variable. Each model was adjusted for demographic and lifetime clinical variables that significantly differed between groups in univariate analysis.

3.3 Results

3.3.1 Adverse childhood life events and postpartum psychosis

3.3.1.1 Demographics

Table 3.1 summarises the demographic characteristics of women in the sample according to postpartum psychiatric outcome. Women in the PP group were significantly younger at interview (median 47 years vs 52 years respectively, $p < 0.001$), more likely to have completed further education (defined as achieving equivalent to A-Level qualifications or above; 73.1%, $n = 141/193$ vs 59.2%, $n = 129/218$ respectively, $p = 0.003$) and be recruited non-systematically (75.9%, $158/207$ and 62.9%, $n = 141/224$ respectively, $p = 0.003$) compared with women in the No PME group.

Table 3.1: Demographic characteristics according to postpartum psychiatric outcome in the ACEs subset of parous women with BD-I in the BDRN retrospective sample ($n = 432$)

	PP ($n = 208$)	No PME ($n = 224$)	Test statistic	p-value ^b
<i>Demographic</i>				
Age at interview (years)				
Median (IQR)	47 (16)	52 (16)	U = 18519.000, Z = -3.685	<0.001
Range	21-79	24-73		
Education			χ^2 (1) 8.754	0.003
No further education	52 (26.9%)	89 (40.8%)		
Further education ^a	141 (73.1%)	129 (59.2%)		
Method of Recruitment			χ^2 (1) 8.574	0.003
Non-systematic	158 (75.9%)	141 (62.9%)		
Systematic	50 (24.1%)	83 (37.1%)		

Ns differ due to unknown data. **BD-I:** Bipolar I disorder, **No PME:** No lifetime history of any perinatal mood episode, **PP:** Lifetime history of postpartum psychosis. ^aFurther education defined as equivalent to A-Level qualification or above. ^bPearson's Chi-Square or Mann Whitney-U test.

3.3.1.2 Lifetime clinical features

As shown in **Table 3.2**, women in the PP group were significantly younger at age of illness onset (median 23 years; defined as age at first impairment due to BD illness) compared to women in the No PME group (27 years, $p < 0.001$). While women in the PP

group had on average experienced significantly fewer episodes of depression per illness year (0.21 episodes) compared to the No PME group (0.28 episodes, $p=0.039$), there was no significant difference between the PP and No PME groups in the average number of episodes of mania per illness year (0.25 and 0.23 episodes respectively, $p=0.452$).

Table 3.2: Lifetime clinical characteristics according to postpartum psychiatric outcome in the ACEs subset of parous women with BD-I in the BDRN retrospective sample ($n=432$)

	PP ($n=208$)	No PME ($n=224$)	Test statistic	p- value ^b
<i>Lifetime clinical characteristic</i>				
Age at illness onset (years)				
Median (IQR)	23 (10)	27 (17)	U= 18092.000,	<0.001
Range	10-39	10-45	Z = -4.016	
Number of episodes of mania per illness year (avg.)				
Median (IQR)	0.25 (0.32)	0.23 (0.34)	U=20701.500,	0.452
Range	0.04-3.16	0.02-10.87	Z = -0.753	
Number of episodes of depression per illness year (avg.)				
Median (IQR)	0.21 (0.42)	0.28 (0.43)	U= 16677.500,	0.039
Range	0-6.10	0-10.87	Z = -2.064	

BD-I: Bipolar I disorder, **No PME:** No lifetime history of any perinatal mood episode, **PP:** Lifetime history of postpartum psychosis. ^bMann Whitney-U test.

3.3.1.3 Lifetime perinatal characteristics

Table 3.3 summarises lifetime perinatal characteristics of the sample within the PP and No PME groups. Women in the PP group were significantly older at the age of their first pregnancy (median 27 years) compared to women in the No PME group (median 24.5 years, $p=0.019$). However, the median number of deliveries did not statistically differ between women in the PP (2) and No PME groups (2, $p=0.561$).

Table 3.3: Lifetime perinatal characteristics according to postpartum psychiatric outcome in the ACEs subset of parous women with BD-I in the BDRN retrospective sample (n=432)

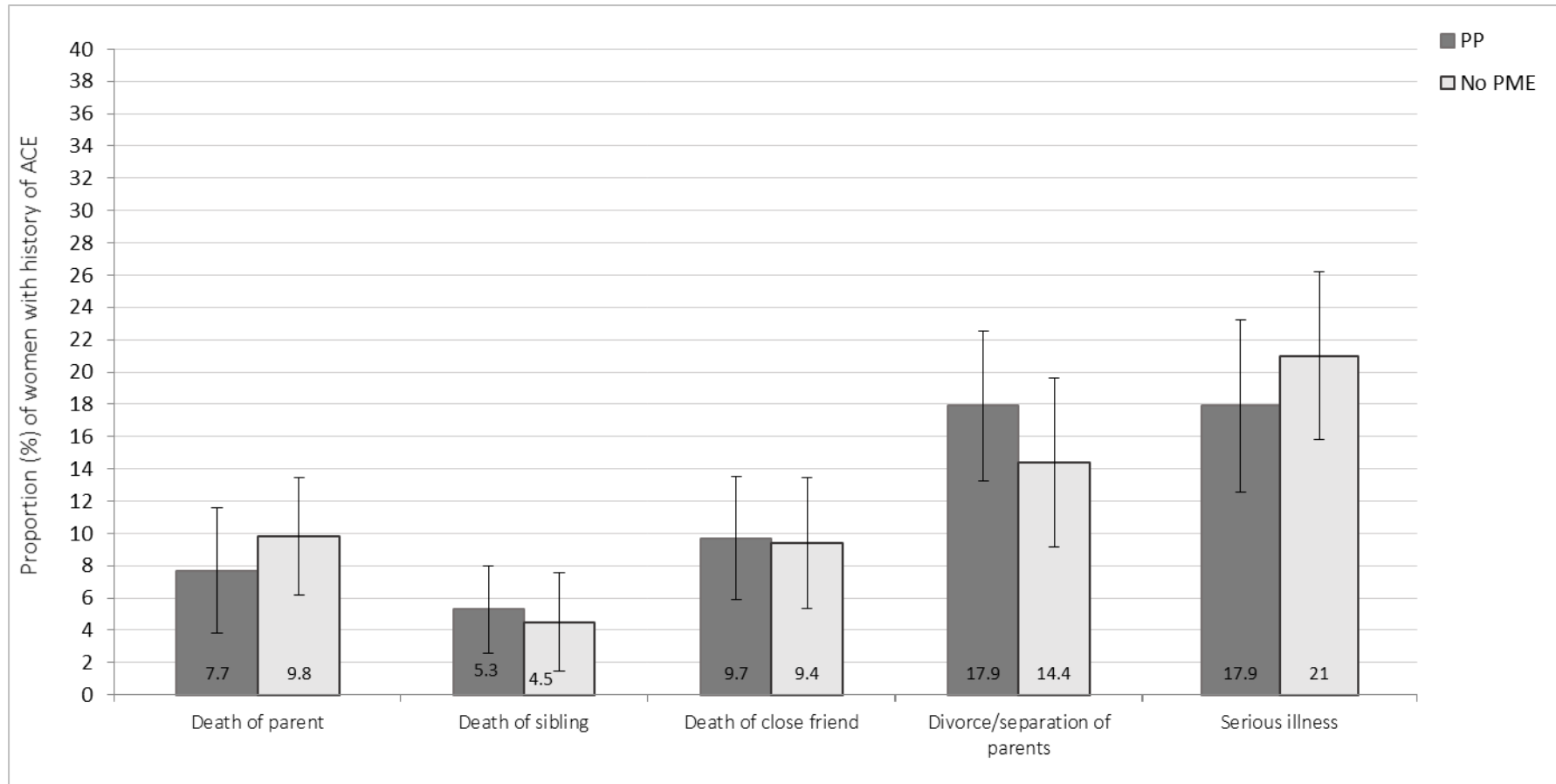
	PP (n=208)	No PME (n=224)	Test statistic	p- value ^b
<i>Lifetime perinatal characteristic</i>				
Age at 1st pregnancy (years)				
Median (IQR)	27 (5)	24.5 (7)	U= 873.000,	0.019
Range	19-38	13-38	Z = -2.342	
Number of deliveries				
Median (IQR)	2 (1)	2 (1)	U= 22395.000,	0.561
Range	1-9	1-6	Z = -0.581	

BD-I: Bipolar I disorder, **No PME:** No lifetime history of any perinatal mood episode, **PP:** Lifetime history of postpartum psychosis. ^bMann Whitney-U test.

3.3.1.4 Adverse childhood experiences

Figure 3.4 shows the proportion of women in the PP and No PME groups who experienced each non-abuse ACE. As shown in **Table 3.4**, unadjusted comparisons between the groups revealed women in the PP group were not significantly more likely to experience any of the following non-abuse related ACEs compared to women in the No PME group (proportions are presented respectively); death of a parent (7.7%, n=16/207 vs 9.8%, n=22/224, p=0.444, OR 0.77 95% CI 0.39-1.51), death of a sibling (5.3%, 11/207 vs 4.5%, n=10/224, p=0.682, OR 1.20 95% CI 0.50-2.89), death of a close friend (9.7%, n=20/207 vs 9.4%, n=21/224, p=0.919, OR 1.03 95% CI 0.54-1.97), divorce or separation of parents (17.9%, n=37/207 vs 14.4%, n=32/222, p=0.330, OR 1.29 95% CI 0.77-2.17) and a serious physical illness requiring hospitalisation (17.9%, n=37/207 vs 21%, n=47/224, p=0.416, OR 0.82 95% CI 0.51-1.32).

Figure 3.4: Prevalence of each non-abuse ACE according to postpartum psychiatric outcome in the ACEs subset of parous women with BD-I in the BDRN retrospective sample (n=432)



ACE: Adverse childhood experience; Bars represent 95% confidence intervals

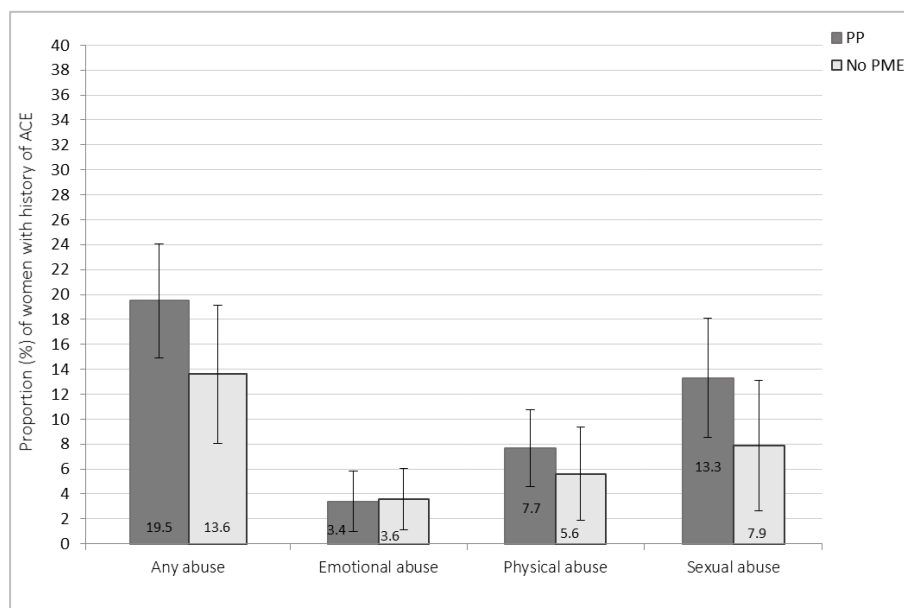
Table 3.4: Prevalence of non-abuse ACEs according to postpartum psychiatric outcome in the ACEs subset of parous women with BD-I in the BDRN retrospective sample (n=432)

Type of non-abuse ACE	PP (n=208)	No PME (n=224)	Test statistic	p- value ^b
Death of a parent				
Yes	16 (7.7)	22 (9.8)	χ^2 (1) 0.586	0.444
No	191 (92.3%)	202 (90.2%)		
Death of a sibling				
Yes	11 (5.3%)	10 (4.5%)	χ^2 (1) 0.168	0.682
No	196 (94.7%)	214 (95.5%)		
Death of a close friend				
Yes	20 (9.7%)	21 (9.4%)	χ^2 (1) 0.010	0.919
No	187 (90.3%)	203 (90.6%)		
Divorce/separation of parents				
Yes	37 (17.9%)	32 (14.4%)	χ^2 (1) 0.950	0.330
No	170 (82.1%)	190 (85.6%)		
Serious physical illness requiring hospitalisation				
Yes	37 (17.9%)	47 (21.0%)	χ^2 (1) 0.662	0.416
No	170 (82.1%)	177 (79.0%)		

Ns differ due to unknown data. **ACEs:** Adverse childhood experiences, **BD-I:** Bipolar I disorder, **No PME:** No lifetime history of any perinatal mood episode, **PP:** Lifetime history of postpartum psychosis. ^bPearson’s Chi-Square

Figure 3.5 shows the proportion of women in the PP and No PME groups who experienced any and each type of abuse during childhood.

Figure 3.5: Prevalence of childhood abuse according to postpartum psychiatric outcome in the ACEs subset of parous BD-I women in the BDRN retrospective sample (n=432)



ACE: Adverse childhood experience; Bars represent 95% confidence intervals

Compared to the No PME group, women in the PP group were not significantly more likely to experience the following types of childhood abuse (see **Table 3.5**): any form of childhood abuse (defined as any emotional, physical or sexual abuse, 19.5%, n=38/195 vs 13.6%, n=29/214, p=0.416, OR 1.54 95% CI 0.91-2.61), emotional abuse (3.4%, n=7/208 vs 3.6%, n=8/224, p=0.907, OR 0.94 95% CI 0.34-2.64), physical abuse (7.7%, n=15/195 vs 5.6%, n=12/214, p=0.396, OR 1.403 95% CI 0.64-3.08) or sexual abuse (13.3%, n=26/195 vs 7.9%, n=17/214, p=0.076, OR 1.78 95% CI 0.94-3.40).

Table 3.5: Prevalence of each type of childhood abuse according to postpartum psychiatric outcome in the ACEs subset of parous women with BD-I in the BDRN retrospective sample (n=432)

	PP (n=208)	No PME (n=224)	Test statistic	p- value ^b
<i>Type of childhood abuse</i>				
Any abuse				
Yes	38 (19.5%)	29 (13.6%)	$\chi^2(1)$ 0.662	0.416
No	157 (80.5%)	185 (86.4%)		
Emotional abuse				
Yes	7 (3.4%)	8 (3.6%)	$\chi^2(1)$ 0.014	0.907
No	201 (96.6%)	216 (96.4%)		
Physical abuse				
Yes	15 (7.7%)	12 (5.6%)	$\chi^2(1)$ 0.719	0.396
No	180 (92.3%)	202 (94.4%)		
Sexual abuse				
Yes	26 (13.3%)	17 (7.9%)	$\chi^2(1)$ 3.150	0.076
No	169 (86.6%)	197 (92.1%)		

Ns differ due to unknown data. **ACEs:** Adverse childhood experiences, **BD-I:** Bipolar I disorder, **No PME:** No lifetime history of any perinatal mood episode, **PP:** Lifetime history of postpartum psychosis. ^b Pearson's Chi-Square

To examine whether a dose-response relationship existed between ACEs and the occurrence of PP, the median total number of ACEs was further compared between the PP and No PME groups. The number of ACEs did not significantly differ between the two groups (median of one ACE, range 0-4, p=0.561).

3.3.1.5 Multivariate binary logistic regression models

After controlling for clinical and demographic factors found to significantly differ between women in the PP and No PME groups in univariate analyses (age at interview, education, method of recruitment, age at illness onset, average number of episodes of depression per illness year and age at first pregnancy), there remained no significant association between history of any ACE (including each subtype of childhood abuse) and the occurrence of PP (see **Table 3.6** for adjusted p-values and odds ratios).

Table 3.6: Unadjusted and adjusted odds ratios for ACEs according to postpartum psychiatric outcome in the ACEs subset of parous women with BD-I in the BDRN retrospective sample (n=432)

ACE	Unadjusted		Adjusted*	
	p value	OR (95% CI)	p value	OR (95% CI)
Death of a parent	0.444	0.77 (0.39-1.51)	0.479	0.74 (0.33-1.69)
Death of a sibling	0.682	1.20 (0.50-2.89)	0.401	1.70 (0.50-5.83)
Death of a close friend	0.919	1.03 (0.54-1.97)	0.944	1.00 (0.45-2.20)
Divorce/separation of parents	0.330	1.29 (0.77-2.17)	0.094	1.76 (0.91-3.40)
Serious illness requiring hospitalisation	0.416	0.82 (0.51-1.32)	0.949	1.02 (0.55-1.88)
Any abuse	0.105	1.54 (0.91-2.62)	0.168	1.60 (0.82-3.10)
Emotional abuse	0.907	0.94 (0.34-2.64)	0.485	0.62 (0.16-2.36)
Physical abuse	0.396	1.40 (0.64-3.08)	0.617	1.29 (0.48-3.49)
Sexual abuse	0.076	1.78 (0.94-3.40)	0.063	2.12 (0.96-4.67)

ACE: Adverse childhood experience; **95% CI**: 95% confidence intervals, **OR**: Odds ratio, *****Adjusted for age at interview, education, method of recruitment, age at onset of impairing BD, average number of episodes of depression per illness year and age at first pregnancy.

3.3.2 Lifetime anxiety disorders and postpartum psychosis

3.3.2.1 Demographics

Table 3.7 summarises the demographic characteristics of women in the anxiety subset according to postpartum psychiatric outcome. Women in the PP group were significantly younger at interview (median 47 years vs 51 years respectively, $p < 0.001$) and more likely to have completed further education (77.5%, $n = 117/151$ vs 61.9%, $n = 99/160$ respectively, $p = 0.003$) compared with women in the No PME group. The method of recruitment did not significantly differ between the PP and No PME groups ($p = 0.058$).

Table 3.7: Demographic characteristics according to postpartum psychiatric outcome in the anxiety subset of parous women with BD-I in the BDRN retrospective sample ($n = 327$)

<i>Demographic</i>	PP ($n = 162$)	No PME ($n = 165$)	Test statistic	p- value ^b
Age at interview (years)				
Median (IQR)	47 (18)	51 (17)	U= 10375.500, Z = -3.499	<0.001
Range	21-76	24-73		
Education			χ^2 (1) 8.921	0.003
No further education	34 (22.5%)	61 (38.1%)		
Further education ^a	117 (77.5%)	99 (61.9%)		
Method of Recruitment			χ^2 (1) 3.589	0.058
Non-systematic	126 (77.8%)	113 (68.5%)		
Systematic	36 (22.2%)	52 (31.5%)		

Ns differ due to unknown data. **BD-I:** Bipolar I disorder, **No PME:** No lifetime history of any perinatal mood episode, **PP:** Lifetime history of postpartum psychosis. ^aFurther education defined as equivalent to A-Level qualification or above. ^bMann Whitney-U or Chi-Squared test.

3.3.2.2 Lifetime clinical features

As shown in **Table 3.8**, women in the PP group were significantly younger at the age of onset of BD compared with women in the No PME group (median 23 years vs 26 years respectively, $p < 0.001$). The median (average) number of episodes of mania or depression per illness year did not significantly differ between the two groups ($p = 0.931$ and $p = 0.079$ respectively).

Table 3.8: Lifetime clinical characteristics according to postpartum psychiatric outcome in the anxiety subset of parous women with BD-I in the BDRN retrospective sample (n=327)

<i>Lifetime clinical characteristic</i>	PP (n=162)	No PME (n=165)	Test statistic	p-value^a
Age at illness onset (years)				
Median (IQR)	23 (10)	26 (16.3)	U= 10629.000,	<0.001
Range	10-39	10-45	Z = -3.203	
Number of episodes of mania per illness year (avg.)				
Median (IQR)	0.22 (0.32)	0.24 (0.36)	U=12176.000,	0.931
Range	0.04-3.16	0.03-4.18	Z = -0.86	
Number of episodes of depression per illness year (avg.)				
Median (IQR)	0.21 (0.41)	0.30 (0.48)	U= 9381.500,	0.079
Range	0-6.10	0-5.30	Z = -1.759	

BD-I: Bipolar I disorder, **No PME:** No lifetime history of any perinatal mood episode, **PP:** Lifetime history of postpartum psychosis. ^a Mann Whitney-U test.

3.3.2.3 Lifetime perinatal features

Women in the PP group were significantly older at age of first pregnancy compared to women in the No PME group (median age of 27 years vs 25 years, $p < 0.001$, **Table 3.9**). The lifetime number of deliveries did not significantly differ between the two groups ($p = 0.523$).

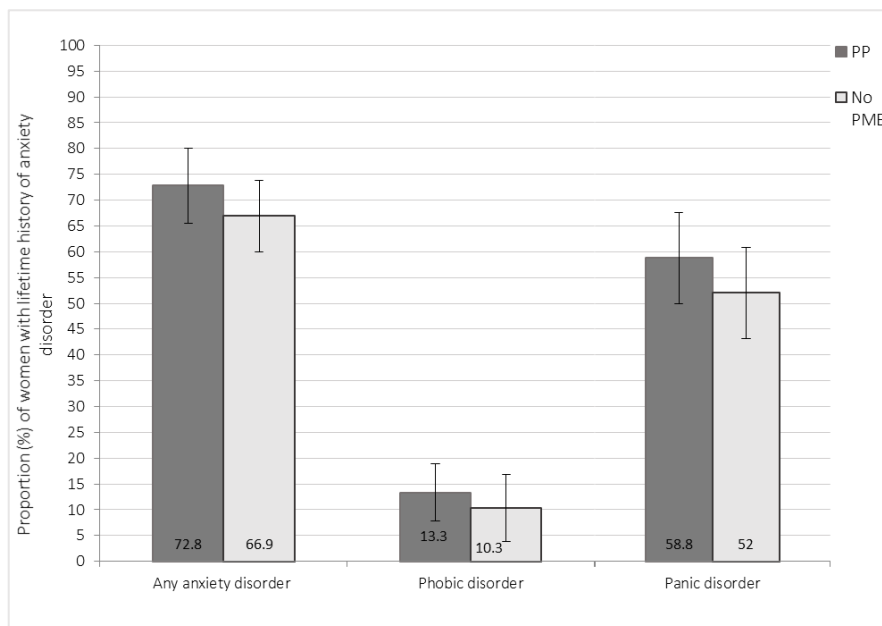
Table 3.9: Lifetime perinatal characteristics according to postpartum psychiatric outcome in the anxiety subset of parous women with BD-I in the BDRN retrospective sample (n=327)

<i>Lifetime perinatal characteristic</i>	PP (n=162)	No PME (n=165)	Test statistic	p- value ^a
Age at 1st pregnancy (years)				
Median (IQR)	27 (8)	25 (7)	U= 8430.500,	<0.001
Range	18-41	16-39	Z = -4.465	
Number of deliveries				
Median (IQR)	2 (1)	2 (1)	U= 12703.000,	0.523
Range	1-9	1-6	Z = -0.639	

BD-I: Bipolar I disorder, **No PME:** No lifetime history of any perinatal mood episode, **PP:** Lifetime history of postpartum psychosis. ^a Mann Whitney-U test.

3.3.2.4 Lifetime anxiety disorders

Figure 3.6 shows the proportion of women with a lifetime history of each type of anxiety disorder. Compared to the No PME group, women in the PP group were not significantly more likely to report a lifetime history of the following anxiety disorders

Figure 3.6: Prevalence of lifetime anxiety disorders according to postpartum psychiatric outcome in the anxiety subset of parous women with BD-I in the BDRN retrospective sample (n=327)

Bars represent 95% confidence intervals

(see **Table 3.10**): any anxiety disorder (72.8%, n=118/162 vs 66.9%, n=109/163, p=0.241, OR 1.33 95% CI 0.83-2.14), phobic disorder (13.3%, n=14/105 vs 10.3%, n=12/116, p=0.491, OR 1.33 95% CI 0.59-3.03) or panic disorder (58.8%, n=70/119 vs 52%, n=64/123, p=0.288, OR 1.32 95% CI 0.79-2.19).

Table 3.10: Prevalence of each type of anxiety disorder according to postpartum psychiatric outcome in the anxiety subset of parous women with BD-I in the BDRN retrospective sample (n=327)

<i>Type of anxiety disorder</i>	PP (n=162)	No PME (n=165)	Test statistic	p- value ^a
Any anxiety disorder				
Yes	118 (72.8%)	109 (66.9%)	χ^2 (1) 1.374	0.241
No	44 (27.2%)	54 (33.1%)		
Phobic disorder				
Yes	14 (13.3%)	12 (10.3%)	χ^2 (1) 0.474	0.491
No	91 (86.7%)	104 (89.7%)		
Panic disorder				
Yes	70 (58.8%)	64 (52.0%)	χ^2 (1) 1.129	0.288
No	49 (41.2%)	59 (48.0%)		

BD-I: Bipolar I disorder, **No PME:** No lifetime history of any perinatal mood episode, **PP:** Lifetime history of postpartum psychosis. ^a Pearson chi-square test

3.3.2.5 Multivariate binary regression models

After controlling for clinical and demographic factors found to significantly differ between women in the PP and No PME groups in univariate analyses (age at interview, education, age at onset of impairing BD and age at first pregnancy), there remained no significant association between history of any lifetime anxiety disorder (including specifically phobia and panic disorder) and the occurrence of PP (see **Table 3.11** for adjusted and unadjusted odds ratios).

Table 3.11: Unadjusted and adjusted odds ratios for lifetime anxiety disorder according to postpartum psychiatric outcome in the anxiety subset of parous women with BD-I in the BDRN retrospective sample (n=327)

	Unadjusted		Adjusted*	
	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)
Anxiety disorder				
Any anxiety disorder	0.241	1.33 (0.83-2.14)	0.468	1.22 (0.72-2.08)
Phobic disorder	0.491	1.33 (0.59-3.03)	0.225	1.75 (0.71-4.33)
Panic disorder	0.288	1.32 (0.79-2.19)	0.532	1.20 (0.68-2.14)

95% CI: 95% confidence intervals, **OR:** Odds ratio, *Adjusted for age at interview, education, age at onset of impairing BD and age at first pregnancy.

3.4 Discussion

3.4.1 Adverse childhood experiences

In this study, I examined the relationship between a range of ACEs and the lifetime occurrence of PP within a large sample of parous women with BD-I. Though women in the PP group were more likely to report a history of any childhood abuse and specifically childhood sexual abuse compared to women without a lifetime history of any perinatal mood episode, this difference was not statistically significant.

Furthermore, I did not find significant associations between any other ACLE assessed or the total number of ACEs experienced and PP in this sample. Even after controlling for differences in demographic and clinical differences between the groups (including age at interview, education, recruitment method, age at illness onset, lifetime number of episodes of depression and age at first pregnancy) the type and number of ACEs did not significantly differ. These findings suggest that over and above any effect on course of illness of BD more generally, ACEs do not appear to increase vulnerability for PP.

While research in this area is limited, the findings of the current study are consistent with those that have also found no significant association between ACEs and the

occurrence of broadly defined PP among a small diagnostically heterogeneous clinical sample (Dowlatshahi and Paykel 1990) and among the general population in a recent Danish register study (Meltzer-Brody et al. 2018). Importantly however, in contrast to this study, neither Dowlatshahi and Paykel (1990) nor Meltzer-Brody et al. (2018) examined the role of childhood abuse or used a narrow definition of PP (restricted only to cases of mania or affective psychoses with onset within six weeks of delivery). Furthermore, this study is the first to examine the relationship between ACEs and PP specifically among a sample of women with BD (i.e. women with BD comprised both the case and control group for this analysis).

The lack of an association between ACEs and the occurrence of PP is also consistent with the wider literature. To date, there is no clear evidence to suggest a role for adverse life events occurring during adulthood or within the 12 months prior to pregnancy in the occurrence of PP (Brockington et al. 1990; Dowlatshahi and Paykel 1990; Marks et al. 1992). While these studies were based on small diagnostically heterogeneous samples (ranging from 12-88 women defined as cases of PP), considered together with the findings of the current study, this would suggest that life stressors in general, nor the timing of these events appear to influence risk of PP. Conversely, it has been reported that women with PP are somewhat less likely to report history of adverse life events at any time compared with control groups (Meltzer-Brody et al. 2018).

In contrast to episodes of PP, previous studies have shown ACEs and in particular, childhood sexual abuse, to increase risk of PND (Dennis and Vigod 2013; Meltzer-Brody et al. 2018; Plaza et al. 2012). Furthermore, a dose-response relationship between the number of ACEs experienced and risk of PND has also been demonstrated (Meltzer-Brody et al. 2018), a finding which has not been observed in relation to PP in the current study or in others (Meltzer-Brody et al. 2018). These findings are consistent with previous literature suggesting that overall, biological factors may be more important in the aetiology of PP. As discussed in the introductory chapter to this thesis, evidence has implicated obstetric complications (Hellerstedt et al. 2013), primiparity (Di

Florio et al. 2014), genetic factors (Jones and Craddock 2001; Jones et al. 2007), immunological factors (Bergink et al. 2013, 2015a) and sleep deprivation (Lewis et al. 2018; Sharma 2003; Sharma, Smith and Khan 2004) in the aetiology and triggering of PP.

3.4.2 Lifetime history of anxiety disorders

To my knowledge, this research was the first to investigate whether lifetime comorbidity of anxiety disorders increases lifetime vulnerability to PP in women with BD. Even after controlling for significant differences in demographic and clinical factors between the PP and No PME group (age at interview, education, age at onset of impairing BD and age at first pregnancy), there remained no significant association between a lifetime history of any anxiety disorder or type of anxiety disorder (phobia or panic disorder) and the occurrence of PP in this sample. These findings are in contrast to those of PND, which has been frequently associated with a history of anxiety disorders, occurring both prior to (Guintivano et al. 2018) and during pregnancy (Austin, Tully and Parker 2007; Heron et al. 2004; Skouteris et al. 2009). If replicated, this might suggest that unlike PND, aetiological factors involved in determining lifetime risk of anxiety disorders may be less important in the pathogenesis of PP.

Though evidence to suggest an association between lifetime history of anxiety disorders and PP is lacking, these findings do not preclude the possibility that anxiety disorders that have onset during the perinatal period increase risk of PP. However, given that anxiety disorders and PP were assessed on a lifetime basis within this sample, it was not possible to further examine the specific relationship between antenatal anxiety and risk of PP (within the same perinatal period). Studies examining the potential relationship between antenatal anxiety and PP are required for several reasons. As discussed in section 2.6.2.4 in the background chapter of this thesis, an association between antenatal anxiety and postpartum depression has been demonstrated (Austin, Kildea and Sullivan 2007; Heron et al. 2004, 2009). While the influence of anxiety during

pregnancy has been associated with broadly defined PP (of an affective and non-affective nature (McNeil 1988), this has not been specifically examined in women with BD. Furthermore, given that the perinatal context is unique in terms of biological, psychological and psychosocial factors, the aetiology of anxiety disorders related to pregnancy and childbirth may be distinct from anxiety disorders with onset at other times. Evidence also suggests that anxiety disorders and BD can both be exacerbated and triggered by childbirth, therefore these disorders (or subtypes of these disorders) may share underlying aetiological factors that are specific to childbirth.

3.4.3 Limitations

The findings presented within this chapter are subject to several limitations. Firstly, all women were interviewed in adult life and data were obtained cross-sectionally. Retrospective assessment of potential risk factors may therefore have increased the likelihood of recall errors or bias, leading to over or underestimates of the presence of these factors. However, risk of recall bias may have been compensated for, given that women in this study were selected from the wider BDRN sample, and were not specifically recruited to assess the effects of anxiety or childhood trauma (or other psychological factors) on psychiatric outcomes. Thus, it is less likely these women were primed to report these factors at interview simply due to recruitment bias.

It is also possible that ACEs in particular were underreported. During assessment, participants were not asked directly about their experiences of childhood abuse, but were instead required to voluntarily disclose any such history. Thus, women may have been less inclined to discuss these experiences freely at interview. Nonetheless, it has been demonstrated that disclosure of abuse is more likely when the word 'abuse' is not used in questions pertaining to childhood experiences (Thombs et al. 2006). Notably, self-completed questionnaires were also screened for any mention of childhood abuse that was not disclosed during the face-to-face interview. Furthermore, in an effort to obtain additional information and also remedy any sources of error or bias that may

result from a cross-sectional methodology, psychiatric case-notes were screened to supplement all data obtained at interview.

A second limitation, is that despite the modest sample size, stratification of participants according to postpartum psychiatric outcome considerably reduced statistical power of subsequent analyses. This is possibly a reason I did not find a significant association between ACEs, and specifically childhood abuse and PP. Post-hoc power analysis based on published effect sizes in relation to PND in non-bipolar samples (Plaza et al. 2012) showed that the sample size in this study of 432 women (208 PP; 224 No PME) has >95% power to detect a significant ($p < 0.05$) between-group difference in the frequency of childhood sexual abuse. However, based on the effect sizes I observed, a total minimum sample of 1018 women with BD would be required to achieve the recommended minimum of 80% power to detect a significant ($p < 0.05$) between group difference in the frequency of childhood sexual abuse. Nevertheless, this study remains one of the largest to examine the relationship between ACEs and PP, and to my knowledge, the only study to examine these factors specifically within women with BD. The findings of this study therefore extend those of previous literature, providing further clues to the aetiological and triggering factors of a currently poorly understood disorder.

Thirdly, I was only able to explore the relationship between a limited range of ACEs and anxiety disorders and PP. It is plausible that ACEs or specific anxiety disorders not measured within the BDRN sample (such as severe bullying or obsessive-compulsive disorder) play a more important role in increasing vulnerability for PP in women with BD. In an effort to address both the second and third limitation discussed here, future research should aim to replicate the current study in a larger sample of women with BD, whilst also examining a wider range of ACEs and anxiety disorders that are yet to be investigated. Fourthly, it is important to consider that women within this sample were all of UK/Eire white ethnicity and so the results may not be generalisable to other populations.

3.5 Importance of prospective studies for investigating risk of postpartum psychosis

This study and much of the previous literature has focused on investigating risk factors for PP using a cross-sectional study design. While there are considerable benefits of this methodology (such as enabling recruitment of larger samples of women, increasing power of analyses and generalisability of findings), there are also several key limitations. As discussed in section 3.4.3, risk of recall error and bias is increased when using a retrospective methodology. Moreover, accurately identifying and characterising historical episodes of psychiatric illness becomes more challenging. For example, in the BDRN retrospective sample, milder episodes of perinatal recurrence of BD may be underreported compared with more severe episodes. Women with a history of less impairing postpartum recurrences of BD would therefore be more likely to be included in the No PME group, potentially introducing further heterogeneity within the sample.

Arguably, the most important limitation of cross-sectional research is that it is not possible to establish causal relationships between potential risk factors and the outcome of interest. Due to this limitation, the nature of the relationship between several potential risk factors and PP remains inconclusive. For example, sleep disruption has been implicated in retrospective studies as a potential triggering factor of PP (Lewis et al. 2018; Sharma, Smith and Khan. 2004; see section 2.6.2.1 for full description). Nevertheless, based on cross-sectional data, it is not possible to infer whether sleep loss acted as a triggering factor for PP or occurred as an early onset symptom marking the prodromal phase of illness. Furthermore, our research group has shown risk of PP to be significantly higher among women with BD-I compared to BD-II (Di Florio et al., 2013; see section 2.5.2 for a full description). However, given that women with BD-II who experience an episode of postpartum mania subsequently meet diagnostic criteria for BD-I, risk of PP among women with BD-II may be currently underestimated. To establish the direction of potential relationships and determine causality, it is therefore crucial to identify the presence of potential risk factors during pregnancy and prior to the onset of PP.

In contrast to cross-sectional research, temporality can be determined using a prospective cohort-design. Prospective studies are also less vulnerable to limitations of recall error or bias, and as such, are considered the gold standard study design for observational research. Studies which aim to investigate risk of PP are prime candidates for use of a prospective methodology, given that the perinatal period offers a unique, narrowly defined timeframe during which we can reliably predict the event of childbirth. In particular, this method is ideal for assessing potential within-pregnancy risk factors for PP (such as antenatal anxiety and psychotropic medication use), that are yet to be investigated or have predominantly been examined retrospectively. The findings of such a study would further extend those of previous research, given that prospective identification of risk factors would provide stronger evidence of causality than cross-sectional methods. For these reasons, studies which investigate risk factors for PP among women with BD using a prospective follow-up methodology are required.

3.6 Summary and conclusions

In this chapter, I investigated the role of ACEs and of lifetime anxiety disorders in the occurrence of PP in parous women with BD-I. Even after controlling for differences in clinical and demographic factors, I found no association between ACEs, or lifetime history of anxiety disorders and PP in this sample. The lack of evidence for an association between ACEs and PP in BD is consistent with studies of PP that have been conducted in diagnostically heterogeneous samples. To my knowledge, this study is the first to examine the role of lifetime anxiety disorders in PP. These findings are in contrast to studies of PND, in which ACEs and anxiety disorders have been associated with an increased risk of these episodes. If replicated, this may provide further evidence for a distinct aetiology between PP and PND.

To date, the majority of research (including this study) has investigated risk factors for PP using a cross-sectional study design. However, based on this methodology, it has not been possible to identify causal relationships between potential aetiological or

triggering factors and the occurrence of PP. Establishing temporality between potential risk factors and PP would have important clinical implications for individualising risk prediction of these episodes among women with BD. To address these limitations, prospective follow-up studies in this area are required. In particular, focus should be placed on investigating the influence of a range of within-pregnancy factors on risk of PP, which to date are yet to be investigated or have primarily been studied retrospectively.

To further extend the findings of this thesis thus far, subsequent chapters will therefore focus on examining a range of within-pregnancy potential risk factors for PP among pregnant women with BD using a prospective follow-up design. Results of this analysis will be presented in Chapter 7. Chapter 4 will provide further context for this research by reviewing the existing literature that has investigated the risk of recurrence of BD during the perinatal period using a prospective methodology.

Chapter 4

The BDRN Pregnancy Study: Introduction

4.1 Overview of chapter

In Chapter 3, I examined the relationship between potential risk factors (anxiety disorders and ACEs) and lifetime occurrence of PP in a large sample of parous women with BD. While the majority of literature has focused on investigating lifetime correlates of PP, relatively little is known about factors occurring within-pregnancy that may also influence risk of these episodes. Moreover, of within-pregnancy factors that have been examined, these have primarily been investigated using a retrospective methodology. As discussed, cross-sectional data are subject to several key methodological limitations, in particular recall bias and being unable to establish causal relationships between potential risk factors and the outcome of interest. To address these limitations, I argued the need for further research investigating risk factors for PP using a prospective follow-up methodology. In this chapter, I provide context for a prospective follow-up study of pregnant women with BD that was conducted as part of this thesis (The BDRN Pregnancy Study, described and discussed in Chapters 5, 6 and 7). Literature examining the course of BD during the perinatal period using a prospective follow-up design will be reviewed, followed by a description of the aims of The BDRN Pregnancy Study.

4.1.1 Literature search

Consistent with the purpose of this literature review (and due to a paucity of prospective research in this area), a systematic review was not conducted. Methods used to search the literature outlined in Chapter 2 (see table 2.2; page 6) were also utilised here. The additional following search terms were used in combination with those highlighted in Chapter 2: pregnancy, prospective and longitudinal. Relevant literature was subsequently collated and summarised in the following sections of this chapter.

4.2 Prospective pregnancy studies of the perinatal period in bipolar disorder

4.2.1 Recurrence of bipolar disorder during pregnancy

As in retrospective research, estimates of antenatal recurrence vary widely across prospective studies, with new onset mood episodes reported to occur in between 11.2% and 71% of women with BD (see **Table 4.1**; Abdel-Hay, El-Sawy and Badawy 2011; Bergink et al. 2012; Rosso et al. 2016; Sharma, Sommerdyk and Campbell 2013; Viguera et al. 2007). Recurrence during pregnancy was found to be highest among a Canadian sample of 89 women with BD-I and BD-II (Viguera et al, 2007), in which the onset of DSM-IV defined mood episodes were assessed at each trimester of pregnancy through to 12 months postpartum. The authors reported as many as 71% of women to experience at least one recurrence of BD during pregnancy. Incidence of antenatal recurrence was found to be considerably lower in a Danish sample of women with BD-I and BD-II (n=41), being identified in almost a quarter of all women (24.4%; Bergink et al. 2012). Variation in findings are potentially due to methodological heterogeneity between the two studies. For example, though the proportion of women with BD-I and BD-II was similar in both studies (approximately two thirds of women with BD-I), in the Danish sample, a higher proportion of women remained on lithium prophylaxis throughout pregnancy (73.1% compared to 61.8% in Viguera et al.'s study). Moreover, women in the Danish sample were also followed up more frequently throughout pregnancy and therefore may have had increased opportunity to receive clinical intervention had symptoms emerged, subsequently reducing risk of clinically impairing recurrence. Cultural differences between studies may also have influenced findings.

To date, few studies have examined antenatal recurrence in samples of women with BD-I and BD-II independently. As discussed in Chapter 3 (section 2.5.2), little is known regarding risk of perinatal recurrence (and factors influencing risk) across BD subtypes. This is poorly understood among women with BD-II in particular, given that

Table 4.1: Prospective cohort studies investigating risk of recurrence during pregnancy in women with BD

Author	Country	Sample	Duration of follow-up/assessments	Potential risk factors assessed	Outcomes	Findings
<i>Prospective cohort studies investigating risk factors for recurrence during pregnancy only</i>						
Viguera et al. (2007)	U.S.A	89 pregnant women with DSM-IV BD-I and BD-II stratified to two groups: a) Use of at least one mood stabiliser at conception and continued at least through the first 12 weeks of pregnancy a) Discontinuation of mood stabiliser treatment in the 6 months prior to conception or during first 12 weeks of pregnancy	From baseline (<24 weeks of pregnancy) to 12 months postpartum. • Structured clinical interview at baseline. • Follow-up assessments at each trimester of pregnancy and at 6, 12, 24, 52 weeks postpartum	<ul style="list-style-type: none"> • <i>Demographic and pregnancy variables:</i> ethnicity, education status, marital status, planning of pregnancy, parity • <i>Illness history factors:</i> BD subtype, age at onset, polarity of first episode, time since last episode, number of illness episodes per year, psychiatric comorbidity, history of suicide attempt, history of mixed affective episodes, family history of mood disorders, perinatal psychiatric history, presence of rapid cycling • <i>Prophylactic mood stabiliser use including:</i> polytherapy with two or more psychotropic drugs, antidepressant use, primary mood stabiliser other than lithium, affective switch during antidepressant use, abrupt discontinuation of mood stabiliser 	<ul style="list-style-type: none"> • Occurrence of DSM-IV mania, depression, hypomania or mixed affective state during pregnancy only • Time to recurrence of new DSM-IV affective episode 	<p><i>Risk of recurrence:</i> 71% (n=63/89);</p> <ul style="list-style-type: none"> • 41.3% depression • 38.1% mixed state • 11.1% hypomania • 9.5% mania <ul style="list-style-type: none"> • Withdrawal of medication significantly associated with recurrence during pregnancy: <ul style="list-style-type: none"> ▪ 37% medication group ▪ 85.5% no medication group • Abrupt medication withdrawal associated with 4x shorter time to recurrence and 5x duration of illness <p><i>Other predictors of recurrence:</i> BD-II diagnosis, earlier onset, more recurrences/year, recent illness, antidepressant use and use of anticonvulsants vs lithium.</p>
Newport et al (2008)	U.S.A	26 pregnant women with DSM-IV BD (BD-I, BD-II or BD-NOS): Stratified to two groups: a) Continued prophylactic lamotrigine during pregnancy a) Discontinued prophylactic mood stabilisers within 8 weeks of last menstrual period	From first trimester of pregnancy to delivery. • Structured clinical interview at baseline. • Follow-up clinical assessments monthly during pregnancy.	<ul style="list-style-type: none"> • Lamotrigine use/discontinuation • Rate of mood stabiliser discontinuation 	Weeks from conception to occurrence of DSM-IV mania, depression, hypomania or mixed affective state during pregnancy only	<ul style="list-style-type: none"> • Withdrawal of medication significantly associated with recurrence during pregnancy: <ul style="list-style-type: none"> ▪ 30% in lamotrigine group ▪ 100% in no medication group • Withdrawal of medication significantly associated with shorter time to recurrence during pregnancy: <ul style="list-style-type: none"> ▪ 28 weeks in lamotrigine group ▪ 2 weeks in no medication group

BD: Bipolar disorder, **BD-I**: Bipolar I disorder, **BD-II**: Bipolar II disorder, **BD-NOS**: bipolar disorder not otherwise specified

Table 4.2: Prospective cohort studies investigating risk of recurrence during the perinatal period in women with BD

Author	Country	Sample	Duration of follow-up/ assessments	Potential risk factors assessed	Outcomes	Findings
<i>Prospective cohort studies investigating risk factors for recurrence during pregnancy/postpartum</i>						
Van Gent and Verhoeven (1992)	Netherlands	15 pregnant women with DSM-III BD-I and BD-II taking prophylactic lithium (n=12), carbamazepine (n=2) or haloperidol (n=1) at the start of pregnancy	From preconception (planning pregnancy) to 12 months postpartum Routine clinical assessments	-	Occurrence of affective episode (defined clinically) during pregnancy or within 12 months postpartum	Of 16 deliveries to 11 women who reached follow-up, recurrence rates were: During pregnancy: • 13% (n=8) in medication group • 41% (n=8) no medication group Within 3 months postpartum: • 27% (n=11) in medication group • 60% (n=5) no medication group 3-12 months postpartum: • 27% (n=11) in medication group • 20% (n=5) no medication group
Wisner et al. (2004)	U.S.A	26 pregnant women (<35 weeks gestation) with DSM-IV BD-I and BD-II stratified to two groups: a) Use of prophylactic sodium valproate plus postpartum monitoring (consisting of psychoeducation and weekly mood monitoring, n=15) b) Postpartum mood monitoring only (without any psychotropic medication, n=11)	From delivery to 20 weeks postpartum Baseline assessments included a structured clinical interview and measures of current mood state. Follow up assessments at each week postpartum for 20 weeks	Prophylactic medication use (focus on sodium valproate)	• Occurrence of DSM-IV mania, depression, hypomania or mixed affective state within 2 weeks postpartum • Time to recurrence of new DSM-IV affective episode	• No significant difference in recurrence rates between the groups ▪ 70% valproate group (n=10/15) ▪ 73% no valproate group (n=8/11) • No significant difference in time to recurrence between the two groups
Sharma, Smith and Mazmanian (2006)	Canada	25 pregnant women with BD-I and BD-II stratified to two groups: a) Use of prophylactic olanzapine (alone or in combination with other psychotropic medication) for at least four weeks postpartum (n=11) a) No prophylactic olanzapine within the first four postpartum weeks (including women using other psychotropic medication or no medication, n=14)	From baseline in the first trimester of pregnancy to 4 weeks postpartum. • Baseline assessments included a semi-structured diagnostic interview. • Follow up assessments conducted at each trimester of pregnancy and in six postpartum visits (including 1 week and 1 month postpartum).	• Use of prophylactic olanzapine	Occurrence of DSM-IV mania, depression, hypomania or mixed affective state within 4 weeks postpartum	• No significant difference between the two groups (likely due to 23% power): ▪ Olanzapine group: 18.2% (n=2/11) ▪ No olanzapine group: 57.1% (n=8/14)

BD: Bipolar disorder, BD-I: Bipolar I disorder, BD-II: Bipolar II disorder

Table 4.1: Prospective cohort studies investigating risk of recurrence during the perinatal period in women with BD

Author	Country	Sample	Duration of follow-up/ assessments	Potential risk factors assessed	Outcomes	Findings
<i>Prospective cohort studies investigating risk factors for recurrence during pregnancy/postpartum</i>						
Abdel-Hay, El-Sawy and Badawy (2011)	Egypt	83 pregnant women with DSM-IV BD-I	Through pregnancy to 4 weeks postpartum. • Structured clinical interview at baseline. • Clinical assessments at each trimester.	<ul style="list-style-type: none"> • <i>Demographic variables:</i> age, education, employment status • <i>Illness history factors:</i> age at illness onset, number of episodes, number of hospitalisations, history of suicide attempts, time since last episode, treatment history • <i>Obstetric complications:</i> during pregnancy and delivery 	Occurrence of affective episode during pregnancy or within 4 weeks postpartum	<p><i>Risk of recurrence:</i> 65%;</p> <ul style="list-style-type: none"> • 33.7% during pregnancy • 31.3% postpartum <p><i>Predictors of any perinatal recurrence:</i> discontinuation of medication, longer duration of illness, increased number of episodes, increased frequency of episodes in pregnancy, obstetric complications during pregnancy and labour, unplanned pregnancy and increased number of hospitalisations.</p> <p><i>Predictors of postpartum recurrence:</i> younger age at onset, more frequent episodes in pregnancy, complication during labour, increased number of hospitalisations and less time since last episode.</p>
Bergink et al. (2012)	Netherlands	29 pregnant women with PP only (i.e. without a history of mood episodes unrelated to childbirth) 41 pregnant women with BD-I and BD-II, stratified to two groups: a) Use of lithium in perinatal period b) No lithium use during perinatal period	Through pregnancy to 4 weeks postpartum • Structured clinical interview and case-note review at baseline to confirm diagnosis. • Assessed every 4-6 weeks during the perinatal period, including daily screening up to 4 weeks postpartum by psychiatric nurse.	<ul style="list-style-type: none"> • Lithium withdrawal during perinatal period 	Occurrence of DSM-IV mania, depression, hypomania or mixed affective state	<p><i>PP only group</i></p> <ul style="list-style-type: none"> • No recurrence in pregnancy (no medication during pregnancy) • 13.8% recurrence postpartum <ul style="list-style-type: none"> ▪ Withdrawal of lithium use significantly associated with postpartum recurrence: (0% in medication group vs 44% in no medication group) <p><i>BD group:</i></p> <ul style="list-style-type: none"> • 24.4% recurrence in pregnancy (2/10 episodes of depression) <ul style="list-style-type: none"> ▪ 60% also had recurrence postpartum • 22% recurrence postpartum (66% were hospitalised) <ul style="list-style-type: none"> ▪ 50% in history of puerperal episodes group ▪ 27.3% in history of non-puerperal episodes only. ▪ Withdrawal of lithium significantly associated with recurrence in pregnancy (19.4% in medication group vs 40% in no medication group) • Withdrawal of lithium significantly associated with recurrence postpartum (7.7% in medication group vs 20% in no medication group)

BD: Bipolar disorder, BD-I: Bipolar I disorder, BD-II: Bipolar II disorder

Table 4.1: Prospective cohort studies investigating risk of recurrence during the perinatal period in women with BD

Author	Country	Sample	Duration of follow-up/ assessments	Potential risk factors assessed	Outcomes	Findings
Prospective cohort studies investigating risk factors for recurrence during pregnancy/postpartum						
Sharma et al. (2013)	Canada	37 pregnant women with BD-II	From 24 weeks of pregnancy to 12 months postpartum • Structured clinical interview at baseline (between weeks 24-32 of pregnancy) to confirm diagnosis. • Assessed at week 34 of pregnancy, 2 weeks postpartum and months 1, 2, 3, 6 and 12 postpartum	• Psychotropic medication use	Occurrence of DSM-IV depression or hypomania Symptom scores on screening measures of depression and mania	Psychotropic medication use: • 54% no psychotropic medication in pregnancy • 11% two or more psychotropic medications during pregnancy; 50% two or more postpartum • 3% no psychotropic medication during pregnancy or postpartum • 14% no psychotropic medication postpartum Recurrence rates: • 51% during pregnancy (3 hypomania, 16 depression) • 70.3% during postpartum (10 hypomania, 16 depression) • Significantly higher symptom scores of depression and mania (indicating greater severity of symptoms) at 3 months postpartum in women not using prophylactic psychotropic medication compared to women who did
Rosso et al. (2016)	Italy	17 pregnant women with lithium responsive DSM-IV BD-I (all remained on prophylactic lithium)	Through pregnancy to 12 weeks postpartum Assessed monthly during routine clinical appointments	-	Occurrence of affective episodes (clinical criteria unspecified) during pregnancy and within 12 weeks postpartum	Recurrence rates: • 11.2% during pregnancy ▪ One episode of depression ▪ One episode of hypomania • 27.8% during postpartum ▪ 2 episodes of depression ▪ 1 episode of hypomania ▪ 2 episodes of anxiety disorder NOS
Driscoll et al (2017)	U.S.A	159 pregnant women with DSM-IV bipolar disorder (bipolar I, II or not otherwise specified). • 152 followed through pregnancy stratified to 3 groups: a) Psychotropic medication during first trimester only b) Psychotropic medication during second or third trimester c) No psychotropic medication use during pregnancy • 107 followed through to the postpartum, stratified to two groups: a) Medication use postpartum b) No medication use postpartum	Through pregnancy to 12 months postpartum • Structured clinical interview at baseline to confirm diagnosis. • Symptom screening measures administered at 20, 30 and 36 weeks of pregnancy and at 2, 12, 26 and 52 weeks postpartum.	• Psychotropic medication use	• Mania and depression symptom scores indicated by self-report screening tools, during pregnancy and within 12 months postpartum	Psychotropic medication use: • 58% receiving psychotropic medication during pregnancy ▪ 26% discontinued medication in the first trimester ▪ 74% continued medication throughout pregnancy or to the second and third trimester. • 73% used psychotropic medication postpartum Risk of recurrence: • No significant difference between medication and no medication groups in symptoms of mania or depression during pregnancy or the postpartum period.

BD: Bipolar disorder, BD-I: Bipolar I disorder, BD-II: Bipolar II disorder, BD-NOS: bipolar disorder not otherwise specified

retrospective measurements are likely to underestimate recurrence in this group. Only one study has investigated perinatal recurrence in women with BD-II using a prospective follow-up design (Sharma, Sommerdyk and Campbell 2013). Sharma, Sommerdyk and Campbell (2013) assessed recurrence of mood disorder during pregnancy in 37 women with BD-II. 51% of women in this sample experienced an episode of illness, though episodes that had onset prior to 24 weeks of pregnancy were assessed retrospectively.

In one of two prospective studies of women with BD-I, 83 Egyptian women were assessed at each trimester of pregnancy through to four weeks postpartum (Abdel-Hay, El-Sawy and Badawy 2011). Almost 34% of women were reported to experience the onset of a mood episode during pregnancy, though it was not clear how episodes of recurrence were defined in this sample. In the second study, compared to findings of other prospective research, incidence of antenatal recurrence was lower in a small Italian sample of 17 women with BD-I (Rosso et al., 2016). Following monthly assessments during pregnancy at routine clinical appointments (which continued to 12 months postpartum), 11.2% of women were described as having experienced an episode of mood disorder during pregnancy. Notably however, all women remained on lithium, were considered clinically to be lithium responsive and were also receiving regular psychiatric monitoring throughout pregnancy. Women in this sample may therefore have had a form of BD that was especially well managed during pregnancy compared to those in other prospective studies.

4.2.1.1 Phenomenology of mood episodes with onset during pregnancy

Mood episodes with onset during pregnancy have been shown in all but one study (Bergink et al. 2012) to most frequently present as depression or a mixed affective state (Abdel-Hay, El-Sawy and Badawy 2011; Van Gent and Verhoeven 1992; Newport et al. 2008; Sharma, Sommerdyk and Campbell 2013; Viguera et al. 2007). Van Gent and Verhoeven (1992) followed a sample of 15 women with DSM-III BD-I and BD-II recruited

from a preconception counselling service, through pregnancy to 12 months postpartum. The authors found that of 16 pregnancies to 11 women who were successfully followed up, three of four pregnancies affected by a recurrence were depressive in polarity, with only one episode presenting as mania. Similarly, in an American sample of 26 pregnant women with broadly defined BD (BD-I, BD-II and BD-NOS), episodes of depression represented the majority of recurrences during pregnancy (68.4%), with 15.8% being comprised of mixed affective states, 10.5% mania and 5.3% hypomania (Newport et al., 2008). This pattern is also consistent to that found within other prospective studies (Abdel-Hay, El-Sawy and Badawy 2011; Viguera et al. 2007), in which episodes with onset during pregnancy were predominantly of depression 41.3-57.1% and 28.6-38.1% mixed affective states. In contrast, only 14.3-20.6% of episodes were found to be episodes of mania or hypomania.

4.2.1.2 Factors influencing risk of recurrence during pregnancy

Consistent with data from cross-sectional studies, when followed prospectively, a significant proportion of women with BD (between 42-54%) do not use any psychotropic medication during the course of their pregnancy (Driscoll et al. 2017; Sharma, Smith and Mazmanian 2006, respectively). Of 159 pregnant women with broadly defined BD (BD-I, BD-II and BD-NOS), more than a quarter of women (26%) who were using psychotropic medication at the start of their pregnancy subsequently discontinued all medication within the first trimester of pregnancy (Driscoll et al., 2017). The destabilising effect of medication withdrawal on mood during pregnancy has been investigated in several prospective studies, with evidence indicating that discontinuation of medication prior to or during pregnancy increases risk of antenatal recurrence in women with BD (Bergink et al. 2012; Van Gent and Verhoeven 1992; Newport et al. 2008; Viguera et al. 2007). In addition, discontinuation of psychotropic medication, and of mood stabilisers in particular, has also been associated with a reduced latency to illness onset (Newport et al. 2008; Viguera et al. 2007) and longer duration of episodes within-pregnancy (Viguera et al. 2007). As described in Chapter 2

(section 2.6.2.2), latency to illness onset has been shown to be more than four times shorter among women who discontinue mood stabilisers rapidly (within two weeks) compared to those who withdraw mood stabilisers more gradually (over a period of more than two weeks (Viguera et al. 2007).

Other factors reported to be associated with antenatal recurrence include an earlier age at onset of BD, a BD-II diagnosis, a history of more frequent mood episodes per year (prior to pregnancy), reduced time since last episode and use of antidepressants or anticonvulsants compared to lithium (Viguera et al. 2007).

4.2.1.3 Section summary

Based on the literature thus far, discontinuation of mood stabilisers during pregnancy and markers of a more severe, preconception course of BD (such as an earlier age at onset and a history of more frequent mood episodes) may be useful indicators of recurrence of BD during pregnancy. Given that childbirth is an event associated with unique physiological and psychosocial changes, it is plausible that the pathophysiology of episodes triggered by childbirth differs from episodes occurring antenatally or unrelated to childbirth. As discussed in the background chapter of this thesis, prospective studies examining risk of postpartum recurrence of BD are crucial, given that the risk of mania or affective psychosis is significantly greater following delivery compared to any other time in a woman's life. Studies examining postpartum recurrence of BD using a prospective methodology are discussed further below.

4.2.2 Recurrence of bipolar disorder in the postpartum period

Consistent with retrospective literature, the risk of recurrence of BD (within the same samples of women) has been shown to be higher following childbirth compared to pregnancy in several prospective studies (Bergink et al. 2012; Van Gent and Verhoeven 1992; Rosso et al. 2016; Sharma, Sommerdyk and Campbell 2013), but not in all (Abdel-

Hay, El-Sawy and Badawy 2011; Bergink et al. 2012). Overall estimates suggest that between 22-31.3% of women with BD experience the onset of at least one mood episode within the first 3 months of delivery (Abdel-Hay, El-Sawy and Badawy 2011; Bergink et al. 2012; Rosso et al. 2016), increasing to 70.3% of women within the first postpartum year (Sharma, Sommerdyk and Campbell 2013). As with estimates of recurrence during pregnancy, direct comparison of risk of postpartum mood disorders across BD subtypes is difficult, given that studies stratifying by diagnosis are limited and there is substantial heterogeneity in the temporal definition used to define the postpartum period. For example, Rosso et al. (2016) reported postpartum mood episodes to occur in 27.8% of women with BD-I within four weeks of delivery, compared with 31.3% in an independent sample of women with BD-I within the first three months (Abdel-Hay, El-Sawy and Badawy 2011). In their unique study of women with BD-II, Sharma, Sommerdyk and Campbell (2013) defined the postpartum period as the first 12 months following childbirth, during which 70% of women were reported to experience a clinically impairing mood episode.

4.2.2.1 Phenomenology of mood episodes with onset in the postpartum period

In contrast to episodes with onset during pregnancy, reports regarding the clinical presentation of postpartum mood episodes have been inconsistent across literature. Several prospective studies have observed a predominance of episodes with manic features following delivery (PP, mixed episodes, hypomania; Abdel-Hay, El-Sawy and Badawy 2011; Bergink et al. 2012; Van Gent and Verhoeven 1992), particularly in cases with early onset within four weeks of delivery (Abdel-Hay, El-Sawy and Badawy 2011; Bergink et al. 2012). Conversely, a number of studies have reported episodes of postpartum depression to be especially frequent (Rosso et al. 2016; Sharma, Smith and Mazmanian 2006; Sharma, Sommerdyk and Campbell 2013; Wisner et al. 2004), despite in some cases restricting onset criterion to within 12 (Rosso et al. 2016) and 4 weeks of delivery (Sharma, Smith and Mazmanian 2006; Wisner et al. 2004). Nevertheless, of those studies which have directly compared the phenomenology of perinatal episodes

within the same sample of women, risk of PP and hypomania was higher within the first three months postpartum compared to pregnancy in all (Abdel-Hay, El-Sawy and Badawy 2011; Bergink et al. 2015a; Van Gent and Verhoeven 1992; Sharma, Sommerdyk and Campbell 2013) but one study (Rosso et al. 2016). In the study by Sharma, Sommerdyk and Campbell (2013), risk of hypomania in their sample of women with BD-II was three times higher in the postpartum period compared to during pregnancy. Notably, none of the women experienced an episode of mania or affective psychosis during the study period, supporting evidence from retrospective studies which indicate risk of PP to be considerably lower in women with BD-II than in BD-I.

4.2.2.2 Predictors of recurrence of bipolar disorder in the postpartum period

4.2.2.2.1 Mood stabiliser prophylaxis of postpartum mood episodes

Well-designed, cohort studies that have prospectively examined risk factors for postpartum recurrence of BD are scarce. Similar to studies discussed previously, the majority of research in this area has been limited to assessing the influence of psychotropic medication only, the findings of which have been inconsistent (Bergink et al. 2012; Driscoll et al. 2017; Sharma, Smith and Mazmanian 2006; Sharma, Sommerdyk and Campbell 2013; Wisner et al. 2004). While lack of efficacy of prophylactic mood stabilising medication during the postpartum period has been demonstrated by several studies (Driscoll et al. 2017; Sharma, Smith and Mazmanian 2006; Wisner et al. 2004), others have reported the opposite (Abdel-Hay, El-Sawy and Badawy 2011; Bergink et al. 2012; Sharma, Sommerdyk and Campbell 2013).

Wisner et al. (2004) investigated use of prophylactic sodium valproate for the prevention of postpartum mood episodes in a sample of 26 pregnant women with BD. The authors reported no significant effect of using this particular medication, finding that 70% of women who remained on sodium valproate experienced the onset of a mood episode within two weeks of delivery, compared to 73% of women not using this

medication. There was also no significant association between use of sodium valproate and time to onset of postpartum recurrence. In their study, Abdel-Hay, El-Sawy and Badawy 2011, found discontinuation of sodium valproate to significantly increase risk of any mood episode during the perinatal period, but not specifically of those with postpartum onset.

These findings are further supported by those of Driscoll et al. (2017), in which symptoms of depression and mania during the first postpartum year (assessed by screening measures in 107 women with BD who completed follow-up) were found to be comparable between women who remained on prophylactic psychotropic medication and those who did not, suggesting that psychotropic medication had little influence on risk of postpartum psychopathology. Nonetheless, these findings may only be generalisable to women with a less severe form of BD, given that all symptoms of recurrence were noted to be mild in severity. This may be explained by 40% of the sample having a diagnosis of BD-II or BD-NOS, both of which by definition, typically present with a less severe illness course than BD-I or SA-BD. As discussed previously, these subtypes are also potentially less vulnerable to severe postpartum recurrence. Moreover, 30% of women recruited during pregnancy were subsequently lost to attrition at postpartum follow-up. It is therefore possible that women who did not participate at follow-up were those who experienced the onset of a severe mood episode following delivery.

Driscoll et al.'s (2017) study is also limited by the use of brief symptom screening measures to assess the presence of perinatal psychopathology. These particular measures were not designed specifically for use within populations of women within the perinatal period, and as such can be less reliable due to the inclusion of items which assess somatic features of mood episodes (for example changes in sleep patterns or appetite) that are common in pregnant women or new mothers. The nature of these behavioural changes may therefore be misattributed by the participant (Ross et al. 2003), potentially leading to an over or underestimation of psychopathology within this

sample. In addition, as perinatal psychopathology was not defined according to standard diagnostic criteria, it was also not possible to determine whether discontinuation of medication in early pregnancy specifically increases risk of severe postpartum mood episodes, and in particular of PP.

In contrast to the findings outlined above, the efficacy of prophylactic mood stabilisers during the perinatal period has been demonstrated in other research. In a sample of 25 pregnant women with BD, postpartum recurrence within the first month of delivery was strikingly less frequent among women using prophylactic olanzapine (18.2%), compared to those who were not using this medication (57.1%; Sharma, Smith and Mazmanian 2006). Though this finding was not statistically significant, post-hoc analyses showed this study was considerably underpowered (at 23%) to detect this between group difference, thus highlighting the need for replication of this finding within a larger sample of women with BD.

Moreover, Sharma, Sommerdyk and Campbell (2013) compared the severity of symptoms of mania and depression (indicated by scores from screening measures) between BD-II women who were not taking any psychotropic medication and women that were. The authors reported severity of mood symptoms to be significantly greater at three months postpartum among women who were not using psychotropic medication. Importantly however, the authors did not restrict their definition of psychotropic medication use to mood stabilisers only, also including women who were receiving antidepressant or anxiolytic monotherapy which has been shown to increase risk of recurrence of BD during the perinatal period (Viguera et al. 2007).

Bergink et al. (2012) found that among the 41 women with BD in their sample, compared to those who remained on lithium, discontinuation of lithium was associated with a significantly increased risk of any DSM-IV mood episode within the first postpartum month (7.7% vs 20%). Furthermore, despite treatment and subsequent maintenance with mood stabilisers, antenatal recurrence was associated with a 14

times greater risk of postpartum recurrence, with 60% of women who experienced a mood episode during their pregnancy also becoming clinically unwell following delivery. Within the same study, the effect of lithium prophylaxis was also examined in a separate sample of 29 pregnant women with a history of PP only (i.e. women who had never experienced any episodes of mood illness unrelated to childbirth). Interestingly, unlike women in the BD group, none of the women with a history of PP experienced an episode of mood illness during pregnancy, despite all remaining medication free. At follow-up however, 44% of women who discontinued all medication experienced a mood episode postpartum, compared to none of the women who commenced lithium immediately following delivery. This suggests that lithium may be less effective at preventing postpartum mood episodes among women with BD than those with a history of PP only. Thus, despite phenotypic similarities between the two groups of women, the pathophysiology and triggering of postpartum mood episodes is potentially distinct across these sub-groups.

4.2.2.2 Non-medication related risk factors for postpartum recurrence

Despite emerging evidence suggesting efficacy of mood stabilising medication for the prophylaxis of postpartum mood episodes, findings within the literature also suggest that risk of postpartum recurrence in women with BD remains high despite medication use. This potentially indicates that factors other than medication are also likely to influence risk of episodes following childbirth within women with BD. Currently, only one prospective study has examined medication and a range of non-medication related factors that may influence risk of postpartum recurrence of BD (Abdel-Hay, El-Sawy and Badawy, 2011). Potential risk factors investigated in this study (in addition to psychotropic medication use) included pre-pregnancy clinical characteristics of BD and obstetric complications. Though other within-pregnancy potential risk factors (such as social support or sleep disruption) were not explored. In this sample, risk of postpartum recurrence was significantly greater among women who had a younger age at onset of BD, experienced more frequent mood episodes during pregnancy, experienced an

increased number of psychiatric hospitalisations prior to pregnancy, a reduced time since last episode and obstetric complications during delivery.

However, the findings of this study are subject to several limitations. For example, it was not clear how perinatal recurrence was assessed in this sample and whether standard diagnostic criteria were used to define episodes of recurrence. Furthermore, it was not clear how use of psychotropic medication use defined. Specifically, the timing of medication use was not specified (i.e. during pregnancy and/or postpartum) and it is unknown whether the medication group only included women who were using medication prophylactically. Finally, factors previously implicated in postpartum recurrence of BD (such as previous history of PP or primiparity) were not adjusted for, or risk factors for PP specifically assessed.

4.3 Summary

Following a review of the literature, it is evident that prospective pregnancy studies of the perinatal period in women with BD are lacking. Those which have been conducted have been limited by use of a descriptive methodology (Van Gent and Verhoeven 1992; Viguera et al. 2007), small unrepresentative samples (ranging from 15-83 women, with the exception of Driscoll et al. 2017), heterogeneity in the definition of the postpartum period (from 4 weeks to 12 months postpartum) and lack of standardised diagnostic criteria to define episodes of recurrence (Abdel-Hay, El-Sawy and Badawy 2011; Driscoll et al. 2017; Van Gent and Verhoeven 1992; Rosso et al. 2016). Consequently, estimates of perinatal recurrence vary widely between studies, with little known regarding risk of perinatal recurrence and specifically postpartum recurrence across BD subtypes.

Furthermore, prospective studies investigating potential risk factors for postpartum mood disorders in BD have primarily focused on examining the influence of a limited range of psychotropic medications, none of which have specifically been assessed in relation to PP. The role that other potential risk factors, specifically those occurring

within the perinatal period may have in the occurrence of PP in BD therefore remains to be investigated. Moreover, no prospective pregnancy studies in this area have been conducted in a UK population of women with BD.

4.4 Further aims of this thesis

In addition to investigating potential lifetime correlates of PP (the findings of which were presented and discussed in Chapter 3), a further aim of this thesis was to examine potential within-pregnancy risk factors for PP in BD using a prospective follow-up design. Few within-pregnancy risk factors for PP have been examined using a prospective methodology, and/or within a UK population, using standardised diagnostic criteria or by comparison with an appropriate diagnostic control group. To address the gaps identified within the literature, this study (The BDRN Pregnancy Study) aimed to examine the influence of a wide-range of within-pregnancy factors for PP in a UK sample of pregnant women with well-defined BD, using a prospective follow-up design.

Specifically, the current study aimed to:

1. Describe psychotropic medication use and psychiatric outcomes across the perinatal period within the BDRN pregnancy sample (*this step would allow further phenotypic refinement of perinatal psychiatric outcomes to effectively address Aim 2*).
2. Investigate a wide range of within-pregnancy potential risk factors for PP within the BDRN pregnancy sample (*differences observed in the occurrence of PP according to the presence or absence of within-pregnancy factors would identify factors that potentially influence risk of these episodes*).

The following chapter (Chapter 5) describes the methods used within the BDRN Pregnancy Study, following which the results of investigations conducted to address the aims outlines above will be reported and discussed in Chapters 6 and 7.

Chapter 5

The BDRN Pregnancy Study: Methods

5.1 Overview of chapter

As discussed in previous chapters of this thesis, research identifying factors influencing risk of PP are crucial for individualised risk prediction of these episodes within BD. Prospective follow-up studies allow for directional relationships between predictors and illness outcomes to be established and as such are considered the gold standard of observational research. Nevertheless, there is a paucity of prospective research investigating potential risk factors for PP in BD. For these reasons, risk of recurrence during the perinatal period was assessed using a prospective-follow up design in 106 pregnant women with a pre-conception diagnosis of BD.

This chapter focuses on the methods of recruitment and assessment utilised within this study. First, an outline of the study design, details of ethical approval and inclusion criteria are described, followed by a summary of approaches used to maximise the identification and recruitment of women with BD during pregnancy. Detailed descriptions of clinical assessments conducted across the perinatal period are also documented and approaches to the statistical analysis of potential risk factors for episodes of postpartum recurrence are presented.

5.2 Design

This study utilised a prospective follow-up design. Potential risk factors for postpartum mood episodes were assessed at baseline during pregnancy in women with a lifetime history of BD. Follow-up measures were conducted at three months postpartum to assess the occurrence of perinatal psychopathology. The follow-up period was defined in accordance with the literature indicating the first three postpartum months to be the period of greatest risk for severe recurrence of mood episodes.

Baseline assessments conducted during pregnancy consisted of:

- A semi-structured psychiatric research interview to assess pre-conception lifetime history of perinatal and non-perinatal psychopathology.
- An interview completed during the third trimester to assess the presence or absence of a range of potential risk factors for postpartum recurrence in the current perinatal period.

Postpartum follow-up assessments included:

- A postal questionnaire completed by the participant's General Practitioner (GP) and/or psychiatrist at two months postpartum.
- A semi-structured telephone interview with the participant at three months following their expected delivery date to assess the presence or absence of psychopathology within the current postpartum period.

Psychiatric case-notes were also reviewed at three months postpartum to supplement all data gathered at each assessment. **Figure 5.1** provides an overview of the study design.

Figure 5.1 Flow chart summarising the timing of assessments conducted in The BDRN Pregnancy Study

5.3 Ethical approval

This study received a favourable Multi region Research Ethics Committee (MREC) opinion for conduct in the NHS and received local Research and Development approval in 9 Health Boards and NHS Trusts nationwide (MREC 97/07/001, amendment AM04). Participants were provided with a Participant Information Sheet (Appendix D) and written consent was obtained prior to participation (Appendix E).

5.4 Inclusion criteria

Women were included in the current study if they:

- a) met DSM-5 criteria for lifetime BD
- b) were at least 18 years of age
- c) were at least 12 weeks pregnant.

5.5 Recruitment

To maximise the identification and recruitment of women with BD during pregnancy, a combination of different recruitment methods was employed. A summary of systematic and non-systematic methods of recruitment is provided in this section and in **Figure 5.2**.

5.5.1 Systematic approach

5.5.1.1 NHS perinatal mental health services

The majority of women were recruited to the BDRN Pregnancy Study via NHS perinatal psychiatric services across the UK. **Figure 5.3** summarises recruitment within each perinatal service involved in this study. Perinatal psychiatric services were selected within Trusts and Health Boards in which BDRN either had existing or historical ethical approval or contact with clinicians interested in facilitating recruitment. In NHS Trusts and Health Boards in which perinatal services are available, ideally all women with a history of BD or PP are referred for specialist psychiatric care during pregnancy. Women who met the study inclusion criteria (n=64) were identified by members of the perinatal psychiatric team or NHS Clinical Studies Officers (CSOs) during the referral process or via attendance at outpatient clinic appointments. Eligible women were approached by their clinician or a CSO and asked if they would be interesting in receiving further information about the study from a member of the BDRN study team. Of those who expressed an interest in the study, 39 (61%) women subsequently participated.

Figure 5.2 Flow chart summarising methods of recruitment of women to The BDRN Pregnancy Study

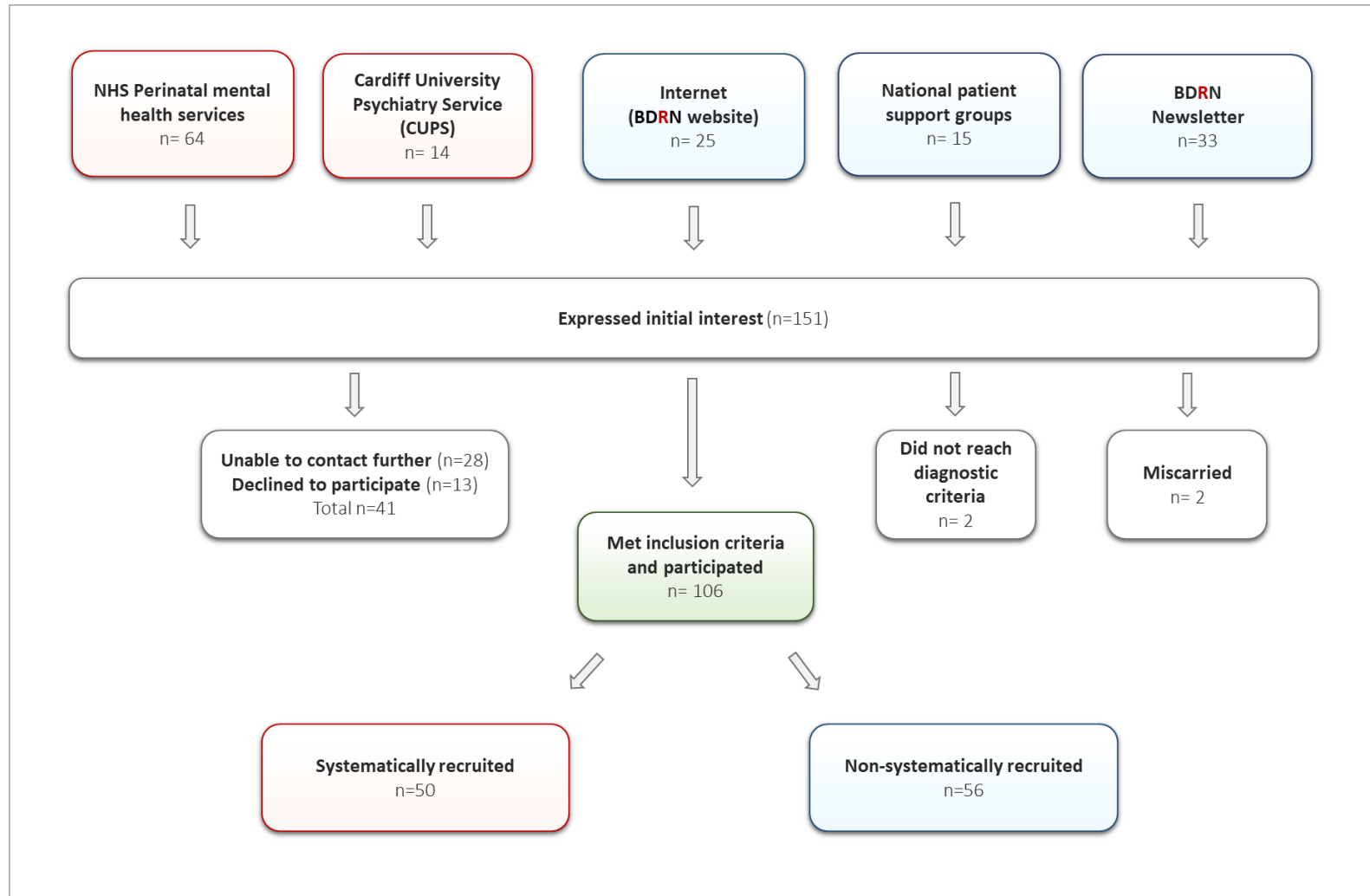
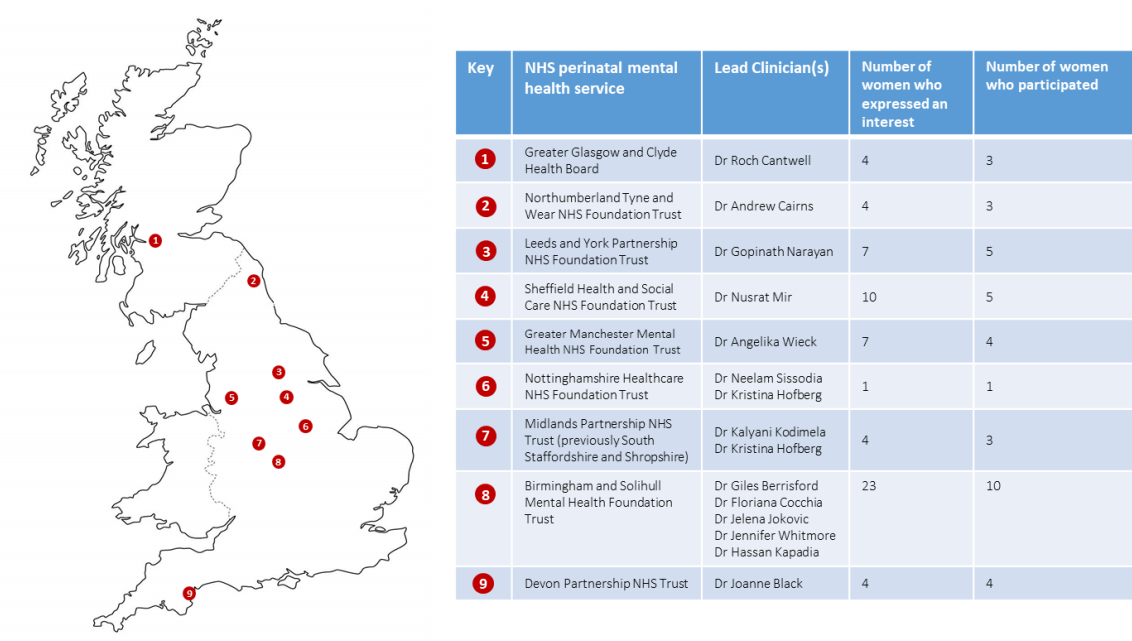


Figure 5.3: Perinatal mental health services involved in the recruitment of women to The BDRN Pregnancy Study



5.5.1.2 Cardiff University Psychiatry Service (CUPS)

The CUPS clinic is a free second opinion psychiatry service run jointly by Cardiff University and Cardiff and Vale University Health Board. Within this service Professor Ian Jones operates a specialist perinatal clinic for women with BD. Women seeking further advice while in the stages of planning a pregnancy, or during their pregnancy may be referred to CUPS via their psychiatric team. This service is typically utilised by women who do not have access to specialist perinatal psychiatric services in their local area. Through CUPS, Professor Ian Jones identified 14 women who were eligible for participation in the study and asked if they would be interested in receiving further information. 11 (79%) of these women subsequently participated in the study.

5.5.2 Non-systematic approach

5.5.2.1 BDRN website

Information about the BDRN Pregnancy Study was provided on the BDRN website (www.BDRN.org), along with downloadable participant information leaflets (see Appendix F) and contact details for the study team. Women who had received initial information about the study via advertisements or news broadcasts in local or national media were directed to the BDRN website for further information. 25 women expressed an interest in the study via the BDRN website, of whom 20 (80%) participated.

5.5.2.2 National patient support groups

Adverts were placed on the websites of the national patient support charities APP and Bipolar UK. Articles were also produced for Bipolar UK's quarterly magazine, Pendulum, which was distributed to all subscribing members. Participant information leaflets were distributed at patient support group meetings attended by myself or other members of the Mood Disorders Research Group.

In collaboration with Bipolar UK, Professor Ian Jones, Clare Dolman (Vice Chair of Bipolar UK) and I also organised a series of information workshops for women with BD seeking advice about pregnancy and childbirth. Workshops were organised as a session within the Bipolar UK annual conference held in the summer of 2015 and as a stand-alone session in summer 2016. Women planning pregnancy or those pregnant at the time of the workshop were provided with information and invited to participate. 15 women expressed an interest in the study after receiving information via their support group, of whom 10 (66%) participated.

5.5.2.3 BDRN participant newsletter

All participants involved in the BDRN programme of research were sent an annual research newsletter by post, informing them of study updates and advertising current projects, including the BDRN Pregnancy Study. 33 women involved in BDRN responded to study adverts included in the newsletters, of whom 26 (79%) subsequently participated.

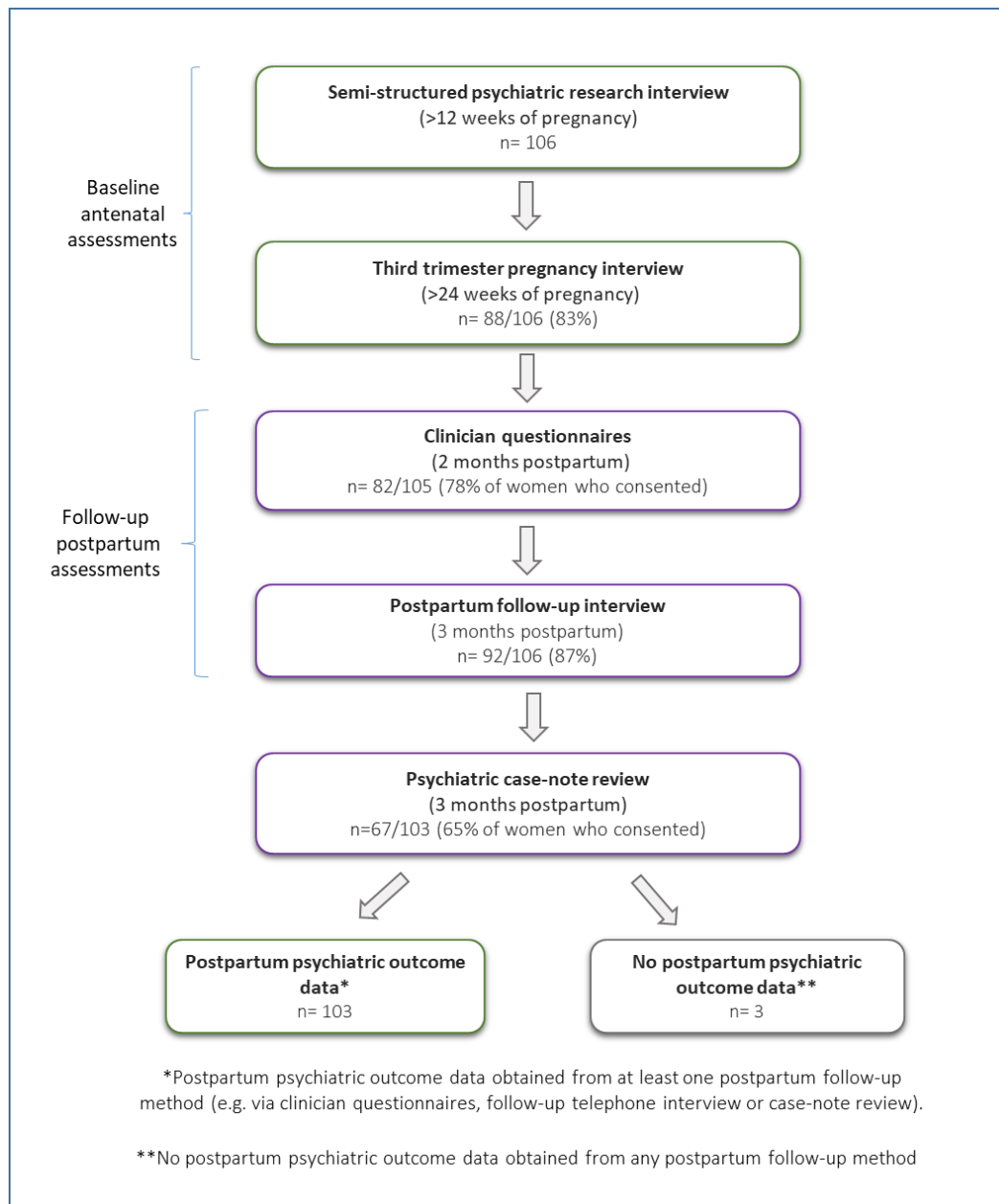
5.6 Participants

As shown in **Figure 5.2**, 151 women expressed an interest in participating in this study and were screened by telephone to confirm eligibility (see appendix G). Despite their initial interest, 28 women did not respond to further contact, a further 13 later declined to participate following the telephone screen and two women did not meet diagnostic inclusion criteria. An additional two women unfortunately miscarried prior to completing the baseline semi-structured interview. Though women were not asked to provide an explanation for refusal to participate in the study, reasons volunteered included having too many commitments during pregnancy, the short length of time to delivery and concerns that discussing past illness experiences may increase risk of recurrence in the perinatal period. The final sample comprised 106 women with BD.

5.7 Procedures

All procedures and assessments utilised within this study are described below. **Figure 5.4** provides a summary of the number and proportion of women that participated in each stage of assessment.

Figure 5.4: Flow chart summarising data collected at each assessment in The BDRN Pregnancy Study



5.7.1 Baseline antenatal assessments

5.7.1.1 Semi-structured psychiatric research interview

Once eligibility for participation in the study was confirmed, baseline semi-structured research interviews (Appendix H) were conducted in participant's homes from week 12 of pregnancy (lasting approximately 1.5-2 hours). Interviews were arranged after the first trimester to ensure women were beyond the period considered highest risk of miscarriage. A minority of women resided in Ireland (n=3) and it was not feasible to conduct these interviews in person. Therefore, in these cases interviews were completed via telephone. In total, 106 women completed the semi-structured interview at baseline.

The semi-structured interview was used to assess lifetime psychopathology and was adapted from that designed and used in the BDRN programme of research (see Chapter 3, page 53 for a full description). The baseline assessment consisted of a modified version of the SCAN (Wing et al., 1990) to assess lifetime occurrence of mania and depression, psychotic symptoms and anxiety disorders occurring prior to the current pregnancy.

5.7.1.2 Third trimester pregnancy interview

To assess potential predictors of postpartum recurrence present within the current pregnancy, an additional interview (Appendix I) informed by previous literature was completed in the third trimester of pregnancy (lasting approximately 10 minutes). Women who were less than 24 weeks pregnant at the time of the baseline semi-structured interview subsequently completed the pregnancy interview by telephone once in the third trimester. This time frame was selected to capture the presence of potential predictors occurring within each trimester of pregnancy.

The third trimester interview consisted of the following measures:

- **SCAN (Wing et al., 1990):** Relevant sections of the SCAN were used to assess the presence of psychopathology during the current pregnancy.
- **Pregnancy Risk Questionnaire (PRQ, Austin et al. 2005):** Three items extracted from the PRQ were used to assess participant's subjective experience of pregnancy and emotional support during pregnancy. Participants were asked to rate their experience of pregnancy on a Likert scale ranging from one indicating that pregnancy was 'not at all a positive experience' to five 'very much a positive experience'. They were also asked to rate the perceived level of emotional support that would be provided by their partner (if applicable) and by significant others following the birth of their baby. Both variables were rated on a Likert scale from one indicating 'not at all emotionally supportive' to five 'very emotionally supportive'.
- **Brief Life Events Questionnaire (BLEQ, Brugha et al., 1985):** A range of 11 adverse life events occurring during the previous six months of pregnancy were assessed using a modified version of the BLEQ. An open-ended question also asked participants 'In the last six months, other than being pregnant, has any other significant event happened in your life?' For a more detailed description of the BLEQ, please refer to Chapter 3, page 56.
- **Pittsburgh Sleep Quality Index (PSQI, Buysse et al. 1989):** A closed ended question extracted from the PSQI was used to assess subjective experience of sleep quality in the third trimester of pregnancy. The PSQI is a widely used and well validated self-report instrument assessing sleep quality and disturbance over a one-month period. Participants were asked 'during the last month, how would you rate your sleep quality overall?' Responses were coded categorically as 'very good', 'fairly good', 'fairly bad' and 'very bad'.

In addition, participants were asked a series of questions about planning of the current pregnancy, any psychotropic medication use during the current perinatal period (in the six months prior to and/or during pregnancy) and any alcohol and smoking use within the current pregnancy. In total, 88 (83%) women completed the third trimester interview.

5.7.2 Follow-up postpartum assessments

Follow-up data were gathered from multiple sources in the postpartum period to maximise the likelihood of obtaining postpartum psychiatric outcome data and to corroborate information collected antenatally. These assessments are described further below.

5.7.2.1 Clinician questionnaires

For women who had provided explicit written consent (n=105), a postal questionnaire was sent to their GP (Appendix J)/and or psychiatrist (Appendix K) at two months following their expected delivery date. The questionnaires asked clinicians about participants' use of psychotropic medication and the occurrence of any episodes of psychiatric illness within the current perinatal period. Questionnaires were sent at two months postpartum to obtain details of any adverse outcome of the pregnancy prior to the participant being contacted for a follow-up telephone interview at three months postpartum. This step was taken to avoid causing unnecessary distress to participants should an adverse outcome have occurred. In total, questionnaires were completed by the GP and/or psychiatrist for 82 (78%) women.

5.7.2.2 Postpartum follow-up interview

Participants were contacted at three months following their expected delivery date for a telephone interview lasting approximately 20 minutes (Appendix L). The follow-up interview was designed to assess perinatal psychiatric outcomes, in addition to potential predictors of postpartum recurrence which had occurred since completion of the third trimester interview. The postpartum interview comprised the following measures:

- *SCAN (Wing et al. 1990)*: Relevant sections of the SCAN were administered to obtain information about any episodes of psychiatric illness that had occurred during late pregnancy and/or within three months postpartum.
- *Psychotropic medication use*: Women were asked about any changes in psychotropic medication use since the third trimester interview.
- *Smoking and alcohol use*: Women were asked about any smoking or alcohol use in pregnancy since the third trimester interview
- *BLEQ (Brugha et al., 1985)*: The BLEQ was re-administered at postpartum follow-up to assess the occurrence of any adverse life events since the third trimester interview.

Women were also asked at postpartum follow-up about a range of other factors specific within the current pregnancy such as sleep loss during labour and obstetric factors relating to pregnancy and delivery. In total, 92 (87%) women completed the follow-up interview. Of those women who did not complete the postpartum telephone interview, 13 were unable to be contacted and one woman was contacted but declined to participate further.

5.7.3 Psychiatric case-note review

For women who provided written consent, psychiatric case-notes where available were reviewed at three months postpartum to supplement and corroborate all data gathered at each assessment (n=67/103, 65%). This period was chosen so that information could also be gathered about any episodes of psychiatric illness occurring with onset within three months postpartum.

5.8 Clinical Ratings

Data gathered at each assessment were combined with psychiatric case note information to produce detailed, clinical vignettes. Vignettes summarised participants' lifetime and perinatal psychopathology, demographic and social information, lifetime substance use, obstetric history and family history of psychiatric illness. From the vignettes, ratings were made for demographic characteristics, key lifetime psychiatric features, potential within-pregnancy predictors of postpartum recurrence and perinatal psychiatric outcome data. A summary of each variable cluster is provided below, followed by detailed descriptions of all variables rated.

- ***Demographic characteristics:*** Ratings were made of demographic variables including age at baseline interview, ethnicity, relationship status, highest educational achievement, highest level of occupation and method of recruitment.
- ***Preconception lifetime psychiatric history:*** Ratings were made for key lifetime clinical variables for the period from illness onset to conception of the current pregnancy. These included DSM-5 diagnoses, illness course characteristics, family history of postpartum mood illness and sleep loss as a trigger of affective episodes.

- *Within-pregnancy potential predictors of postpartum recurrence relating to the current pregnancy:* Ratings were made for potential predictors of postpartum recurrence that were specific within the current pregnancy. Variables rated included psychotropic medication use during the current perinatal period, psychopathology in pregnancy, perceived experience of pregnancy, perceived emotional support, substance use in pregnancy, adverse life events in the perinatal period, sleep quality in pregnancy, sleep loss during delivery and obstetric factors relating to the current pregnancy and delivery.
- *Perinatal psychiatric outcomes:* Ratings were made for any episodes of psychiatric illness with onset during pregnancy and within three months of delivery.

Table 5.1 provides an overview of the source assessment(s) from which data regarding potential predictors and perinatal psychiatric outcomes were obtained.

Methodological considerations

To ensure reliability of clinical data, Christine Fraser (CF, a research psychologist and senior member of BDRN) and I made independent lifetime ratings of diagnoses, key lifetime clinical variables and perinatal psychiatric outcomes. CF was selected as an independent rater for the study, due to having considerable experience of conducting psychiatric assessments of participants with BD and of rating lifetime clinical data and psychiatric diagnoses. CF and I met regularly to review all ratings and consensus was agreed through discussion. In cases of doubt, ratings were discussed and agreed with senior members of the BDRN team (Professor Ian Jones, Professor Lisa Jones and Dr Katherine Gordon-Smith).

Table 5.1: Summary of source(s) of assessment from which all data were obtained in the BDRN Pregnancy Study

<i>Data collected</i>	Semi-structured research interview	Third trimester pregnancy interview	Clinician questionnaires	Postpartum follow-up interview	Psychiatric case-notes
Preconception lifetime psychiatric history					
Pre-conception best estimate main DSM-5 diagnosis	X				X
Pre-conception illness course characteristics	X				X
Family history of postpartum psychiatric illness	X				X
Pre-conception sleep loss as a lifetime trigger of affective episodes	X				X
Within pregnancy potential predictors of postpartum recurrence in the current perinatal period					
Prophylactic medication use in the current perinatal period	X	X	X	X	X
Antenatal psychopathology within the current pregnancy	X	X	X	X	X
Psychosocial factors relating to the current pregnancy		X		X	X
Smoking and alcohol use in the current pregnancy		X		X	X
Adverse life events in the current perinatal period		X		X	X
Sleep quality and sleep loss in the current perinatal period		X		X	X
Obstetric factors in the current perinatal period		X	X	X	X
Psychiatric outcomes within the current postpartum period					
DSM-5 mood episodes with onset during the postpartum period			X	X	X
Timing of onset of DSM-5 episodes of mood episodes during the current postpartum period			X	X	X

5.8.1 Demographic characteristics

Ratings were made for the following demographic variables according to definitions described below:

- *Age at interview*: age at participation in the baseline semi-structured interview.
- *Ethnicity*: rated according to the following groups; White British/White other.
- *Lifetime marital status*: rated as a) ever married/lived as married or b) never married/lived as married.
- *Highest educational achievement*: rated as a) achieving higher education level qualifications (defined as Advanced Level [A-Level] qualification or equivalent and above) or b) no higher education level qualifications (defined as General Certificate of Secondary Education [GCSE] or equivalent and lower).
- *Highest occupational status*: lifetime highest occupational status was rated according to The International Standard Classification of Occupations (ISCO-88, International Labour Organisation). Responses were coded as a) having a lifetime history of a professional occupation (ISCO-88 groups 1-3) or b) a lifetime history of a non-professional occupation(s) only (all other groups).
- *Method of recruitment*: rated as a) systematic (defined as recruitment via NHS Trust/Health Boards or the CUPS clinic) or b) non-systematic (all other methods).

5.8.2 Preconception lifetime psychiatric history

Key lifetime clinical characteristics for the period prior to the current pregnancy were rated as detailed below.

5.8.2.1 Lifetime psychopathology

Best estimate DSM-5 main diagnosis:

Ratings of best-estimate main psychiatric diagnoses were made for all participants according to standard operationalised diagnostic criteria of the DSM-5. In cases where multiple diagnoses were indicated, these were rated hierarchically according to level of functional impairment. The diagnosis causing the highest level of functional impairment was rated as the primary diagnosis. Diagnoses discussed in subsequent chapters relating to this study are primary diagnoses rated according to the DSM-5.

Lifetime illness course characteristics:

- *Age at illness onset:* defined as the age at which affective symptoms first caused impairment in daily occupation or social functioning.
- *History of psychotic symptoms:* rated as present or absent. Presence was defined as a history of experiencing at least one psychotic symptom prior to the current pregnancy.
- *Number of episodes of mania/depression:* defined as the number of episodes of mania and depression per illness year prior to the current pregnancy (calculated for the period between the age of onset of impairing BD and conception of the current pregnancy).
- *Family history of postpartum mood illness:* rated as a) present (defined as a known history of postpartum mood illness among a first degree relative) or b) absent (no known presence of postpartum affective illness among a first degree relative).

5.8.2.2 Lifetime history of postpartum psychosis

Lifetime history of PP (prior to the current pregnancy) was rated as present or absent. PP was defined as a DSM-5 episode of mania, mixed affective state or affective psychosis with onset within six weeks of a previous delivery. The cut-off used to define the postpartum period was expanded to be consistent with both DSM-5 and ICD-10 criteria.

5.8.2.3 Sleep loss as a lifetime trigger of episodes of affective illness

Lifetime history of an affective episode triggered by sleep loss was rated as present or absent. Presence was defined as having a self-reported history of at least one episode of affective illness triggered by sleep loss.

5.8.3 Potential within-pregnancy predictors of postpartum recurrence in the current pregnancy

A range of factors occurring specifically within the current pregnancy was rated as potential predictors of postpartum recurrence. Detailed descriptions of rating procedures for each of these variables is provided below.

5.8.3.1 Psychotropic medication use in the current perinatal period

Data regarding psychotropic medication use during the perinatal period were highly complex and subject to substantial variation between participants but also across each individual perinatal period. For this reason, I developed a visual timeline tool for each participant as a means of graphically representing this data longitudinally and simply across the perinatal period (Perry et al. 2017, see Appendix M for examples of perinatal timelines). In combination with clinical vignettes, these timelines were used as an aid

from which to make ratings of psychotropic medication use during the current perinatal period.

Given the complexity of medication data, definitions of ‘prophylactic’ and of ‘mood stabilising medication’ (i.e. what medications would be defined as a mood stabiliser) were discussed and agreed through consensus with senior members of BDRN (Prof. Lisa Jones, Dr Katherine Gordon-Smith, Prof. Ian Jones and Dr Marisa Casanova-Dias), two of whom were consultant perinatal psychiatrists (Prof. Ian Jones and Dr Marisa Casanova-Dias). Prophylactic mood stabilising medication was subsequently defined as the use of any medication (during the perinatal period) intended for the purpose of mood stabilisation, which was commenced or continued for reasons other than treatment. Based on clinical and research expertise, medications included in this definition were lithium, anticonvulsants and antipsychotics (typical and atypical). Timelines for each participant were subsequently reviewed and the presence/absence of prophylactic mood stabilising medication in the postpartum period agreed through discussion and consensus according to the definition described above. Specifically, ratings were made for the following medication related factors:

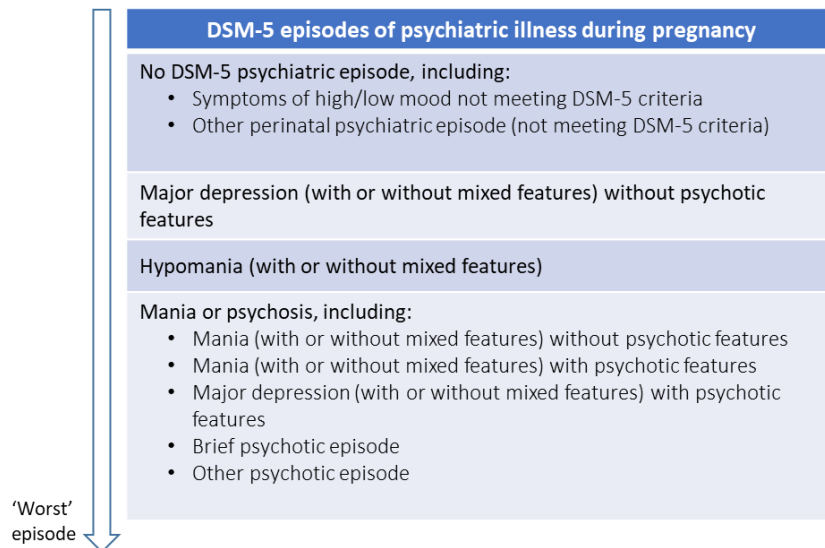
- ***Use of any psychotropic medication as a mood stabiliser:*** rated as present or absent within each of the following time periods; the six months immediately preceding pregnancy, each month of pregnancy and each postpartum month. Presence included any medication used for purposes of treatment or prophylaxis.
- ***Withdrawal of mood stabilising medication:*** rated as present or absent in women who were using mood stabilising medication within the six months immediately preceding pregnancy. Presence was defined as the discontinuation of all mood stabilising medication either within the six months prior to pregnancy or during pregnancy, which was not recommenced at any point during pregnancy.

- *Use of prophylactic mood stabilising medication in the postpartum period*: rated as present or absent. Absence was defined as use of any other psychotropic medication not consistent with the definition of those that were ‘mood stabilising’ (as outlined in section 5.8.3.1; such as antidepressants or anxiolytics) or no psychotropic medication. Rating were made specifically for the use of:
 - a) any prophylactic mood stabilising medication (including lithium, anticonvulsants, typical or atypical antipsychotics)
 - b) prophylactic lithium
 - c) prophylactic quetiapine
 - d) prophylactic olanzapine
- *Timing of use of prophylactic mood stabilising medication in the postpartum period*: rated as a) use within-pregnancy which was continued into the postpartum or b) postpartum use only (i.e. medication was only commenced following delivery).

5.8.3.2 Antenatal psychopathology within the current pregnancy

- *Clinically impairing symptoms of anxiety*: Ratings were made for the presence/absence of any DSM-5 defined clinically impairing symptoms of anxiety disorder and specifically, the presence/absence of panic disorder and generalised anxiety disorder.
- *DSM-5 episodes of psychiatric illness within the current pregnancy*: Ratings were made for the presence/absence, type and timing of onset of DSM-5 psychiatric episodes with onset during the current pregnancy.
- *DSM-5 worst episode of psychiatric illness within the current pregnancy*: Ratings of individual psychiatric episodes were used to code the ‘worst’ DSM-5 psychiatric episode with onset during pregnancy according to a hierarchy as indicated below **Table 5.2**.

Table 5.2 Hierarchy of rating categories for the ‘worst’ DSM-5 episode of psychiatric illness with onset in pregnancy within the current perinatal period in The BDRN Pregnancy Study



5.8.3.3 Psychosocial factors relating to the current pregnancy

- **Planning of pregnancy:** rated as planned or unplanned
- **Experience of the current pregnancy:** Responses to the PRQ (Austin et al. 2005, as described in section 5.7.1.2) were collapsed to the following categories, indicating the experience of pregnancy to be perceived as ‘positive’ (defined as scores of three to five) or ‘not positive’ (defined as scores of one or two).
- **Partner in the current pregnancy:** rated as yes or no.
- **Perceived emotional support from partner during current pregnancy:** Among women who reported a partner as being present in the current pregnancy, responses to the PRQ item were collapsed to the following categories, indicating the perceived level of emotional support from their partner during pregnancy to be ‘very supportive’ (defined as scores of three to five) or ‘not supportive’ (defined as scores of one or two).

- *Perceived emotional support from others in the current pregnancy*: responses to the PRQ item were collapsed to the following categories, indicating the perceived level of emotional support during pregnancy from people other than their partner to be 'very supportive' (defined as scores of three to five) or 'not supportive' (defined as scores of one or two).

5.8.3.4 Smoking and alcohol use during the current pregnancy

- *Smoking during the current pregnancy*: Smoking of cigarettes during the current pregnancy was rated as present or absent.
- *Alcohol use during the current pregnancy*: Regular alcohol use during pregnancy (on a weekly basis) exceeding the NHS recommended amount of 14 units per week, rated as present or absent.

5.8.3.5 Adverse life events in the current perinatal period

Each specified adverse life event item assessed by the BLEQ (Brugha et al. 1985) was rated as present or absent during the current pregnancy. Consistent with the definition used by Brugha et al. (1985), only events subjectively reported as being 'moderately bad' or 'very bad' experiences were considered sufficiently adverse to be rated as present.

5.8.3.6 Sleep quality and loss during the current perinatal period

Ratings were made for the following sleep variables related to the current pregnancy and labour:

- *Sleep quality in the 3rd trimester*: responses to the PSQI item assessing perception of sleep quality in the third trimester of the current pregnancy were

coded categorically as ‘very good/fairly good’ or ‘fairly bad/very bad’ (see section 5.7.1.2 for a full description of the PSQI).

- *Any missed sleep during labour*: self-reported sleep loss of any duration during labour was coded as present or absent.
- *At least one night of missed sleep due to labour*: self-reported sleep loss of at least one complete night was rated as present or absent
- *Time of delivery*: To enable comparisons with previous literature (Sharma et al. 2004) the time of delivery and length of labour (in hours) were considered proxy measures of sleep loss during delivery. Therefore, in accordance with the definition used by Sharma et al. (2004), time of delivery was categorised as having occurred during the day (between 7:31am and 12.29pm) or night (between 12.30am and 7:30am).

5.8.3.7 Obstetric factors relating to the current perinatal period

Women were asked about a wide range of obstetric factors relating to the recent pregnancy and delivery. Ratings were made for the following variables:

Pregnancy related factors

- *IVF treatment*: the use of IVF treatment to facilitate conception of the current pregnancy was rated as present or absent.

Infant related variables

- *Infant sex*
- *Breastfeeding following delivery* (defined as present or absent)
- *Duration of breastfeeding* (defined as weeks)

Obstetric complications

- ***Obstetric complications during pregnancy:*** rated as present or absent. Obstetric complications were defined as any maternal or infant medical condition severe enough to warrant treatment as an outpatient or via hospital admission.
- ***Pre-eclampsia:*** rated as present or absent. Presence was defined as symptoms or a diagnosis of pre-eclampsia in pregnancy that warranted treatment as an outpatient or via hospital admission.
- ***Obstetric complications during delivery:*** rated as present or absent. Complications were defined according to the ICD-10 (codes 60-77) and included the baby being breech, in distress or involved in cord accidents during labour.
- ***Problems identified with baby at birth:*** rated as present or absent. Presence was defined as any medical condition severe enough to warrant treatment as an outpatient or via hospital admission within 28 days of delivery.

Delivery factors:

- ***Maternal age at delivery***
- ***Parity:*** rated as number of current delivery
- ***Pre-term delivery:*** rated as present or absent. Consistent with the World Health Organisation definition, pre-term delivery was defined as any delivery occurring prior to 37 weeks gestation.
- ***Induction or augmentation of labour:*** rated as present or absent. Presence was defined as history of any method or intervention used to induce or augment labour in the current pregnancy.
- ***Emergency caesarean section:*** rated as present or absent.

- *Assisted delivery*: rated as present or absent. Presence was defined as any delivery requiring the use of forceps/ventouse or caesarean section.
- *Duration of labour*: rated in hours from the onset of contractions to time of birth.

5.8.4 Postpartum psychiatric outcomes in the current perinatal period

Postpartum psychiatric outcome data were obtained for 103 of 106 women (97%).

Ratings were made for the following outcomes:

- *DSM-5 episodes of postpartum psychiatric illness*: The presence or absence and type of any DSM-5 episodes of psychiatric illness with onset within three months of the recent delivery. Episodes with onset during pregnancy that continued postpartum were only rated as a recurrence during pregnancy.
- *DSM-5 worst episode of postpartum psychiatric illness*: Ratings of individual psychiatric episodes were used to code the 'worst' DSM-5 episode experienced within the postpartum period. For this variable, a hierarchy was used as shown within **Table 5.3**.
- *Timing of onset of DSM-5 episodes of postpartum psychiatric illness*: The time of onset of DSM-5 episodes of postpartum psychiatric illness (including the worst episode) were rated as the number of days and/or weeks following delivery at which symptoms first became impairing.

Table 5.3: Hierarchy of rating categories for the ‘worst’ DSM-5 episode of postpartum psychiatric illness within the current perinatal period in the BDRN Pregnancy Study

DSM-5 episodes of postpartum psychiatric illness	
↓ ‘Worst’ episode	No DSM-5 psychiatric episode, including: <ul style="list-style-type: none"> • Symptoms of high mood not meeting DSM-5 criteria • Postpartum ‘baby blues’ • Other perinatal psychiatric episode (not meeting DSM-5 criteria)
	Major depression (with or without mixed features) without psychotic features
	Hypomania (with or without mixed features)
	Mania or psychosis, including: <ul style="list-style-type: none"> • Mania (with or without mixed features) without psychotic features • Mania (with or without mixed features) with psychotic features • Major depression (with or without mixed features) with psychotic features • Brief psychotic episode • Other psychotic episode

5.9 Statistical Analysis

All data were analysed using the statistical package SPSS version 24. As continuous data were non-normally distributed (as indicated by the Kolmogorov-Smirnov test), non-parametric tests were used to assess the relationship between within-pregnancy potential risk factors and postpartum psychiatric outcome. All tests were deemed significant at a p-value of <0.05 (two-tailed). Due to the modest sample size (thus reducing power) and exploratory nature of the current study, corrections were not made for multiple testing. For this reason, significant findings were interpreted with caution and emphasis placed on examining trends within the data.

5.9.1 Continuous Data

Relationships between continuous data were assessed using Mann Whitney-U tests. Medians, range and inter-quartile ranges are therefore reported for each continuous variable.

5.9.2 Categorical Data

Relationships between categorical data were assessed using Pearson's Chi Square tests. In cases where 20% or more of cells within a chi-square table had a cell count lower than the expected five; Fisher's exact tests were used. For each variable, the number of cases and proportions within each group are reported.

5.9.3 Logistic Regression Analyses

Associations between potential within-pregnancy potential risk factors and postpartum psychiatric outcome were further assessed in two binary logistic regression models (using the enter method) with No PP/PP as the outcome variable. In the first, the model adjusted for lifetime correlates of PP as identified within the BDRN retrospective sample; preconception lifetime history of PP (including women who were primiparous), primiparity at time of conception of the current pregnancy, family history of postpartum affective illness in a first degree relative and sleep loss as a self-reported lifetime trigger for preconception episodes of mania. In the second model, use of prophylactic mood stabilising medication in the postpartum period was also included to investigate potential moderating effects of this factor on relationships between within-pregnancy factors and PP.

Results of investigations of potential risk factors for episodes of PP within this sample are described and discussed further in Chapter 7. First however, patterns of psychotropic medication use and psychiatric outcomes within the current perinatal period in 103 women in the BDRN Pregnancy Sample are reported in Chapter 6.

Chapter 6

The BDRN Pregnancy Study: Describing psychotropic medication use and psychiatric outcomes across the perinatal period

6.1 Introduction

This chapter describes 103 pregnant women with BD recruited to the BDRN Pregnancy Study. Demographic, preconception clinical and within-pregnancy characteristics of the sample are first described. This is followed by a description of patterns of psychotropic medication use and psychiatric outcomes during pregnancy and within the first three postpartum months in all women in the sample and also according to subtype of BD. The final part of this chapter focuses on discussion of findings in relation to the literature.

6.2 Sample characteristics

6.2.1 Demographics

Table 6.1 summarises the demographic characteristics of the sample. The median age of women at the time of interview (and of the current pregnancy) was 34 years (range 18-44). Women were predominantly of white ethnicity (92.2%, n=95/103) and just over half were recruited to the study non-systematically (52.4%, n=54/103). Most women had, during their lifetime married or lived as married (98.0%, n=99/101). The majority of the sample were educated to a degree level qualification or higher (62.1%, n=64/103) and had a lifetime history of working in a professional occupation (52.4%, n=54/103).

Table 6.1. Demographic characteristics of the BDRN pregnancy sample (n=103)

<i>Demographic variable</i>	BDRN pregnancy sample (n=103)
Age at interview/pregnancy (years) Median (IQR) Range	34 (6) 18-44
Ethnicity White ethnicity Non-white ethnicity	95 (92.2%) 8 (7.8%)
Method of recruitment Systematic Non-systematic	54 (52.4%) 49 (47.6%)
Lifetime marital status ^a Married/lived as married Never married/lived as married	99 (98.0%) 2 (2.0%)
Highest education level Degree level qualification or higher No degree level qualification	64 (62.1%) 39 (37.9%)
Highest occupation level Professional Non-professional	54 (52.4%) 49 (47.6%)

^aLifetime marital status unknown for two women. **IQR:** Interquartile range. **BDRN:** Bipolar Disorder Research Network

6.2.2 Preconception lifetime clinical characteristics

Table 6.2 summarises the key lifetime clinical characteristics of the BDRN pregnancy sample prior to the current pregnancy (n=103). 78.6% (n=81/103) women met DSM-5 criteria for a main, best-estimate lifetime diagnosis of BD-I, 16.5% (n=17/103) BD-II, 2.9% (n=3/103) SA-BD and 1.9% (n=2/103) BD-NOS. The median age of onset BD, defined as age of first impairment, was 20 years (range 11-36). Women had experienced a median number of 0.36 episodes of mania (range 0.06-3.42) and 0.47 episodes of depression (range 0-9.81) per preconception illness year (defined as episodes occurring between the onset of the first impairing episode of BD to time of conception of the current pregnancy). Most women had a preconception lifetime history of psychotic symptoms (69.9%, n=72/103).

Table 6.2: Preconception lifetime clinical characteristics of the BDRN pregnancy sample (n=103)

<i>Preconception clinical variable</i>	BDRN pregnancy sample (n=103)
Main preconception lifetime DSM-5 diagnosis	
BD-I	81 (78.6%)
BD-II	17 (16.5%)
SA-BD	3 (2.9%)
BD-NOS	2 (1.9%)
Age at onset of impairment of bipolar disorder (years)	
Median (IQR)	20 (10)
Range	11-36
Number of episodes of mania experienced per preconception illness year	
Median (IQR)	0.36 (0.39)
Range	0.06-3.42
Number of episodes of depression experienced per preconception illness year	
Median (IQR)	0.47 (0.66)
Range	0.00-9.81
Preconception history of psychotic features	
Present	72 (69.9%)
Absent	31 (30.1%)

DSM-5: Diagnostic and Statistical Manual of Mental Health Disorders (5th edition); **BD-I:** bipolar I disorder, **BD-II:** bipolar II disorder, **SA-BD:** schizoaffective disorder bipolar type, **BD-NOS:** bipolar disorder not otherwise specified. **IQR:** Interquartile range. **BDRN:** Bipolar Disorder Research Network

6.2.3 Within-pregnancy characteristics

As indicated in section 6.2.1, the median age of women at the time of the current pregnancy was 34 years (range 18-44). Additional within-pregnancy characteristics of the sample are summarised in **Table 6.3**. 50.5% (n=52/103) of women were primiparous, with the majority reporting their pregnancy as being planned (76.7%, n=66/86). Only 3.6% (n=3/84) of women conceived their pregnancy via IVF and nearly all women reported having a partner present (i.e. being involved in a relationship) during their current pregnancy (99.0%, n=102/103).

Table 6.3: Within-pregnancy characteristics of the BDRN pregnancy sample (n=103)

<i>Within-pregnancy variable</i>	BDRN pregnancy sample (n=103)
Age at pregnancy (years) Median (IQR) Range	34 (6) 18-44
Primiparous Yes No	52 (50.5%) 51 (49.5%)
Planned pregnancy ^a Planned Unplanned	66 (76.7%) 20 (23.3%)
Conception by IVF ^a Yes No	3 (3.6%) 81 (96.4%)
Partner present in pregnancy Present Absent	102 (99.0%) 1 (1.0%)

^aNumbers differ due to unknown data. **IQR:** Interquartile range, **IVF:** In-vitro fertilisation. **BDRN:** Bipolar Disorder Research Network

6.2.3.1 Preconception perinatal characteristics in parous women

Among the sample of parous women (n=51), the median number of deliveries occurring prior to the current pregnancy was one (range 1-6, **Table 6.4**). 30% of women had experienced their first impairing episode of BD with onset during the postpartum period (n=15/50). 50% (n=25/50) of parous women had experienced PP following a previous delivery and for 10% (n=5/50), PP was the only episode of mood illness experienced (i.e. no history of mood episodes unrelated to childbirth). For one woman, the presence/absence of a previous PP episode could not be determined (due to insufficient information obtained at baseline interview and lack of psychiatric case-notes).

Table 6.4: Preconception perinatal characteristics of parous women in the BDRN pregnancy sample (n=51)

<i>Preconception perinatal variable</i>	Parous women (n=51)
Parity (number of deliveries) Median (IQR) Range	1 (1) 1-6
Onset of bipolar disorder occurred in postpartum period ^a Yes No	15 (30.0%) 35 (70.0%)
History of PP within 6 weeks ^a Yes No	25 (50.0%) 25 (50.0%)
PP only prior mood episode ^a Yes No	5 (10.0%) 45 (90.0%)

PP: defined as an episode of mania or affective psychosis within 6 weeks of delivery, ^aNumbers differ due to postpartum psychiatric history being unknown for one woman. IQR: Interquartile range

6.3 Psychotropic medication use during the perinatal period

As discussed in Chapter 5 (section 5.8.3.1), detailed data were gathered for all women regarding psychotropic medication use during the perinatal period. These data were highly complex and varied considerably between women and also within each individual perinatal period. **Figure 6.1** is an example of a timeline showing the complexity of medication data gathered across a perinatal period for one woman in this study (Participant 42, Appendix M). The proportion of women taking medication for the purpose of mood stabilisation (specifically those prescribed for treatment or prophylaxis of manic episodes) in the six months prior to pregnancy, during each month of pregnancy and within each of the first three postpartum months is summarised in **Figure 6.2**. Medications used for the purposes of mood stabilisation included traditional mood stabilisers such as lithium and anticonvulsants, in addition to atypical and typical antipsychotics (see section Chapter 5, page 120 for full definition).

Figure 6.1: Psychotropic medication use across the perinatal period in one woman in the BDRN Pregnancy sample

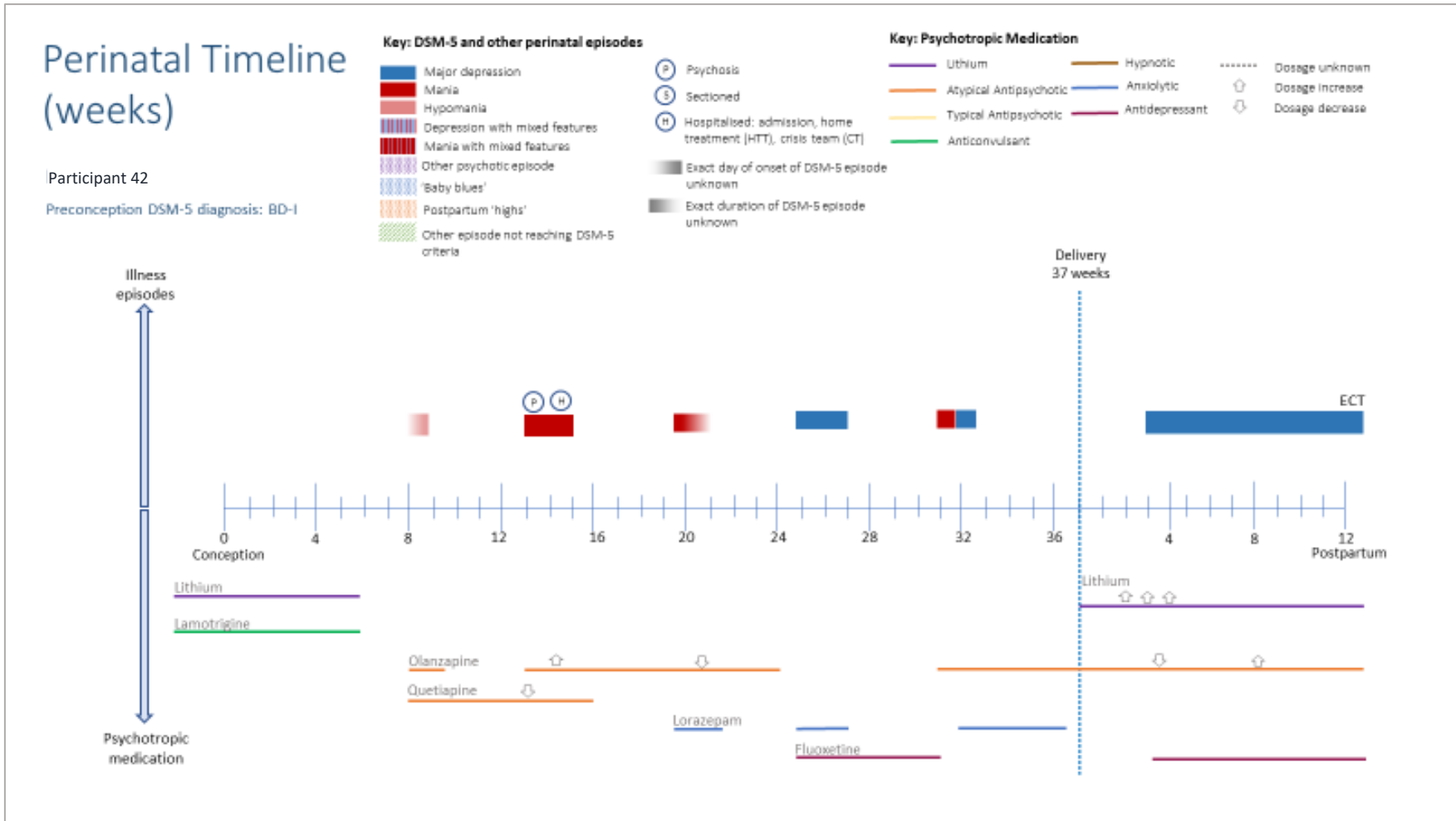


Figure 6.2: Proportion of women in the BDRN pregnancy sample (n=103) using any psychotropic medication for mood stabilisation during the perinatal period

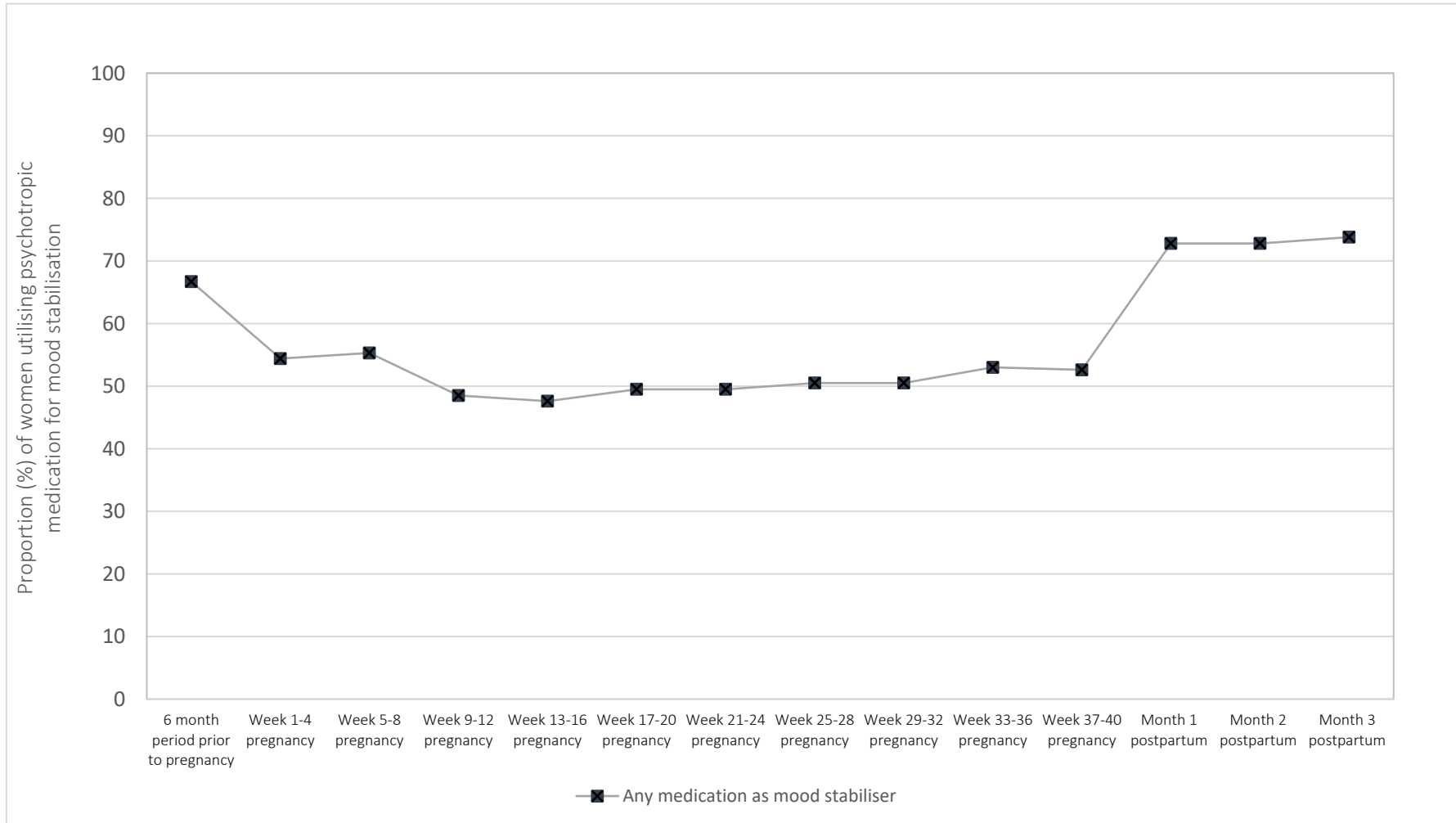
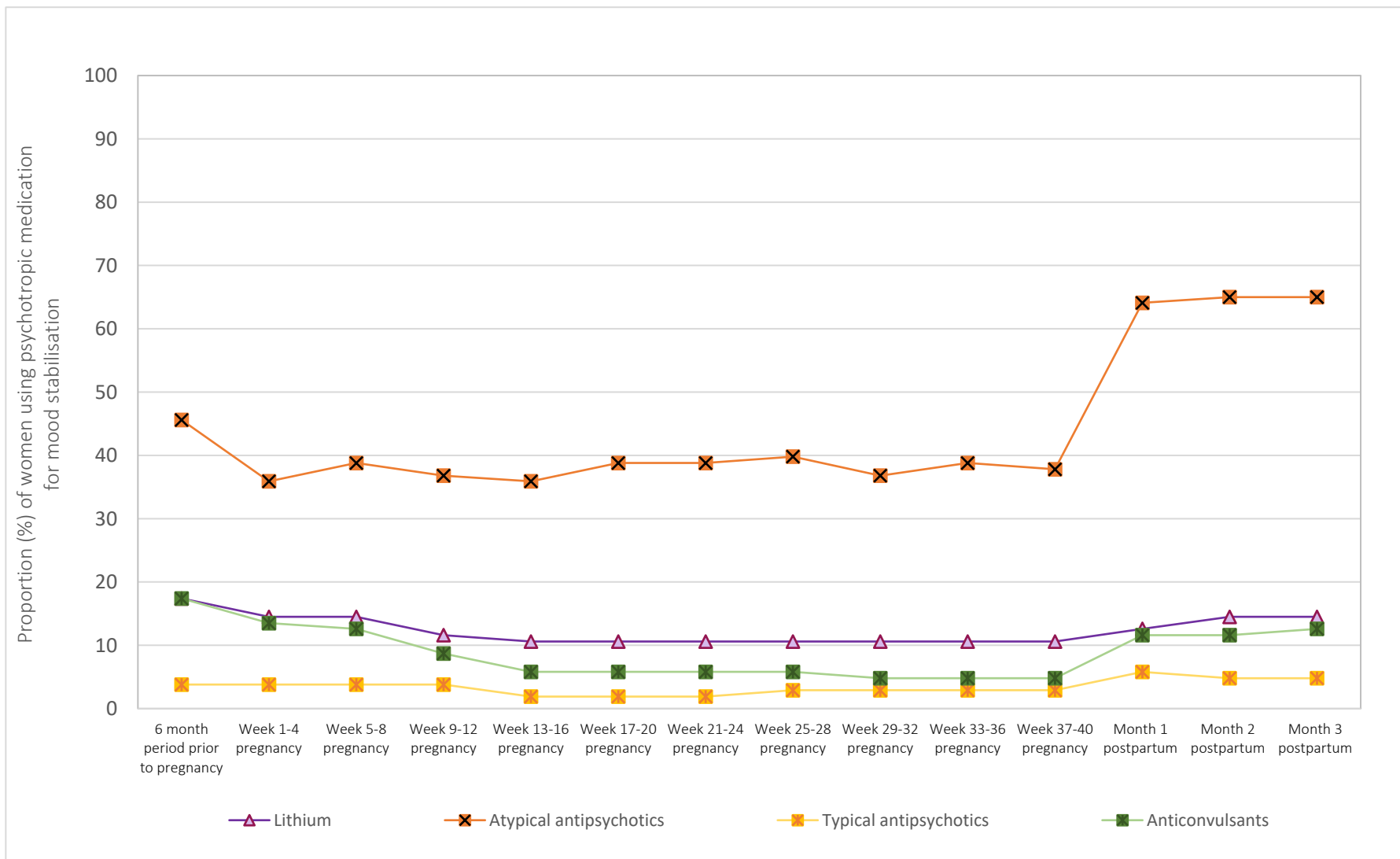


Figure 6.3. Proportion of women in the BDRN pregnancy sample (n=103) using each type of psychotropic medication for mood stabilisation during the perinatal period



The majority of women were using at least one psychotropic medication as a mood stabiliser (with or without adjunctive therapy with antidepressants or anxiolytics) during the six-month period prior to pregnancy (67.6%, $n=69/102$), during pregnancy (61.2%, $n=63/103$) and within the first three postpartum months (73.8%, $n=76/103$). The presence/absence of use of medication for mood stabilisation in the six months prior to pregnancy could not be determined for one woman in the sample (due to insufficient information obtained at interview and a lack of relevant information in psychiatric case-notes and clinician questionnaires). **Figure 6.3** provides a breakdown of medication use across the perinatal period according to type/class of medication. Detailed descriptions of patterns of medication use during the perinatal period are provided in the following sections.

6.3.1 Use of mood stabilising medication during pregnancy

6.3.1.1 Continuation/withdrawal of medication for mood stabilisation from the period prior to pregnancy

Of the 69 women who were taking medications for mood stabilisation in the six months prior to their pregnancy, 40.6% ($n=28/69$) continued their existing medication regime during pregnancy without any significant changes to this medication (i.e. no withdrawal of any medications used as a mood stabiliser). Almost one in five women (18.8%, $n=13/69$) withdrew at least one mood stabilising medication but continued to use an additional or alternative medication as a mood stabiliser during their pregnancy. In contrast, 39.1% ($n=27/69$) of women using mood stabilising medication within the six-month period preceding pregnancy withdrew all mood stabilising medications (26.4% of all women in the sample); 15 women doing so prior to pregnancy and 12 during their pregnancy (11 during the first trimester and one during the third trimester).

Among the 27 women who had discontinued all mood stabilising medication prior to pregnancy, 29.6% ($n=8/27$) subsequently recommenced medication for mood stabilisation during pregnancy. One woman, commenced quetiapine prophylactically

during the first trimester of pregnancy (Participant 88) while an additional seven women utilised mood stabilising medication as treatment for a recurrence of affective symptoms during pregnancy (Participants 4, 11, 14, 16, 39, 42 and 46).

6.3.1.2 Medication for mood stabilisation during pregnancy in women who were not using mood stabilising medication prior to pregnancy

A third of women (32.4%, n=33/102) were not using any mood stabilising medication in the six-month period prior to pregnancy, the majority of whom had a preconception diagnosis of BD-I or SA-BD (78.8%, n=26/33). Most women who were not using any mood stabilising medication prior to pregnancy did not commence any medication as a mood stabiliser during the remainder of their pregnancy (81.8%, n=27/33). Six women (18.2%, n=6/33) subsequently commenced mood stabilising medication during their pregnancy, four prophylactically (Participants 13, 44, 75 and 92) and one following a recurrence of affective illness (Participant 56). One woman commenced mood stabilising medication later in pregnancy (Participant 1), however, the precise time at which this medication was commenced (in relation to the onset of a mood episode) was unclear. For this reason, it was not possible to determine if medication was prescribed prophylactically or as treatment.

6.3.1.3 Use of sodium valproate during pregnancy

As sodium valproate is a known teratogen and is typically advised against in women of childbearing age (National Institute for Health and Clinical Excellence 2014), the proportion of women using this medication during the perinatal period was specifically examined in this sample. Seven women (6.9%, n=7/102) were identified as using sodium valproate as a mood stabiliser in the six months prior to pregnancy (Participants 14, 16, 38, 55, 63, 81 and 82), four of whom were under the care of specialist perinatal psychiatric services (Participants 55, 63, 81 and 82). Three of the seven women reported having planned their pregnancy (two of whom were under perinatal

psychiatric services), subsequently discontinuing use of sodium valproate; two prior to conception (Participants 38 and 63) and one woman at four weeks of pregnancy (Participant 81). None of these women recommenced sodium valproate within the study period.

Of the four women who did not plan their pregnancy, three (Participants 14, 16 and 82) discontinued sodium valproate within the first eight weeks of pregnancy (one of whom subsequently recommenced this medication during the second trimester of pregnancy, participant 82). A fourth woman continued use of sodium valproate through the majority of her pregnancy, discontinuing at 28 weeks of pregnancy to commence an alternative mood stabiliser (Participant 55).

6.3.1.4 Antidepressant monotherapy during the perinatal period

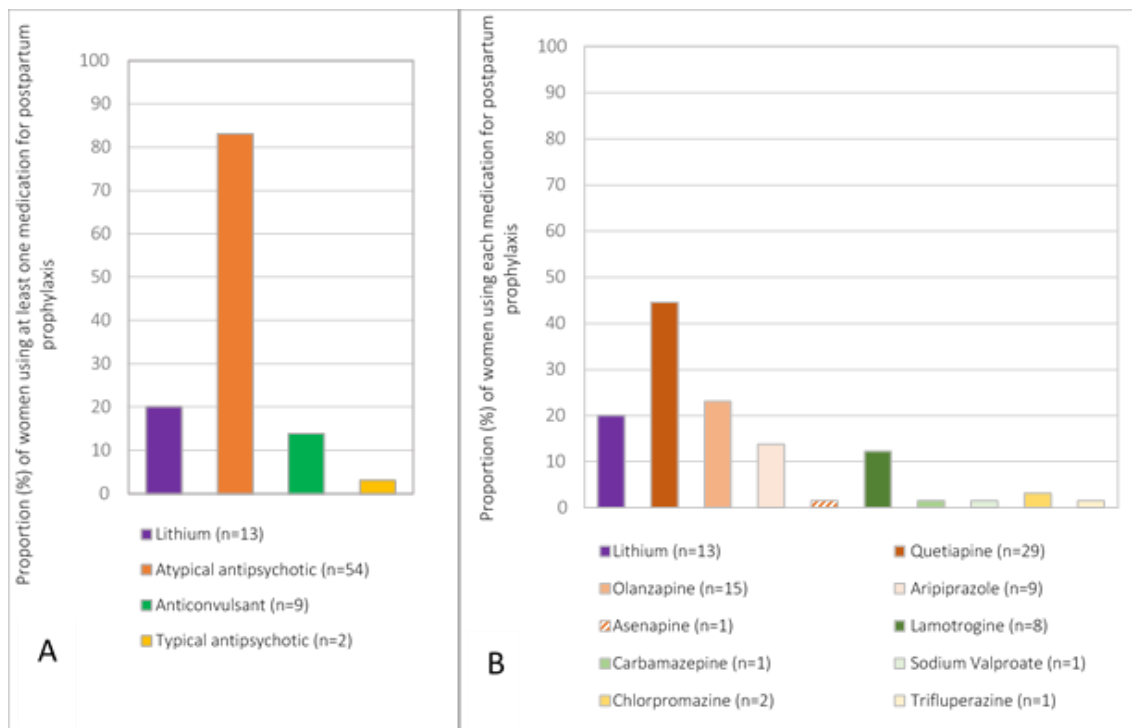
Antidepressant monotherapy is also typically advised against in BD, given the potential for triggering of a manic episode. Therefore, the proportion of women using antidepressant medications without concomitant mood stabilising medication during pregnancy and the postpartum period was further examined. Nine women (8.8%, $n=9/102$) reported using antidepressants without adjunctive medication for mood stabilisation during pregnancy, four women throughout the entire duration of their pregnancy (Participants 10, 34, 41 and 70) and five for a duration of at least one month during their pregnancy (Participants 13, 42, 44, 68 and 86). Furthermore, seven women (Participants 10, 24, 53, 68, 71, 79 and 97) took only antidepressants in the first three months following delivery.

6.3.2 Prophylactic mood stabilising medication in the postpartum period

As described in section 5.8.3.1, postpartum prophylaxis was defined as the use of any psychotropic medication during the postpartum period intended for the purpose of mood stabilisation (lithium, anticonvulsants, typical or atypical antipsychotics), that was

commenced or continued for reasons other than treatment. It was not possible to determine if mood stabilising medications were commenced prophylactically or as treatment for two women in the sample, given that the time at which medications were commenced (in relation to the onset of a postpartum mood episode) could not be established (Participants 2 and 22). Of those for whom data were available (n=101), the majority of women used at least one medication prophylactically as a mood stabiliser in the postpartum period (64.4%, n=65/101). Most women (76.9%, n=50/65) used only one prophylactic mood stabilising medication (with or without the use of other psychotropic medications, such as antidepressants), with multiple mood stabilising medications being used concurrently in 23.1% (n=15/65) of women. The proportion of women using at least one of each class and individual medication for prophylactic mood stabilisation in the postpartum period is illustrated in **Figure 6.4**.

Figure 6.4: Medications used for prophylaxis of postpartum mood episodes in the BDRN Pregnancy sample (n=65)



*Numbers do not sum 65 due to polypharmacy of medications in some women.

Of the 65 women for whom the presence of at least one prophylactic mood stabilising medication could be determined, 20.0% (n=13/65) were using lithium, 83.1% (n=54/65) at least one atypical antipsychotic, 13.8% (n=9/65) at least one anticonvulsant and 3.1% (n=2/65) at least one typical antipsychotic (**Figure 6.4a**). In addition to lithium, quetiapine and olanzapine were the most commonly used medications for prophylaxis of mood episodes in the postpartum period (44.6%, n=29/65 and 23.1%, n=15/65 respectively, **Figure 6.4b**). In most cases (78.5%, n=51/65), prophylactic mood stabilising medications were continued from pregnancy through the postpartum period, while 21.5% women (n=14/65) commenced mood stabilising medication following delivery. Nearly all women who commenced prophylactic mood stabilising medication in the postpartum period did so on the day of delivery (92.9% n=13/14). The remaining woman (Participant 70) did not commence lamotrigine prophylactically until two weeks postpartum.

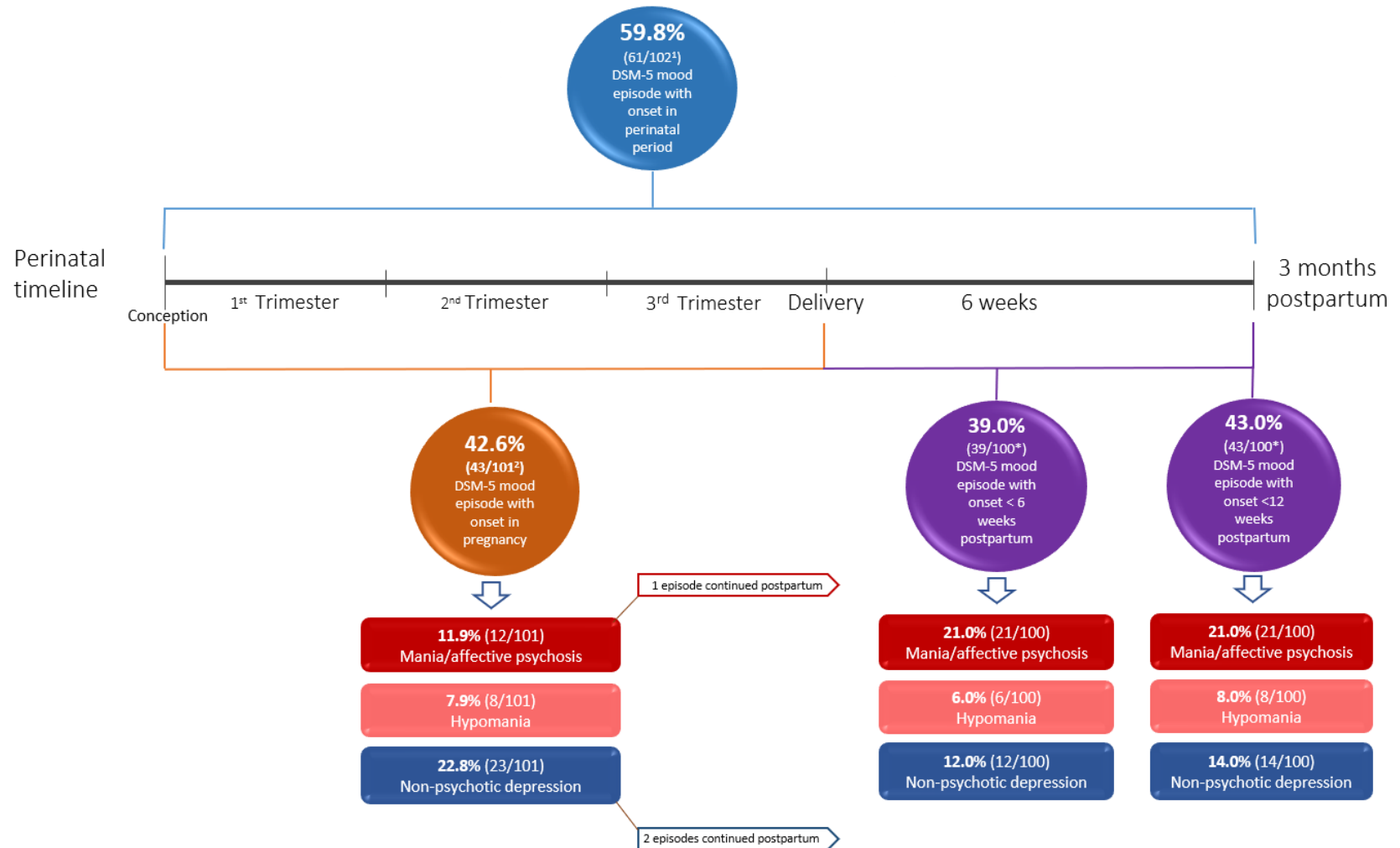
6.4 Perinatal psychiatric outcomes

As described earlier in this thesis (see Chapter 5, section 5.8.3.2), ratings were made for the presence (and type) or absence of the worst DSM-5 affective episode with onset during the current pregnancy and postpartum period. **Figure 6.5** summarises proportions and frequencies of the worst DSM-5 affective episode experienced according to time of onset within the perinatal period. The presence/absence of at least one DSM-5 episode during the perinatal period could not be determined for one woman in the sample. In this case, there was no postpartum recurrence of BD, however, the definite presence/absence of a mood episode during pregnancy could not be established. Of the remaining sample, 59.8% (n=61/102) women experienced at least one episode of affective illness meeting DSM-5 diagnostic criteria with onset during the perinatal period. The occurrence of DSM-5 episodes during pregnancy and the postpartum period are described further in the following sections.

6.4.1 Occurrence of DSM-5 affective episodes with onset during pregnancy

The presence or absence of an affective episode of illness during pregnancy could not be determined for 1.9% (n=2/103) of women. In both cases, insufficient information was obtained at interview and neither psychiatric case-notes nor clinician questionnaires could be obtained. As shown in **Figure 6.5**, 42.6% (n=43/101) of women experienced at least one clinically impairing affective episode with onset during pregnancy, of which 11.9% (n=12/101) was a worst episode of mania or affective psychosis, 7.9% (n=8/101) hypomania and 22.8% (n=23/101) an episode of non-psychotic depression. 57.4% (n=58/101) of the sample did not experience recurrence of a DSM-5 affective episode during pregnancy. Three women who experienced an onset of a DSM-5 episode during pregnancy continued to remain unwell throughout the entire postpartum period. As shown in **Figure 6.6**, one woman (Participant 16) experienced a prolonged episode of psychotic mania with mixed affective features and two women episodes of non-psychotic depression (Participant 68 and 96).

Figure 6.5: Recurrence rates of DSM-5 mood episodes with onset during the current perinatal period in the BDRN pregnancy sample



Total N's differ for each period due to missing data. ¹One women excluded as the presence/absence of at least one perinatal episode could not be determined. ²Two women excluded as the presence/absence of at least one episode during pregnancy could not be determined. *excluding cases in which an episode occurred with onset during pregnancy and continued postpartum

Figure 6.6: Timelines showing mood episodes with onset in pregnancy that continued postpartum in three women in the BDRN pregnancy sample

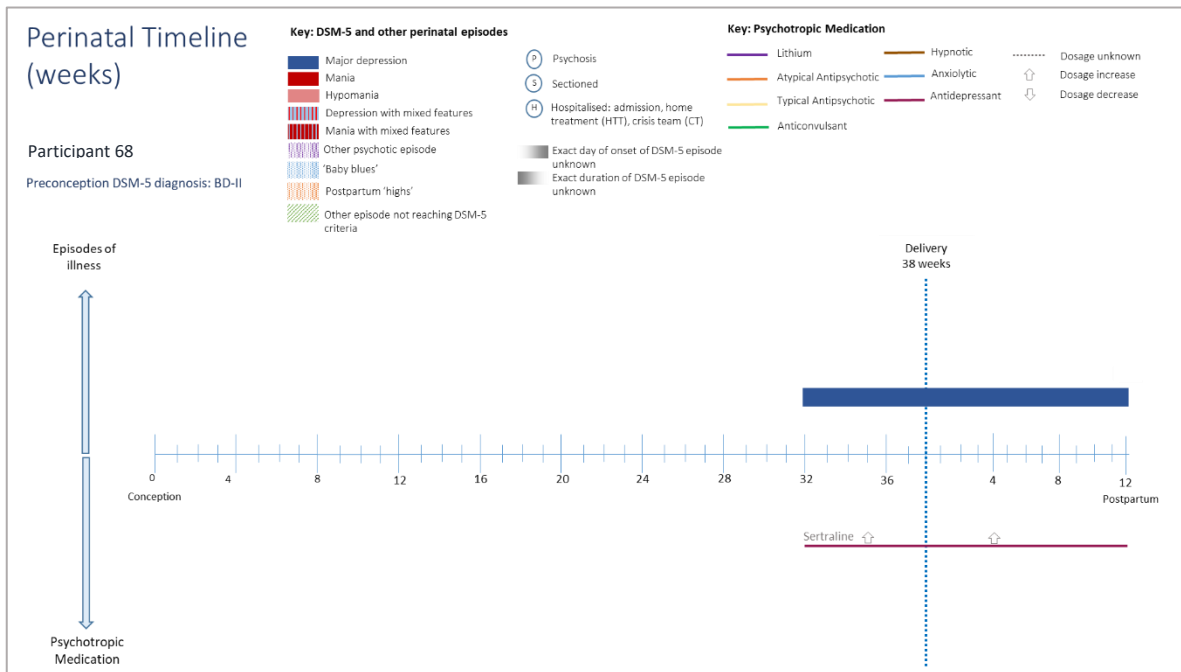
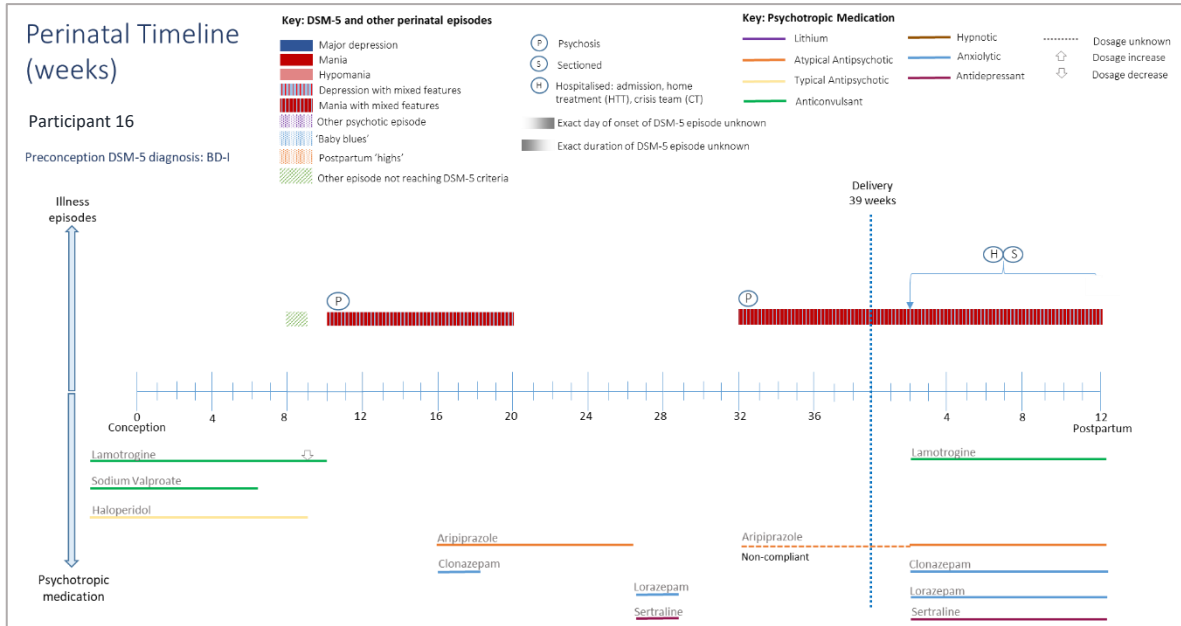
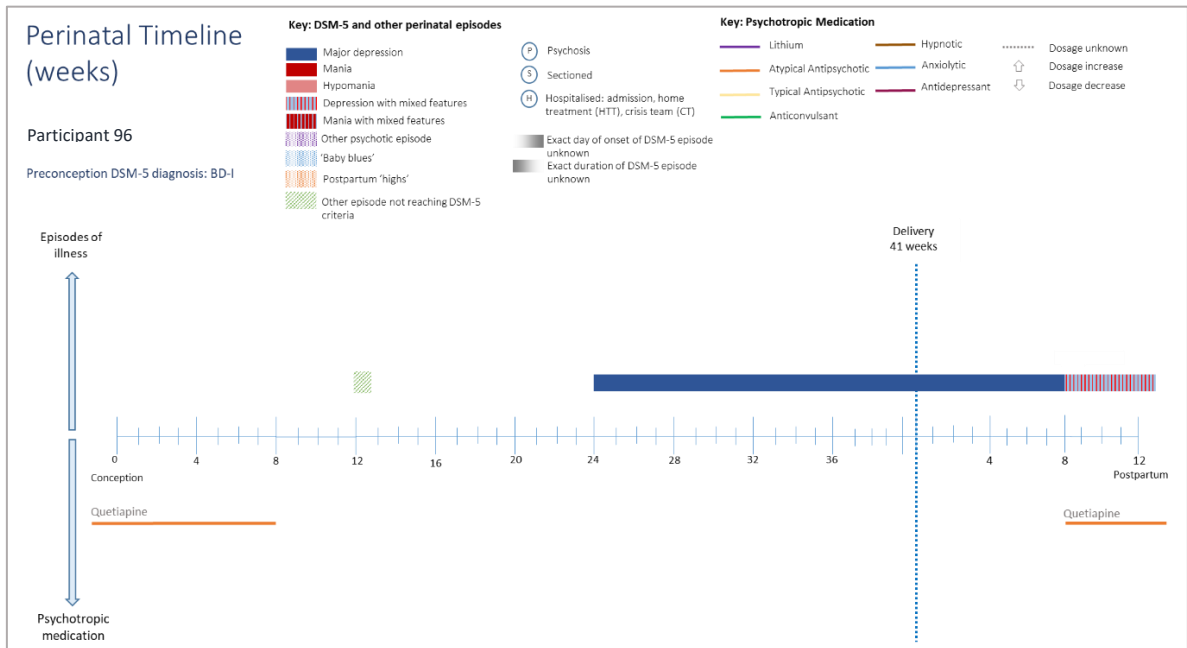


Figure 6.6 continued. Timelines showing mood episodes with onset in pregnancy that continued in to the postpartum period in three women in the BDRN pregnancy sample



6.4.2 DSM-5 affective episodes with onset within three months postpartum

The occurrence of the worst DSM-5 affective episode of illness with onset within three months of delivery is presented in **Figure 6.5**. Women who remained unwell in the postpartum period following the onset of an episode during pregnancy ($n=3/103$, see **Figure 6.6**) were excluded from subsequent analyses. This decision was made on the assumption that these women did not have an opportunity to experience the onset of a new episode in the postpartum period. Overall, 43.0% ($n=43/100$) of women experienced an onset of an affective episode within three months of delivery, 21.0% ($n=21/100$) were episodes of mania or affective psychosis, 8.0% ($n=8/100$) episodes of hypomania and 14.0% ($n=14/100$) non-psychotic depression. 57.0% ($n=57/100$) women did not experience a DSM-5 recurrence in the postpartum period. A small proportion of the total sample (6.0%, $n=6/100$) experienced the onset of more than one DSM-5 episode of postpartum psychiatric illness within the three-month follow-up period (Participants 21, 65, 72, 85, 86 and 103, see **Figure 6.7**).

Figure 6.7: Timelines showing onset of multiple postpartum mood episodes within the current perinatal period in six women in the BDRN pregnancy sample.

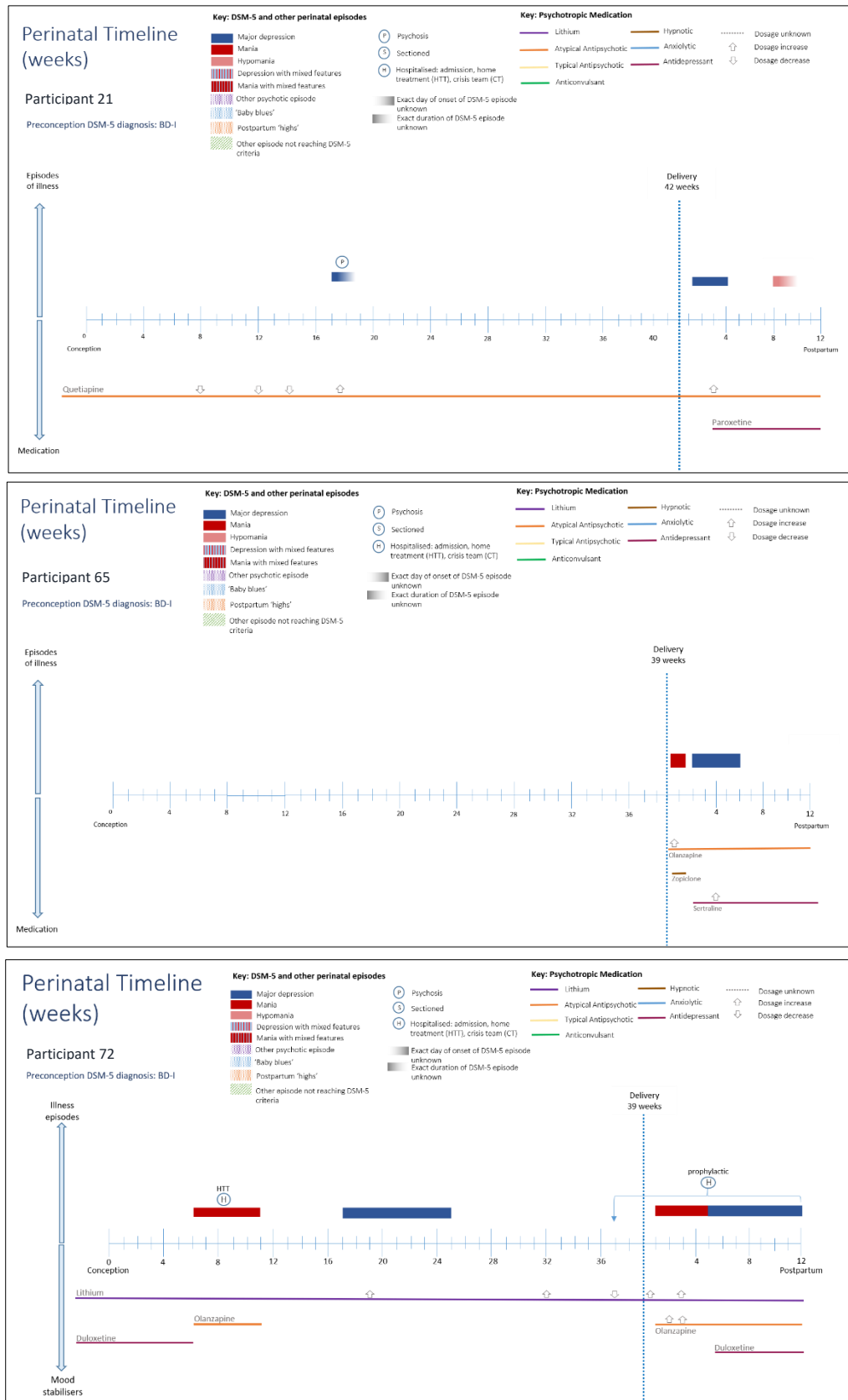
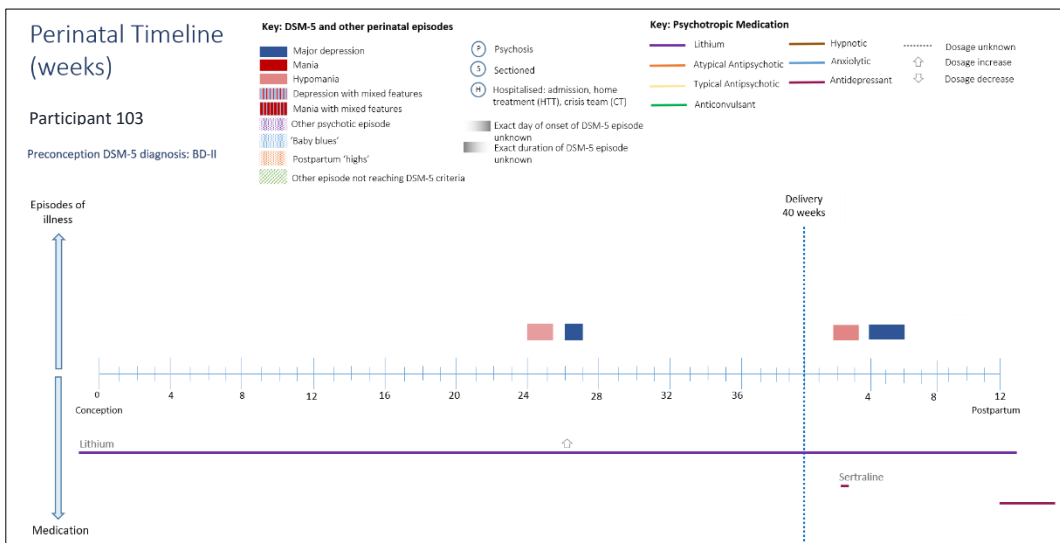
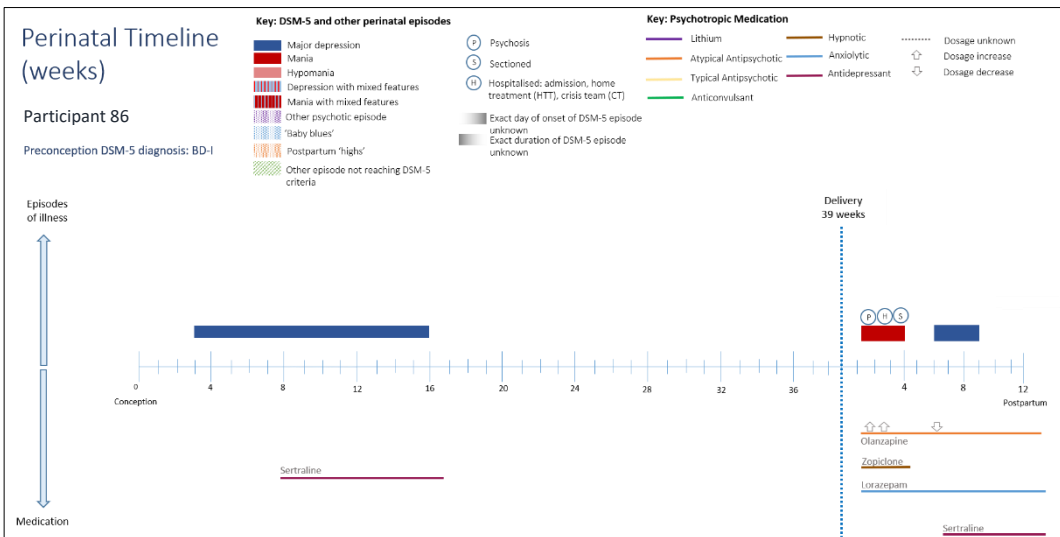
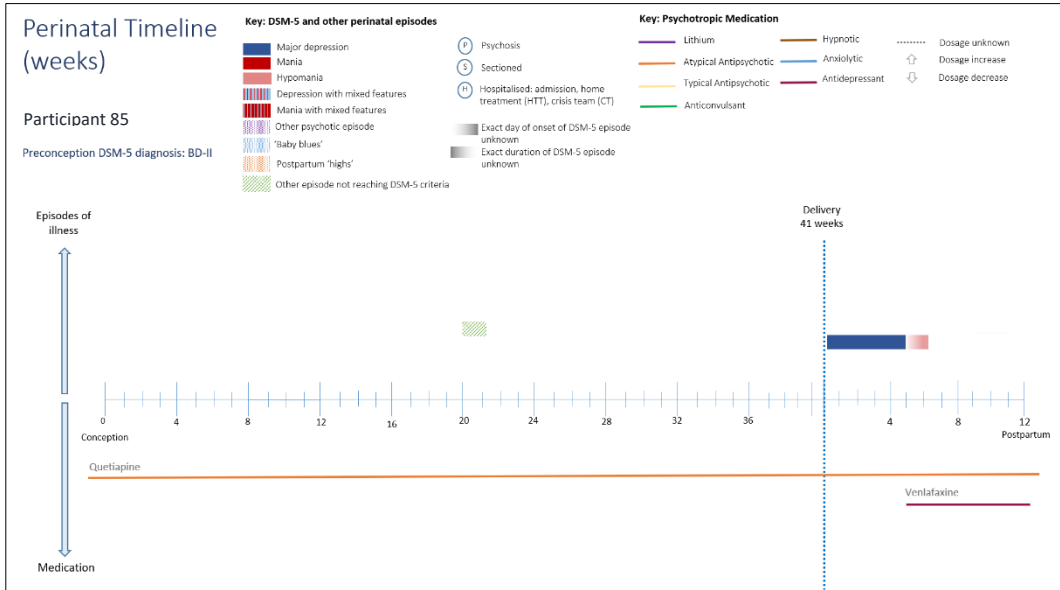


Figure 6.7 continued: Timelines showing onset of multiple postpartum mood episodes within the current perinatal period in six women in the BDRN pregnancy sample

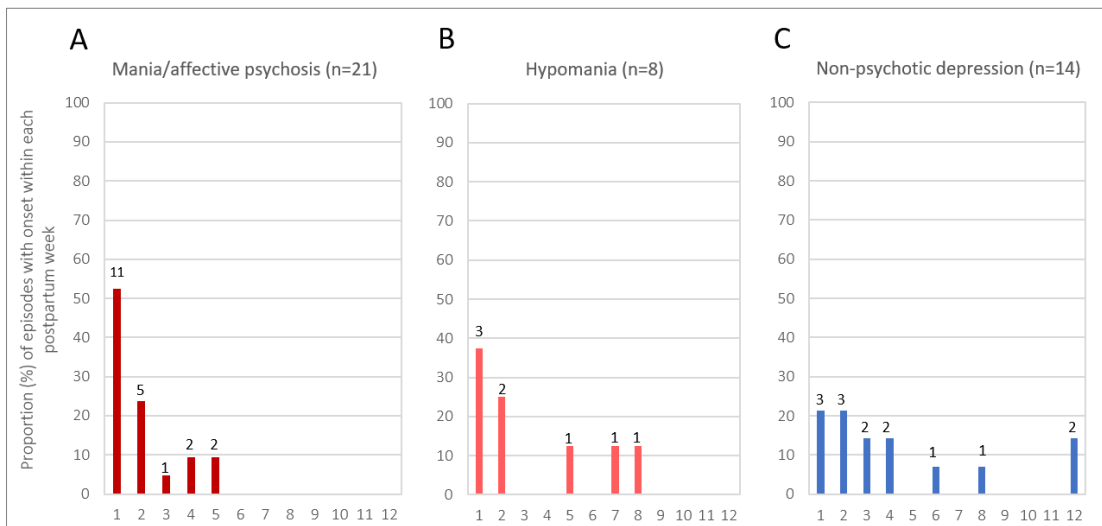


As shown in **Figure 6.7**, all six women experienced an episode of both mania/hypomania and depression. Two women experienced an affective switch without a period of euthymia between episodes (participants 72 and 85).

6.4.2.1 Timing of onset of worst postpartum affective episode

Figure 6.8 indicates the week of onset of the worst episode of affective illness experienced within three months of delivery. Of psychiatric episodes with an early onset (i.e. within two weeks of delivery ($n=27$), 59.3% ($n=16/27$) were a manic or affective psychosis, 18.5% ($n=5/27$) hypomania and 22.2% ($n=6/27$) a non-psychotic depression. 76.2% ($n=16/21$) of all episodes of mania/affective psychosis had onset within two weeks of delivery. **Figure 6.8a** shows a particularly marked peak in the onset of episodes of mania or affective psychosis within the first two postpartum weeks, compared to between weeks three and five postpartum.

Figure 6.8: Week of onset of worst DSM-5 postpartum mood episode within the current perinatal period in the BDRN pregnancy sample



Notably, no episodes of mania or affective psychosis had an onset beyond five weeks of delivery within this sample. The pattern of onset of episodes of hypomania (**Figure 6.8b**) was similar to that of mania and affective psychoses, with the majority of episodes having onset within the first two postpartum weeks (62.5%, $n=5/8$). However, the remainder of episodes had an onset later in the postpartum period, between weeks five and eight following delivery (37.5%, $n=3/8$). In comparison, the onset of episodes of non-psychotic depression (**Figure 6.8c**) was more widely distributed across the follow-up period, with 57.1% ($n=8/14$) of cases occurring after two weeks postpartum.

6.4.2.2 Onset of worst DSM-5 episode within 6 weeks postpartum

As shown in **Figure 6.9**, using a narrow temporal definition of the postpartum onset period (consistent with both DSM-5 and ICD-10 definitions), 39.0% ($n=39/100$) women experienced onset of the worst mood episode within the first six weeks of delivery. The worst episodes with onset within this time period were as follows; 21.0% ($n=21/100$) mania or affective psychosis, 6.0% ($n=6/100$) hypomania and 12.0% ($n=12/100$) non-psychotic depression. Two cases of PP which had particularly early onset are described in **Figure 6.10**.

Figure 6.9: Recurrence rates of DSM-5 mood episodes with onset within six weeks of delivery in the BDRN pregnancy sample

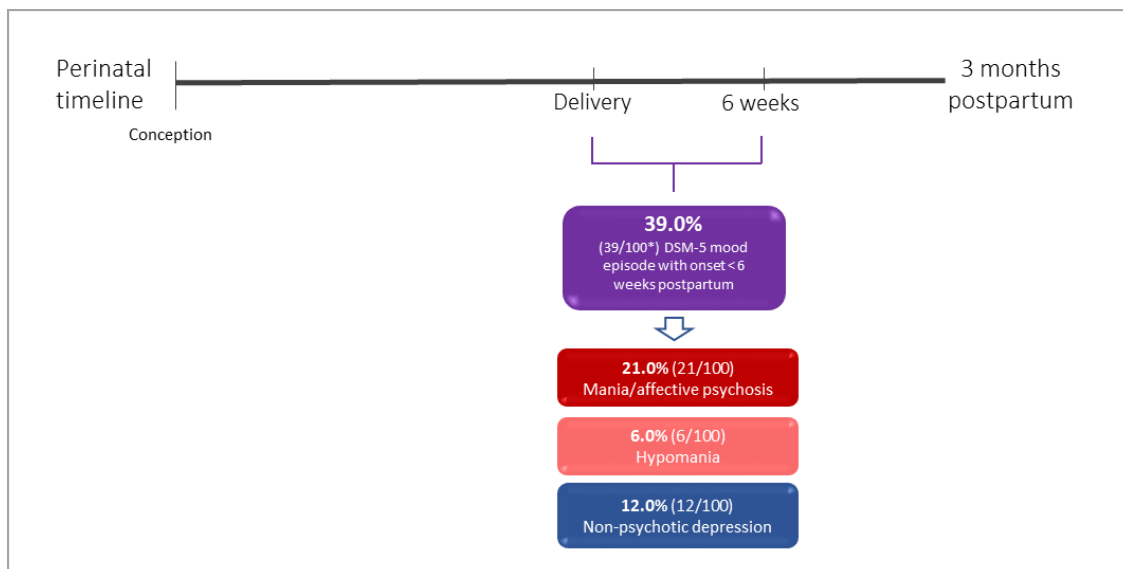


Figure 6.10: Descriptions of two cases of PP with early onset within two weeks of delivery in the BDRN pregnancy sample

Case 77

Participant 77 was a mother of seven children, with a history of BD-I and PP. She had a family history of severe, unspecified psychiatric disorder and of suicide.

Her current pregnancy was unplanned, but her partner and family were described as supportive. She remained well in mood until 37 weeks of pregnancy, when she experienced some mild symptoms of hypomania that subsequently resolved around the time of delivery. Risperidone was taken only intermittently throughout pregnancy.

Her baby was delivered via normal vaginal delivery and was healthy. Within two weeks of delivery, she had completely discontinued all medication and her mood subsequently began to fluctuate from being elated and grandiose to being tearful and concerned that there was something wrong with her baby. Her presentation was noted to be chaotic and her mood labile. She experienced paranoid delusional beliefs and delusional ideas that she was still pregnant. She was admitted under section for several months and was subsequently treated with risperidone by depot amid concerns of non-compliance. Lithium was also commenced.

Case 86

Participant 86 was a young mother of one with a previous history of PP meeting DSM criteria for BD-I. She had no prior history of psychiatric illness before the birth of her first baby. She did however have a family history of affective illness (including PND and suspected BD) and suicidal behaviour.

Her current pregnancy was unplanned but reported to be a positive experience during which her partner was deemed supportive. Despite this, she unfortunately experienced a moderately severe episode of depression during the first trimester of her pregnancy, and was subsequently commenced on sertraline. She had recovered from this episode by week 16 of pregnancy.

Her baby was delivered normally at 39 weeks with no complications. She had been prescribed olanzapine and zopiclone to commence prophylactically immediately following delivery, but did not take it. On day nine postpartum, she became manic, being unable to sleep, instead cleaning and tidying excessively. Her mood was elated with prominent features of irritability, which was directed towards her husband in particular. Perplexity and dysphoric features were also present, with symptoms including feeling low and scared. Her mood was labile, being tearful and then quickly becoming elated once more. Ideas of reference were reported that were grandiose in content. She was admitted under section for three weeks, during which time delusions of misinterpretation were prominent, believing that members of clinical staff were police officers in disguise and that everything was a test or game constructed for her benefit. She reported feeling euphoric and became increasingly spiritual.

Participant 86 recovered from the initial episode following treatment with olanzapine, zopiclone and lorazepam before experiencing an episode of depression soon after (from weeks 6-9 postpartum).

6.4.3 Perinatal psychiatric outcomes according to preconception lifetime diagnosis

To examine differences in perinatal psychiatric outcomes between BD subtypes, recurrence rates across the perinatal period are also reported separately in women with BD-I/SA-BD and those with BD-II/BD-NOS in the following sections.

6.4.3.1 BD-I and SA-BD

Figure 6.11 shows recurrence rates of worst DSM-5 episodes with onset across the perinatal period in the sample of women with BD-I and SA-BD (n=84). As described previously in this section (page 147), total sample sizes differ for each phase of the perinatal period due to unknown outcomes or exclusion of cases in which postpartum mood episodes had onset during pregnancy. 60.2% (n=50/83) of women with BD-I/SA-BD experienced at least one DSM-5 episode with onset during the perinatal period; 43.9% (n=36/82) during pregnancy, 42.7% (n=35/82) within three months and 39% (n=32/82) within six weeks of delivery. During pregnancy, 14.6% of women (n=12/82) experienced an episode of mania/affective psychosis, 6.1% (n=5/82) an episode of hypomania and 23.2% (n=19/82) an episode of non-psychotic depression.

In the postpartum period, all episodes of PP (24.4%, n=20/82) occurred within six weeks of delivery. 6.1% (n=5/82) of women experienced an episode of postpartum hypomania within three months and 3.7% (n=3/82) within six weeks of delivery. An additional 12.2% (n=10/82) women experienced an episode of non-psychotic depression, of which all but one case had onset within six weeks of delivery (90%, n=9/10).

Figure 6.11: Recurrence rates of worst DSM-5 mood episodes with onset during the current perinatal period in women with BD-I/SA-BD in the BDRN pregnancy sample (n=84)

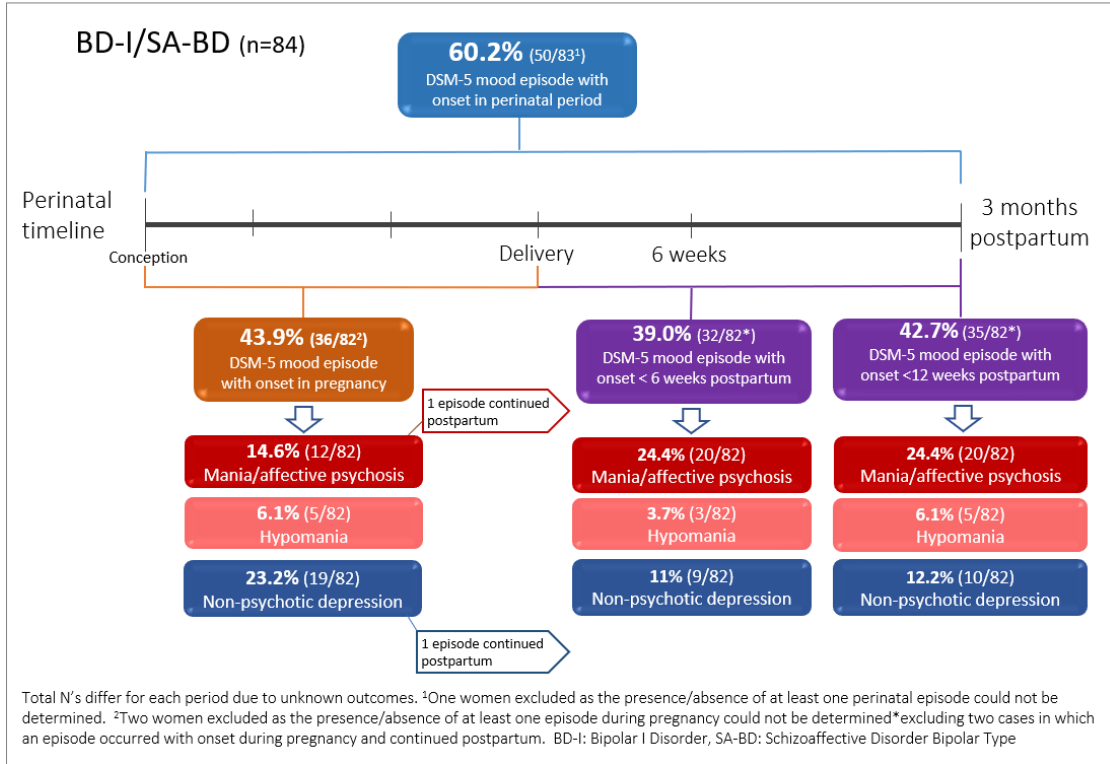
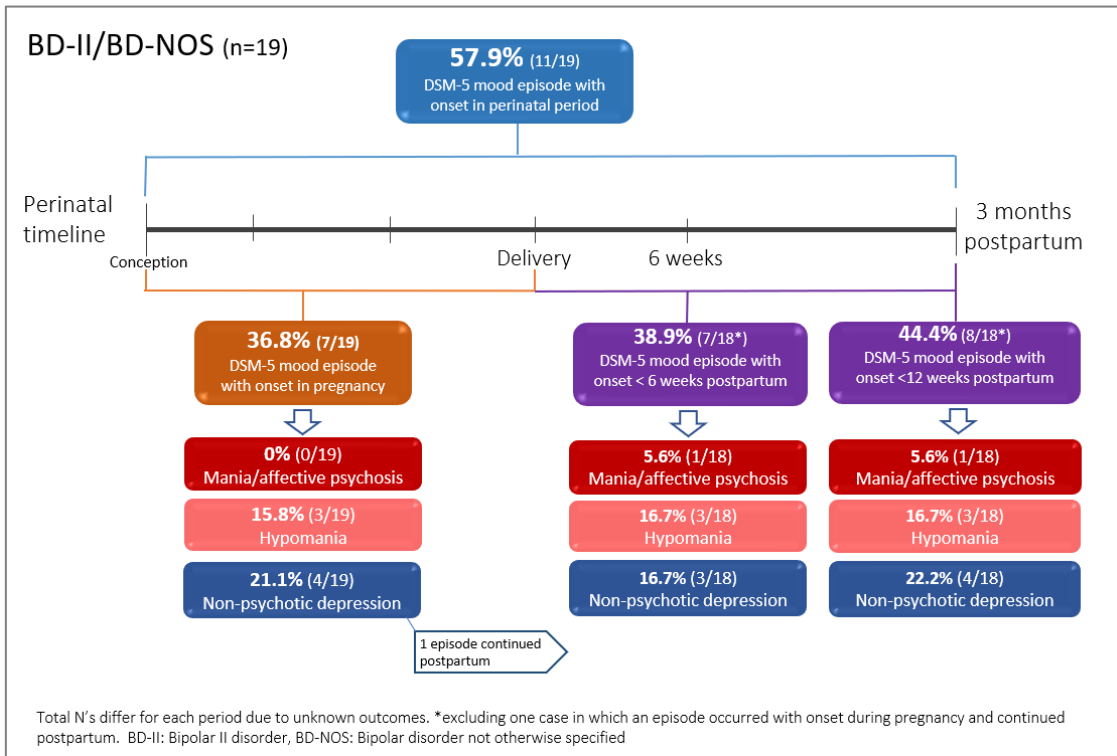


Figure 6.12 Recurrence rates of worst DSM-5 mood episodes with onset during the current perinatal period in women with BD-II/BD-NOS in the BDRN pregnancy sample (n=19)



6.4.3.2 BD-II and BD-NOS

Among the sample of 19 women with BD-II and BD-NOS, 57.9% (n=11/19) experienced a recurrence of at least one DSM-5 mood episode during the perinatal period; 36.8% (n=7/19) during pregnancy, 44.4% (n=8/18) within three months and 38.9% (n=7/18) within six weeks of delivery (see **Figure 6.12**). No women with BD-II or BD-NOS experienced a worst episode of mania/affective psychosis during pregnancy, while episodes of hypomania occurred in 15.8% (n=3/19) and non-psychotic depression within 21.1% (n=4/19) of pregnancies.

Following delivery, only one woman with a preconception diagnosis of BD-II experienced an episode of PP within six weeks of delivery (Participant 93, see **Figure 6.13**), subsequently meeting DSM-5 criteria for a lifetime diagnosis of BD-I disorder. This case is also described in **Figure 6.14**. A further 16.7% (n=3/18) of women experienced an episode of hypomania postpartum (all with onset within the first six weeks) and an additional 22.2% (n=4/8) an episode of non-psychotic depression within three months of delivery. As observed in women with BD-I, nearly all episodes of non-psychotic depression had an onset within six weeks postpartum (75%, n=3/4).

Figure 6.13: Timeline showing onset of PP within the current perinatal period in a woman with a preconception lifetime diagnosis of BD-II in the BDRN pregnancy sample

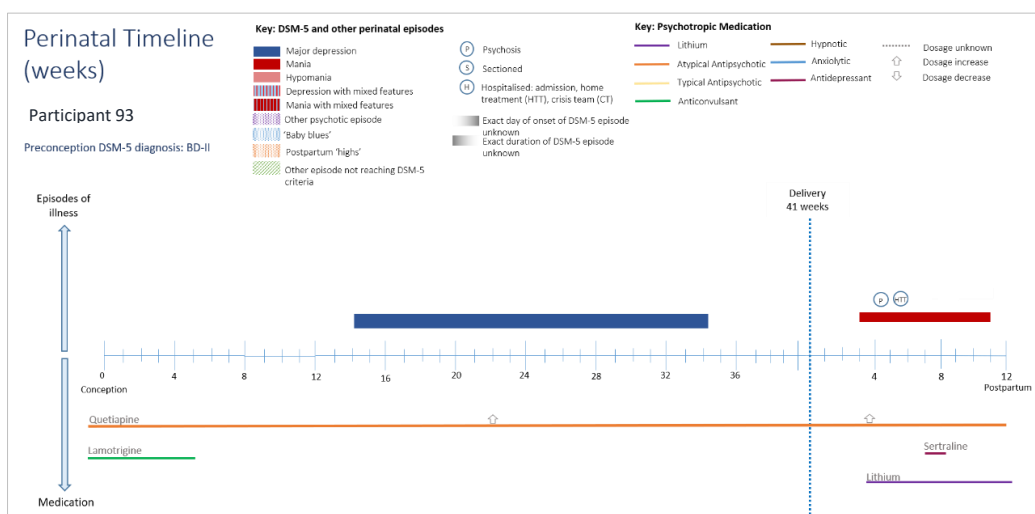


Figure 6.14: Description of a case of PP that occurred in a woman with a preconception history of BD-II in the BDRN pregnancy sample

Case 93

Participant 93 was a young mother of two children with a history of BD-II. She had a strong family history of affective disorders occurring both perinatally (PND) and non-perinatally (BD). A severe episode of depression with psychotic features (but no features of mania) occurred following the birth of her second child, for which she required admission.

Her current pregnancy was unplanned and while she did not experience any physical complications, several life stressors were present throughout pregnancy and contributed to pathological symptoms of antenatal anxiety. Upon learning of her pregnancy, she discontinued lamotrigine at 12 weeks of pregnancy, while continuing quetiapine throughout pregnancy which was subsequently increased at 29 weeks gestation.

Her baby was born normally with no complications, though unfortunately experienced some health complications within a month of delivery, which further contributed to increased levels of anxiety. Sertraline was prescribed as treatment, triggering an episode of mania at 3 weeks postpartum. Her mood quickly became elated, with increased libido, excessive activity (such as cleaning obsessively) and problematic excessive spending also being reported. Dysphoric symptoms were also present, particularly feeling 'on edge' and paranoid that someone would harm her baby.

Psychotic features further developed, including auditory and visual hallucinations that were congruent with dysphoric mood. Delusion beliefs included ideas of reference that she perceived were occurring to 'make her more depressed'. Delusions of grandiosity, jealousy and misinterpretation were prominent features. Persecutory ideas centred on the belief that clinical members of staff who were government agents in disguise, attempting to harm her because 'she was special'. Classical magical thinking was also observed.

Participant 93 recovered following admission to psychiatric hospital at 4 weeks postpartum. During which time, quetiapine was increased and lithium commenced.

6.4.3.3 Comparing risk of perinatal recurrence across diagnostic subtypes

6.4.3.3.1 Recurrence with onset during pregnancy

As shown in **Table 6.5**, women in the BD-I/SA-BD group were more likely to experience *any* DSM-5 mood episode and specifically an episode of mania/affective psychosis with

onset during pregnancy compared to those in the BD-II/BD-NOS group, however these trends did not reach statistical significance (43.9%, n=36/82 vs 36.8%, n=7/19, χ^2 (1), n=103, 3.15, p=0.575, OR=1.34, 95% CI 0.48-3.76 and 14.6%, n=12/82 vs 0%, 0/19, p=0.116, OR=1.17, 95% CI 1.07-1.28 respectively). In contrast, women with BD-II/BD-NOS were more likely to experience episodes of hypomania (15.5%, n=3/19 vs 7.3%, n=6/82, p=0.364, OR=0.42, 95% CI 0.10-1.86) and non-psychotic depression compared to women with BDI-/SA-BD (36.8%, n=7/19 vs 28%, n=23/82, p=0.450, OR=0.67, 95% CI 0.23-1.91), though again, these findings were not statistically significant. Post-hoc calculations indicated power to detect between groups differences in the rates of recurrence during pregnancy to range between 7.7%-34.7%.

6.4.3.3.2 Recurrence with onset within six weeks of delivery

The rate of recurrence of *any* DSM-5 mood episode with onset within six weeks of delivery did not significantly differ between the two groups (39.0%, n=32/82 vs 38.9%, n=7/18, χ^2 (1), n=100, 0.000, p=0.991, OR=1.01, 95% CI 0.35-2.86). However, episodes of hypomania and non-psychotic depression occurred more frequently in women BD-II/BD-NOS compared to those with BD-I/BD-NOS group (16.7%, n=3/18 vs 6.1%, n=5/82 and 33.3%, n=6/18 vs 15.9%, n=20/82 respectively), yet neither difference was statistically significant (p=0.153, OR=0.33, 95% CI 0.70-1.51 and p=0.103, OR=0.38, 95% CI 0.12-1.18 respectively). Similarly, women in the BD-I/SA-BD group were more likely to experience an episode of PP (24.4%, n=20/82) compared with women in the BD-II/BD-NOS group (5.6%, n=1/18), though this finding was also not significant (Fisher's Exact Test, p=0.11, OR=5.48, 95% CI 0.69-43.84). Post-hoc power to detect between group differences within this set of analyses was calculated to be between 2.5% and 41.2%.

Table 6.5: Recurrence of mood episodes with onset during the current perinatal period according to BD subtype in the BDRN Pregnancy sample

	BD-I/SA-BD (n=82)	BD-II/BD-NOS (n=19)	Test statistic	p-value^a	OR (95% CI)	Post-hoc Power
<i>DSM-5 mood episode with onset during pregnancy</i>						
Any mood episode	36 (43.9%)	7 (36.8%)	$\chi^2 (1) 3.15$	0.575	1.34 (0.48-3.76)	7.7%
Any hypomania	6 (7.3%)	3 (15.8%)	-	0.364 ^F	0.42 (0.10-1.86)	25.9%
Any non-psychotic depression	23 (28.0%)	7 (36.8%)	-	0.450 ^F	0.67 (0.23-1.91)	12.4%
Any mania/affective psychosis	12 (14.6%)	0 (0%)	-	0.116 ^F	1.17 (1.07-1.28)	34.7%
<i>DSM-5 mood episode with onset within 6 weeks postpartum</i>						
	BD-I/SA-BD (n=82)	BD-II/BD-NOS (n=18)	Test statistic	p-value^a	OR (95% CI)	Post-hoc Power
Any mood episode	32 (39.0%)	7 (38.9%)	$\chi^2 (1) 0.000$	0.991	1.01 (0.35-2.86)	2.5%
Any hypomania	5 (6.1%)	3 (16.7%)	-	0.153 ^F	0.33 (0.70-1.51)	36.2%
Any non-psychotic depression	13 (15.9%)	6 (33.3%)	-	0.103 ^F	0.38 (0.12-1.18)	41.2%
Any mania/affective psychosis	20 (24.4%)	1 (5.6%)	-	0.110 ^F	5.48 (0.67-43.84)	39.1%

^F Fisher’s exact test, **OR (95% CI)**: Odds ratio (95% confidence intervals), **BD-I/SA-BD**: Bipolar I disorder/schizoaffective disorder, **BD-II/BD-NOS**: Bipolar II disorder/bipolar disorder not otherwise specified

6.5 Summary of main findings

The first aims of this naturalistic study were to describe patterns of psychotropic medication use and psychiatric outcomes during the perinatal period in a well-characterised sample of 103 pregnant women with BD using a prospective follow-up design. Key findings from this chapter are summarised below.

6.5.1 Use of mood stabilising medication across the perinatal period

- Use of psychotropic mood stabilising medication varied considerably across the perinatal period.
- 26.4% of all women in the sample discontinued all mood stabilising medications prior to or during pregnancy.
- 81.8% of women who were not using any mood stabilising medication within the six-month period prior to pregnancy, also did not use any mood stabilising medication during pregnancy.
- Overall, the majority of women (61.2%) used at least one mood stabilising medication during pregnancy, with more than two thirds of women (64.4%) using mood stabilising medication for prophylaxis of PP in the postpartum period. Atypical antipsychotics (and specifically quetiapine) were the most commonly used mood stabilising medications.
- 6.9% of women were using sodium valproate for mood stabilisation within the six months prior to pregnancy; of which 71% continued to use this medication through at least the first month of pregnancy (duration of use ranged from 4-28 weeks of pregnancy). 8.8% of women received antidepressant monotherapy for at least one month during the perinatal period.

6.5.2 Perinatal psychiatric outcomes

- The risk of recurrence of mood disorder during the perinatal period was high, with 59.8% of all women experiencing an onset of at least one DSM-5 mood episode during pregnancy or the postpartum period. Risk of experiencing any DSM-5 mood episode with onset within the first three postpartum months was similar to that during pregnancy (43.0% and 42.6% respectively).
- The risk of mania or affective psychosis was especially high in the postpartum period. More than one in five women (21%) experienced an episode of PP, compared to 14% who experienced PND and 8% an episode of hypomania. Risk of PP was almost double that of mania/affective psychosis during pregnancy (11.9%). In contrast, risk of hypomania following delivery was comparable with that of pregnancy (7.9%), while episodes of depression were considerably less frequent postpartum compared to pregnancy (22.8%).
- All PP episodes had onset within six weeks of delivery, whereas the onset of episodes of hypomania and in particular, non-psychotic depression was more widely distributed throughout the postpartum period. Moreover, PP occurred within the first two postpartum weeks in 76% of cases, compared to 63% of episodes of hypomania and 43% of PND.
- Episodes of hypomania and non-psychotic depression occurred more frequently during pregnancy and the postpartum period in women with BD-II/BD-NOS compared to women with BD-I/SA-BD. However, episodes of mania or affective psychosis during pregnancy and of PP were especially prevalent among women with BD-I and SA-BD. PP occurred following 24.4% of deliveries in women with BD-I/SA-BD compared to only 5.6% of those with BD-II and BD-NOS. Due to limitations of power, these trends were not statistically significant.

6.6 Discussion

The first aim of this study was to describe patterns of medication use and psychiatric outcomes across the perinatal period in a sample of 103 pregnant women with BD using a prospective follow-up design. This prospective study is one of the largest such studies conducted to date and also the first to characterise the perinatal period among a UK sample of women with BD. I also examined perinatal psychiatric outcomes across BD subtypes, which has rarely been investigated using a prospective methodology. In this section, I discuss the results of the current study in relation to previous literature. First, patterns of psychotropic medication use during the perinatal period will be compared with findings reported in independent samples of BD. This is followed by a discussion of psychiatric outcomes during the perinatal period, with a subsequent focus on observed differences within BD subtypes. Finally, the implications for further analyses conducted within this thesis will be discussed.

6.6.1 Patterns of psychotropic medication use across the perinatal period

In this study, patterns of psychotropic medication use for mood stabilisation were found to be complex and highly variable across the perinatal period. The proportion of women using mood stabilising medications reduced during pregnancy compared with the six-month period prior to conception (from 67.6% to 61.2%), before increasing following delivery to 73.8%. Nevertheless, the majority of women continued to use at least one medication as a mood stabiliser at some point during their pregnancy or the postpartum period. Specifically, almost two thirds of women (64.4%) were using at least one medication in the postpartum period for prophylaxis of mania or psychosis. Atypical antipsychotics were the most commonly prescribed psychotropic medications during the perinatal period. Surprisingly, sodium valproate was used as a mood stabiliser prior to pregnancy in 6.9% of women, with the majority (71%) continuing this medication through at least one month of pregnancy. Moreover, antidepressant monotherapy was used for at least one month during the perinatal period in 8.8% of women. Overall, the

findings of this naturalistic study are likely to reflect the complex scenarios and decisions faced by clinicians in practice when managing BD during the perinatal period. The decision to continue or withdraw mood stabilising medication during or planning pregnancy is based on several factors, ranging from individual preferences (of both the clinician and the patient), teratogenicity and efficacy of medications, to the perceived risk of recurrence (National Institute for Health and Clinical Excellence 2014).

To date, only one published study has described patterns of psychotropic medication use during the perinatal period in a sample of 336 women with BD (Broeks et al. 2017). In their Danish study, psychotropic medication use was defined as the redemption of prescriptions (as indicated in national case registers) from 12 months preconception to 12 months postpartum. Similar to the pattern of psychotropic medication use observed in this study, Broeks et al. (2017) found redemption of prescriptions for any psychotropic medication to decrease during pregnancy (to 36.6% from 54.8% in the three months preconception), before increasing again (to 40%) at three months postpartum. They observed this pattern for all psychotropic medication types, including those used for mood stabilisation, thus being consistent with the pattern of use of mood stabilising medications I observed. The overall pattern observed across both studies (decreased use of medication during pregnancy and subsequent increase postpartum) is likely to reflect women opting to withdraw medication before or during pregnancy due to fears of teratogenic effects on the foetus or because of plans to breastfeed. Some of these women may instead choose to commence prophylactic medication following delivery, while a proportion of women only use mood stabilising medication for treatment of emergent mood symptoms.

Indeed, I found 26% of all women to withdraw mood stabilising medications, with 17.6% of women doing so during pregnancy. Broeks et al. (2017) reported a higher rate of withdrawal of any psychotropic medication during pregnancy (27.9%), however the proportion of women who withdrew mood stabilising medications prior to pregnancy was not stated. It is therefore reasonable to assume that the proportion of women who

withdrew all mood stabilising medications in Broeks et al.'s (2017) study is likely closer to the figure I observed within the BDRN pregnancy sample.

Though the pattern of medication use across the perinatal period was similar between this study and that reported by Broeks et al. (2017), the proportion of women using medication during each phase of the perinatal period was higher in the BDRN pregnancy sample. For example, I found 61.2% of women to be using at least one mood stabilising medication during pregnancy, compared to 36.6% of women (as indicated by redemption of prescriptions) in Broeks et al.'s study (2017). I also found the proportion of women using mood stabilising medication in the postpartum period for any purpose (73.8%, i.e. for treatment or prophylaxis) and specifically for prophylaxis of mood episodes (64.4%) to be higher compared to the use of any psychotropic medication (40%) in the Danish population. This difference is despite both studies adopting the same temporal definition of the postpartum period (i.e. within the first three months).

There are several potential explanations for this difference. First, in the study by Broeks et al. (2017), analyses were restricted to primiparous women only. If these women had not previously experienced a postpartum mood episode, the perceived need for prophylaxis of postpartum mood episodes would likely be lower than for women who did have such history. Due to the increased uncertainty of risk of postpartum recurrence, women in the Danish study may have preferred to instead withdraw medication and adopt a 'wait and watch' approach before commencing any medication. In contrast, as indicated in section 6.2.3 of this chapter, almost a quarter of women in the BDRN pregnancy sample had a prior history of PP, thus likely being considered particularly high risk of further postpartum recurrence (24%, $n=25/103$). Additionally, given that approximately 50% of women were recruited to the BDRN pregnancy study via specialist perinatal psychiatric services, it is probable that a higher proportion of women in this sample were advised to remain on medication during the perinatal period.

Alternatively, it is possible that the proportion of women using psychotropic mood stabilising medication during the perinatal period may be underestimated in Broeks et al.'s (2017) study compared to the rates I observed. In their study, it was not possible to identify from case-registers medications prescribed while receiving inpatient care. However, in the current study, when examining use of any mood stabilising medications across the perinatal period, I was able to identify medication utilised as treatment or for prophylaxis, providing a comprehensive picture of overall psychotropic medication use.

Another factor that may have contributed to an underestimation of psychotropic medication use in the Danish sample is that diagnosis of BD was confirmed only by review of case-registers and made according to ICD criteria. As such it was not possible for Broeks et al. (2017) to establish the presence/absence of subtypes of BD within their sample. Though speculative, their sample may have comprised a higher proportion of women with subtypes of BD (such as BD-II or BD-NOS) for whom the risk of perinatal recurrence is often perceived to be lower for those with a diagnosis of BD-I or SA-BD. This is further suggested by the high rate of antidepressant monotherapy observed in their sample (50%), which is typically avoided in individuals with a history of manic episodes. In comparison, the vast majority of women in this study (approximately 80%) had a preconception diagnosis of BD-I, who by definition are considered at greater risk of manic episodes or psychosis than women with BD-II or BD-NOS. If this were the case, it could be expected that fewer women in the Danish study would have remained on medications for the purpose of mood stabilisation compared to within the BDRN pregnancy sample.

Nevertheless, it is important to note that directly comparing the findings of this study with that of Broeks et al (2017) is difficult, given other key differences in methodology between the two studies. Primarily, the use of a case-register methodology in Broeks et al.'s (2017) study meant it was not possible for the authors to infer whether medication was prescribed prophylactically or as treatment for emergent symptoms. Furthermore, as they were only able to identify medication use by the rate of redemption of

prescriptions, it was unknown whether women were actually compliant with medications prescribed during this time period. In comparison, use of mood stabilising medication in this study was ascertained not only by self-report, but also by information from clinician questionnaires and psychiatric case-notes. Thus, the findings of this study are likely to offer a more reliable and representative picture of psychotropic medication use and specifically of prophylactic mood stabiliser use across the perinatal period in women with BD.

6.6.1.1 Sodium valproate and antidepressant monotherapy in the perinatal period

In this sample, I found 6.9% of women to have used sodium valproate for mood stabilisation (of any duration) within six months prior to pregnancy and a further 7.8% antidepressant monotherapy (for a duration of at least one month) either in the six months prior to pregnancy or during the perinatal period. These findings are surprising, given that both medication regimes are advised against in clinical practice. While the use of antidepressant monotherapy in this sample was considerably lower than the 50% of women observed in Broeks et al.'s (2017) study, as discussed previously, this likely reflects the high proportion of women in the BDRN pregnancy sample who had preconception diagnosis of BD-I and thus would have been perceived at high risk of mania without the use of a concomitant mood stabilising medication (Goodwin et al. 2016).

The proportion of women I found to be using sodium valproate as a mood stabiliser in this sample is particularly concerning. The teratogenic effects of this drug on the foetus have been well-documented (Andrade 2018; Macfarlane and Greenhalgh 2018). Within the UK, evidence based guidelines for NHS practice recommend that sodium valproate should not be used in any woman of childbearing age (National Institute for Health and Clinical Excellence 2014). This finding is therefore particularly surprising, given that three of seven women reported planning their pregnancy and four were receiving care from NHS perinatal psychiatric services. This would suggest that some women (or

potentially their clinicians) may not have been aware of the risks of remaining on sodium valproate during pregnancy. When examining the proportion of women who used sodium valproate specifically during their pregnancy, the rate of use in the BDRN pregnancy sample would decrease to 3.9% (as three women discontinued use of this medication prior to conception). This is comparable to the 2.3% (n=4/176) women observed to be using carbamazepine or sodium valproate during pregnancy in Broeks et al.'s study (2017), though the precise number of women using sodium valproate was not reported. The proportion of women in this sample who were using sodium valproate during pregnancy is however similar to the 5.6% of women with epilepsy who are also reported to use this medication during pregnancy (Petersen et al. 2017). Thus, this finding likely represents prescribing practices across disorders and is not necessarily specific to BD.

6.6.1.2 Section summary

In summary, I found the overall pattern of use of mood stabilising medications to be consistent with the previous literature to date. The findings further demonstrate the complexity of managing BD during the perinatal period, showing that many women undergo significant changes to their medication regime during pregnancy, often withdrawing their use of mood stabilising medication completely or switching to alternative medications. Surprisingly, a notable proportion of women also continue to remain on medication regimes that are advised against by clinical recommendation guidelines, suggesting that not all women may be aware of the risks of remaining on valproic acid during pregnancy or of using antidepressant monotherapy.

Despite variation in patterns of medication use across the perinatal period, I found the majority of women to remain on mood stabilising medication, the proportion of which was higher than has been previously reported (Broeks et al., 2017). Due to methodological differences between studies, direct comparison of these findings is difficult. However, the high proportion of women remaining on prophylactic mood

stabilising medications in this study is likely to reflect women in the current sample being perceived at particularly high risk of postpartum recurrence, given that the majority met criteria for a preconception diagnosis of BD-I and a quarter had a history of severe postpartum mood episodes.

The role of mood stabilising medications in the prevention of severe postpartum recurrence in women with BD is largely unknown. As discussed in the introductory chapter of this thesis (section 2.6.2.2), previous research in this area has been primarily limited to small samples of women and specifically the use of lithium. Furthermore, few studies assessing risk factors for postpartum recurrence have controlled for prophylactic mood stabiliser use. In addition to a range of within-pregnancy factors, the influence of mood stabiliser prophylaxis on risk of PP will therefore be examined in the next chapter of this thesis.

6.6.2 Perinatal recurrence of mood episodes

In this study, more than half of all women (59.8%) experienced at least one DSM-5 affective episode during the perinatal period, defined as the onset of an episode during pregnancy or within three months postpartum. Overall, rates of recurrence during pregnancy were similar to that within the postpartum period (42.6% and 43% respectively). However, unlike episodes of hypomania (8%) or non-psychotic depression (14%), when compared with similar episodes of mania/affective psychosis during pregnancy (21%), episodes of PP were especially frequent following childbirth. While onset of all episodes of PP occurred within five weeks of delivery (peaking within the first two weeks), the onset of episodes of hypomania and of non-psychotic depression was more widely distributed across the postpartum period. Examining psychiatric outcomes within BD subtypes revealed perinatal episodes of hypomania and non-psychotic depression to be more frequent among women with BD-II or BD-NOS compared to women with BD-I or SA-BD. In contrast, perinatal episodes of mania/affective psychosis were more common among women with BD-I/SA-BD. Almost

a quarter of women (24.4%) with BD-I and SA-BD experienced the onset of PP, compared to only 5.6% of women in the BD-II and BD-NOS group. Though no difference in perinatal psychiatric outcomes across BD subtypes reached statistical significance.

6.6.2.1 Recurrence of bipolar disorder during pregnancy

The rate of recurrence of BD during pregnancy was high in this sample, with 42.6% of women experiencing the onset of at least one DSM-5 mood episode. Episodes of non-psychotic depression were especially frequent, occurring in 22.8% of women, compared with 11.9% who experienced a worst episode of mania or affective psychosis and 7.9% an episode of hypomania. No woman with BD-II experienced the onset of an episode of mania or affective psychosis during pregnancy. The overall recurrence rate I observed during pregnancy (42.6%) is considerably higher than the rate of 10.8% reported by our research group in our retrospective sample of 1212 women with bipolar I and II disorder (Di Florio et al. 2013). This variation is however likely due to key methodological differences between the two studies. Primarily, only the worst mood episode experienced during each perinatal period was reported in our retrospective sample. Perinatal mood episodes were also rated hierarchically, with postpartum episodes rated in favour of those occurring during pregnancy. For example, if a woman experienced mania during pregnancy and the postpartum period, only the episode occurring with onset in the postpartum period was rated, thus likely underestimating recurrence during pregnancy. Another contributory factor may be the retrospective method in which perinatal outcomes were assessed in our cross-sectional study. This likely increased the possibility of recall bias, with milder forms of disorder with onset during pregnancy being underreported.

Compared with two key studies which have also examined recurrence during pregnancy in women with BD, recurrence in the BDRN pregnancy sample (42.6%) was higher than the rate of 24.4% reported in one retrospective study (Bergink et al. 2012) but

considerably lower than that reported in a prospective study (70.8%, Viguera et al. 2007). The findings of Bergink et al.'s (2012) study were based on a small sample of 41 women, 75.6% of whom had remained on medication during pregnancy and all but one of whom continued to use lithium prophylactically (96.8%, $n=30/31$). This is in striking contrast to the 12% of women taking lithium during pregnancy in this study. While the prophylactic effect of mood stabilising medication on perinatal recurrence in BD requires further investigation (and will be examined in the next chapter of this thesis), lithium remains the gold standard treatment for maintenance of BD (Lähteenvuo et al. 2018). Thus, it is possible that women in Bergink et al.'s (2012) study had a form of BD illness that was better managed during pregnancy than within the current study, reducing risk of recurrence in their sample. It is also noteworthy that I found a higher proportion of women in the BDRN Pregnancy Study to not use any mood stabilising medication at all during pregnancy (38.8%), compared to 24.4% of women in the Danish study (Bergink et al. 2012). Interestingly, when examining women who were not using prophylactic mood stabilisers in pregnancy, Bergink et al. (2012) found the recurrence rate during pregnancy in their sample to increase to 40.0%.

In another study, Viguera et al. (2007) reported 70.8% of 89 women in their sample to relapse during pregnancy. This contrasts with the rate of 42.6% of women in the current sample, despite both studies using a prospective design and DSM criteria to assess psychiatric outcomes. There are a number of potential differences between the two studies that may explain this finding. Firstly, the vast majority of women in the sample studied by Viguera et al. (2007) were identified as not using any mood stabilising medication during pregnancy (70%), compared with only 38.8% women in this sample. It is therefore possible the risk of recurrence may have been greater in their study than in the BDRN pregnancy sample. Furthermore, clinical characteristics of women included in their study suggest these women may have been more vulnerable to recurrence during the perinatal period. The authors reported 89.4% of women in their sample to have a prior history of perinatal episodes, compared to the quarter of women in the current study who had a history of PP. Nevertheless, this is only speculative, given that I

only assessed lifetime history of PP (as opposed to any perinatal episode) and thus could not directly compare studies. Finally, episodes of depression were especially frequent during pregnancy in their study, occurring in 38.2% of pregnancies compared to only 22.8% in this sample. This may reflect the higher proportion of women with BD-II disorder in their sample (31.5%) compared to within this study (16.5%); women who have been shown to be a greater risk of depressive episodes during pregnancy compared to women with BD-I disorder (Di Florio et al. 2013).

6.6.2.2 Recurrence of bipolar disorder in the postpartum period

I found 43% of all women with BD to experience the onset of a mood episode within three months of childbirth. The high rate of postpartum recurrence reported within the BDRN pregnancy sample is similar to the rate of 52.6% previously observed in our retrospective sample (Di Florio et al. 2013). Episodes of PP were found to occur following 21% of all deliveries within six weeks in the current study, which is almost identical to the rate of 19% of deliveries affected in our retrospective sample of 671 women with BD. Notably, the rate reported by Di Florio et al. (2013) only included the onset of episodes of mania or mixed affective states. If episodes of psychotic depression were also included in this definition (as I have reported in this study), the rate of severe recurrence in the retrospective sample would increase to 22.4%, which is in keeping with the 21% of women who experienced these episodes in the BDRN pregnancy sample. Importantly, in both studies, recruitment methods were similar and psychiatric outcomes were assessed by semi-structured clinical interviews and case-note review.

The postpartum recurrence rate of 43% of any mood episode within 12 weeks of delivery observed in this study is also generally consistent with wider research. Based on data from 25 studies, a recent meta-analysis found that 37% of women with BD experienced a postpartum mood episode within 12 months of delivery (Wesseloo et al., 2016). The authors also reported severe recurrence (defined as an episode of mania/mixed affective state or affective psychosis) to occur in 17% of all deliveries up to

12 months following delivery, again being comparable with findings of this study that more than one in five women with BD are at risk of PP.

Again, it is difficult to directly compare outcomes I have reported here with the findings of this meta-analysis, given that the 25 studies from which their data was obtained, all demonstrated considerable heterogeneity in assessment, study design and the temporal period used to define postpartum recurrence (ranging from one month to 12 months postpartum). When studies were grouped by these key methodological differences, rates of postpartum recurrence varied widely. For example, using data only from prospective studies of BD, 33% of women were found to have a postpartum recurrence within the first 12 months following delivery, which is slightly lower than their pooled estimate of 37% when combining all studies of BD (regardless of study design; Wesseloo et al. (2016). This estimate from prospective studies remains lower than the rate of recurrence I observed within this sample (within three months of delivery; 43%). This difference may be indicative of the high proportion of women in this study with BD-I disorder (80%) who may have been at higher risk of recurrence. In contrast, 63% of the combined sample in Wesseloo et al.'s (2016) study was comprised of women with BD-I disorder. Overall however, incidence of postpartum recurrence in this study (39% within six weeks and 43% within three months of delivery) is within the range of overall estimates of postpartum recurrence (within 12 months) reported by Wesseloo et al. (2016) based on all included studies of BD (29-45%) and solely using data from prospective studies (23-45%).

6.6.2.3 Presentation of postpartum mood episodes

Relative to episodes of PP (21%), episodes of PND and hypomania within three months of delivery were relatively less frequent in this sample at 14% and 8% respectively. Previous research has found episodes of non-psychotic depression to be the most frequent presentation of mood disorder in the postpartum period, with prevalence estimates ranging between 18-59.7% in samples of women with BD (Blehar et al. 1998;

Bratfos and Haug 1964; Colom et al. 2010; Di Florio et al. 2013; Maina et al. 2014; Viguera et al. 2011; Wisner et al. 2004). However, I found that even when accounting for all occurrences of PND with onset within three months of delivery (i.e. also including women who experienced a worst episode of mania in addition to an episode of depression), the prevalence of PND remained slightly lower than that of PP (20%). Importantly, much of the previous literature has adopted a broader onset criteria of the postpartum period (up to six months following delivery, Di Florio et al. 2013; Viguera et al. 2011; Wisner et al. 2004), likely identifying episodes of depression which typically have a wider distribution of onset. As the follow-up period in this study was restricted to the first three postpartum months, it was not possible to compare recurrence including episodes which may have a later onset. Furthermore, as stated previously, only 16.5% women in this study had a preconception diagnosis of BD-II disorder, compared to between 20-54.4% in previous studies (Blehar et al. 1998; Bratfos and Haug 1964; Colom et al. 2010; Di Florio et al. 2013; Maina et al. 2014; Viguera et al. 2011; Wisner et al. 2004). Given that evidence suggests women with BD-II may be at increased risk of recurrence during the perinatal period (Di Florio et al. 2013; Viguera et al. 2007), findings of the current study may be more representative of course of illness among women with BD-I.

Episodes of hypomania occurred infrequently postpartum (in 8% of all women within three months of delivery), which is consistent with previous research (Abdel-Hay, El-Sawy and Badawy 2011; Di Florio et al. 2013; Viguera et al. 2011). Given that I assessed recurrence of illness soon after delivery, it is unlikely that episodes of hypomania were underreported due to recall bias. It is plausible that in some cases, milder episodes were difficult for women and their families to distinguish from the joy experienced following the birth of their baby. Postpartum highs are also a common feature in the first few weeks after delivery in the general population (Heron et al. 2009; Smith et al. 2009) and can be present with additional symptoms of the baby blues. Therefore, briefer periods of elated or mixed mood may not have been considered episodes of impairing illness, but rather a common experience of emotional fluctuation associated

with hormonal changes in the early postpartum. The likelihood of this is however reduced, given that case-notes and clinician questionnaires were also used to assess postpartum psychiatric outcomes.

6.6.2.4 Timing of onset of worst postpartum mood episode

Of the worst postpartum mood episodes experienced within the current perinatal period, all episodes of PP occurred within six weeks of delivery, with the majority of these episodes (76.2%) having onset within the first two weeks. This was in contrast to episodes of hypomania and non-psychotic depression, for which the onsets were more widely distributed across the postpartum period. Episodes of hypomania were found to have onset up to 8 weeks postpartum, while episodes of non-psychotic depression occurred up to 12 weeks postpartum.

The pattern of onset observed within the current study is consistent with previous literature, in which studies of clinical samples (McNeil 1986), women with BD (Heron et al. 2008) and large populations (Kendell, Chalmers and Platz 1987; Langan Martin et al. 2016; Munk-Olsen et al. 2006; Nott 1982) have all demonstrated the first two postpartum weeks to be a period of particularly high risk for onset of episodes of PP. This finding has important implications for clinical practice, indicating the first few weeks in particular to be the primary time in which women with BD should be monitored for the onset of early symptoms. Furthermore, the striking excess of episodes of PP that were found to occur early in the postpartum period provides further support for the hypothesis that childbirth has a specific role in the aetiology and/or triggering of severe mood episodes among women with BD.

6.6.2.5 Perinatal recurrence according to preconception BD subtype

The proportion of women who experienced at least one DSM-5 mood episode within six weeks of delivery was almost identical among those with a preconception diagnosis of

BD-I/SA-BD (38.9%) and those with BD-II/BD-NOS (39.0%). However, perinatal episodes of hypomania and non-psychotic depression were observed more frequently among women with a preconception history of BD-II/BD-NOS than those with BD-I/SA-BD. Conversely, women with BD-I/SA-BD were at higher risk of mania/affective psychosis during pregnancy (14.6% vs 0% in BD-II/BD-NOS) and of PP compared to those with BD-II or BD-NOS (24.4% vs 5.6% respectively). While these trends did not reach statistical significance, post-hoc calculations revealed power of these analyses to be low, ranging between 2.5%-41.2%. Based on the observed effect sizes (see page 158 for summary of odds ratios), sample size calculations indicate up to 443 women with BD would be needed within each diagnostic subgroup in future studies to achieve 80% power to detect a between group difference in the type of perinatal recurrence. Given the strong possibility of type II error, these findings provide an important contribution to individualising risk prediction of PP. Women with BD-I may need additional monitoring across the perinatal period, given that these women may be at especially high risk of PP.

To my knowledge, this prospective study is the first to demonstrate that women with BD-II/BD-NOS may be at increased risk of hypomania and non-psychotic depression during pregnancy compared to women with BD-I/SA-BD, and that women with BD-I/SA-BD are at comparatively increased risk of mania/affective psychosis. Nevertheless, the overall trend for women with BD-I/SA-BD to be at greater risk of any mood recurrence during pregnancy compared to BD-II/BD-NOS is in contrast with some previous literature (Di Florio et al. 2015; Viguera et al. 2011, 2007). As discussed, Viguera et al. (2007) found a BD-II diagnosis to be associated with increased risk of at least one DSM-IV defined recurrence during pregnancy. Similarly, in our large retrospective sample (Di Florio et al. 2013), the occurrence of DSM-IV episodes with onset in pregnancy was approximately twice as high among women with BD-II (18.4%) compared to those with BD-I (8.6%), though this difference was not statistically compared. One possible reason for discrepancies between findings may be due to the inclusion of women with SA-BD and BD-NOS within the current sample, groups that were not included in either previous study. Inclusion of women with SA-BD in the BD-I/SA-BD group may have

inflated risk of recurrence during pregnancy within this group, whereas inclusion of women with BD-NOS may have simultaneously reduced risk within the BD-II/BD-NOS group. Risk of antenatal recurrence is also likely underestimated in our BDRN retrospective sample, given that only the worst mood episode within each perinatal period was rated. Using a hierarchy method, postpartum onset episodes were rated in favour of those with onset during pregnancy.

Overall, the pattern of postpartum recurrence I observed across diagnostic subtypes is consistent with the literature. In a recent systematic review and meta-analysis of postpartum recurrence, no difference was found in overall recurrence rates of any postpartum mood episode (within 12 months postpartum) between women with BD-I and BD-II (45% and 50% respectively, Wesseloo et al. 2016). Though importantly, type of postpartum recurrence was not statistically compared across BD subtypes. To date, only two large retrospective studies of women with BD have described the type and polarity of postpartum mood episodes occurring within diagnostic subtypes (both of which were included in the meta-analysis by Wesseloo et al., 2016). Consistent with the current study, episodes of PP occurred more frequently in our BDRN retrospective sample among women with BD-I disorder than those with BD-II (33% vs 9.1% respectively, Di Florio et al., 2013). Furthermore, postpartum episodes of hypomania and non-psychotic depression (within 12 months of delivery) occurred more frequently among women with BD-II (4% and 35.4% respectively) compared to those with BD-I (2.6% and 24.8% respectively). As described earlier in this thesis (section 2.5.2), participants were recruited to both studies using similar methods, and diagnoses and psychiatric outcomes assessed in both BDRN samples according to DSM criteria using the same semi-structured neuropsychiatric interview (SCAN).

Finally, Viguera et al. (2011) assessed psychiatric outcomes of 2232 deliveries to 1162 women with BD (283 BD-I and 338 BD-II), also finding no difference in overall postpartum recurrence rates within six months of delivery between diagnostic groups (38% in BD-I and 34.5% in BD-II). However, when examining recurrence of severe

postpartum episodes, no woman in the BD-II group experienced an episode of PP, compared to 9.8% of women in BD-I group. Viguera et al. (2011) also found mixed affective states to be less frequent in the BD-II group (2.5%) compared to within the BD-I group (6.5%), though the predominant polarity of the episodes was not specified.

6.6.2.6 Section summary

In summary, the findings of this study are consistent with previous research indicating that risk of recurrence is high during the perinatal period in women with BD.

Longitudinal assessment of perinatal psychiatric outcomes indicates that the postpartum period and specifically, the first few weeks following delivery is a time of especially high risk for episodes of mania or affective psychosis. Findings from this study also suggest that this risk may be specifically increased among women with BD-I or SA-BD.

The close temporal relationship between PP and childbirth reinforces the hypothesis that factors specific to childbirth are likely more important in the occurrence of these episodes compared to other postpartum mood disorders. Nevertheless, factors influencing risk of PP (including use of pharmacotherapy) are poorly understood. Identifying factors that place women with BD at greatest risk of severe postpartum recurrence would clearly have important implications for clinical practice. Therefore, in order to examine this further, the next chapter of this thesis will focus on investigating the relationship between a range of within-pregnancy potential risk factors and the occurrence of narrowly defined PP in the BDRN pregnancy sample. Given observed heterogeneity between diagnostic subtypes, these investigations will be conducted in women with a preconception diagnosis of BD-I and SA-BD only (n=82, for whom the presence/absence of postpartum recurrence could be established).

Chapter 7

The BDRN Pregnancy Study: Investigating within-pregnancy risk factors for postpartum psychosis in bipolar disorder

7.1 Introduction

The primary aim of this study was to identify potential risk factors for PP in the sample of women recruited to the BDRN Pregnancy Study (described in Chapter 6). Due to heterogeneity between diagnostic subgroups, this chapter will focus on investigations in women with BD-I and SA-BD only (n=84). First, results of univariate analyses examining the relationship between the occurrence of PP and a range of within-pregnancy potential risk factors will be presented, followed by reports of findings from multivariate binary logistic regression analyses. I extend these analyses, reporting investigations assessing the specificity of potential risk factors to the occurrence of PP by also examining their relationship to episodes of PND. The final section of this chapter focuses on discussion of findings in relation to the literature and implications these may have for future research and clinical practice.

7.2 Sample

As stated, due to heterogeneity between BD subtypes, analyses within this chapter were restricted to participants with a preconception DSM-5 lifetime diagnosis of BD-I or SA-BD only. Of the 84 women with BD-I or SA-BD who were recruited to the BDRN Pregnancy Study, two women had experienced the onset of an affective episode during pregnancy that continued into the postpartum period. As it was not possible to determine if these women would have experienced an episode following childbirth had they been euthymic at the time of delivery, these women were excluded from all subsequent analysis. The final sample therefore comprised 82 women with a diagnosis of BD-I or SA-BD.

7.3 Definition of outcomes

The worst DSM-5 mood episode occurring within six weeks of delivery (as described in Chapter 6, section 6.4.3.3.2) was used to categorise outcomes within the sample according to the presence or absence of PP (PP or No PP respectively, defined within

this thesis as an episode of mania with or without mixed features or affective psychosis). A temporal cut-off of six weeks was used to define the postpartum period to be consistent with both DSM-5 and ICD-10 criteria. According to this definition, 24.4% (n=20/82) of women had experienced an episode of PP and 75.6% No PP (n=62/82).

7.4 Results

7.4.1 Demographic and key clinical characteristics

Demographic and preconception key clinical characteristics of the sample according to the presence or absence of PP are shown in **Table 7.1** and **Table 7.2** respectively. As shown in **Table 7.1**, there were no significant differences between the two groups with regards to age at interview (p=0.820), ethnicity (p=0.591), method of recruitment (p=0.242), lifetime marital status (p=0.435), highest education level (p=1.000) or highest occupational level (p=0.890).

Table 7.1: Demographic characteristics of BD-I/SA-BD women in the BDRN pregnancy sample (n=82) according to the presence or absence of PP

	PP 24.4% (n=20)	No PP 75.6% (n=62)	Test statistic ^a	p-value
<i>Demographic characteristic</i>				
Age at interview (years)				
Median (IQR)	34 (10)	35 (6)	U= 599.000,	0.820
Range	20-44	23-43	Z = -.227	
Ethnicity				
White ethnicity	18 (90.0%)	59 (95.2%)	-	0.591 ^F
Non-white ethnicity	2 (10%)	3 (4.8%)		
Method of recruitment				
Non-systematic	13 (65.0%)	31 (50.0%)	χ^2 (1) 1.368	0.242
Systematic	7 (35.0%)	31 (50.0%)		
Lifetime marital status				
Married/lived as married	19 (95.0%)	60 (98.4%)	-	0.435 ^F
Never married/lived as married	1 (5.0%)	1 (1.6%)		
Highest education level				
Degree level qualification or higher	17 (85.0%)	51 (82.3%)	-	1.000 ^F
No degree level qualification	3 (15.0%)	11 (17.7%)		
Highest occupation level				
Professional	11 (55.0%)	33 (53.2%)	χ^2 (1) 0.019	0.890
Non-professional	9 (45.0%)	29 (46.4%)		

Numbers differ due to unknown data. **PP**: postpartum psychosis, **No PP**: No postpartum psychosis. **IQR**: Interquartile range. ^a p-values calculated via Mann-Whitney U test for continuous variables. p-values for categorical variables calculated by Pearson's Chi-Square or Fisher's exact test. ^FFisher's exact test.

As shown in **Table 7.2**, there was no significant association between the occurrence of PP and age at onset of impairing BD ($p=0.709$) or preconception lifetime number of episodes of mania ($p=0.434$) and depression per illness year ($p=0.916$). Women who experienced PP were significantly more likely to have a preconception history of psychotic symptoms (95%, $n=19/20$) compared to women who did not experience PP (71%, $n=44/62$; $p=0.032$, OR 7.77 95% CI 0.97-62.49).

Table 7.2: Key preconception clinical characteristics of BD-I/SA-BD women in the BDRN pregnancy sample ($n=82$) according to the presence or absence of PP

	PP 24.4% (n=20)	No PP 75.6% (n=62)	Test statistic ^a	p-value
<i>Key preconception clinical characteristics</i>				
Age at onset of impairment of BD				
Median (IQR)	21 (11)	20 (10)	U= 528.500,	0.709
Range	13-36	11-35	Z = -.374	
Preconception lifetime number of episodes of mania per illness year				
Median (IQR)	0.31 (0.33)	0.38 (0.44)	U= 450.000,	0.434
Range	0.11-2.01	0.05-7.37	Z = -.782	
Preconception lifetime number of episodes of depression per illness year				
Median (IQR)	0.40 (0.93)	0.45 (0.35)	U= 514.000,	0.916
Range	0.00-1.85	0-4.34	Z = -.105	
Preconception lifetime history of psychotic symptoms				
Present	19 (95.0%)	44 (71.0%)	-	0.032
Absent	1 (5.0%)	18 (29%)		

BD-I: Bipolar I disorder. PP: postpartum psychosis, No PP: No postpartum psychosis. IQR: Interquartile range. ^a p-values calculated via Mann-Whitney U test for continuous variables. p-values for categorical variables calculated by Fisher's exact test.

7.4.2 Within-pregnancy potential risk factors for postpartum psychosis

This section presents results of analyses examining the relationship between the following range of within-pregnancy potential risk factors and occurrence of PP; psychosocial factors, adverse life events, smoking and alcohol use, perinatal sleep factors, obstetric factors, antenatal psychopathology and prophylactic medication use for mood stabilisation.

7.4.2.1 Psychosocial factors relating to pregnancy

Table 7.3 summarises postpartum psychiatric outcomes according to the presence or absence of psychosocial factors specific within the current pregnancy. As shown, there were no significant differences between the two groups in the proportion of women who experienced PP with regards to the planning of pregnancy (23.5% planned, $n=12/51$ vs 40.0% unplanned, $n=6/15$; $p=0.322$, OR 2.17 95% CI 0.64-7.33) or women's perceived experience of pregnancy (26.3% positive experience, $n=10/38$ vs 22.7% negative experience, $n=10/44$; $p=0.706$, OR 1.21 95% CI 0.44-3.33). Due to the small sample size in one of the groups, the occurrence of PP according to the presence/absence of a partner during pregnancy or the perceived level of emotional support from partner or others could not be statistically compared.

Table 7.3: Occurrence of PP according to psychosocial factors specific within the current pregnancy in BD-I/SA-BD women in the BDRN pregnancy sample ($n=82$)

	PP	No PP	Test statistic ^a	p- value
Planned pregnancy				
Planned ($n=51$)	12 (23.5%)	39 (76.5%)	-	0.322 ^f
Unplanned ($n=15$)	6 (40.0%)	9 (60.0%)		
Perceived experience of pregnancy				
Positive ($n=38$)	10 (26.3%)	28 (73.7%)	$\chi^2(1) 0.142$	0.706
Not positive ($n=44$)	10 (22.7%)	34 (77.3%)		
Partner in pregnancy^b				
Present ($n=81$)	20 (24.7%)	61 (75.3%)	-	-
Absent ($n=1$)	0 (0%)	1 (100%)		
Perceived emotional support from partner^b				
Supportive ($n=66$)	18 (27.3%)	48 (72.7%)	-	-
Not supportive ($n=2$)	0 (0%)	2 (100%)		
Perceived emotional support from others^b				
Supportive ($n=68$)	19 (27.9%)	49 (72.1%)	-	-
Not supportive ($n=2$)	0 (0%)	2 (100%)		

Numbers differ due to unknown data. **BD-I:** Bipolar I disorder, **SA-BD:** Schizoaffective disorder bipolar type, **PP:** Postpartum psychosis; **No PP:** No postpartum psychosis. ^a p-values for categorical variables calculated by Pearson's Chi-Square or Fisher's exact test. ^b Statistical comparisons not performed due to small sample sizes. ^f Statistic calculated using Fisher's Exact Test

7.4.2.2 Adverse life events during pregnancy

Table 7.4 summarises comparisons of the occurrence of PP according to the presence/absence of adverse life events experienced during pregnancy. As shown, episodes of PP did not occur significantly more frequently among women who reported the presence of any (i.e. at least one) adverse life event during their pregnancy compared to those who did not (28.3%, n=13/46 vs 16.7%, n=4/24 respectively; p=0.283, OR=1.97, 95% CI 0.56-6.88). There was also no significant association between the total number of adverse life events experienced during pregnancy and the occurrence of PP (p=0.64).

The proportion of women who experienced PP did not significantly differ according to the presence/absence of any of the following adverse events during pregnancy: a serious illness or injury to themselves (50.0%, n=3/6 vs 21.0%, n=13/62; p=0.137, OR 3.77 95% CI 0.68-20.91), a serious illness or injury to a close relative (23.1%, n=3/13 vs 23.6%, n=13/55; p=1.000, OR 0.97, 95% CI 0.23-4.06) bereavement of a close friend or relative (38.5%, n=5/13 vs 20.4%, n=11/54; p=0.274, OR 2.44, 95% CI 0.67-8.96) or the presence of at least one other adverse life event (see page 124 for a full description of questionnaire item (19.4%, n=6/31 vs 29.7%, n=11/37; p=0.235, OR=0.57, 95% CI 0.18-1.77).

Due to small sample sizes across groups, the occurrence of PP could not be statistically compared according to the presence/absence of the breakdown of a relationship during pregnancy, a serious problem with friends or relatives or problems with the police involving a court appearance. No woman in the sample reported losing a job during pregnancy, experienced a financial crisis equating to three months lost wages or the theft or loss of a valued item.

Table 7.4: Occurrence of PP according to the presence or absence of adverse life events during pregnancy in BD-I/SA-BD women in the BDRN pregnancy sample (n=82)

	PP	No PP	Test statistic ^a	p- value
Adverse event during pregnancy				
Any adverse life event experienced				
Present (n=46)	13 (28.3%)	33 (71.7%)	χ^2 (1) 1.153	0.283
Absent (n=24)	4 (16.7%)	20 (83.3%)		
Serious illness/injury				
Present (n=6)	3 (50.0%)	3 (50.0%)	-	0.137 ^f
Absent (n=62)	13 (21.0%)	49 (79.0%)		
Serious illness/injury to close relative				
Present (n=13)	3 (23.1%)	10 (76.9%)	-	1.00 ^f
Absent (n=55)	13 (23.6%)	42 (76.4%)		
Bereavement of close friend/relative				
Present (n=13)	5 (38.5%)	8 (61.5%)	-	0.274 ^f
Absent (n=54)	11 (20.4%)	43 (79.6%)		
Breakdown of relationship ^c				
Present (n=3)	0 (0%)	3 (100%)	-	-
Absent (n=65)	16 (24.6%)	49 (75.4%)		
Serious problem with friends/relatives ^c				
Present (n=2)	1 (50.0%)	1 (50.0%)	-	-
Absent (n=68)	15 (23.1%)	50 (76.9%)		
Problems with the police involving court appearance ^c				
Present (n=1)	0 (0%)	1 (100.0%)	-	-
Absent (n=67)	16 (23.9%)	51 (76.1%)		
Any other adverse event^b				
Present (n=31)	6 (19.4%)	25(80.6%)	χ^2 (1) 0.968	0.235
Absent (n=37)	11 (29.7%)	26 (70.3%)		
Total number of adverse life events experienced				
Median (IQR)	1 (1)	1 (1)	U= 378.000, Z = -0.472	0.637
Range	0-4	0-3		

Numbers differ due to unknown data. **BD-I:** Bipolar I disorder, **SA-BD:** Schizoaffective disorder bipolar type, **PP:** Postpartum psychosis; **No PP:** No postpartum psychosis. ^a p-values for categorical variables calculated by Pearson's Chi-Square or Fisher's exact test. ^b Variable formed from responses to the open-ended question 'In the last 6 months, other than being pregnant, did any other significant event happen in your life?'. ^c Statistical comparison not performed due to small sample sizes ^f statistic calculated by Fisher's Exact Test

7.4.2.3 Smoking and alcohol use in the current pregnancy

The proportion of women who experienced PP did not significantly differ between those who reported smoking during pregnancy (22.2%, $n=4/18$, see **Table 7.5**) and those who did not smoke during pregnancy (25.0%, $n=16/64$; $p=1.000$, OR 0.86 95% CI 0.25-2.98). The influence of alcohol use on risk for PP could not be examined, as no woman in the sample consumed more than the recommended limit of units (14 units) of alcohol per week during their pregnancy (specifically, no woman regularly consumed more than one unit of alcohol within a week).

Table 7.5: Occurrence of PP according to self-reported smoking during pregnancy in BD-I/SA-BD women in the BDRN pregnancy sample ($n=82$)

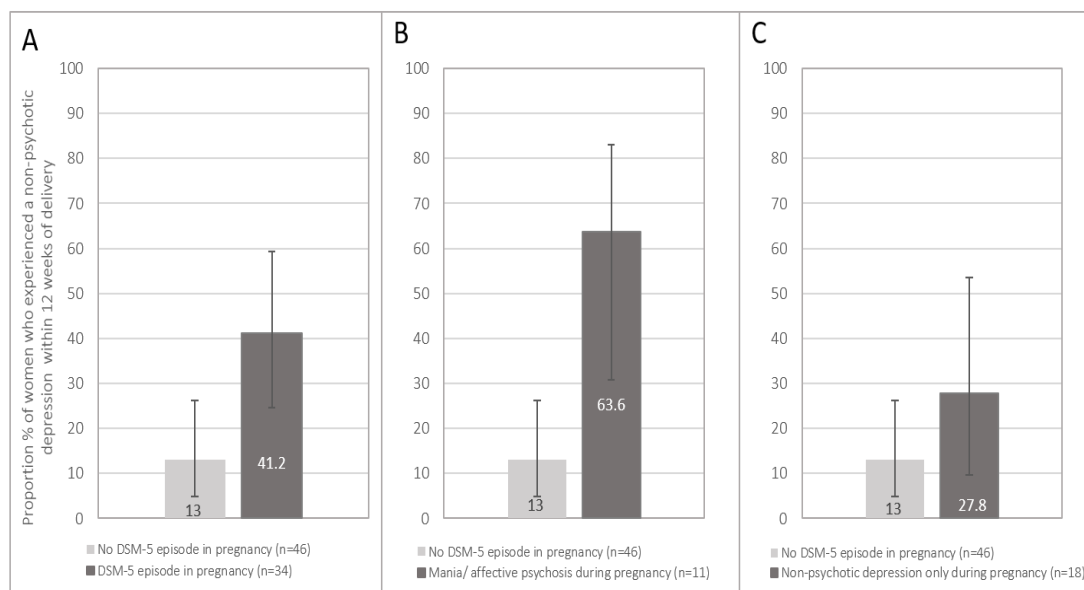
	PP	No PP	Test Statistic ^a	p-value
Smoking in pregnancy				
Present ($n=18$)	4 (22.2%)	14 (77.8%)	-	1.000 ^a
Absent ($n=64$)	16 (25.0%)	48 (75.0%)		

BD-I: Bipolar I disorder, SA-BD: Schizoaffective disorder bipolar type, PP: Postpartum psychosis; No PP: No postpartum psychosis. ^a p-value calculated by Fisher's exact test

7.4.2.4 Psychopathology within the current pregnancy

The occurrence of PP was compared between women according to the presence or absence of a DSM-5 episode of mood illness with onset during pregnancy (see **Figure 7.1a**). In addition to two women who were previously excluded from the PP/No PP groups (see page 178), an additional two women were excluded from this analysis as the occurrence of a DSM-5 episode during pregnancy could not be determined. Of the remaining sample ($n=80$), 41.2% ($n=14/34$) of women who experienced a clinically impairing episode of mood illness during pregnancy subsequently experienced PP, compared with 13.0% ($n=6/46$) of women who did not experience an affective episode during pregnancy. This finding was statistically significant ($p=0.004$; OR=4.67, 95% CI 1.56-13.97).

Figure 7.1: Occurrence of PP according to the presence/absence of a DSM-5 mood episode in pregnancy in BD-I/SA-BD women in the BDRN pregnancy sample (n=80).



BD-I: Bipolar I disorder, SA-BD: Schizoaffective disorder bipolar type, PP: postpartum psychosis. Bars represent 95% confidence intervals.

7.4.2.4.1 Polarity of mood episode in pregnancy

Further analyses were conducted to assess the relationship between the polarity of DSM-5 episode experienced in pregnancy (mania/psychosis or non-psychotic depression) and the occurrence of PP. The relationship between hypomania during pregnancy and PP was not examined, as only five women experienced the onset of hypomania during pregnancy. **Figure 7.1b** shows the proportion of women who experienced an episode of PP among women who experienced an episode of mania/affective psychosis and those who did not experience any DSM-5 mood episode during pregnancy. Women who experienced an episode of mania or affective psychosis during pregnancy were significantly more likely to experience PP compared to women who did not experience any DSM-5 mood episode during pregnancy (63.6%, n=7/11 and 13%, n=6/46; $p=0.001$, OR=11.67, 95% CI 2.61-52.21).

Episodes of PP also occurred more frequently among women who experienced episodes of non-psychotic depression during pregnancy (27.8%, n=5/18) compared to those who

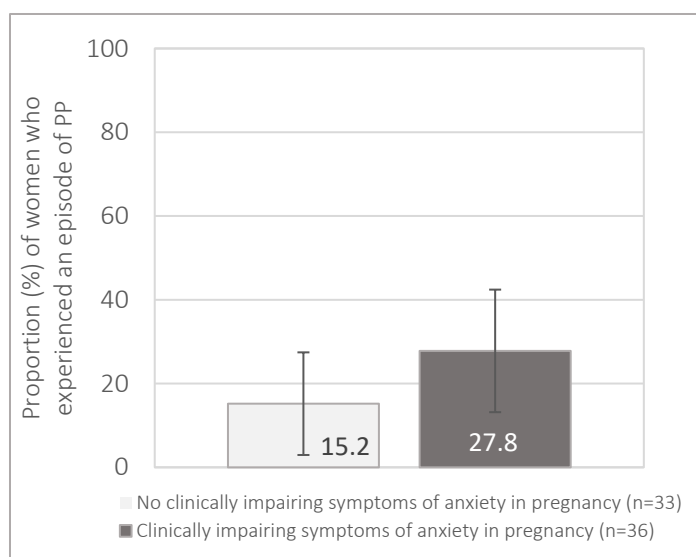
did not experience any DSM-5 mood episodes during pregnancy (13.0%, n=6/46, **Figure 7.1c**), however this finding did not reach statistical significance ($p=0.27$; OR=2.56, 95% CI 0.67-9.81). PP occurred more frequently among women who experienced an episode of mania/affective psychosis during pregnancy (63.6%) compared to those who experienced non-psychotic depression during pregnancy (27.8%), however this difference was not statistically significant ($p=0.119$; OR=4.55, 95% CI 0.92-22.63).

To investigate whether severity of BD (indicated by lifetime frequency of mood episodes) prior to pregnancy explained the relationship between mania during pregnancy and PP, the number of preconception lifetime episodes of mania and depression per illness year were compared between women who experienced an episode of mania during pregnancy and those who did not experience any mood episode during pregnancy. Compared to women who remained euthymic during pregnancy, the occurrence of mania or affective psychosis during pregnancy was significantly associated with a greater number of episodes of mania per illness year (median number 0.314 and 0.625 respectively; $p=0.009$) but not of depression (median number 0.375 and 0.555 respectively; $p=0.178$).

7.4.2.4.2 Anxiety during pregnancy

As shown in **Figure 7.2**, the occurrence of PP did not statistically differ between those who experienced clinically impairing symptoms of anxiety during pregnancy (see page 119 full definition; 27.8%, n=10/36) and those who did not (15.2%, n=5/33; $p=0.204$, OR=2.15, 95% CI 0.65-7.14).

Figure 7.2: Occurrence of PP according to the presence/absence of clinically impairing symptoms of anxiety in BD-I/SA-BD women in the BDRN pregnancy sample (n=69).



BD-I: Bipolar I disorder, **SA-BD:** Schizoaffective disorder bipolar type, **PP:** postpartum psychosis.

7.4.2.5 Obstetric factors relating to pregnancy and labour in the current perinatal period

Table 7.6 summarises the proportion of women who experienced PP according to obstetric factors relating to pregnancy and labour within the current perinatal period. No significant associations were found between any of the obstetric factors studied and the occurrence of PP. There was however an overall trend for PP to occur more frequently among women who did not experience obstetric complications during the perinatal period. Specifically, PP occurred more frequently among women who did *not* experience; any obstetric complication during pregnancy (29.8% vs 13.3%; $p=0.100$, $OR=2.76$, 95% CI 0.81-9.38), symptoms or diagnosis of pre-eclampsia (27.3% vs 7.7%; $p=0.171$, $OR=4.50$, 95% CI 0.55-37.14), pre-term delivery (25.7% vs 14.3%; $p=0.674$, $OR=2.08$, 95% CI 0.23-18.44), any obstetric complication during delivery (28.2% vs 19.4%; $p=0.375$, $OR=1.63$, 95% CI 0.55-4.80), caesarean section (28% vs 17.9%; $p=0.317$, $OR=1.79$, 95% CI 0.57-5.64) and any form of assisted delivery (31.6% vs 17.5%; $p=0.148$, $OR=2.18$, 95% CI 0.75-6.31). However, PP occurred more frequently among women

Table 7.6. Occurrence of PP according to obstetric factors relating to pregnancy and labour in the current perinatal period in BD-I/SA-BD women in the BDRN pregnancy sample (n=82)

	PP	No PP	Test statistic ^a	p-value
Pregnancy complications				
Yes (n=30)	4 (13.3%)	26 (86.7%)	χ^2 (1) 2.77	0.100
No (n=47)	14 (29.8%)	33 (70.2%)		
Pre-eclampsia				
Symptoms/diagnosis (n=13)	1 (7.7%)	12 (92.3%)	-	0.171 ^F
No symptoms or diagnosis (n=66)	18 (27.3%)	48 (72.7%)		
Induction/augmentation of labour				
Yes (n=29)	8 (27.6%)	21 (72.4%)	χ^2 (1) 0.43	0.514
No (n=43)	9 (20.9%)	34 (79.1%)		
Length of labour (hours)				
Median (IQR)	13.5 (19)	12 (17)	U= 193.00	0.898
Range	1-48	2-48	Z = -0.129	
Pre-term delivery (<37 weeks)				
Yes (n=7)	1 (14.3%)	6 (85.7%)	-	0.674 ^F
No (n=70)	18 (25.7%)	52 (74.3%)		
Delivery complications				
Yes (n=36)	7 (19.4%)	29 (80.6%)	χ^2 (1) 0.79	0.375
No (n=39)	11 (28.2%)	28 (71.8%)		
Caesarean Section				
Caesarean section (n=28)	5 (17.9%)	23 (82.1%)	χ^2 (1) 1.00	0.317
Vaginal delivery (n=50)	14 (28.0%)	36 (72.0%)		
Assisted delivery^c				
Non-assisted delivery (n=38)	12 (31.6%)	26 (68.4%)	χ^2 (1) 2.10	0.148
Assisted delivery (n=40)	7 (17.5%)	33 (82.5%)		
Age at delivery (years)				
Median (IQR)	34 (7)	35 (6)	U= 521.000,	0.447
Range	20-44	19-43	Z = -0.760	
Delivery number of current pregnancy				
Median (IQR)	2 (1)	1 (1)	U= 554.500,	0.440
Range	1-7	1-5	Z = -0.773	
Sex of baby				
Male (n=36)	6 (16.7%)	30 (83.3%)	χ^2 (1) 1.70	0.192
Female (n=41)	12 (29.3%)	29 (70.7%)		
Problems with baby at birth				
Yes (n=24)	7 (29.2%)	17 (70.8%)	χ^2 (1) 0.38	0.538
No (n=53)	12 (22.6%)	41 (77.4%)		

Numbers differ due to unknown data. **BD-I:** Bipolar I disorder, **SA-BD:** Schizoaffective disorder bipolar type, **PP:** Postpartum psychosis; **No PP:** No postpartum psychosis. ^a p-values calculated via Mann-Whitney U test for continuous variables. p-values for categorical variables calculated by Pearson's Chi-Square or Fisher's exact test. ^b Statistical comparisons not performed due to small sample sizes. ^c Assisted delivery defined as any delivery requiring forceps/ventouse or caesarean section ^F Statistic calculated by Fisher's Exact Test

whose babies experienced health problems at birth, though this difference was not significant (29.2% vs 22.6%; $p=0.538$, $OR=1.41$, 95% CI 0.41-4.19). A non-significant association was also observed between PP and deliveries to female babies (29.3%, $n=12/41$ compared to 16.7% of deliveries to male babies, $n=6/36$; $p=0.192$, $OR=2.07$, 95% CI 0.69-6.25).

7.4.2.6 Breastfeeding within the current postpartum period

As indicated in **Table 7.7**, there was no significant association between breastfeeding status (18.7%, $n=9/48$ vs 32.1%, $n=9/28$; $p=0.185$, $OR=0.49$, 95% CI 0.17-1.43) or the duration of breastfeeding and the occurrence of PP (median 1.3 vs 6 weeks, $p=0.598$).

Table 7.7: Occurrence of PP according to breastfeeding status in the current postpartum period among BD-I/SA-BD women in the BDRN pregnancy sample ($n=76$)

	PP	No PP	Test statistic ^a	p-value
Breastfed baby				
Yes ($n=48$)	9 (18.7%)	39 (81.3%)	$\chi^2 (1) 1.76$	0.185
No ($n=28$)	9 (32.1%)	19 (67.9%)		
Duration of breastfeeding (weeks)				
Median (IQR)	1.3 (11)	6.0 (10.75)	U= 140.500, Z = -0.640	0.598
Range	0.5-12	0.1-12		

Numbers differ due to unknown data. **BD-I:** Bipolar I disorder, **SA-BD:** Schizoaffective disorder bipolar type, **PP:** Postpartum psychosis; **No PP:** No postpartum psychosis. ^a p-values calculated via Mann-Whitney U test for continuous variables. P-values for categorical variables calculated by Pearson's Chi-Square.

7.4.2.7 Sleep factors relating to pregnancy and labour in the current perinatal period

Table 7.8 summarises the proportion of women who experienced PP according to sleep related factors within the current perinatal period. Women who reported missing at least one complete night of sleep due to labour and delivery (defined as at least one

complete night without any sleep between the onset of labour and the first night's sleep) were significantly more likely to experience PP (43.3%, n=13/30) compared to those who did not miss a complete night's sleep (12.5%, n=4/32; p=0.007, OR=5.35, 95% CI 1.50-19.11).

Table 7.8: Occurrence of PP according to the presence/absence of sleep factors within the current perinatal period in BD-I/SA-BD women in the BDRN pregnancy sample (n=82)

	PP	No PP	Test Statistic ^a	p-value
Sleep quality in the 3rd trimester				
Good/very good (n=20)	6 (30.0%)	14 (70.0%)	$\chi^2(1) 0.25$	0.875
Fairly bad/very bad (n=28)	9 (32.1%)	19 (67.9%)		
Day/night time delivery				
Day time delivery (n=42)	11(26.2%)	31 (73.8%)	-	0.661 ^f
Night time delivery (n=8)	1 (12.5%)	7 (87.5%)		
Any sleep loss during labour				
Yes (n=38)	14 (36.8%)	24 (63.2%)	$\chi^2(1) 1.71$	0.191
No (n=16)	3 (18.8%)	13 (81.3%)		
At least one complete night of missed sleep during labour				
Yes (n=30)	13 (43.3%)	17 (56.7%)	$\chi^2(1) 7.40$	0.007
No (n=32)	4 (12.5%)	28 (87.5%)		

Numbers differ due to unknown data. **BD-I:** Bipolar I disorder, **SA-BD:** Schizoaffective disorder bipolar type, **PP:** Postpartum psychosis; **No PP:** No postpartum psychosis. ^a p-values for categorical variables calculated by Pearson's Chi-Square or Fisher's exact test. ^f Statistic calculated by Fisher's Exact Test

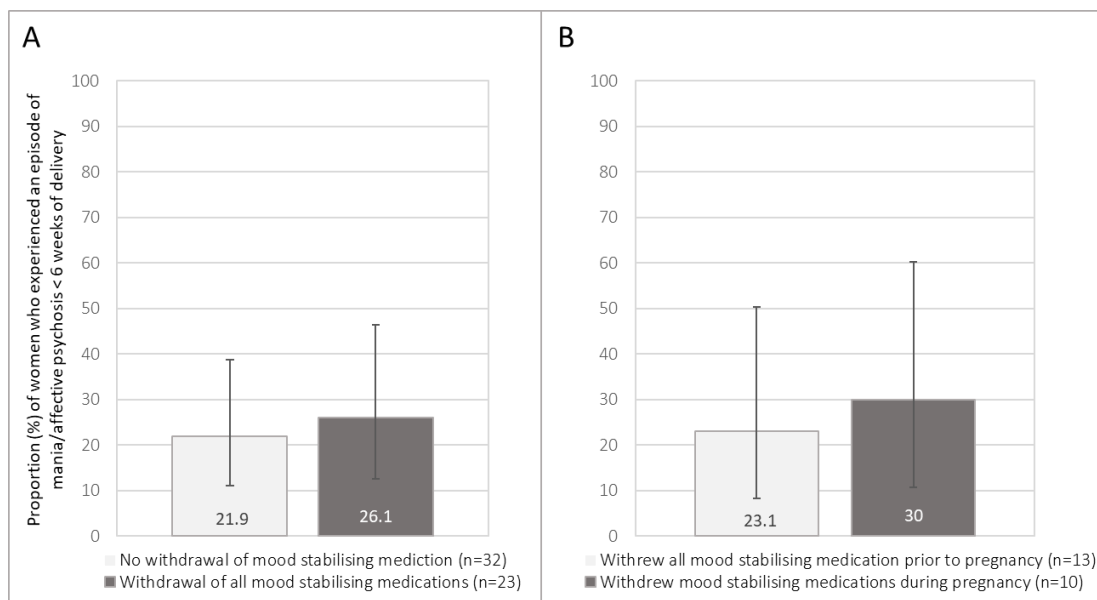
However, the proportion of women who experienced PP was comparable between those who self-reported their quality of sleep within the third trimester to be 'good/very good' (30.0%, n=6/20) and 'fairly bad/very bad' (32.1%, n=9/28; p=0.875, OR=0.91, 95% CI 0.26-3.13). There was also no significant difference in the occurrence of PP between women who gave birth during the daytime (26.2%, n=11/42) versus the night time (12.5%, n=1/8; p=0.661, OR 2.48 95% CI 0.27-22.54) or between those who reported *any* sleep lost due to labour (36.8%, n=14/38) and those who did not report this (18.8%, n=3/16; p=0.191, OR=2.53, 95% CI 0.61-10.44).

7.4.2.8 Prophylactic mood stabilising medication in the perinatal period

7.4.2.8.1 Withdrawal of mood stabilising medication before and during pregnancy

As discussed previously, for reasons which include teratogenicity of medications, many women with BD choose to withdraw mood stabilising medication during the perinatal period. Given that the purpose of prophylactic mood stabilisers is primarily to prevent manic episodes, the influence of withdrawal of mood stabilising medications (lithium, anticonvulsants, typical or atypical antipsychotics) in the six months prior to or during pregnancy (that were not recommenced at any time during pregnancy) on risk for PP was examined. Of 55 women with BD-I/SA-BD known to be using mood stabilising medication in the six months prior to pregnancy, withdrawal of mood stabilising medications was not associated with an increased occurrence of PP (26.1%, n=6/23 vs 21.9%, n=7/32 respectively; p=0.72, OR=1.26, 95% CI 0.36-4.41, **Figure 7.3a**).

Figure 7.3: Occurrence of PP according to withdrawal of mood stabilising medication during the perinatal period in BD-I/SA-BD women in the BDRN pregnancy sample (n=55).



BD-I: Bipolar I disorder, **SA-BD:** Schizoaffective disorder bipolar type, **PP:** postpartum psychosis. Bars represent 95% confidence intervals.

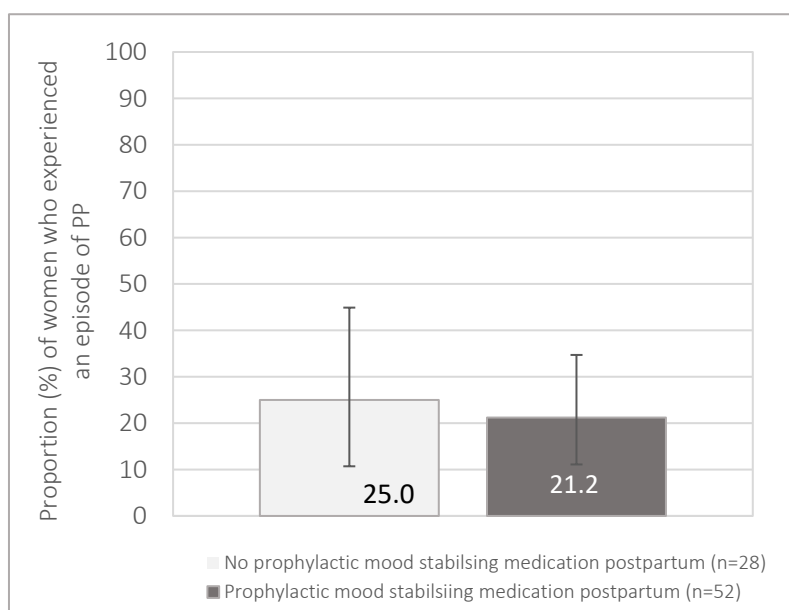
Of women who withdrew all mood stabilising medication (n=23), there was no significant difference in the occurrence of PP between women who withdrew mood

stabilising medications in the six months prior to pregnancy compared to those who withdrew mood stabilising medication during pregnancy (23.1%, $n=3/13$ vs 30.0%, $n=3/10$ respectively; $p=1.00$, $OR=1.43$, 95% CI 0.22-9.26, **Figure 7.3b**).

7.4.2.8.2 Prophylactic mood stabilising medication in the postpartum period

Figure 7.4 shows the proportion of women who experienced PP among those who did and did not use prophylactic medication as a mood stabiliser in the postpartum period (see page 120 for full definition). Two women were excluded from this analysis as it was not clear whether medications used postpartum were commenced prophylactically or as treatment for onset of mood symptoms.

Figure 7.4: Occurrence of PP according to use of any prophylactic medication as a mood stabiliser in the postpartum period in BD-I/SA-BD women in the BDRN pregnancy sample



BD-I: Bipolar I disorder, **SA-BD:** Schizoaffective disorder bipolar type, **PP:** postpartum psychosis. Bars represent 95% confidence intervals.

Within the remaining sample ($n=80$), 25.0% ($n=7/28$) of women who were not using prophylactic medication as a mood stabiliser experienced an episode of PP, compared to 21.2% ($n=11/52$) of those who were. Use of prophylactic mood stabilising medication

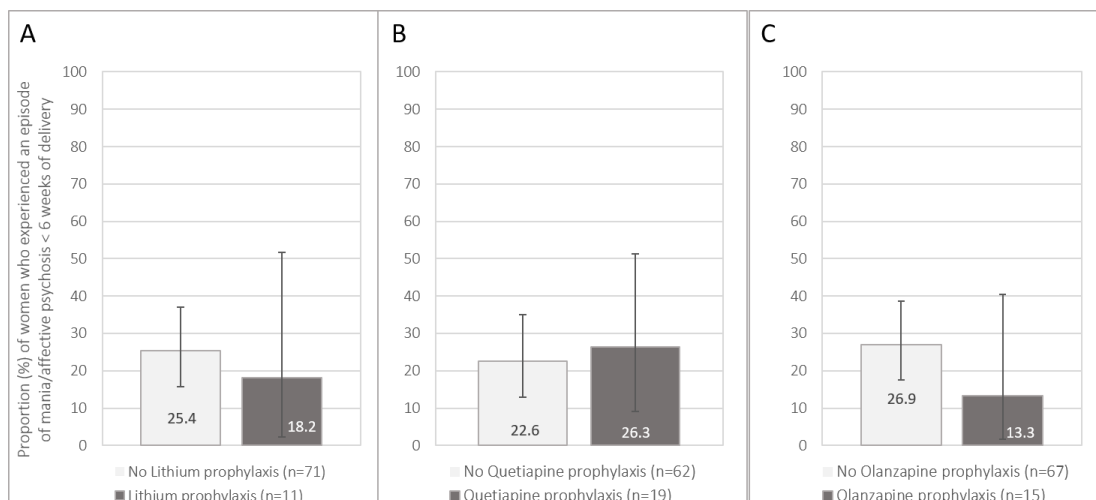
in the postpartum period was not significantly associated with a reduced likelihood of developing PP ($p=0.69$, $OR=0.80$, $95\% CI 0.27-2.38$).

7.4.2.8.3 Type of prophylactic mood stabilising medication in the postpartum period

To examine whether use of the three most commonly prescribed medications for postpartum prophylaxis of mania was associated with a reduced recurrence of PP, further statistical comparisons were made between groups of women who did and did not use the following medications: lithium, quetiapine and olanzapine. As highlighted in the previous section, two women were excluded from the overall analysis assessing postpartum prophylaxis for PP (due to inability to determine whether medication was prescribed prophylactically or as treatment). However, of these, one woman could be included in the control group for all analyses reported here, given that she had not used any of the specified medications during the postpartum period. The second woman was excluded only from analyses assessing the use of prophylactic quetiapine in the postpartum period (as she had only been using quetiapine, but it was not clear if this was commenced prophylactically or as treatment). **Figure 7.5** shows the proportion of women who experienced PP according to use of each of the three medications.

Women who were using quetiapine (**Figure 7.5b**) for postpartum prophylaxis of mood episodes were not significantly less likely to experience PP compared to women who were not using this medication (26.3%, $n=5/19$ vs 22.6%, $n=14/62$ respectively; $p=0.76$, $OR=1.22$, $95\% CI 0.38-4.00$). As shown in **Figure 7.5a** and **Figure 7.5c**, there were trends for women who were using lithium or olanzapine to be less likely to experience PP compared to women who were not using these medications, however, neither difference was statistically significant (18.2%, $n=2/11$ vs 25.4%, $n=18/71$; $p=1.00$, $OR=0.65$, $95\% CI 0.13-3.32$ and 13.3%, $n=2/15$ vs 26.9%, $n=18/67$; $p=0.34$, $OR=0.42$, $95\% CI 0.09-2.04$ respectively).

Figure 7.5 Occurrence of PP according to prophylactic use of the most commonly prescribed mood stabilising medications in the postpartum period in BD-I/SA-BD women in the BDRN pregnancy sample (n=82)



BD-I: Bipolar I disorder, **SA-BD:** Schizoaffective disorder bipolar type, **PP:** postpartum psychosis. Bars represent 95% confidence intervals.

7.4.2.8.4 Timing of use of prophylactic mood stabilising medication

Among women who used medication for postpartum prophylaxis of mood episodes (n=52), similar rates of recurrence of PP were observed between women who had continued mood stabilising medication from pregnancy into the postpartum period (20.0%, n=8/40) and those who had commenced medication following delivery (25.0%, n=3/12). There was no significant difference between the two groups ($p=0.70$, $OR=1.33$, 95% CI 0.29-6.09).

7.4.2.9 Section summary

In this section, I presented results of univariate analyses investigating the relationship between a range of within-pregnancy factors and PP among women with BD-I/SA-BD in the BDRN pregnancy sample. Findings indicated episodes of mania or affective psychosis during pregnancy and the loss of at least one complete night of sleep during labour to significantly increase risk of PP by 11.67 and 5.35 times respectively (Table 7.9).

Table 7.9: Summary of within-pregnancy variables significantly associated with the occurrence of PP in BD-I/SA-BD women in the BDRN pregnancy sample

	Occurrence of PP % (n)	P-value	OR (95% CI)
DSM-5 episode of mania/affective psychosis in pregnancy			
Mania/affective psychosis (n=11)	63.6% (7)	0.001	11.67 (2.61-52.21)
No DSM-5 episode (n=46)	13% (6)		
At least one complete night of missed sleep during labour			
Present (n=30)	43.3% (13)	0.007	5.35 (1.50-19.11)
Absent (n=32)	12.5% (4)		

BD-I: bipolar I disorder, **SA-BD:** schizoaffective disorder bipolar type, **PP:** postpartum psychosis. **OR:** Odds-ratios, **95% CI:** 95% confidence intervals.

Due to limitations of multiple testing, it is important to consider that these findings may be at increased risk of type-I error. If Bonferroni Correction is applied to these analyses ($p=0.05/51$), the observed relationships would no longer reach the adjusted significance level of $p=0.0009$. Nevertheless, given the exploratory nature of this study, this significance level was deemed too conservative and thus a p-value of 0.05 was considered acceptable. In the following section, I will further examine these potential relationships using multivariate logistic regression models, controlling for lifetime correlates found to be associated with PP within the BDRN retrospective sample.

Notably, there were also several trends of within-pregnancy factors influencing risk of PP that did not reach statistical significance (**Table 7.10**). Factors indicated to non-significantly increase risk of PP included:

- an unplanned pregnancy
- occurrence of any adverse life event during pregnancy (and specifically the occurrence of a serious illness or injury or a bereavement of a close friend or relative)
- clinically impairing symptoms of anxiety during pregnancy
- no obstetric complications during pregnancy or delivery (and specifically, no symptoms or diagnosis of pre-eclampsia, no pre-term delivery and a non-assisted delivery)
- vaginal delivery
- delivery during the day-time
- loss of any sleep attributed to labour and delivery
- the birth of a female baby

The following within-pregnancy factors showed a trend for reducing risk of PP:

- Use of prophylactic lithium during the postpartum period
- Use of prophylactic olanzapine during the postpartum period

These factors will not be assessed further in multivariate models.

Table 7.10: Within-pregnancy factors demonstrating a trend towards an association with PP in BD-I/SA-BD women in the BDRN pregnancy sample

	PP % (n)	P-value	OR (95% CI)	Power (%)	Sample size required *
Psychosocial variables					
Planned pregnancy					
Planned (n=51)	23.5% (12)	0.322 ^F	2.17 (0.64-7.33)	20%	n=248
Unplanned (n=15)	40.0% (6)				
Adverse life events during pregnancy					
Any adverse life event					
Any event (n=46)	28.3% (13)	0.283 ^x	1.97 (0.56-6.88)	38%	n=404
No event (n=24)	16.7% (4)				
Serious illness or injury					
Yes (n=6)	50.0% (3)	0.137 ^F	3.77 (0.68-20.91)	32%	n=84
No (n=62)	21.0% (13)				
Bereavement of close friend/relative					
Yes (n=13)	38.5% (5)	0.274 ^F	2.77 (0.67-8.96)	23%	n=196
No (n=54)	20.4% (11)				
Psychopathology during pregnancy					
Anxiety during pregnancy^a					
Present (n=36)	27.8% (10)	0.204 ^x	2.15 (0.65-7.14)	43%	n=332
Absent (n=33)	15.2% (5)				
Non-psychotic depression during pregnancy					
Yes (n=18)	27.8% (5)	0.270 ^x	2.56 (0.67-9.81)	31%	n=230
No (n=46)	13.0% (6)				
Obstetric factors					
Obstetric complications during pregnancy					
Yes (n=30)	13.3% (4)	0.100	2.76 (0.81-9.38)	38%	n=203
No (n=47)	29.8% (14)				
Symptoms/diagnosis of pre-eclampsia					
Symptoms/diagnosis (n=13)	7.7% (1)	0.171	4.50 (0.55-37.14)	26%	n=116
No symptoms or diagnosis (n=66)	27.3% (18)				
Pre-term delivery (<37 weeks)					
Yes (n=7)	14.3% (1)	0.674	2.08 (0.23-18.44)	6%	n=384
No (n=70)	25.7% (18)				
Any delivery complications					
Yes (n=36)	19.4% (7)	0.375	1.63 (0.55-4.80)	5.6%	n=732
No (n=39)	28.2% (11)				
Caesarean section					
Caesarean section (n=28)	17.9% (5)	0.317	1.79 (0.57-5.64)	16%	n=542
Vaginal delivery (n=50)	28.0% (14)				
Assisted delivery					
Non-assisted delivery (n=38)	31.6% (12)	0.148 ^x	2.18 (0.75-6.31)	30%	n=290
Assisted delivery (n=40)	17.5% (7)				

BD-I: bipolar I disorder, **SA-BD:** schizoaffective disorder bipolar type, **PP:** postpartum psychosis. **OR:** Odds-ratios, **95% CI:** 95% confidence intervals. * Minimum total sample size estimation (based on observed effect size) to achieve 80% power to detect a statistical difference using a two-tailed hypothesis with a significance value of $p < 0.05$. ^a DSM-5 clinically impairing symptoms of anxiety during pregnancy. ^F P-value calculated by Fisher's Exact Test. ^x P-value calculated by Pearson's Chi Square

Table 7.10 continued: Within-pregnancy factors demonstrating a trend towards an association with PP in BD-I/SA-BD women in the BDRN pregnancy sample

	PP % (n)	P-value	OR (95% CI)	Power (%)	Sample size required*
Sex of baby					
Male (n=36)	16.7% (6)	0.192 ^x	2.07 (0.69-6.25)	44%	n=348
Female (n=41)	29.3% (12)				
Labour/delivery related sleep factors					
Day/night time delivery					
Day time delivery (n=42)	26.2% (11)	0.661 ^f	2.48 (0.27-22.54)	2%	n=258
Night time delivery (n=8)	12.5% (1)				
Any sleep loss during labour					
Yes (n=38)	36.8% (14)	0.191 ^x	2.53 (0.61-10.44)	46%	n=192
No (n=16)	18.8% (3)				
Prophylactic mood stabilising medication in the postpartum period					
Prophylactic lithium					
Prophylactic lithium (n=11)	18.2% (2)	1.000 ^f	1.53 (0.30-7.74)	2%	n=1030
No prophylactic lithium (n=71)	25.4% (18)				
Prophylactic olanzapine					
Prophylactic olanzapine (n=15)	13.3% (2)	0.340 ^f	2.39 (0.49-11.64)	11%	n=270
No prophylactic olanzapine (n=67)	26.9% (18)				

BD-I: bipolar I disorder, **SA-BD:** schizoaffective disorder bipolar type, **PP:** postpartum psychosis. **OR:** Odds-ratios, **95% CI:** 95% confidence intervals. * Minimum sample size estimation (based on observed effect size) to achieve 80% power to detect a statistical difference using a two-tailed hypothesis with a significance value of $p < 0.05$. ^a DSM-5 clinically impairing symptoms of anxiety during pregnancy. ^f P-value calculated by Fisher's Exact Test. ^x P-value calculated by Pearson's Chi Square

7.4.3 Regression model of within-pregnancy potential risk factors for postpartum psychosis

The presence or absence of mania or affective psychosis during pregnancy was assessed as a predictor of PP in a binary logistic regression model with the presence/absence of PP as the outcome variable. The loss of at least one complete night of sleep due to labour and delivery was excluded from the model due to the limited number of cases. A significance level of $p < 0.05$ was considered an acceptable cut-off for inclusion of within-pregnancy predictor variables. Potential lifetime predictors found to be significantly associated with PP within our BDRN retrospective sample were also included in the model as covariates (**Table 7.11**), with the exception of preconception history of psychotic symptoms due to evidence of multicollinearity (with preconception history of PP). An additional regression model was performed to assess potential moderating effects of prophylactic mood stabilising medication in the postpartum period on the potential relationship between mania and affective psychosis during pregnancy and the occurrence of PP (summarised in section 7.4.3.2 and in **Table 7.13**).

Table 7.11: Lifetime covariates included in the within-pregnancy regression model due to their association with PP in the BDRN retrospective sample

<i>Lifetime covariate</i>	Relevant citation demonstrating significant relationship between lifetime factor and PP
Preconception lifetime history of PP within 6 weeks	Di Florio et al. (2018); Robertson et al. (2005)
Family history of postpartum mood illness in 1st degree relative	Jones and Craddock (2001)
Sleep loss as a lifetime preconception self-reported trigger of manic episodes	Lewis et al. (2017)
Primiparous at conception of current pregnancy	Di Florio et al. (2014)

7.4.3.1 Regression model of within-pregnancy potential risk factors controlling for lifetime correlates of PP

The relationship between mania/affective psychosis with onset during pregnancy (with no mania/affective psychosis as the control group) and PP was assessed in a regression

model, which also included the following lifetime covariates (meeting recommendations of a minimum of 10 cases per independent variable to prevent overfitting of the data, Peduzzi et al. 1996): preconception lifetime history of PP (including women who were primiparous, coded as no lifetime history of PP to maximise the sample size), primiparity at time of conception of the current pregnancy (yes/no), family history of postpartum affective illness in a first degree relative (present/absent) and sleep loss as a self-reported lifetime ever trigger for preconception episodes of mania (present/absent). Results of this model are summarised below in **Table 7.12**.

After controlling for lifetime correlates associated with PP in the BDRN retrospective sample, onset of mania or affective psychosis during pregnancy ($\beta=2.803$, $p=0.002$, OR 16.49, 95% CI 2.76-98.48) significantly predicted PP within six weeks of delivery. This model explained 35.1% of the variance of PP (Nagelkerke R Square) and correctly classified 82.6% of cases ($p=0.002$).

Table 7.12: Regression model predicting PP within the BDRN pregnancy sample

	Wald	DF	p-value	OR (95% CI)
DSM-5 episode of mania/affective psychosis in pregnancy	9.449	1	0.002	16.49 (2.76-98.48)
Preconception lifetime history of PP within 6 weeks	3.385	1	0.066	5.67 (0.89-35.99)
Family history of postpartum mood illness	1.612	1	0.204	3.07 (0.54-17.32)
Primiparous at conception of current pregnancy	0.302	1	0.583	1.61 (0.30-8.71)
Sleep loss as a trigger for preconception mania	2.040	1	0.153	0.33 (0.07-1.51)

DF: degrees of freedom. OR: odds ratio. 95% CI: 95% confidence intervals

7.4.3.2 Regression model adjusting for prophylactic mood stabilising medication in the postpartum period

After further adjusting for use of prophylactic mood stabilising medication in the postpartum period, mania or affective psychosis during pregnancy ($\beta=2.72$, $p=0.006$, OR 15.24, 95% CI 2.23-104.32) and preconception history of PP significantly predicted the

occurrence of PP within the current perinatal period ($\beta=2.75$, $p=0.031$, OR 15.58, 95% CI 1.29-188.18, see **Table 7.13**). This model explained 38.2% of the variance (Nagelkerke R Square) of PP and correctly classified 83.6% of cases ($p=0.003$).

Table 7.13: Regression model of predictors of PP within the BDRN pregnancy sample after adjustment for prophylactic mood stabilising medication in the postpartum period

	Wald	DF	p-value	OR (95% CI)
Preconception lifetime history of PP within 6 weeks	4.656	1	0.031	15.58 (1.29-188.78)
DSM-5 episode of mania/affective psychosis in pregnancy	7.707	1	0.006	15.24 (2.23-104.32)
Primiparous at conception of current pregnancy	1.591	1	0.207	4.70 (0.42-51.96)
Family history of postpartum mood illness	2.090	1	0.148	3.66 (0.63-21.27)
Prophylactic mood stabilising medication in postpartum	0.264	1	0.607	0.67 (0.14-3.16)
Sleep loss as a lifetime ever trigger of preconception mania	1.094	1	0.296	0.44 (0.09-2.06)

DF: degrees of freedom. OR: odds ratio. 95% CI: 95% confidence interval

7.4.4 Predictors of PP and their relationship to postpartum non-psychotic depression

To further examine the specificity of significant predictors of PP, the relationship between the occurrence of mania/affective psychosis in pregnancy, preconception history of PP and postpartum non-psychotic depression was also assessed. For these analyses, outcomes were defined among women with a preconception history of BD-I/SA-BD as:

- a) No DSM-5 mood episode within three months of delivery (no postpartum mood episode 'No PME' group, $n=47$)
- b) An episode of non-psychotic depression within three months of delivery (PND only group, $n=10$).

Women who experienced an episode of PP or of postpartum hypomania were excluded from these analyses ($n=25$). A broader temporal definition of the postpartum period was used to capture episodes of PND which had a wider distribution of onset. As shown

in **Table 7.14** there was a trend for women who experienced an episode of mania or affective psychosis during pregnancy (66.7%, n=2/3) to be more likely to experience an episode of PND compared to women who did not experience any DSM-5 mood episode during pregnancy (10.8%, n=4/37). However, due to small sample sizes, it was not possible to statistically compare this difference. Preconception history of PP (including women who were primiparous) was not significantly associated with PND (Fisher's exact test, p=1.000, OR=0.93, 95% CI 0.17-5.06).

Table 7.14: Predictors of PP and their relationship to PND in BD-I/SA-BD women in the BDRN pregnancy sample

	PND	No PME	Test statistic	p-value ^a
DSM-5 episode of mania/affective psychosis in pregnancy				
Present (n=3)	2 (66.7%)	1 (33.3%)	-	. ^b
Absent (n=37)	4 (10.8%)	33 (89.2%)		
Preconception lifetime history of PP within 6 weeks				
Present (n=12)	2 (16.7%)	10 (83.3%)	-	1.000
Absent (n=45)	8 (17.8%)	37 (82.2%)		

Numbers differ due to unknown data. **BD-I:** bipolar I disorder, **SA-BD:** schizoaffective disorder bipolar type, **PND:** Postpartum non-psychotic depression with onset within three months of delivery. **No PME:** No occurrence of a DSM-5 mood episode with onset within three months of delivery, ^a p-values calculated using Fisher's Exact Test. ^b Statistical comparisons could not be conducted due to small sample sizes.

7.5 Summary of findings

This study investigated potential within-pregnancy risk factors for the occurrence of PP in women with BD-I and SA-BD using a prospective follow-up design. Key findings from these analyses are summarised below.

- Univariate analyses revealed episodes of mania or affective psychosis during pregnancy and the loss of at least one complete night of sleep during labour to be significantly associated with the occurrence of PP.
- In contrast, there was no significant association between within-pregnancy psychosocial or obstetric factors and the occurrence of PP.
- Use of prophylactic mood stabilising medications in the postpartum period was not significantly associated with a reduced risk of PP.
- Over and above known associations between lifetime factors and PP (identified in the BDRN retrospective sample), episodes of mania or affective psychosis with onset during pregnancy significantly predicted PP, increasing risk more than 16 times. After further adjusting for the use of prophylactic mood stabilising medication, women who experienced episodes of mania/affective psychosis during pregnancy remained at least 15 times more likely to experience PP than women who did not experience these episodes during pregnancy.

7.6 Discussion

This chapter aimed to investigate potential within-pregnancy risk factors for PP, over and above known associations between lifetime correlates and PP (such as a preconception history of PP) in a sample of pregnant women with BD-I/SA-BD using a prospective follow-up design. Results of these analyses will be discussed further in this section and considered in the context of the existing literature. Strengths and limitations of the study and the implications of these findings for clinical practice and future research will be presented.

7.6.1 Psychopathology during pregnancy within the current perinatal period

7.6.1.1 DSM-5 recurrence of affective episodes

In this study, antenatal recurrence of a DSM-5 mood episode, specifically of mania or affective psychosis was associated with a more than 15 times increased risk of PP. Episodes of mania or affective psychosis during pregnancy remained a significant risk factor for PP, even after controlling for the use of prophylactic mood stabilising medication within the postpartum period. The relationship between antenatal mood episodes and PP appears unique to episodes of mania or affective psychosis, given that although a trend was observed, no significant association was found between recurrence of non-psychotic depression during pregnancy and of PP.

These findings are consistent with a number of studies indicating high rates of postpartum mood episodes among women who experience recurrence during pregnancy (Akdeniz et al. 2003; Bergink et al. 2012; Doyle et al. 2012; Freeman et al. 2002; Viguera et al. 2011), but this study is the first to demonstrate a specific association between mania in pregnancy and the occurrence of PP. It could be suggested that women who experienced PP had not fully recovered from episodes of mania or psychosis occurring during pregnancy, thus reflecting a continuation of illness

as opposed to the onset of a new episode in the postpartum period. However, the use of a prospective design allowed for the onset and duration of each episode to be more accurately determined than in retrospective studies. In addition to each woman's self-report of perinatal psychopathology, data were further supplemented by case-note review and clinician questionnaires. In particular, clinicians were specifically asked to confirm if a postpartum recurrence was a continuation of an episode with onset during pregnancy. Using these methods, the clear onset/absence of a DSM-5 mood episode in the postpartum period could be determined and independently agreed by consensus in nearly all cases. Additionally, postpartum episodes identified as having onset during pregnancy or those in which onset could not clearly be established were excluded from these analyses.

The association between severe antenatal and postpartum recurrence may also suggest that women who experienced episodes within both phases of the perinatal period had a more severe course of BD overall, marked by an increased vulnerability to more frequent episodes of mania. When examining this further, compared to women who remained well during pregnancy, mania or psychosis during pregnancy was significantly associated with more frequent lifetime episodes of mania prior to pregnancy, but not of depression. Notably however, I also observed trends for episodes of PP to occur more frequently among women who experienced non-psychotic depression during pregnancy, and for episodes of PND to occur more frequently among women who experienced episodes of mania/affective psychosis during pregnancy. This would suggest that an increased susceptibility to mania in general is unlikely to explain the specific relationship between mania/affective psychosis during pregnancy and subsequent PP.

If either factor (i.e. an increased vulnerability to mania or unremitted antenatal mania) were accounting for the observed relationship between antenatal mania/psychosis and PP, we might expect episodes of mania to occur at similar rates across pregnancy and the postpartum period. Yet in this sample, as in others (Di Florio et al. 2013; Munk-

Olsen et al. 2009; Viguera et al. 2011), episodes of mania/affective psychosis were more prevalent following childbirth compared to during pregnancy (Chapter 6, section 6.4). Together, this might suggest that the aetiology of PP is distinct from episodes of mania occurring within-pregnancy. Regardless of the nature of the relationship, the onset of mania or affective psychosis during pregnancy may be an important risk marker of PP in women with BD. This finding also further highlights the importance of planning pregnancy in BD; not only is the risk of recurrence high antenatally but prevention of these episodes may also be crucial for more favourable outcomes postpartum.

7.6.1.2 Anxiety

This study was the first to investigate the relationship between pathological anxiety during pregnancy and risk of PP within BD. Though a significant relationship was not found in this study, women reporting clinically impairing symptoms of anxiety during pregnancy were more likely to experience PP compared to women who did not have such symptoms. These findings are consistent with one other prospective study which has also shown anxiety during pregnancy to significantly increase risk of broadly defined PP (affective or non-affective) within the first three weeks of delivery (McNeil 1988b). Though the relationship between antenatal anxiety and PP was not specifically assessed within women with BD, the majority of episodes with early onset (within 3 weeks postpartum) were predominantly affective. Given that the same relationship was not observed in relation to later onset episodes (which more frequently presented as non-affective), this would suggest a specific relationship between antenatal anxiety and affective PP in particular.

Nonetheless, information regarding anxiety was not gathered for 13 (of 82) women recruited during pregnancy to the sample examined within this thesis (due to this measure being introduced later in the period of data collection). This analysis was therefore underpowered at 43% to detect a statistically significant difference in the occurrence of PP according to the presence or absence of pathological anxiety during

pregnancy. Based on effect sizes within the current sample, sample size calculations indicated at least 332 women would be required in future analyses to achieve sufficient power of 80% to detect a between group difference.

7.6.1.3 Sleep factors within the current perinatal period

7.6.1.3.1 Sleep loss due to labour and delivery

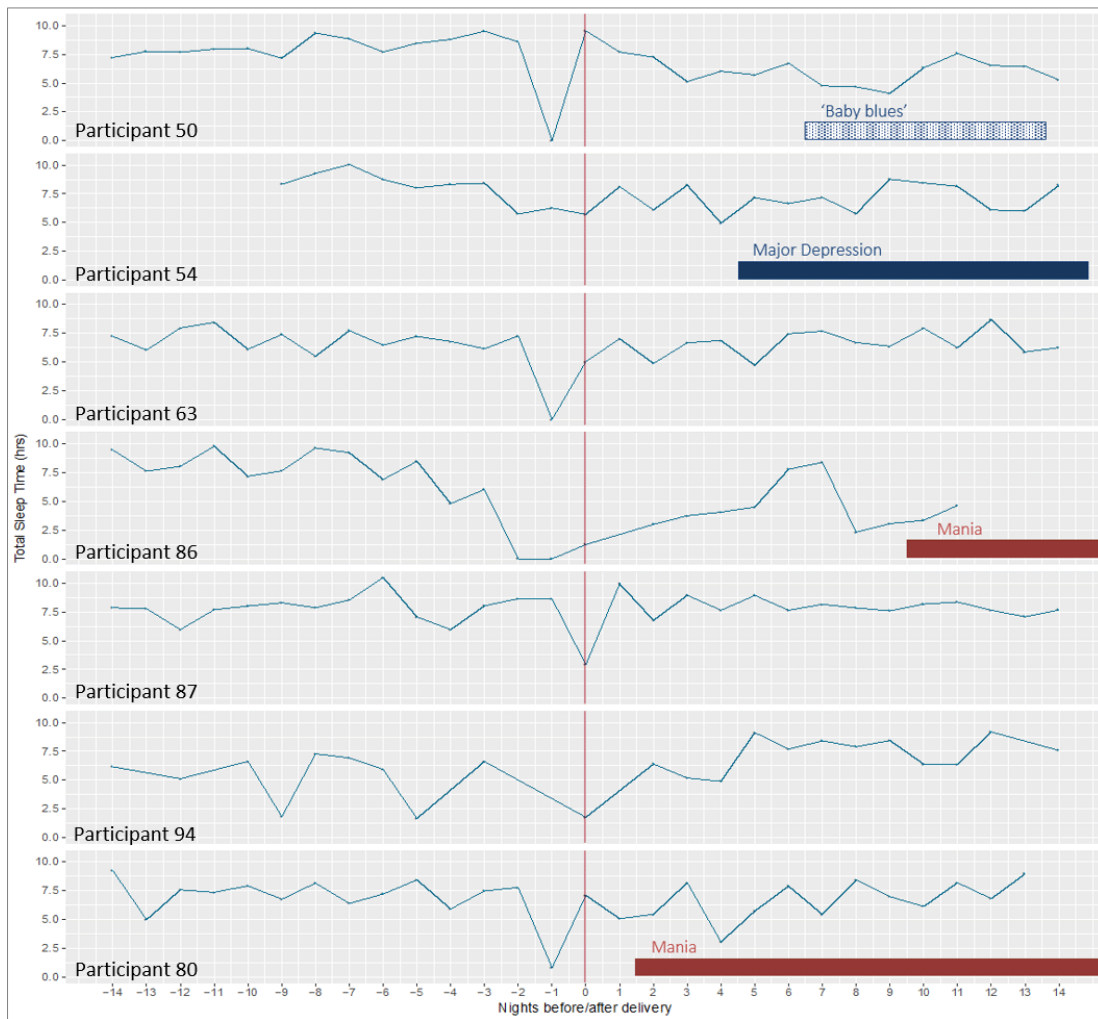
Within this sample, I observed a trend for episodes of PP to occur more frequently among women who self-reported sleep loss (of any duration) during labour compared to those who reported no missed sleep during this period. Furthermore, women who reported losing at least one complete night of sleep were significantly more likely to develop PP compared to women who did not report this. As this data was not gathered for 20 women with BD-I/SA-BD (due to this measure being introduced later in the period of data-collection), sample sizes were too small to assess the predictive effect of this factor for episodes of PP in multivariate analyses, over and above other known risk factors (such as preconception history of PP and FH of postpartum affective illness). Nonetheless, these initial findings might suggest that acute sleep loss experienced during delivery and the early postpartum is an important triggering factor in the onset of PP. If replicated, this finding would also be consistent with evidence indicating sleep loss to also be a trigger of non-postpartum manias (Bauer et al. 2006; Leibenluft et al. 1996; Lewis 2017).

A limitation of this analysis could be that it was difficult for women to distinguish between insomnia as a prodromal symptom of mania from sleep lost specifically due to labour and delivery, particularly in cases of very early onset PP. This is a common limitation of any research which aims to assess the role of self-reported sleep loss in the triggering of manic episodes, given that sleep disturbance is likely both a trigger and symptom of psychopathology. However, in an attempt to distinguish between the early onset of symptoms and sleep loss due to labour/delivery, women were made aware at interview that the question referred specifically to sleep lost due to labour and delivery.

A small subset of women in the BDRN pregnancy sample (n=7) also participated in an actigraphy study during the perinatal period, in which the aim was to assess the causal association, if any, between objectively measured sleep in late pregnancy, the immediate postpartum period and postpartum psychiatric outcomes (Lewis 2017). Data in the current study regarding sleep loss during labour was further validated and corroborated by objective data gathered by Lewis (2017) within some women.

Figure 7.6 (adapted from Lewis 2017) shows the number of hours of sleep per night across the perinatal period (from late pregnancy to the early postpartum) and postpartum psychiatric outcomes in the seven women for whom actigraphy data was collected. For example, the objective measure indicated that participant 86 missed two complete night's sleep prior to the day of delivery (i.e. obtained 0 hours sleep for two consecutive days) with her delivery being followed by an onset of PP. In almost all women (participants 50, 54, 63, 86, 87 and 94), actigraphy data was highly correlated with self-reported sleep data from the current study, irrespective of postpartum psychiatric outcome. Data was not wholly consistent across measures for only one woman (participant 80). In this case, the participant reported missing one complete night's sleep during labour and delivery, while actiwatch data indicated that she slept for approximately one hour the night before delivery. However, as noted by Lewis (2017), actiwatch data typically measures activity and not sleep, therefore is known to overestimate sleep during periods of rest or sitting still. Given that participant 80 self-reported a complete loss of sleep, it is likely this woman received very little, if any sleep during the night indicated. It is also interesting to note that in the two women who experienced an episode of PP (Participants 86 and 80), number of hours of sleep subsequently increased in the immediate period following delivery and the acute period of sleep loss. This would further suggest that women were in fact reporting sleep loss attributed to the period of labour and delivery, as opposed to the onset of manic symptoms.

Figure 7.6: Sleep actigraphy data for the perinatal period in a subset of women in the BDRN prospective sample (n=7), adapted from Lewis (2017)



Interestingly, I also observed a trend for episodes of PP to occur more frequently among women who had given birth during the day time, though no significant association was found between length of labour and occurrence of PP. These findings are in contrast to those of a previous study (Sharma, Smith and Khan 2004), in which sleep disruption during labour was retrospectively compared between a clinical sample of women admitted with PP and a healthy parous control group. The authors reported a significant association between deliveries occurring at night, increased length of labour and episodes of PP, providing indirect evidence to suggest that sleep disruption during labour may be a precipitant of PP. Given the high proportion of primiparous women in

their sample (57%), the authors further postulated that first pregnancies are likely to affect sleep patterns and routines to a greater degree than subsequent pregnancies (Sharma and Mazmanian 2003). However, it was not possible to examine this hypothesis further within the current study, given the small number of women who were primiparous in the BDRN pregnancy sample (n=40).

The discrepancy between findings across studies may be explained by several methodological differences. For example, in the study by Sharma, Smith and Khan (2004), the case group was comprised of a diagnostically heterogeneous sample of women, which in addition to BD, also included women with diagnoses of schizoaffective disorder depressed type and unipolar psychotic depression. Furthermore, comparisons were made with a healthy parous control group rather than a diagnostically homogeneous group of women who were considered at equally high-risk of recurrence. Thus, their findings are likely to have limited generalisability to women with BD and may instead reflect differences in sleep patterns between parous women with psychiatric disorders and parous healthy controls.

Within the current study, the lack of a significant association between night time delivery, duration of labour and PP appears inconsistent with the finding that self-reported sleep loss (of at least one complete night) during labour significantly predicts PP. However, time of delivery and duration of labour can only be considered proxy measures of sleep disruption and do not necessarily equate to duration of sleep loss or indicate if in fact, more acute sleep loss occurred (e.g. complete nights of sleep missed during labour/delivery). Acute sleep loss (as opposed to any sleep disruption) may be a more important risk factor for PP. This is supported by evidence in the current study suggesting that while sleep loss of any duration during labour and delivery was associated with an increased risk of PP by more than 2.5 times, this risk more than doubled when at least one complete night of sleep was missed during labour (OR=5.35).

7.6.1.3.2 Sleep factors related to pregnancy

In contrast to sleep disruption associated with labour, this study found no association between poor self-reported sleep quality in the third trimester of pregnancy and PP. As discussed earlier in this thesis, only one published study has previously attempted to assess sleep patterns prospectively during pregnancy and the relationship with PP (Bilszta, Meyer and Buist 2010). However, given that so few women experienced any postpartum recurrence ($n=3$) the authors were unable to statistically examine the specific association between sleep patterns and occurrence of PP. Consequently, the current study is the first to prospectively assess the association between sleep quality in late pregnancy and occurrence of PP in women with BD.

The finding that poor sleep quality during pregnancy does not appear to increase risk of PP in women with BD is novel but should be interpreted carefully in the context of several possible limitations. Firstly, it could be argued that subjective measures of sleep, especially during pregnancy are not likely to be as reliable as objective measures such as actigraphy. However, it has been previously suggested that objective measures of sleep (particularly those using actigraphy) are not necessarily more accurate than self-report measures when assessing disturbed sleep (Littner et al. 2003). This is especially likely to be the case when assessing quality of sleep, given that as discussed above, actigraphy data typically gathers information regarding periods of activity or rest, thus only indicating number of hours of sleep obtained per period of study. Therefore, for this and reasons regarding feasibility, self-report measures of sleep quality were deemed the most appropriate measure of this factor. Secondly, sleep patterns and quality are known to be highly variable in late pregnancy (Lee 1998). The time at which sleep quality was assessed during the third trimester of pregnancy varied in some cases (depending on the availability of each participant), it is therefore possible that sleep patterns at the start of the third trimester were dissimilar from that in the last week of pregnancy. To remedy this limitation, sleep quality would ideally be assessed at multiple time points during the third trimester and particularly in the last week of pregnancy. However, given the difficulty of predicting the onset of labour, frequent measures of

assessment in late pregnancy would be required, reducing feasibility of the study. These additional assessments would also likely increase risk of attrition prior to postpartum follow-up. A potential compromise for increasing feasibility in future studies may be to offer completion of adjunctive online measures of sleep assessments in the late stages of pregnancy.

7.6.2 Psychosocial factors within the current pregnancy

In this study, I did not find a significant association between any of the within-pregnancy psychosocial factors studied and the subsequent occurrence of PP. To my knowledge, this is the first study to prospectively examine women's perceived experience of pregnancy in relation to PP in BD. The lack of association between women's overall subjective experience of pregnancy and PP is however consistent with a small study of women with broadly defined PP (i.e. including women who experienced affective or non-affective psychoses, McNeil and Blennow, 1988).

Though not significant, I found episodes of PP to occur more frequently among women who reported their pregnancy as being unplanned (40%) compared to women who had planned their pregnancy (23.5%). This analysis was found to be considerably underpowered (at 20%), with sample size estimates indicating at least 248 women with BD would be required to achieve 80% power to detect the observed difference between groups. Nevertheless, the direction of the trend is consistent with previous reports which have found an unplanned pregnancy to increase risk of any postpartum recurrence among women with BD (Abdel-Hay, El-Sawy and Badawy 2011; Doyle et al. 2012) but is inconsistent with one study examining risk factors for PP among a diagnostically heterogeneous clinical sample (Marks et al. 1992). Given the paucity of research investigating this relationship among women with BD, it remains unclear whether this finding may reflect the psychological effects of an unexpected pregnancy or the increased likelihood that these women may be more likely to withdraw medication suddenly during pregnancy. For example, circumstances related to an

unplanned pregnancy (such as pregnancies resulting from reckless behaviour in a manic episode or financial pressures) may act as psychological stressors, increasing vulnerability of PP. Furthermore, while it was not possible to examine the rate of medication withdrawal during pregnancy among women in this sample, rapid discontinuation of mood stabilisers (within 14 days) during pregnancy has been associated with an increased risk of perinatal recurrence of mood disorder among women with BD (Viguera et al. 2000, 2007).

Importantly, few women did not have a partner present during the pregnancy or reported their partner as not being emotionally supportive. For this reason, it was not possible to meaningfully examine the relationship between these factors and the occurrence of PP. While several studies have reported no association between the presence of a partner during pregnancy and PP (McNeil 1987; Protheroe 1969; Wisner, Peindl and Hanusa 1994) others have reported the opposite (Dean and Kendell 1981; Kendell, Chalmers and Platz 1987; Nager, Johansson and Sundquist 2005; Terp and Mortensen 1998; Upadhyaya, Sharma and Raval 2014). In the current study, there was a trend for women who reported having a partner present and emotionally supportive relationships during pregnancy to be more likely to experience PP than women who did not report this. This finding is similar to that of a prospective study of women with a history of functional psychoses, in which rates of PP were higher among women reporting more emotionally supportive relationships during pregnancy (Marks et al. 1992). This would also be consistent with evidence indicating that women who experience PP tend to be high functioning both socially and occupationally (Sit, Rothschild and Wisner 2006). Nevertheless, it was not possible to draw conclusions from this set of analyses, given that only one woman in the current study did not have a partner present during her pregnancy and only two women denied feeling emotionally supported by their partner or others.

Alternatively, these observations may reflect a sample bias, in that women recruited to his study were on the whole particularly high functioning. This is suggested by a number

of factors. Firstly, the rate of single mother pregnancies was low in this sample (1%), compared to estimates of 5.2% in the UK general population (Office for National Statistics 2017) and the few reports among other prospective studies of pregnant women with BD (18%-59%, Driscoll et al. 2017; Viguera et al. 2007). If these women were particularly high functioning, they might be expected to experience less difficulty in maintaining significant relationships compared to women with BD who are lower functioning. Accordingly, most women in the BDRN sample had achieved degree level qualifications or higher (62.1%) and had worked in professional occupations (52.4%) at some point during their lifetime. Given that women were primarily recruited through perinatal services and had reported planning their pregnancy (77%), it is also likely these women planned their pregnancy at a time when circumstances were most convenient for them (i.e. when in a stable and supportive relationship and at a financial advantage).

On the whole, these initial findings do not suggest a significant role of psychosocial factors in the aetiology of PP within BD and is consistent with the previous literature. This is in contrast to episodes of PND, in which a range of psychosocial factors have frequently been reported to significantly increase risk of recurrence (Cantwell and Smith 2009; Leigh and Milgrom 2008; O'Hara and Swain 1996). However, as I was unable to investigate the influence of partner support and single parenthood on risk of PP in this sample, factors which have inconsistently been associated with PP in previous literature, their role in the occurrence of PP requires further study.

7.6.3 Adverse life events within the current pregnancy

Several trends emerged from this study, showing that PP occurred more frequently among women who experienced at least one adverse life event during pregnancy and specifically, among those who experienced a serious illness or injury or a bereavement of a close friend or relative during pregnancy. No significant associations (or trends

towards significance) were found between any other specified adverse life event, nor the total number of adverse life events experienced and subsequent risk of PP. These findings are in contrast to previous literature, which has found no evidence to suggest that adverse life events during pregnancy may increase risk of PP (Brockington et al. 1990; Dowlatshahi and Paykel 1990; Marks et al. 1992). However, the trends observed within this study may be explained by several factors. Specifically, this study is the first to examine the relationship between adverse life events during pregnancy and PP within women with BD. Previous studies have primarily focused on women with broadly defined affective disorder (Marks et al., 1992) or in clinical samples of women with PP with no distinction between those with affective and non-affective psychotic disorders (Brockington et al. 1990; Dowlatshahi and Paykel 1990). Furthermore, I defined life events as being 'adverse' on the basis of women's subjective self-report, including only those events that they perceived to have a moderate to severe negative impact. In comparison, all three previous studies in this area assessed the degree of negative impact objectively (Brockington et al. 1990; Dowlatshahi and Paykel 1990; Marks et al. 1992). It is therefore possible that the adverse, psychological impact of these events were underestimated, explaining the lack of significant findings or trends within their samples. Finally, to ensure I only examined events occurring prior to and within close temporal proximity to childbirth, I assessed only those events which had occurred during pregnancy. In previous studies, the timeframe during which events occurred was either not clear (Brockington et al. 1990) or was considerably broader than in the current study (up to one year prior to pregnancy, Dowlatshahi and Paykel, 1990; Marks et al., 1992). It is plausible that more distally occurring events pose less psychological risk for PP than those occurring closer to childbirth.

This suggestion may be supported by findings reported earlier in this thesis, demonstrating that adverse life events occurring during childhood do not appear to be associated with increased risk of PP in BD (reported in Chapter 3). However, given that sample sizes were small (with some events inevitably occurring infrequently during pregnancy), it was not possible to examine the specific effect of all individual life events

measured. Furthermore, of those that were statistically examined, analyses were largely underpowered to detect a difference. According to sample size calculations, to achieve 80% power, between 84 and 404 women would be required in future studies to detect between group differences in adverse life events during pregnancy.

7.6.3.1 Smoking and alcohol use within the current pregnancy

This study was the first to prospectively examine the relationship between smoking and alcohol use during pregnancy and the occurrence of PP within a sample of women with BD. The influence of alcohol consumption during pregnancy on risk for PP remains unexplored, given that no woman in this study reporting drinking more than the recommended number of units per week. However, no significant association was found between smoking during pregnancy and the occurrence of PP. This finding is in contrast to that previously reported in the BDRN retrospective sample, in which lifetime history of smoking was associated with a significantly reduced risk of experiencing PP (n=653, Di Florio et al. 2015). It is possible that social desirability effects particularly influenced findings within the current study, given that women may be less likely to disclose smoking or drinking behaviour when assessed during their pregnancy.

7.6.3.2 Obstetric factors within the current perinatal period

No significant association was found in this study between any obstetric factor assessed (including pregnancy or delivery complications, method of delivery, sex of baby or gestation period) and the occurrence of PP. There was a trend for episodes of PP to occur more frequently following deliveries of female babies than of male babies (29.3% and 16.7% respectively, see page 195 for summary table), though as these analyses were found to be underpowered at 44%, this difference did not reach statistical significance (sample size estimates suggest 348 women would be required to achieve 80% power). The observed trend is consistent with the findings of a Indian study in which the majority of women (72%) admitted for episodes of PP had given birth to

female babies (Agrawal, Bhatia and Malik 1990). In contrast, investigations within a sub-set of women within our BDRN retrospective sample revealed no association between sex of baby and PP (55% of deliveries to male babies, Blackmore et al. (2006).

The finding that complications during pregnancy or delivery were not found to increase risk of PP, is consistent with investigations in large case-register studies (Meltzer-Brody et al. 2017; Nott 1982; Videbech and Gouliaev 1996) and one prospective study (Bergink et al. 2011a). Interestingly, I observed an overall directional trend for episodes of PP to occur more frequently among women who did *not* experience obstetric complications during the perinatal period, which may suggest that biological factors uniquely associated with giving birth naturally are particularly important in the pathophysiology of PP. Consistent with this theory, there was a trend for women who reported delivering their baby via normal vaginal delivery to be more likely to experience PP (31.6%) compared to women who had delivered their baby by any other mode (17.5%). Nevertheless, this finding did not reach statistical significance (post-hoc power calculated to be 30%, sample size calculation for 80% power to be n=290). Alternatively, women who experience obstetric complications may be more closely monitored by health services, receiving more support and being encouraged to rest more frequently during pregnancy. It is possible these factors may therefore have had an indirect protective effect on risk of PP.

The lack of a significant association between obstetric complications and PP is however in contrast to one study conducted within a sub-set of women in the BDRN retrospective sample (Blackmore et al. 2006). In this study, obstetric complications were compared in 129 women with BD between deliveries affected and unaffected by PP within four weeks of childbirth using a within-subjects design. Due to the small sample sizes, the authors were unable to assess the role of individual obstetric complications in postpartum recurrence of mood episodes, however they did find the occurrence of any obstetric complication during delivery to be significantly associated with increased risk of PP. This finding is inconsistent with the current study, despite the same definition of

obstetric complications being utilised in both studies. This difference may be explained by the retrospective nature of the analysis in the study by Blackmore et al. (2006). Specifically, the retrospective assessment of obstetric factors and postpartum outcomes may have increased the likelihood of recall bias. Women who experienced PP (many of whom were recruited to the study specifically on the basis of having a history of PP) may have been more likely to detect or report obstetric complications than those who did not experience an adverse psychiatric outcome.

7.6.3.3 Medication use for prophylaxis of postpartum mania within the current perinatal period

The findings of this naturalistic study indicate that risk of PP among women with BD-I and SA-BD is high, despite prophylaxis with mood stabilising medications. In this sample, use of any mood stabilising medications was not significantly associated with a reduced risk of experiencing PP. Further investigation also revealed no significant association between the occurrence of PP and specific medications (i.e. lithium or olanzapine), timing of use (for example, in both pregnancy and the postpartum period, compared with the postpartum period only) or a significant change (i.e. withdrawal) of mood stabilising medication during the perinatal period. These findings are consistent with a large case-control study of severe affective disorders (Taylor, Stewart and Howard 2019), in which prophylactic medication use in late pregnancy did not significantly reduce risk of severe postpartum recurrence within three months of delivery. However, much of the literature to date has reported the opposite. In their meta-analysis of eight studies (total n=205), Wesseloo et al (2016) reported the risk of severe postpartum recurrence to be lower among women with BD utilising any mood stabilising medication in the postpartum period compared to women who were medication free (29% and 65% respectively). The discrepancy in findings may be attributed to methodological differences between studies. Specifically, research included in the meta-analysis were primarily descriptive in nature and in contrast to this thesis, had not controlled for

factors previously identified as influencing risk for PP (such as primiparity or previous history of PP).

Efficacy of lithium (Austin 1992; Bergink et al. 2012; Cohen et al. 1995; Van Gent and Verhoeven 1992) and olanzapine (Sharma, Smith and Mazmanian 2006) for prophylaxis of PP has been demonstrated in samples of women with BD. Though associations were not statistically significant, there was a trend for PP to occur less frequently among women using lithium and olanzapine compared to women who were not taking these medications (refer to section 7.5). These analyses were found to be underpowered at only 2% for lithium and 11% for olanzapine. Given the clinical significance of these findings, the prophylactic effect of these medications in particular requires further investigation. Sample size calculations suggest as many as 1030 women with BD would be required to achieve 80% when assessing the prophylactic effect of lithium and at least 270 women to adequately assess efficacy of olanzapine.

The lack of an overall association between any psychotropic medication use and risk of PP was surprising and may be explained by several factors. For example, the definition of mood stabilising medications in this study was wider than that used previously, including medications (such as antipsychotics) which have little or no demonstrable evidence of efficacy for prophylaxis of postpartum recurrence. Of women utilising psychotropic medication in the current sample, more than two thirds were using at least one atypical antipsychotic (primarily quetiapine). The efficacy of this medication for prophylaxis of PP has not yet been examined elsewhere. Moreover, a recent study has shown pharmacokinetic changes in pregnancy to affect serum blood levels of quetiapine and aripiprazole in particular, reducing bioavailability of these drugs across pregnancy. Consequently, higher doses of these medications may be required during the perinatal period to achieve the same therapeutic effect. In the BDRN pregnancy sample, prophylactic quetiapine was the most commonly used mood stabilising medication.

In contrast to randomised controlled trials, it can be difficult in naturalistic studies to distinguish between the effects of illness from those of medication. Women with a more severe preconception course of illness may have been more likely to remain on prophylactic mood stabilising medication during the perinatal period. Personal preferences of women and their clinicians were also likely to have influenced decisions around psychotropic medication use in the perinatal period. Nevertheless, post-hoc comparisons between women using prophylactic mood stabilising medications in the postpartum period compared to those without did not reveal significant differences between the two groups with regards to markers of a more severe preconception course of illness (such as the number of preconception lifetime mood episodes per illness year, number of preconception admissions or of psychotic features (see Appendix N). Conversely, it could be suggested that the high proportion of women recruited through specialist perinatal psychiatric services had an illness that was particularly well-managed. However, no significant differences were observed between women recruited through specialist perinatal services and those recruited through other methods in the rates of postpartum prophylactic medication use (see appendix O).

An alternative explanation is that mood stabilising medications may be less effective at preventing mania in the postpartum period compared to mania occurring at other times. As discussed in the background chapter to this thesis, emerging evidence suggests that postpartum mania may be distinct in aetiology from non-puerperal episodes. This is reflected by differences in the clinical presentation and course of these episodes. Indeed, in our retrospective BDRN sample, we have also found a number of key clinical characteristics to significantly differ between postpartum and non-postpartum manic episodes when using a within-subjects design, with perplexity and dysphoria being more frequently present among episodes of postpartum mania (paper under review for publication). Consequently, postpartum episodes of mania may require a distinct pharmacological approach from that used outside the perinatal period, even within the same woman.

7.6.4 Strengths and limitations

There are a number of key strengths of this study. First is the use of a prospective follow-up design to assess the perinatal period and predictors of postpartum recurrence in a clinically, well defined sample of pregnant women with BD. This is the largest study to investigate such a wide range of potential within-pregnancy risk factors for PP in BD using this gold-standard method. The use of multiple assessments and follow up measures across the perinatal period has a number of benefits compared with a retrospective methodology, such as; reducing the possibility of recall bias, allowing for directional relationships between risk factors and PP to be established and for perinatal mood episodes to be more accurately characterised. Additionally, a combination of measures was used to assess postpartum psychiatric outcomes. Had this study relied on follow-up interviews alone, severe postpartum recurrences many not have been adequately captured, instead being lost to attrition.

A further strength is that in all cases, consensus ratings were made independently by the same two members of the research team (myself and CF) for key clinical and predictor variables such as prophylactic medication use, preconception main best estimate diagnoses and perinatal psychiatric outcomes. In addition, ratings of all key clinical data were made independently via a widely used, psychiatric assessment tool consistent with DSM criteria. Use of DSM criteria allows for comparability between these findings and the wider literature.

Finally, the follow-up period in this study was restricted to the first three postpartum months. This period has been shown in population studies to represent the highest-risk period for severe recurrence of mood disorder. Using a more narrowly defined definition of postpartum onset limits the possibility that episodes unrelated to childbirth were included in prevalence rates of psychiatric outcomes and subsequently in analyses of potential risk factors for PP.

Overall, data from this prospective study are high-quality and provide an important contribution to the literature regarding risk prediction of PP in women with BD. The naturalistic design of this study also likely captured variability in illness course and management that is representative of real-world scenarios encountered by women and their clinicians during the perinatal period.

7.6.4.1 Limitations

Whilst this study has many strengths, it is important to consider the findings in the context of several limitations. For example, despite an intense effort to recruit a representative sample of women with BD using a combination of both systematic and non-systematic methods, approximately two thirds of the sample had a diagnosis of BD-I disorder. Additionally, just over half (52.4%) of all women recruited to this study were identified via specialist perinatal psychiatric services. These women may represent a specific sub-group of BD who were more likely to be referred (or to self-refer) to these services due to having a more severe illness course or as shown previously, prior history of perinatal mood episodes.

In this study, all follow-up interviews were conducted via telephone to increase feasibility of the research. Conducting the interview via telephone increased flexibility of the assessment for women in the early postpartum period, encouraging participation. Interviews could be conducted at any location participants chose (for example, at a friend's or relative's home whilst the baby was being cared for) and were less intrusive than in person interviews. However, despite this benefit, it has been argued that compared to face-to-face interviews, telephone interviews may compromise data quality. Specifically, rapport between the interviewer and participant may be restricted, resulting in increased risk of non-disclosure of emotionally sensitive information (Novick 2008; Shuy 2003). The potential for this effect is however minimised in the current study for several reasons. First, follow-up interviews were conducted after rapport had been established during pregnancy. Almost all women were interviewed in person (at

home) during pregnancy, typically over a period of two hours. The screening assessment and third trimester interview also provided further opportunities for relationship building. Second, follow-up data were gathered from clinicians and psychiatric case notes, corroborating and supplementing information obtained at interview. In addition, no differences have been observed in the quality or quantity of information obtained during psychiatric research interviews conducted by telephone compared to face-to-face methods (Aneshensel et al. 1982; Crippa et al. 2008; Fenig et al. 1993; Simon et al. 1974; Wells et al. 1988).

Another important limitation is the modest sample size of this study, particularly when stratifying according to potential risk factors or potential sub-groups of interest. As indicated in section 7.5 (page 203), it was not possible to adequately assess a number of potential risk factors for PP, given that these analyses would be considerably underpowered to detect a statistically significant difference. Emphasis was therefore placed on examining trends within the data. It is also of note that relationships found to be significant would not survive Bonferroni correction. However, due to the exploratory nature of this study, Bonferroni correction was deemed too conservative and a less stringent p-value of 0.05 was considered more appropriate. Consequently, findings from this study would benefit from replication within a larger sample of women with BD. Depending on the factor of interest (and observed effect sizes), sample size estimates indicated as many as between 98-1080 women with BD would be required in future analyses to achieve sufficient power of 80%.

Due to sample size limitations, it was not possible to examine risk factors for PP according to diagnostic subtype of BD, therefore reducing generalisability of findings to the wider BD population. Investigating aetiological and triggering factors of PP among women with BD-II or BD-NOS is likely to be considered of particular clinical importance, given that despite lack of evidence, these women are generally perceived to be at lower risk of PP. Similarly, there is evidence to suggest that women who experience episodes of mania solely in relation to childbirth may represent a distinct subtype of BD

(Wesseloo et al. 2016). It therefore cannot be assumed that aetiological and triggering factors for PP among such women are similar to those in women who have a more 'typical' bipolar illness (i.e. women who also experience episodes of mania unrelated to childbirth). Narrowly refining samples of women with BD for future studies of PP would not only be of clinical benefit, but would also provide further insight into the nosology of postpartum psychiatric illnesses.

Despite facing unique challenges when recruiting women with BD to this prospective research (for example, the narrow time frame during which women could be recruited and women being less likely to take part compared to other times), the sample size obtained was that which was feasible within the time frame. Moreover, this study remains one of the largest prospective pregnancy studies of BD to date and the first such study to be conducted within a UK population. Recruiting larger samples of women with BD during pregnancy to prospective or longitudinal research would be highly resource intensive and require highly targeted recruitment methods. Women with BD-II or BD-NOS may be less likely to be identified by perinatal specialist services, while isolated PP cases are uncommon. Recruiting these women would likely be achievable, but would rely on continued collaboration with NHS specialist perinatal services and also large, national organisations such as Bipolar UK and Action on Postpartum Psychosis (APP).

7.6.5 Implications

7.6.5.1 Clinical practice

If replicated, the findings of this thesis have potentially important implications for clinical practice. Specifically, these data indicate that risk of recurrence of BD is high across the perinatal period, despite prophylactic medication use. This finding might suggest that in many cases, current pharmacological regimens are suboptimal for managing BD across the perinatal period. Further research is therefore needed to examine medication factors that may contribute to poorer maternal outcomes across

the perinatal period in women who have BD. In particular, focus should be placed on investigating the pharmacokinetic changes that may be induced by pregnancy and childbirth on psychotropic medications commonly used for prophylaxis of BD. Emerging evidence has shown that serum blood levels of lithium and quetiapine can vary considerably across pregnancy (Wesseloo et al. 2017a; Westin et al. 2018), reducing below optimal therapeutic dose. Thus, the authors have highlighted the need for frequent monitoring of blood levels of these medications throughout the perinatal period. Nevertheless, data in this area remains limited. Such research is crucial, given that as demonstrated in this naturalistic sample, a wide range of medications are utilised for prophylaxis of PP, despite having no established evidence base for efficacy. Inevitably, large samples of individuals would be required to conduct these analyses. One way this could be achieved is through the use of large, naturalistic datasets of anonymised clinical records such as that used by the NIHR Maudsley Biomedical Research Centre (<https://www.maudsleybrc.nihr.ac.uk/facilities/clinical-record-interactive-search-cris/>)

While pharmacotherapy is the first line recommended intervention for prevention of PP (National Institute for Health and Clinical Excellence 2014), the findings of this study also highlight the importance of exploring the effectiveness of other non-pharmacological interventions for further managing risk of PP. For example, women in this sample who missed more than at least one night of complete sleep across labour and delivery were found to be at more than five times increased risk of PP. Where possible, strategies to minimise sleep disruption during this period may therefore be beneficial, but require further examination.

Finally, an additional approach to enhance perinatal care in women at high-risk of PP could involve the provision of further specialist education for midwives and health visitors. Indeed, this is a recommendation that has been outlined in the NHS Long Term Plan (NHS England 2019b). As clinical professionals who are in frequent contact with women during pregnancy and the first critical weeks following delivery, midwives and

health visitors are instrumental for identifying women at high-risk of PP and also those who require urgent psychiatric intervention following childbirth. Data derived from this thesis could form the basis of educational programmes regarding risk of PP. For example, case-vignettes could be used to demonstrate the phenomenology of episodes and provide wider context of severe postpartum mood disorders.

7.6.6 Aetiology of postpartum mood episodes

On the whole, findings from this study are consistent with previous literature indicating biological factors related to pregnancy and childbirth to be more important in the aetiology of PP than psychological factors. This is generally in contrast to studies of PND, which have consistently found psychological factors to be robust predictors of these episodes (Cantwell and Smith 2009; Howard et al. 2014). This is also in line with emerging literature which has implicated genetic factors (Jones and Craddock 2001), immunological factors (Bergink et al. 2015a, 2015b) and sensitivity to hormonal changes (Robertson Blackmore et al. 2008) in the pathophysiology of PP. The findings of this study, if replicated, may further suggest that episodes of PP and PND are heterogeneous forms of mood disorder, with PP in particular having a unique relationship to aetiological and triggering factors associated with childbirth. This would have important implications for nosology of these episodes and particularly classification of postpartum mood disorders, given that currently, neither DSM nor ICD-10 criteria recognises PP as being distinct from other perinatal episodes. Additionally, there are also implications for future research, which should aim to investigate risk factors for PND and PP independently in BD, given that these episodes are likely to be heterogeneous forms of mood illness.

7.7 Summary

In summary, the findings of this naturalistic study suggest that women with BD are at high risk of recurrence of mood episodes during the perinatal period and particularly of

PP within the first few weeks after delivery. The risk of PP within this sample remained high, despite the use of prophylactic medications for mood stabilisation in the postpartum period. Over and above risk associated with known lifetime predictors (such as prior history of PP), episodes of mania or affective psychosis during pregnancy significantly increased risk of PP among women with BD-I/SA-BD by more than 15 times. Further analysis revealed that prophylactic mood stabilising medication within the postpartum period did not significantly reduce this risk. Moreover, additional evidence suggests that acute sleep loss (of more than one complete night) associated with labour and delivery may act as a final common-pathway in the triggering of PP. Given that no clear significant relationship was established between any psychosocial factor and the occurrence of PP, this finding suggests biological factors may be especially important in the aetiology of PP.

Chapter 8

Discussion

8.1 Overview of chapter

In this chapter, I review the main findings and final conclusions of this thesis, followed by a discussion of the potential implications of this work for clinical practice. Key limitations of this research will also be discussed, concluding with suggestions for further research.

8.2 Main findings

The primary aim of this thesis was to investigate potential aetiological and triggering factors for episodes of PP among women with well-defined BD. Specifically, the three main aims of this thesis were to:

1. Investigate potential relationships between history of ACEs, anxiety disorders and the lifetime occurrence of PP in a sample of parous women with BD (Chapter 3, The BDRN Retrospective Sample).
2. Describe psychotropic medication use and psychiatric outcomes across the perinatal period in a sample of pregnant women with BD using a prospective follow-up design (Chapter 6, The BDRN Pregnancy Sample)
3. Investigate a wide range of within-pregnancy potential risk factors for PP in a sample of pregnant women with BD using a prospective follow-up design (Chapter 7, The BDRN Pregnancy Sample).

The main findings of this thesis are reviewed in relation to each aim within the following sections.

8.2.1 Aim 1

‘To investigate potential relationships between history of ACEs, anxiety disorders and the lifetime occurrence of PP in a sample of parous women with BD’

In Chapter 3, I examined whether history of ACEs or anxiety disorders was associated with PP in a sample of parous women with BD (The BDRN retrospective sample). This study was the first to examine these relationships among women with well-defined BD. In contrast to studies examining the relationship between these factors and PND, I found no evidence to suggest ACEs or lifetime comorbidity of anxiety disorders are associated with an increased vulnerability to PP in women with BD.

The lack of evidence for a relationship between ACEs and PP is consistent with one small study which also reported no significant relationship between a small range of ACEs and broadly defined PP among a diagnostically heterogeneous sample of women (Dowlatshahi and Paykel 1990) and the findings of a Danish population study (Meltzer-Brody et al. 2018). The findings of the current study also support those of the wider literature, reporting a lack of association between adverse life events occurring during adulthood or within the 12 months prior to pregnancy and the onset of PP. Together, these findings suggest that life stressors, or at least more distal life stress (from the event of childbirth) do not play an important role in the pathogenesis of PP.

Given that the role of anxiety disorders or life stressors occurring within-pregnancy in could not be examined in relation to PP within this sample, these factors were identified as areas of further study in prospective research.

8.2.2 Aim 2

‘To describe psychotropic medication use and psychiatric outcomes across the perinatal period in a sample of pregnant women with BD using a prospective follow-up design’

In Chapter 6, I described psychotropic medication use and psychiatric outcomes across the perinatal period (to three months postpartum) in women with BD using a prospective follow-up design. In this naturalistic study, I found patterns of psychotropic medication use to be highly variable across the perinatal period. Most women (61.2%) used at least one mood stabilising medication during pregnancy, and almost two thirds (64.4%) a prophylactic mood stabilising medication postpartum. 26% of all women discontinued all mood stabilising medication prior to or during pregnancy and did not recommence these medications within the remaining study period.

Despite frequent use of psychotropic medication, risk of at least one new onset DSM-5 mood episode remained high during the perinatal period (59.8%). Risk of recurrence was comparable during pregnancy (43%) and within the first three postpartum months (42.6%). However, compared to pregnancy (11.9%), risk of mania/affective psychosis was greatest following childbirth (21%), and occurred more frequently in women with BD-I/SA-BD (24.4%) compared to those with BD-II/BD-NOS (5.6%). In contrast, risk of postpartum hypomania (8%) was comparable with that of pregnancy (7.9%), while depression was less frequent postpartum (14%) compared to pregnancy (22.8%). All episodes of PP occurred within six weeks of delivery (76% within the first two weeks), while the onset of hypomania and PND was more widely distributed throughout the postpartum period.

These findings are consistent with previous literature that has shown the perinatal period to be a time of high risk of recurrence of BD (Di Florio et al. 2013) and the early postpartum period in particular for episodes of mania/affective psychosis (PP; Wesseloo et al. 2016). Risk of PP remained high despite use of prophylactic mood stabilising medication in the postpartum period, suggesting that factors other than medication are also likely to influence risk of PP in women with BD.

8.2.3 Aim 3

'To investigate a wide range of within-pregnancy potential risk factors for PP in a sample of pregnant women with BD using a prospective follow-up design'

In Chapter 7, I reported findings of investigations examining the influence of a range of within-pregnancy factors on risk of PP in women with BD using a prospective follow-up design. To my knowledge, this prospective study is one of the largest such studies conducted to date and the first to be conducted in a UK sample of women with BD.

In univariate analyses, I found the occurrence of mania/affective psychosis during pregnancy and loss of more than one complete night's sleep during labour/delivery to significantly increase risk of PP. After adjusting for known lifetime correlates of PP (history of mania triggered by sleep loss, prior history of PP, family history of perinatal psychiatric illness and primiparity), mania/affective psychosis during pregnancy remained a significant predictor of PP ($p < 0.01$, OR 16.49, 95% CI 2.76-98.48). When added to the model, prophylactic mood stabilising medication during the postpartum period had little influence in moderating risk of PP ($p = 0.61$, OR 0.67, 95% CI 0.14-3.16).

Given that acute sleep loss across labour/delivery was also associated with PP in univariate analysis (but could not be examined further due to limitations in sample size), this may suggest that sleep disruption across the peripartum period may also act as a final common pathway in the triggering of PP in women with BD. Moreover, despite observing several trends within the data, within-pregnancy psychological and psychosocial factors did not significantly influence risk of PP, suggesting that in contrast to episodes of PND (as demonstrated in the literature), these factors may be less important in the pathophysiology of PP.

8.2.4 Final conclusions

In conclusion, the findings of this thesis suggest that risk of PP is high among women with BD, despite use of prophylactic mood stabilising medication in the postpartum period. Neither history of ACEs nor anxiety disorders were associated with increased risk of lifetime PP. However, an episode of mania/affective psychosis with onset during pregnancy was found to significantly increase risk of PP, over and above associations with known lifetime risk factors. Further evidence suggested that use of prophylactic mood stabilising medication had little influence in reducing risk of PP and that sleep loss associated with labour and delivery may also act as a final common pathway in the triggering of PP. In contrast to studies of PND, no significant associations were found between within-pregnancy psychological or psychosocial factors and PP, further suggesting that aetiological and triggering factors may be distinct across these disorders.

8.3 Implications

If replicated, the findings of this thesis have potential clinical implications for individualising risk prediction and prevention of PP in women with BD and also for understanding the aetiology and nosology of PP and related mood disorders. These implications are discussed further within this section.

8.3.1 Clinical implications

The high prevalence of perinatal recurrence observed in the prospective sample further highlights the need for all women who have BD to be closely monitored and followed throughout pregnancy, as well as the postpartum period. Women with BD should be made aware of the risk of recurrence during both stages of the perinatal period and advised on the importance of planning pregnancy. Ideally, all women with BD should receive care from specialist perinatal psychiatric services from the

preconception/planning stage through at least the first three months postpartum. The findings of this thesis also suggest that psychological and psychosocial factors may be less important when determining individual risk of PP in women with BD.

Given that the risk of PP remains high despite use of prophylactic mood stabilising medication, further research is required to examine medication factors and practices that may be associated with poorer maternal outcomes. Data also indicates that focus should be placed on evaluating the potential effectiveness of non-pharmacological interventions for reducing risk of PP. This may for example include strategies to minimise the impact of acute sleep disruption where possible across labour and delivery. In an effort to ensure women at high risk of PP receive optimal care across all healthcare disciplines during the perinatal period, data derived from this thesis could also be used to form the basis of education programmes about PP for health visitors and midwives. Such healthcare professionals may be instrumental for identifying women at high risk of PP and also those who require urgent psychiatric intervention in the early postpartum period.

8.3.2 Aetiology and nosology of postpartum mood disorders

Together with existing literature, the findings of this thesis support evidence to suggest that the aetiology of PP is potentially distinct from PND. The lack of strong evidence for a role of psychological or social factors in the occurrence of PP is in contrast to studies of PND, which have consistently found these factors to be more robust predictors of non-psychotic depression following childbirth (Cantwell and Smith 2009; Howard et al. 2014). If replicated, the findings of this study might suggest that episodes of PP and PND are heterogeneous forms of mood disorder, which could have important implications for the nosology of these episodes and the classification of postpartum mood disorders more generally.

8.4 Limitations

8.4.1 Potential sample biases

The main limitation of this thesis is the potential for sample bias based on a number of recruitment related factors. Firstly, due to a key focus of BDRN being on genetic studies of mood disorders, it is possible that women who took part in this research were more likely to do so due to having a more biological form of BD or an increased genetic vulnerability to BD or PP (for example, as indicated by a strong family history of mood disorders).

Secondly, as many women were recruited through perinatal psychiatric services and national support charities such as APP (to increase feasibility of the study), it is also possible that these women had a more severe form of BD that required increased psychiatric monitoring, and more specifically, were a group of women who were particularly susceptible to mood disorders triggered by childbirth. However, half of the pregnancy sample were found to be primiparous (50.5%) and so did not have a previous history of PP. Furthermore, to minimise the influence of any such biases, I adopted a range of systematic and non-systematic approaches to recruitment and where relevant, conducted post-hoc analyses to assess and/or control for the influence of recruitment method and preconception psychiatric history on findings.

Thirdly, despite using a range of methods to recruit women to this research, ethnic diversity of the samples remained low. As such, generalisability of the current findings to ethnic minority groups is potentially limited. The predominance of White-British women in these samples is likely explained by several factors. One contributory factor may be the focus of BDRN on genetic studies of mood disorders. Another is that due to the nature of the assessments, women were required to be fluent English speaking. The ethnic diversity of the sample is also likely to reflect general trends in referral patterns and utilisation of perinatal psychiatric services nationally. Specifically, areas of the country in which recruitment to this research was most successful (such as the North

East of England and South Wales) are predominantly comprised of residents who are White British (97.6% and 97.3% respectively; Office for National Statistics 2012). Moreover, evidence indicates being from an ethnic minority background as a strong predictor of disengagement and non-utilisation of services (O'Brien, Fahmy and Singh 2009). Thus, to enhance the representativeness of findings from future studies of PP, recruitment efforts should focus on areas of the country high in ethnic diversity (such as London; Office for National Statistics 2012).

8.4.2 Complications regarding the nosology of postpartum psychosis

A further limitation of this research is that due to uncertainty regarding the most appropriate definition of PP and also the temporal criterion that should be used to define the postpartum period, those adopted within this thesis are essentially arbitrary. As discussed previously, there is disagreement between standardised diagnostic criteria in the temporal definition of the postpartum period (being four weeks in DSM and six weeks in ICD criteria), while in clinical practice and other research, a definition of up to 12 months postpartum is frequently used. However, as a compromise, I chose a temporal cut-off of six weeks to define the postpartum period to include both DSM and ICD criteria. Furthermore, this is more consistent with literature which indicates the early postpartum to be the period of high risk of PP, thus reducing the possibility that I included cases of mood disorder that were unrelated to childbirth.

Similarly, the concept of PP and how to most appropriately define the phenotype that should be captured within this concept (i.e. what forms of mood illness should be included) is not clear. For example, it is uncertain whether episodes of postpartum hypomania or PND occurring within close temporal proximity to childbirth should be included or excluded within the definition of PP or whether episodes of postpartum psychotic depression should be considered distinct from episodes of psychotic or non-psychotic mania. However, given that evidence primarily suggests that childbirth is most closely related to affective psychoses, predominantly those that typically present with

manic or mixed features, I narrowly defined PP as any severe episode of mania (excluding hypomania) or affective psychosis only, regardless of polarity. This definition is also widely used within clinical practice and other research studies, thus ensuring these findings could be more directly compared with other literature within this area.

8.5 Further research

As the investigations presented and discussed within this thesis are novel, further independent replication of these findings is required in a larger sample of women with BD. Given the considerable heterogeneity in research findings between existing studies of PP (likely due to methodological differences), future research should aim to replicate these investigations using a similar methodology to that used within this thesis. Specifically, future studies should adopt the same definition of PP and temporal cut-off used to define the postpartum period, in addition to using a similar standardised psychiatric research tool to assess perinatal psychiatric outcomes according to clinical diagnostic criteria. This would further enable comparability of findings between studies.

Further research is also needed to assess other within-pregnancy factors that may influence risk for PP, but could not be investigated within this thesis. For example, the role of neurobiological factors specific within-pregnancy (such as hormonal or immunological) in the occurrence of PP has been little studied in samples of women with BD, particularly using a prospective methodology. Moreover, it would be of great clinical and personal benefit (for women with BD) to examine other medication related factors that may explain the lack of association I observed between use of prophylactic mood stabilising medications postpartum and risk of PP. Specific areas identified for further investigation include assessing the influence of dosage and serum blood levels of medications across the perinatal period (to ensure therapeutic dose is being achieved). Additionally, due to limitations of sample size, efficacy of commonly used psychotropic medications for mood stabilisation could not be examined effectively and as such, warrant further study.

In order to extend the findings of this thesis further, another area of research would be to investigate risk (and potential risk factors) of PP across other subtypes of BD. The findings of this study indicate that although risk is low, a small proportion of women who have BD-II at conception experience PP and thus, potentially a more severe long-term course of illness. Being able to predict risk of PP within this group may provide early indication of long-term course of BD, but would be particularly beneficial for the clinical management of BD-II during the perinatal period. This may be especially important, given that risk of PP is often perceived to be low for women with BD-II (by women themselves and clinicians), and may result in these women being less likely to use medication or be under the care of psychiatric services during the perinatal period.

Similarly, emerging evidence indicates that some women have a distinct, 'pure puerperal' form of BD, in which episodes of mania/affective psychosis only occur in relation to childbirth. It would therefore be of interest to examine potential risk factors for PP within this sub-group, as refining the phenotype further may provide additional clues to the aetiology and triggering of these episodes. However, to be able to conduct these investigations across subtypes of BD, more intensive effort would be required to recruit women into future studies, given that a 'pure puerperal form' of BD is less common and that women with BD-II are less likely to be under the care of perinatal psychiatric services during pregnancy. Thus, highlighting the need for targeted recruitment of these women via non-systematic methods in particular, which may be best achieved through continued close collaboration with national patient support charities such as Bipolar UK and APP.

Based on the findings of this thesis and in combination with existing literature, a final recommendation for further research is that additional focus should be placed on investigating genetic factors that may be involved in the pathogenesis of PP. Despite indication that susceptibility to PP may be hereditary in some cases, specific genes are yet to be identified. However, collection of genetic material from women with BD and a history of PP is ongoing in the BDRN programme of research. It is anticipated that in the

future, through international collaboration with other research groups, sample sizes will be sufficient to conduct a genome wide association study of PP. Furthermore, given the overlap in roles of the endocrine and neurotransmitter function in mood regulation, parturition and sleep, the role of sleep disruption in the occurrence of PP should also be a prime candidate for further study. Specifically, studies should assess sleep disruption using objective methods of assessment (such as with actigraphy), to further distinguish between sleep loss as a trigger for PP and the prodromal phase of illness.

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Appendices

Appendix A: Childhood Life Events Questionnaire (CLEQ)

Self / Interviewer rated (please circle)

Did you experience as a child (up to age 16 years) any of the following life events?

	<i>Please circle:</i>		<i>If yes, how old were you?</i>
	Yes	No	_____
1. Death of parent	Yes	No	_____
2. Death of a brother/sister	Yes	No	_____
3. Death of a close friend	Yes	No	_____
4. Divorce of parents	Yes	No	_____
5. Marital separation of parents	Yes	No	_____
6. Marriage of parent to step parent	Yes	No	_____
7. Serious illness needing hospitalisation	Yes	No	_____
8. Hospitalisation of a parent	Yes	No	_____
9. Acquiring a visible deformity	Yes	No	_____
10. Jail sentence of a parent for a year or more	Yes	No	_____
11. Teenage pregnancy/fatherhood	Yes	No	_____
12. Suspension from school	Yes	No	_____
13. Are there any other significant life events you experienced as a child that are not mentioned about?	Yes	No	_____

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Appendix B: Lifetime psychiatric history questionnaire

3. (b) Has a doctor or health professional ever told you that you have any of the following? (please cross one answer for each item):

	Yes	No	Not sure	FOR OFFICE USE
21. Attention Deficit Disorder (ADHD)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	21 <input type="checkbox"/>
22. Autism	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	22 <input type="checkbox"/>
23. Depression	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	23 <input type="checkbox"/>
24. Bipolar Disorder	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	24 <input type="checkbox"/>
25. Obsessive Compulsive Disorder (OCD)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	25 <input type="checkbox"/>
26. Agoraphobia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	26 <input type="checkbox"/>
27. Schizophrenia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	27 <input type="checkbox"/>
28. Panic Disorder	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	28 <input type="checkbox"/>
29. Phobias	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	29 <input type="checkbox"/>
30. Anxiety	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	30 <input type="checkbox"/>
31. Alcohol Abuse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	31 <input type="checkbox"/>
32. Other Substance Abuse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	32 <input type="checkbox"/>
33. Anorexia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	33 <input type="checkbox"/>
34. Bulimia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	34 <input type="checkbox"/>
35. Any other psychiatric illness. Please specify:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	35 <input type="checkbox"/>

Appendix C: The Brief Life Events Questionnaire (BLEQ)

13. In the 6 months prior to your illness onset, do you think that anything happened which contributed to your becoming unwell? If yes, what was it? Yes No

14. Do you think that there is anything that has happened to you during your life which contributed to your becoming unwell? If yes, what was it? Yes No

Appendix D: Participant information sheet



INFORMATION ABOUT RESEARCH INTO MOOD DISORDERS

INTRODUCTION

We are a team of psychiatrists and psychologists who work in the Department of Psychological Medicine at the University of Worcester and the Department of Psychological Medicine at Cardiff University. We are conducting research (funded by the Wellcome Trust and the Stanley Medical Research Institute) into the causes of mood disorders and work closely with other research groups both in Europe and the United States. We would like to ask you if you would be willing to take part in our research. Before you decide whether or not you would like to take part, please take the time to read the following information carefully.

WHAT IS THE PURPOSE OF THE RESEARCH?

Mood disorders sometimes run in families but in other cases only one member of a family is affected. Unfortunately no-one understands enough about the illnesses to know what causes particular individuals to become unwell. The main aim of our research is to look for genes and other factors, such as stressful life events, which make some people more likely than others to become ill. We hope that our study will improve understanding of mood disorders and help other workers find better treatments in the future.

WHO IS BEING ASKED TO TAKE PART IN THE STUDY?

Over 6000 individuals have already taken part in our ongoing research into mood disorders. It is important for us to see many more people in order that we can get the best possible understanding of the causes of mood disorders. We are hoping to recruit individuals who have experienced one or more episodes of high mood (often called mania, hypomania or bipolar disorder) at some point in their lives and would be extremely grateful if you would be kind enough to help with this study.

WHERE DOES THE STUDY TAKE PLACE?

If you agree to take part, a member of our research team will arrange a suitable time to visit you in your home or at another place convenient for you, or to interview you over the phone.

WHAT DOES TAKING PART INVOLVE?

Taking part involves:

- An interview by a trained member of our research team who will spend up to an hour and a half asking you about your experiences and the kinds of symptoms you have had in the past. If you are willing we would like to audio record part of the interview for consistency and training purposes.
- Completing a set of questionnaires (which will take around half an hour).
- In some cases, giving a blood sample from your arm (2 standard blood tubes).

With your permission, we would like to look at your medical records in strict confidence in order to gain further information about the kinds of symptoms you have experienced. We only need to see you once but may contact you again in the future if we need to collect more information for the research. However, you will be free to decline if you do not want to participate further. Once you have agreed to take part in the study we will ask you to sign a consent form and will give you a copy to keep along with this information sheet.

If you are pregnant, we will also ask you to complete an additional questionnaire about your pregnancy (which will take around 10 minutes). With your permission, two months after your expected date of delivery we would like to contact your GP and psychiatrist to request information about the pregnancy and postnatal period. Unless your doctors advise us otherwise, we will then arrange an additional telephone

interview with you (which will take about 20 minutes) to ask about any symptoms you may have experienced in relationship to pregnancy and childbirth.

You can decline to participate in this part of the study. You do not have to take part when contacted after the delivery and this will not affect the care you receive.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART? ARE THERE ANY RISKS?

- By taking part in the study you will not gain any direct benefit. However, your help will be of great value in allowing us to learn more about the causes of mood disorders and we hope this will lead to important advances in the treatment and prevention of mood disorders.
- This study does not include any treatment changes or invasive techniques. Some people experience mild discomfort when giving a blood sample and sometimes there is mild bruising afterwards.
- Most people find talking about their illness beneficial, but some may find it distressing. If at any time during the interview you feel distressed, you can ask the interviewer to move onto another question, take a break or end the interview.
- If you have a concern about any aspect of this study, please speak to Dr Katherine Gordon-Smith. Her contact details are provided at the end of this information sheet.

DECLINING AND WITHDRAWING FROM THE STUDY

- You do not have to take part in this study. If you do decide to take part you are still free to withdraw at any time and without giving a reason.
- A decision to withdraw at any time, or a decision not to take part, will not alter the care you receive.
- If you decide to withdraw from this study, all information and samples you have provided will be destroyed and not used further in the research.

DATA CONFIDENTIALITY

- All interviews and results will be strictly confidential.
- The interview data, audio recordings of interviews and blood samples will be stored in accordance with the General Data Protection Regulation (GDPR). The data will be stored for a minimum of 10 years, but probably for longer as this is an ongoing long-term programme of research.
- The blood sample you provide will be coded and stored safely in a laboratory. It will be analysed to identify genetic variations that might cause some people to develop mood disorders. The results of your blood test are for research purposes only and will not be available to anybody on an individual basis.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

- It is our intention to publish the results of this study in academic journals. Participants will not be identifiable in any report or publication.
- We will keep in touch with you by sending a regular newsletter to let you know how our research is progressing and to ask you to let us know about any important changes in your health since we last saw you.

FURTHER INFORMATION AND CONTACT DETAILS

If you have any further questions about this research, please contact the Mood Disorders Research Team and ask for Dr Katherine Gordon-Smith (Research Psychologist). Our address appears below, our telephone number is 01905 54 2880, and our e-mail address is moodresearch@worc.ac.uk

This study was given a favourable ethical opinion for conduct in the NHS (or other) by the West Midlands Multi-centre Research Ethics Committee (MREC/97/7/01).

Mood Disorders Research Group, University of Worcester, Henwick Grove, Worcester, WR2 6AJ
Tel: 01905 54 2880 Fax: 01905 85 5589 Email: moodresearch@worc.ac.uk

Version 5 03.12.10

Appendix E: Participant consent form

AGREEMENT TO TAKE PART IN THE STUDY OF MOOD DISORDERS

STUDY ID: _____ BDRN use only

Please initial boxes

- 1 I have read the attached information sheet (version 5, dated 03.12.10) on the above project and have been given a copy to keep. I have had the opportunity to ask questions about the project and understand why the research is being done.
- 2 I agree to give a sample of blood for research in the above project.
- 3 I agree to part of the interview being audio recorded
- 4 I understand that participation in this project is voluntary and that I am free to withdraw from the study without giving a reason and without my medical treatment being affected
- 5 I give permission for my medical records to be looked at in strict confidence by responsible people from the Mood Disorders Research Group
- 6 I understand that the tests done as part of this research are not clinically diagnostic and I will not be informed of any specific results
- 7 I understand that I will not benefit personally from taking part in this research
- 8 I understand that the information and blood sample I have donated for this study will be held in a confidential and anonymised form by the research team and may be made available to researchers at other centres who are carrying out similar work
- 9 I agree that I may be contacted again, in connection with the research, in the future
- 10 I know how to contact the research team if I need to

If you are pregnant:

- 11 I give permission for my GP and psychiatrist to be contacted 2 months after my expected delivery date to request information about the pregnancy and postnatal period
- 12 I agree to be contacted 3 months following my expected delivery date to be invited to take part in a telephone interview about my pregnancy and the postnatal period. I understand that I am free to decline this invitation

Name	Signed	Date
_____	_____	_____
Witnessed	Signed	Date
_____	_____	_____

Appendix F: Participant information leaflet



Thank you for taking the time to read this leaflet and for considering joining our bipolar disorder, pregnancy and childbirth research.

The BDRN Research Team





If you would like to be involved in our bipolar disorder, pregnancy and childbirth research or would like further information about taking part our contact details are:

Mood Disorders Research Group
 ☎ 01905 54 2880
 ✉ moodresearch@worc.ac.uk

✉ If you would like to return a completed form or write to us, simply address a sealed envelope to:

Freepost MOOD RESEARCH

This is our new simplified freepost address provided by Royal Mail - please write the address carefully exactly as shown above. You must not include any further address details and your envelope does not need a stamp. Your envelope should look like this:



Please visit our website: www.bdrn.org





Bipolar Disorder, Pregnancy and Childbirth Research



Version 1 12.05.14

Who are BDRN?

BDRN is the largest network of individuals with bipolar disorder in the world. 6000 individuals in the UK with bipolar disorder have now taken part in our studies and continue to help us with our ongoing research through the network.

Bipolar disorder, pregnancy and childbirth.

In our current research we are hoping to find out more about the factors that make some women with bipolar disorder more or less likely to experience episodes of illness in relation to childbirth. We hope this research will lead to better prediction and treatments for these episodes.



Who is invited to participate?

We would be delighted to hear from you if:

You have bipolar disorder and are currently pregnant.

What does taking part involve?

One of our researchers will visit you in your own home during your pregnancy for an interview lasting around an hour and a half.



If you are willing, during this visit we will ask you to complete some questionnaires and also to provide a blood sample.



Three months after you have had your baby, your researcher will then contact you by telephone for a brief interview. Your researcher will ask about any symptoms you may have experienced in relation to childbirth.

If you would like to be involved in our study of bipolar disorder, pregnancy and childbirth, or would like more information about taking part you can either:

- Email, telephone or write to us – our contact details are on the back of this leaflet.
- Fill in the form below, detach this page and return it to us in a sealed envelope to the FREEPOST address on the back of this leaflet.

Name: _____

Address: _____

Tel. Number: _____

Email: _____



Appendix G: Participant telephone screen

Telephone Screen for Prospective Pregnancy Study

Study ID..... Initials: DOB:
 Date of TS: Due date:

Thank you very much for your interest in our research into pregnancy and bipolar disorder and related mood disorders. The overall aim of the research is to find out more about what makes some women more or less likely than others to become unwell in their mood after having a baby.

1. Could I please ask if you are currently pregnant?
 Yes (If yes go to Q2) No (go to Box 1)

BOX 1 WOMEN WHO ARE NOT PREGNANT BUT REPORT POST NATAL MOOD EPISODES

a) Have you ever experienced an episode of postpartum psychosis, puerperal psychosis or any mood episode following childbirth?
 Yes (go to q.b) No/Unsure (cut off)

b) Was this a high or low mood? How soon after delivery was this episode?

c) Were you admitted or received hospital treatment?
 Yes (ask if OK to pass details to Christine) No/Unsure (Cut off)

<CUT OFF> If NO

I am very sorry but our criteria for the current research project is quite strict and at the moment we are only able to interview women who are currently pregnant or have had an episode of puerperal psychosis that required hospital treatment.. However, it is possible that we may have studies in the future that you could become involved in if you are still willing. Would you like to be included on our newsletter mailing list so that we can keep you updated with the findings of the research and of any future research we are carrying out?

YES (add details to box 4) No (End of TS)

2. Could I ask how you heard about our research?.....

First of all I'll just tell you a bit about what taking part involves:

I usually visit women in their homes during their pregnancy for an interview that lasts about an hour and a half. During the interview I will ask about the kinds of mood symptoms you have experienced in the past, the types of treatments you have received and questions relating to your current pregnancy and any previous pregnancies you may have had. Following the interview, I will also leave you with a set of questionnaires to complete and return in your own time. As we are interested in identifying genetic factors that make some individuals more susceptible than others to mood symptoms, this study does involve providing a small blood sample from your arm which I would take when I come to visit you. Then, if you are willing, approximately 3 months after your baby is born, I will arrange to contact you by telephone to ask you some questions about your delivery and also how you have been since I met with you during your pregnancy. This usually lasts around 20 minutes.

3. How does that sound to you? Do you think you may be interested in participating?

Yes (go to Q.4) No (Cut off)

<CUT OFF> If NO
Thank you very much for your interest in our research. Would you like to be included on our newsletter mailing list so that we can keep you updated with the findings of the research?
Yes (add details to Box 4) No (end of TS)

We are interested in seeing women who have experienced at least one period of high mood (often called mania or hypomania) in their life. Can I ask you a few questions about the mood symptoms you have experienced in the past just to make sure you are suitable to take part in the study?

4. Have you ever been diagnosed with bipolar disorder by a psychiatrist?

Yes (go to q.5) No (go to box 2)

BOX 2. NO KNOWN DIAGNOSIS OF BIPOLAR DISORDER

a) Would you say that you have experiences periods where you have felt very high in mood, or when you have felt very energetic or more irritable than usual?
Yes (go to q.b) No/Unsure (cut off)

b) During the same period did you find that your thoughts were racing , that you were talking more than usual , that you were more distractible than usual . Did you feel that you slept less than usual ?

c) Was this different to how you usually feel? Yes (go to d) No/Unsure (cut off)

d) How long would you say these periods lasted?.....

5. One of our study inclusion criteria is that individuals are over the age of 18, can I just check that you are 18 or older?

BOX 2. CONTINUED

<CUT OFF> If no high or irritable mood OR less than 3 additional symptoms OR episodes are not different from usual OR lasting less than 4 days in duration

I am very sorry but the symptoms you have described during your high moods do not sound as if they meet the criteria for our current research project, as our criteria are quite strict. Would you like to be included on our newsletter mailing list so that we can keep you updated with the findings of the research?

YES (add details to box 4) No (End of TS)

Yes (go to Q6) No Can I ask the date when you will be 18?

<CUT OFF> If NO AND PARTICIPANT WILL NOT BE 18 DURING PREGNANCY

Thank you very much for your interest. I am very sorry but we will be unable to interview you for this study as you are under 18.

Our research has been running for many years and we like to check individual's details with our database just to check if they have taken part in our studies previously.

6. Would you mind if I ask your date of birth?

DOB.....

7. Do you know if any of your family members have participated in this study?

Yes No

Details if biological relatives (Initials, DOB, Date participated if known):

.....

8. Can I ask how many weeks pregnant you currently are?.....

9. When is you expected due date?.....

(If less than 12 weeks): *Thank you for agreeing to take part in our pregnancy study. We usually feel it is best to interview women when they are at least 12 weeks pregnant. Is ok if I contact you in about ? weeks/months time to arrange an interview?*

Date to contact when 12 weeks pregnant.....

BOX 5. RISK ASSESSMENT

To be completed within **two weeks** before the interview date.

There are 2 important issues to consider:

1. That the potential participant is well enough in their mood to be seen within the next 2 weeks.
2. The level of risk to a lone interviewer conducting the interview at the participant's home.

Would you mind if I just asked you a few questions about how you have been feeling over the last month and any treatment you may have received?

How are you feeling in your mood at the moment?

.....

.....

.....

.....

Have you received inpatient hospital treatment or intensive home treatment for your mood disorder within the last month?

YES (If yes ask if it is OK to call again in one month) NO

Are you currently under the care of a CMHT? YES NO

Who are you in contact with within the team and how often.....

If participants are recruited non-systematically: We feel it is important to let an individual's key worker know that they are taking part in the study? Are you happy for me to let your key worker know?

Details (e.g. name and address).....

.....

Appendix H: Semi-structured psychiatric research interview

STUDY NUMBER: _____

PREGNANCY AND POSTPARTUM INTERVIEW

SUMMARY SHEET

Interviewer: _____

	Date (or N/A)	Comments
INTERVIEW COMPLETED		
BLOOD PACK GIVEN		
BLOOD SAMPLE RECEIVED		
QUESTIONNAIRES GIVEN		
QUESTIONNAIRE 2 WK REMINDER LETTER		
QUESTIONNAIRE REMINDER PHONE CALL		
QUESTIONNAIRES RECEIVED		
CASE NOTES REQUESTED (PP only see below)		
CASE NOTES RECEIVED (PP only see below)		

PROSPECTIVE PREGNANCY STUDY ADDITIONAL DATA

	Date (or N/A)	Comments
ANTENATAL QUESTIONNAIRE COMPLETED		
2 MONTH GP LETTER AND QUESTIONNAIRE SENT		
2 MONTH GP QUESTIONNAIRE RECEIVED		
2 MONTH PSYCHIATRIST LETTER AND QUESTIONNAIRE SENT		
2 MONTH PSYCHIATRIST QUESTIONNAIRE RECEIVED		
POSTNATAL TELEPHONE INTERVIEW COMPLETED		
CASE NOTES REQUESTED		
CASE NOTES RECEIVED		

PERSONAL INFORMATION

Initials _____

DOB (DD/MMM-three letters/YY) _____

INTERVIEW DATE (DD/MMM-three letters/YY)

AGE AT INTERVIEW (YEARS) _____

SEX	1	Male
	2	Female
	9	Unknown

GP (Surgery name and address)

Name and contact details of consultant psychiatrist and/or community mental health team R is currently or has previously been in contact with (note how long since last seen)

PLACE INTERVIEWED (CIRCLE ONE)

0	Not interviewed	4	Hospital Ward
1	Home	5	GP Surgery
2	QEPH	6	Relative's home
3	Psychiatric Clinic	7	Other
		8	Telephone
		9	Unknown
		10	UHW

METHOD OF RECRUITMENT (CIRCLE ONE)

1	Internet	12	Systematic CMHT
2	Media-Press	13	Other Self-help group
3	Media-Radio	14	Consultant
4	Media-TV	15	Poster/leaflet
5	Self-help literature	16	Other
6	MDF	17	APP
7	Depression Alliance	18	Genesis(DeCC) Controls
8	Local MHT Referral	19	Newcastle
9	National MHT Referral	20	Systematic GP Surgery
10	Lithium Clinics		screen
11	Relatives	21	Dublin
		22	F-series
		23	Aberdeen
		99	UNKNOWN

ETHNIC ORIGIN (CIRCLE ONE)

- | | | | |
|---|-------------------------|---|----------------|
| 1 | South Wales Caucasian | 5 | Afro-Caribbean |
| 2 | UK/Eire Caucasian | 6 | Asian |
| 3 | West European Caucasian | 7 | Mixed race |
| 4 | Other Caucasian | 9 | Unknown |

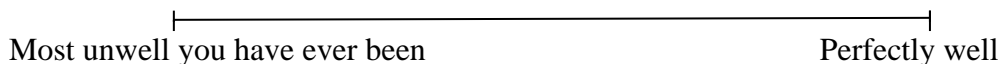
ORIGIN OF FATHER’S FAMILY (CIRCLE ONE)

- | | | | |
|---|-------------------------|---|----------------|
| 1 | South Wales Caucasian | 5 | Afro-Caribbean |
| 2 | UK/Eire Caucasian | 6 | Asian |
| 3 | West European Caucasian | 7 | Mixed race |
| 4 | Other Caucasian | 9 | Unknown |

ORIGIN OF MOTHER’S FAMILY (CIRCLE ONE)

- | | | | |
|---|-------------------------|---|----------------|
| 1 | South Wales Caucasian | 5 | Afro-Caribbean |
| 2 | UK/Eire Caucasian | 6 | Asian |
| 3 | West European Caucasian | 7 | Mixed race |
| 4 | Other Caucasian | 9 | Unknown |

Ask R to make a mark on the line to show how they feel today:



CURRENT MENTAL STATE

How long have you been well for?(circle one)

- | | | | |
|---|-------------------|---|-------------------|
| 1 | Currently unwell | 5 | 7-12 months |
| 2 | Less than 1 month | 6 | More than 1 year |
| 3 | 1-3 months | 7 | More than 5 years |
| 4 | 4-6 months | 9 | Unknown |

How long has it been since your last discharge from hospital? (circle one)

- | | | | |
|---|-----------------------|---|--------------------------------------|
| 1 | Currently in hospital | 5 | 7-12 months |
| 2 | Less than 1 month | 6 | More than 1 year |
| 3 | 1-3 months | 7 | More than 5 years |
| 4 | 4-6 months | 8 | Not applicable (never been admitted) |
| | | 9 | Unknown |

Life chart



OBSTETRIC HISTORY (For all past pregnancies)

PREGNANCY # _____ **Date** _____

OUTCOME:

- | | | |
|---------------------------------|---------------|--------------------|
| 1 Normal vaginal delivery | 3 Stillbirth | 5 Termination |
| 2.1 Elective caesarean section | 4 Miscarriage | 6 Forceps/Ventouse |
| 2.2 Emergency caesarean section | | |

GESTATION: _____ wks **MATERNAL AGE AT OUTCOME:** _____ yrs

SEX OF BABY:

- | | | | |
|-----------------------|--------------------------|-------------------------|--------------------------|
| 1 Male | <input type="checkbox"/> | 5 Twins – male & female | <input type="checkbox"/> |
| 2 Female | <input type="checkbox"/> | 6 Other _____ | <input type="checkbox"/> |
| 3 Twins – both male | <input type="checkbox"/> | 7 Unknown | <input type="checkbox"/> |
| 4 Twins – both female | <input type="checkbox"/> | | |

Pregnancy planned? Y / N/UK **IVF?** Y / N/UK

Rating of psychiatric sequelae (any symptoms occurring within 6 months):

- | | | | |
|---|--------------------------|---|-------------------------|
| 0 | No problems | 5 | “Baby blues” |
| 1 | Mania (including Mixed) | 6 | Cycloid |
| 2 | Hypomania | 7 | Other psychotic episode |
| 3 | Psychotic depression | 8 | Other perinatal episode |
| 4 | Non-psychotic depression | 9 | Unknown |

Admitted Y / N /UK

Psychotic symptoms? Description and congruence

Onset: _____ wks If immediate or as soon as baby born rate 1 week unless day of onset clearly stated. 0.3 = 3 days. Use negative number for onset before term e.g. – 8 weeks = 32 wks.

Duration: _____ wks Use decimal place for days eg 0.3 = 3 days. Use 2nd decimal place for hours eg 0.03 = 3 hours. If > 9 hours round up to one day.

Medication Timeline: (starting 6 months before conception, to 3 months after delivery)

ASK FOLLOWING FOR LIVE DELIVERYS ONLY

PREGNANCY:

Any complications during pregnancy (maternal or baby medical condition severe enough to warrant treatment either as an out patients or hospital admission)? Y / N/UK If yes give details

Pre-eclampsia diagnosis Y / N/UK

Pre-eclampsia symptoms? Y / N/UK If yes give details of symptoms

Smoke during pregnancy? Y/ N/UK

Overall, was your pregnancy a positive experience for you?

1 Not at all 2 3 Somewhat 4 5 Very much

Did you feel you had people you could depend on for emotional support when you got home with your baby (other than partner)?

1 Not at all 2 3 Somewhat 4 5 Very much

Did you have you a partner in this pregnancy? Yes No

If yes, was your relationship with your partner an emotionally supportive one?

1 Not at all 2 3 Somewhat 4 5 Very much

DELIVERY:

Labour: Induction Y / N If yes, select method: IV Pessary Other _____
 Augmentation Y / N If yes, select method: IV Pessary Other _____

Time contractions started ____ **Time of delivery** ____ **Length of labour (hrs)** ____

Sleep loss during labour: Y / N/UK **Total number of nights missed sleep** ____

Pain relief given: Epidural Pethidine
 Gas & Air TENS Other _____

Pain score_(At worst during labour / delivery): _____ 1 = mild discomfort, 10 = worst pain imaginable

Complications during delivery? (breech, distress, cord accidents): Y / N/UK If yes give details

Any problems identified with the baby at birth or following birth? Y / N/UK If yes give details

Birth weight _____ (g or lb, oz and then convert)

BREASTFEEDING: Y / N If yes, duration _ wks

Any episodes in relation to stopping breastfeeding: Yes No Don't know

Details (high/low mood? Mixed features? Psychotic symptoms? Anxiety/panic?):

SYMPTOMS EXPERIENCED DURING EPISODES OF MANIA/HYPOMANIA

NB: For women who have had a postnatal illness please rate the worst postnatal episode independent of polarity, preferentially mania if they have had both depression and mania, however there may be exceptions - hypomania vs severe PND. If the worst postnatal episode is mania/mixed please also rate the worst non-puerperal episode of mania/mixed and worst episode of depression. If the worst postnatal episode is depression please also rate the worst episode of non-puerperal depression and worst episode of mania/mixed.

Use 0, 1, 2, 8, 9 unless where indicated

Episode to be rated WE-NPN _____	Episode to be rated WE-PN _____	Episode to be rated WE-M _____			
			WE- NPN	WE- PN	WE-M
10.001 Expansive (elevated) mood			___	___	___
Did you feel intensely happy or elated without reason? So elated it was unnatural for you					
10.02 Irritable mood			___	___	___
During that time did you find that you were easily irritated, that any little thing provoked you? Did others comment you were too impatient?					
Perplexity					
<i>During this episode did you feel confused? Did you have difficulty getting your thoughts in order? Did you understand clearly what was going on?</i>					
			___	___	___
10.004 Pressing and racing thoughts			___	___	___
Did you find thoughts crowding and racing through your mind, speeding up and have too many compared to usual? Describe? How long did this last?					
10.005 Over-talkativeness			___	___	___
Did people say you talked too fast/ too much so you weren't understood? Could others understand you? Did you feel a pressure to keep talking?					
10.006 Distractibility			___	___	___
Could you concentrate or keep your attention on one thing so that you could complete the task or deal with something properly? Were you distracted by irrelevant things around you/ environmental surroundings?					
10.007 Self-reported overactivity			___	___	___
Were you more active than usual/normal? So active that others thought that there was something wrong? Did you have tremendous energy? Was it unnatural and out of character for you?					
Increased energy			___	___	___
Did you find that you have a lot more energy than usual?					
10.010 Exaggerated self esteem			___	___	___
Did you seem especially efficient or really good at work or in your daily activities- as though you had super powers or talents? Superbly healthy, high intelligence, extraordinary abilities? How did you explain this? How did you opinion compare to others?					

Age first received treatment for high mood _____ years or UK

3. *Have you ever been admitted to hospital, day hospital or had intensive home treatment for your episodes of high mood?* Y N UK

IF YES

Total number of admissions for high mood _____ number or UK

Age first admitted to hospital for high mood _____ years or UK

Ever been sectioned under the mental health act for high mood Y N UK

Proportion of hypomanic/manic episodes experienced _____
Have any of the following triggered episodes of high mood?

	Ever
Sleep loss e.g. long haul flights, shift work, Specify situation:	Y / N / UK / NA
Alcohol	Y / N / UK / NA
Menstrual Cycle	Y / N / UK / NA
Contraceptive Pill/Implant	Y / N / UK / NA
Drugs (non-prescription) Specify:	Y / N / UK / NA
Medication Specify:	Y / N / UK / NA
Other Specify:	Y / N / UK / NA

SECTION 6: DEPRESSED MOOD AND IDEATION

Episode to be
rated WE-NPN _____

Episode to be
rated WE-PN _____

Episode to be
rated WE-D _____

Use 0,1, 2, 8, 9 unless where indicated

- | | | WE-
NPN | WE-
PN | WE-D |
|-------|---|------------|-----------|------|
| 6.001 | Depressed mood
How would you describe your mood during this period? Sad, gloomy, despairing, deeply depressed? Mild/ moderate/ severe? How much of the time were you in reasonable spirits/ really low? When did you last feel your usual self? | ___ | ___ | ___ |
| 7.004 | Loss of interests
What were your interests before? Did you lose interest in work, recreation, appearance? To what extent- did you lose interest altogether? | ___ | ___ | ___ |
| 6.005 | Capacity for enjoyment
Was there anything you enjoyed doing that lifted your spirits? Were you able to positively enjoy things, interests, hobbies? Or were you unable to find pleasure in things you would normally enjoy? | ___ | ___ | ___ |
| 6.012 | Tedium vitae
Did you feel that life was not worth living, or you didn't care if you wake up? Ever wish you had a fatal disease? Recurrent death thoughts? | ___ | ___ | ___ |
| 6.011 | Suicide or self-harm [0-5]
Did you ever think about harming yourself or make an attempt at suicide?
0=absent, 2=suicidal ideation, 3=suicide attempt unlikely to result in death, 4=attempt likely to result in death, 5=multiple attempts likely to result in death | ___ | ___ | ___ |
| | Number of attempts _____ | | | |
| | Worst attempt _____ | | | |
| | Extra question for WE PN episode: Did you have any thoughts about harming your baby? | | ___ | |
| 6.009 | Morning depression [0-1]
When did it feel worse? Any time less severe?
0= not worse early/ 1= worse early in day | ___ | ___ | ___ |
| 6.017 | Loss of self-esteem
What was your opinion of yourself compared to others? Did you feel less competent than them? Inferior or worthless? | ___ | ___ | ___ |
| 6.013 | Pathological guilt
Did you blame yourself for things you had done? Feel guilty or ashamed? What had you done? Would you feel the same now? Out of proportion. | ___ | ___ | ___ |

3.006 **Agitated anxiety** (in the context of depression) _____
 Were you so fidgety and restless that you couldn't sit still?
 Did you have to keep pacing up and down?
 [fidgety = mild; restlessness = moderate; pacing = severe]

4.001 **General rating of anxiety** (in the context of depression) _____
 Now I would like to ask you about feelings of anxiety or panic during PERIOD. When people get anxious or panicky they often feel fearful. They may feel their heart beating fast, or they may start shaking or sweating, or feel they can't get their breath. Have you had feelings like that? Can you describe it? [0/1]

Mixed episodes

During episodes of depression, did you ever also experience (even for brief periods) manic-type symptoms such as elevated mood, increased energy, racing thoughts and increased self esteem? _____

DEPRESSED MOOD AND IDEATION

1. Duration of longest episode of depression? _____ days/weeks (delete one) or UK
2. *How many of these episodes have you experienced in your life?* _____
 (only include episodes lasting at least 2 weeks put UK if unknown or 0 if none)

Go to next page if all episodes of depression have lasted less than two weeks

3. *At what age did these depressions start to cause impairment in your life for example you had to take time off work/school, you saw your GP, or your high mood caused problems with family or friends?* _____ years or UK
4. *Have you ever received treatment for your episodes of depression either from your GP, a psychiatrist or other health professional?* Y N UK

Age first received treatment for depression _____ years or UK

5. *Have you ever been admitted to hospital for your episodes of depression?* Y N UK

IF YES

Total number of admissions for depression _____ number or UK

DEPRESSED MOOD AND IDEATION

Have any of the following triggered episodes of depressed mood?

	Ever
Sleep loss e.g. long haul flights, shift work Specify situation:	Y / N / UK / NA
Alcohol	Y / N / UK / NA
Menstrual Cycle	Y / N / UK / NA
Contraceptive Pill/Implant	Y / N / UK / NA
Drugs (non-prescription) Specify:	Y / N / UK / NA
Medication Specify:	Y / N / UK / NA
Other Specify:	Y / N / UK / NA

AFFECTIVE SYMPTOMS ADDITIONAL INFORMATION

Have you ever had 4 or more mood episodes (depression or mania) in one year?

Y N UK

Has anyone ever told you that you have rapid cycling

Y N UK

Suicidal Ideation (LE)

If R has been asked about suicidal ideation and attempts in the depression section, make rating based on the answers to these items

For individuals who were not asked the depression section:

Have you ever thought that life was not worth living, or you didn't care if you wake up?

Have you ever thought about harming yourself or even made an attempt at suicide?

Rate most severe lifetime-ever:

- 0 Absent
- 1 Tedium vitae
- 2 Suicidal ideation
- 3 Suicide attempt unlikely to result in death
- 4 Suicide attempt likely to result in death
- 5 Multiple suicide attempts likely to result in death
- 9 Unknown

NB: Suicidal ideation/attempt does NOT have to be in the context of depression to be rated here.

Details: _____

Polarity of first episode: If age of first impairment is the same for mania and depression, please indicate which occurred first

Mania Depression Unknown N/A

HALLUCINATIONS, THOUGHT DISORDER, REPLACEMENT OF WILL & DELUSIONS

• Probe question: Hearing noises/voices

Have you ever heard noises or voices when there was nobody around and no ordinary explanation seemed possible?

IF YES brief description

PN Mania/mixed
Non PN Mania/mixed
PN Depression

17.009 **Third person Auditory Hallucinations** Did you ever hear voices talking about you between themselves or did you ever hear a single voice talking about you?

IF YES brief description

PN Mania/mixed
Non PN Mania/mixed
PN Depression

17.008 **Voice(s) commenting on thoughts or actions** Did a voice comment on your thoughts or actions?

IF YES brief description

PN Mania/mixed
Non PN Mania/mixed
PN Depression

Probe question: Visual Hallucinations

Have you ever had visions or seen things other people couldn't see?

IF YES brief description

PN Mania/mixed
Non PN Mania/mixed
PN Depression

Other hallucinations (17.022, 17.026, 17.028)

Have you ever noticed any unusual smells that you couldn't account for or any unusual sexual sensations or noticed any other strange or inexplicable sensations of touch, taste, or temperature, or pain, or floating? Or like a crawling sensation under the skin?

IF YES brief description

PN Mania/mixed
Non PN Mania/mixed
PN Depression

Probe Question: Interference with thoughts

Have you ever felt some outside force or person was interfering with or controlling your thoughts or felt that your thoughts were being read? Have you ever experienced a thought in your mind repeating over, like an echo? Has it ever seemed that the thoughts in your mind were not your own, and they seemed to come from somewhere else? How did they get in your mind? Have you ever felt your thoughts were somehow public, not private, so that others know what your thinking? Did you feel the thoughts leaving? Have you ever experienced your thoughts actually been taken out or sent out of your mind?

IF YES brief description

PN Mania/mixed
Non PN Mania/mixed
PN Depression

Probe Question: Experience of Replacement of Will Have you ever felt some outside force or person was controlling your actions?

IF YES brief description

PN Mania/mixed
Non PN Mania/mixed
PN Depression

19.004 Delusions of reference

Have you ever felt the TV, radio or newspaper were talking about you? or giving messages to you? Have people ever seemed to drop hints meant for you, or say things with double meanings?

IF YES brief description

PN Mania/mixed
Non PN Mania/mixed
PN Depression

• **19.003 Delusions of being spied upon**

Have people seemed to talk about you, check up on you, or follow you about, or record your movements?

IF YES brief description

PN Mania/mixed
Non PN Mania/mixed
PN Depression

• **19.007 Delusions of misidentification**

Are there people about who are not what they seem? Perhaps in disguise? (strangers are people from the past, nursing staff are impostors/or police)

IF YES brief description

PN Mania/mixed
Non PN Mania/mixed
PN Depression

- **19.008 Familiar people impersonated (by strangers)**

Did you feel that the appearance of people you know well had changed in ways that suggested someone was impersonating them?

IF YES brief description

PN Mania/mixed
Non PN Mania/mixed
PN Depression

- **19.012 Delusions of persecution**

Have you ever experienced the feeling that someone or some organisation was trying to harm you?

IF YES brief description

PN Mania/mixed
Non PN Mania/mixed
PN Depression

- **19.014 Delusional jealousy**

Were you jealous of your friend or spouse? What did you do to convince yourself nothing was wrong?

IF YES brief description

PN Mania/mixed
Non PN Mania/mixed
PN Depression

19.017 Delusional lover

Have you believed that someone important was in love with you, even though there was no evidence? Are you loved by someone who does not publicly acknowledge it? Who is it? What evidence to you have of these advances? Do you try to make contact?

IF YES brief description

PN Mania/mixed
Non PN Mania/mixed
PN Depression

Have you ever been unusually preoccupied with religious ideas for example thoughts about God or the Devil?

IF YES brief description

PN Mania/mixed
Non PN Mania/mixed
PN Depression

• 10.016/19.029 Delusions of grandiose ability or 10.017/19.030 identity

Have you ever felt that you or your baby have had special powers? or thought you were somebody special?

IF YES brief description

PN Mania/mixed
Non PN Mania/mixed
PN Depression

• **Delusions of guilt or worthlessness (6.018/19.025)**

Have you ever felt responsible for a crime, evil or harm to others?

IF YES brief description

PN Mania/mixed
Non PN Mania/mixed
PN Depression

• (OPCRIT item 57) **Delusions of poverty**

Have you ever believed that you have lost all of your money or property?

IF YES brief description

PN Mania/mixed
Non PN Mania/mixed
PN Depression

• (OPCRIT item 58) **Nihilistic delusions**

Have you ever felt that part of your body had disappeared or was rotting away or was affected by some devastating or malignant disorder or did you ever believe that you were dead?

IF YES brief description

PN Mania/mixed
Non PN Mania/mixed
PN Depression

General probe question

Have you ever had any other unusual or abnormal experiences when your mind has played tricks on you that looking back now seems strange or unusual?

IF YES brief description

PN Mania/mixed
Non PN Mania/mixed
PN Depression

AGE FIRST PSYCHOSIS _____

SECTION 4: PANIC, ANXIETY AND PHOBIAS

Use scale 1 (0-3) unless stated otherwise

4.001 General rating of anxiety

When people get anxious or panicky they often feel very fearful. They may feel their heart beating fast, or they may start shaking or sweating, or feel they can't get their breath.

_[0/1]

PANIC ATTACKS

4.020 Frequency of panic attacks with autonomic symptoms

Have you had any attacks of panic, or sudden attacks of anxiety which very quickly become intolerable?

[number in a 4 week period] —

Note symptoms in 4.003-4.019

4.021 **Enduring apprehension of having an attack-** *after an attack do you worry about its effects or about getting another attack ?* —

4.022 **Action to prevent or to end panic attack** *—do you have to do something to end an attack, like leaving a bus, or anything to prevent attacks?*

0=absent, 1=action to prevent, 2=action to end, 3 prevent and end —

ALL (0/1) anxiety	Panic	Generalised
4.003 <i>can't get breath and smothering feeling</i>	—	—
4.004 heart pounding, missing beats, faster	—	—
4.005 <i>dizzy, light-headed, faint, unsteady</i>	—	—
4.006 <i>tingly, numbness in face/fingers</i>	—	—
4.007 <i>tightness, discomfort or pain in chest</i>	—	—
4.008 dry mouth not due to medication or dehydration	—	—
4.009 <i>difficulty in swallowing, lump in throat,</i>	—	—
4.010 sweating e.g. palms	—	—
4.011 trembling or shaking e.g. hands or limbs	—	—
4.012 <i>hot or cold sweats or flushes</i>	—	—
4.013 <i>unreality, 'not really here' like an actor</i>	—	—
4.014 <i>churning stomach, nausea, butterflies</i>	—	—
4.015 <i>fear of dying</i>	—	—
4.016 <i>fear of choking</i>	—	—

- 4.17 *fear of going crazy, or fear of losing emotional control or passing out* — —
- 4.018 *apprehension, jumpiness, or increased startle response* — —
- 4.019 *other e.g. increase urinary frequency* — —

Did panic attacks form a prominent part of the WE PN episode (Y, N , UK) _____

GENERALISED ANXIETY

4.023 Free floating anxiety

- *Have you ever had anxiety periods for longer periods not just in attacks (include only anxiety with no apparent reason)*
0=none, 1=mild occasional anxiety, 2= moderately severe 3= severe anxiety —

4.025 *Duration of free floating anxiety – number of months* —

PERIOD RATED _____

***Note symptoms in 4.003-4.019* and also the following all rated (rating scale 1 0-3)**

3.001 Worrying – *did you worry a great deal? did unpleasant thoughts go round and round in your mind, could you stop worrying by looking at the TV or reading or thinking about something you enjoy*

—

3.002 Feeling of nervous tension- *did you often felt on edge or keyed up or mentally strained, everyday problems get on top of you?. Did you Startle too easily?* —

3.003 General muscular tension- *did you have difficulty relaxing, muscles feel tensed up?* —

3.005 Localised tension pains- *did you have aches and pains, like headache, backache, aching muscles? Exclude migraine* —

3.006 Subjective describes restlessness- *were you fidgety and restless?*
fidgety=mild restless=moderate, pacing=restless —

3.07 Fatigability and exhaustion- *were you exhausted and worn out during the day even when you hadn't been working very hard* —

3.010 Irritability – *were you more impatient or irritable than usual*
1= mild irritability, brief domestic quarrels mood, 2= raised voice, anger, shouting,
3=pushing hitting, lost control —

3.012 Depersonalisation and derealisation *Did you feel that things around you or you yourself were unreal* —

7.002 Loss of concentration *was your concentration as good as usual?* —

Did your sleep pattern alter during this episode of anxiety [0/1] —

Did generalised anxiety form prominent part of the WE PN episode (Y, N , UK) _____

FAMILY HISTORY

Draw a family tree of 1ST DEGREE RELATIVES- parents, children, siblings
Have any of these relatives suffered with their nerves, had a nervous breakdown, seen a psychiatrist, tried to harm themselves, committed suicide or had a problem with drugs or alcohol? For female relatives ask whether there is any known family history of postnatal illness

NB: REMEMBER TO CHECK THAT RELATIVES ARE BIOLOGICAL RELATIVES

Are you adopted? Y N UK Are you a twin? Y N UK

Is there anyone else in the family, such as grandparents, aunts, uncles, nieces or nephew that have suffered with their nerves, had a nervous breakdown, seen a psychiatrist tried to harm themselves, committed suicide or had a problem with drugs or alcohol? For female relatives ask whether there is any known family history of postnatal illness

.....
.....

HIGHEST EDUCATIONAL ATTAINMENT (circle as many as necessary)

- 0 None
- 1 11+
- 2 CSE (includes NVQ level 1, GNVQ, GSVO foundation level, other RSA/City & Guilds qualifications, Youth Training Certificate).
- 3 O-Level/GCSE (includes NVQ level 2, GNVQ Intermediate, RSA diploma, City & Guilds craft)
- 4 A-Level/AS levels/Scottish Highers/HND/BTEC (includes Scottish certificate of sixth year studies, NVQ levels 3&4, GNVQ Advanced, SCOTVEC, HNC, RSA Higher/Advanced Diploma, City & Guilds Advanced Craft)
- 5 Degree (includes NVQ level 5)
- 6 Post-graduate degree
- 9 Unknown

Current Occupation (if individuals are not currently working, check whether they are unable to work due to sickness and whether they are receiving incapacity benefit)

.....

Previous Occupation (please indicate whether they are receiving incapacity benefit)

.....

Occupation at time first became unwell (please indicate the individuals occupation at illness onset or if they were a full time student or if they were unemployed at that time)

.....

ALCOHOL/SMOKING/DRUGS QUESTIONNAIRE

1. Have you ever been a regular smoker? (please circle) YES NO
If YES at what age did you begin to smoke? _____ years

2. ALCOHOL

a. Have you ever used alcohol regularly? (please circle) YES NO

IF YES please continue, if NO please go to question 3 on the next page

b. How old were you when you first used alcohol regularly? _____(please put age or unknown)

c. At your heaviest ever, how many units of alcohol did you consume on average per week (NB 1 unit of alcohol is equal to one small glass of wine, a single measure of spirits or half a pint of beer/larger/cider)
_____Number of units per week

d. Did you experience any associated problems through alcohol usage at that time e.g. psychiatric, medical, financial, relationship, occupational? (please circle)
YES NO NOT SURE

Brief details if YES

e. During the year before the onset of your illness, how many units of alcohol did you consume on average per week?
Number of units per week _____

f. Did you experience any associated problems through alcohol usage at that time e.g. psychiatric, medical, financial, relationship, occupational? (please circle)
YES NO NOT SURE

Brief details if YES

3. DRUGS

a. Have you ever used **cannabis** regularly? (please circle)
YES NO NOT SURE

IF YES please continue, if NO please go to question 4 on this page

b. Did you use cannabis regularly in year before the onset of your illness? (please circle)
YES NO NOT SURE

- c. Did you ever experience any associated problems through cannabis usage e.g. psychiatric, medical, financial, relationship, occupational? (please circle)
 YES NO NOT SURE

Brief details if YES

.....

4. NON-PRESCRIPTION DRUGS

- a. Have you ever used any **other non-prescription/non-over the counter drugs** - such as sedatives, *tranquilizers, valium*, stimulants, *speed, ecstasy*, volatile substances, *glue, solvents*, cocaine, opioids, *heroin, methadone*? (please circle)
 YES NO NOT SURE

If YES please continue if NO end of the questionnaire please go to next questionnaire on the next page

- b. Which **non-prescription drugs** have you taken regularly?

.....

- c. Did you use any of these regularly during the year before the onset of your illness? (please circle)
 SURE YES NO NOT SURE

- d. Did you ever experience any associated problems through drug usage e.g. psychiatric, medical, financial, relationship, occupational? (please circle)
 SURE YES NO NOT SURE

Brief details if YES

.....

.....

HORMONAL CONTRACEPTION

Hormonal contraception: Yes No

		Mini	Combined	Injection	Implant	Mirena coil
Symptoms worse	Name _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Symptoms improve	Name _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
No change <input type="checkbox"/>						

Episodes related to Hormonal Contraception: Yes No Don't know

Details (starting/stopping/changing):

.....
.....

MENOPAUSE

Natural menopause: Yes Oophorectomy: Yes

Age (range) of Menopause: _____

Any episodes in relation to menopause: Yes No Don't know

Details (high/low mood? Mixed features? Psychotic symptoms? Anxiety/panic?):

.....
.....

HORMONE REPLACEMENT THERAPY

HRT: Yes No

Name of HRT medication: _____

Any episodes in relation to HRT: Yes No Don't know

Details (high/low mood? Mixed features? Psychotic symptoms? Anxiety/panic?):

.....
.....

PREMENSTRUAL SYMPTOMS Do you experience some or any of the following premenstrual symptoms which start before your period and stop within a few days of bleeding?

Symptom	Not at all	Mild	Moderate	Severe
Anger/irritability				
Anxiety/tension				
Tearful/increased sensitivity to rejection				
Depressed mood/hopelessness				
Decreased interest in work activities				
Decreased interest in home activities				
Decreased interest in social activities				
Difficulty concentrating				
Fatigue/lack of energy				
Overeating/food cravings				
Insomnia				
Hypersomnia (needing more sleep)				
Feeling overwhelmed or out of control				
Physical symptoms: breast tenderness, headaches, joint/muscle pain, bloating, weight gain				

Have your symptoms, as listed above, interfered with:

	Not at all	Mild	Moderate	Severe
Your work efficiency or productivity				
Your relationship with coworkers				
Your relationships with your family				
Your social life activities				
Your home responsibilities				

CLEQ QUESTIONNAIRE

Self / Interviewer rated (please circle)

Did you experience as a child (up to age 16 years) any of the following life events?

	<i>Please circle:</i>		<i>If yes, how old were you?</i>
	Yes	No	_____
1. Death of parent			_____
2. Death of a brother/sister			_____
3. Death of a close friend			_____
4. Divorce of parents			_____
5. Marital separation of parents			_____
6. Marriage of parent to step parent	Yes	No	_____
7. Serious illness needing hospitalisation			_____
8. Hospitalisation of a parent			_____
9. Acquiring a visible deformity			_____
10. Jail sentence of a parent for a year or more			_____
11. Teenage pregnancy/fatherhood			_____
12. Suspension from school			_____
13. Are there any other significant life events you experienced as a child that are not mentioned about?			Yes No

.....

Appendix I: Third-trimester pregnancy interview

PROSPECTIVE ANTENATAL QUESTIONNAIRE

TO BE COMPLETED AT THE END OF THE INTERVIEW IF PAST 24 WEEKS OR AT A LATER DATE VIA TELEPHONE ONCE THE WOMAN HAS REACHED 24 WEEKS

STUDY ID _____ INITIALS _____ DOB _____

Date completed

Questions about your pregnancy:
 What date is your baby due?

How many weeks pregnant are you?

Questions about your feelings about your pregnancy and the support you are receiving

Overall, has this pregnancy been a positive experience for you? (please circle one)

1 2 3 4 5
 Not at all Somewhat Very much

Do you feel you will have people you can depend on for emotional support when you go home with your baby? (other than partner) (please circle one)

1 2 3 4 5
 Not at all Somewhat Very much

Have you a partner in this pregnancy? (please tick one) Yes No

If yes, is your relationship with your partner an emotionally supportive one? (please circle one)

1 2 3 4 5
 Not at all Somewhat Very much

Pregnancy planned? Y / N/UK IVF? Y / N/UK

Questions about smoking, drugs and alcohol in pregnancy

In this pregnancy have you smoked cigarettes?

Yes No

If YES, on average, how many cigarettes a day have you smoked?

In this pregnancy, have you drunk alcohol regularly?

Yes No

If YES, how many units of alcohol have you consumed on average per week? (1 unit of alcohol is equal to one small glass of wine, a single measure of spirits or half a pint of beer/lager/cider)

During this pregnancy have you used any of the following substances when they have not been prescribed by a doctor?

- Sedatives Yes No
- Cannabis Yes No
- Speed Yes No
- Ecstasy Yes No
- Glue Yes No
- Solvents Yes No
- Cocaine Yes No
- Heroin Yes No
- Methadone Yes No
- Other non prescription/over the counter drugs Yes No

If yes please give brief details

PANIC, ANXIETY AND PHOBIAS

4.001 *General rating of anxiety*

When people get anxious or panicky they often feel very fearful. They may feel their heart beating fast, or they may start shaking or sweating, or feel they can't get their breath. ___[0/1]

PANIC ATTACKS

4.020 *Frequency of panic attacks with autonomic symptoms*

Have you had any attacks of panic, or sudden attacks of anxiety which very quickly become intolerable during this pregnancy?

[number in a 4 week period] ___

Note symptoms in 4.003-4.019

4.021 *Enduring apprehension of having an attack- after an attack do you worry about its effects or about getting another attack ?* ___

4.022 *Action to prevent or to end panic attack –do you have to do something to end an attack , like leaving a bus, or anything to prevent attacks?*

0=absent, 1=action to prevent , 2=action to end, 3 prevent and end ___

ALL (0/1)	Panic	Generalised anxiety
4.003 <i>can't get breath and smothering feeling</i>	___	___
4.004 <i>heart pounding, missing beats, faster</i>	___	___
4.005 <i>dizzy, light-headed, faint, unsteady</i>	___	___
4.006 <i>tingly, numbness in face/fingers</i>	___	___
4.007 <i>tightness, discomfort or pain in chest</i>	___	___
4.008 <i>dry mouth not due to medication or dehydration</i>	___	___
4.009 <i>difficulty in swallowing, lump in throat,</i>	___	___
4.010 <i>sweating e.g. palms</i>	___	___
4.011 <i>trembling or shaking e.g. hands or limbs</i>	___	___
4.012 <i>hot or cold sweats or flushes</i>	___	___
4.013 <i>unreality, 'not really here' like an actor</i>	___	___
4.014 <i>churning stomach, nausea, butterflies</i>	___	___
4.015 <i>fear of dying</i>	___	___
4.016 <i>fear of choking</i>	___	___

- 4.17 *fear of going crazy, or fear of losing emotional control or passing out* — —
- 4.018 *apprehension, jumpiness, or increased startle response* — —
- 4.019 *other e.g. increase urinary frequency* — —

GENERALISED ANXIETY

4.023 Free floating anxiety

- *Have you ever had anxiety periods for longer periods during this pregnancy not just in attacks? (include only anxiety with no apparent reason)*
0=none, 1=mild occasional anxiety, 2= moderately severe 3= severe anxiety —

4.025 *Duration of free floating anxiety – number of months* —

PERIOD RATED _____

***Note symptoms in 4.003-4.019* and also the following all rated (rating scale 1 0-3)**

3.001 Worrying – *did you worry a great deal? did unpleasant thoughts go round and round in your mind, could you stop worrying by looking at the TV or reading or thinking about something you enjoy*
 —

3.002 Feeling of nervous tension- *did you often felt on edge or keyed up or mentally strained, everyday problems get on top of you?. Did you Startle too easily?* —

3.003 General muscular tension- *did you have difficulty relaxing, muscles feel tensed up?* —

3.005 Localised tension pains- *did you have aches and pains, like headache, backache, aching muscles? Exclude migraine* —

3.006 Subjective describes restlessness- *were you fidgety and restless?*
fidgety=mild restless=moderate, pacing=restless —

3.007 Fatigability and exhaustion- *were you exhausted and worn out during the day even when you hadn't been working very hard* —

3.010 Irritability – *were you more impatient or irritable than usual*
1= mild irritability, brief domestic quarrels mood, 2= raised voice, anger, shouting, 3=pushing hitting, lost control —

3.012 Depersonalisation and derealisation *Did you feel that things around you or you yourself were unreal* —

7.002 Loss of concentration *was your concentration as good as usual?* —

Did your sleep pattern alter during this episode of anxiety [0/1]
 —

Sleep Before Pregnancy:

The following questions are about what your sleep was like **in the last few weeks before you became pregnant**. Answer each question **independently** of others and please **select the answer that best described you**.

1. During the **first half hour** after you woke up in the morning, how did you **usually** feel?

- Very tired Fairly tired Fairly refreshed Very refreshed

2. At **approximately** what time in the evening did you feel tired, and, as a result, in need of sleep? (*Please circle*):

8:00PM – 9:00PM	9:00PM – 10:15PM	10:15PM – 12:45AM	12:45AM – 2:00AM	2:00 – 3:00 AM
-----------------	------------------	-------------------	------------------	----------------

3. At **approximately** what time of day did you usually feel your best? (*Please circle*):

5:00 – 8:00 AM	8:00 – 10:00 AM	10:00 AM - 5:00 PM	5:00 – 10:00 PM	10:00PM – 5:00AM
----------------	-----------------	--------------------	-----------------	------------------

4. **Approximately** what time would you have gotten up if you had been entirely free to plan your day? (*i.e. if you had no other commitments that day*):

5:00 AM – 6:30 AM	6:30 AM – 7:45 AM	7:45 AM – 9:45 AM
9:45 AM – 11:00 AM	11:00 AM – 12:00 noon	12:00 noon – 5:00 PM

5. One hears about “morning types” and “evening types.” Which one of these types do you consider yourself to be? (*Please circle*):

Definitely a morning type	Rather more a morning type than an evening type	Rather more an evening type than a morning type	Definitely an evening type
---------------------------	---	---	----------------------------

6. Before you became pregnant, did you have a regular work schedule? *If YES, distinguish between work days and free days (below). If NO, distinguish between weekdays and weekends.* Yes No

On your work days/weekdays:

- a) What time did you usually fall asleep? (*NB: this may be different from the time you got into bed*) _____
- b) What time did you usually wake up? (*NB: this may be different from the time you got out of bed*) _____

On your free days/weekends:

- a) What time did you usually fall asleep? (*NB: this may be different from the time you got into bed*) _____
- b) What time did you usually wake up? (*NB: this may be different from the time you got out of bed*) _____

7. How many hours of sleep do you think you need (when not pregnant) in order to feel refreshed? _____

Sleep Quality Over the Last Month:

In the **last month**, how would you rate your sleep quality overall?

- Very good Fairly good Fairly bad Very bad

BLEQ (last 6 months)

1. In the last 6 months, did you suffer from a serious illness, injury or an assault?
Yes No
- If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
2. In the last 6 months, did a serious illness, injury or assault happen to a close relative?
Yes No
- If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
3. In the last 6 months, did a parent, spouse (or partner), child, brother or sister of yours die?
Yes No
- If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
4. In the last 6 months did a close family friend or relative die, such as an aunt, cousin or grandparent?
Yes No
- If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
5. In the last 6 months, did you have a separation due to marital difficulties or break off a steady relationship?
Yes No
- If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
6. In the last 6 months, did you have a serious problem with a close friend, neighbour or relatives?
Yes No
- If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
7. In the last 6 months were you made redundant or sacked from your job?
Yes No
- If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
8. In the last 6 months were you seeking work without success for more than one month?
Yes No
- If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
9. In the last 6 months did you have a major financial crisis such as losing the equivalent of three months income?
Yes No
- If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
10. In the 6 months, did you have problems with the police involving a court appearance?
Yes No
- If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
11. In the 6 months, was something you valued lost or stolen?
Yes No
- If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
12. In the last 6 months other than being pregnancy
any other significant event happened in your life?
Yes No
- If yes, what was it? _____

Appendix J: Postpartum GP questionnaire

STUDY ID _____ INITIALS _____ DOB _____

Pregnancy and Childbirth Questionnaire

Q 1. Date of delivery

Q 2. Pregnancy outcome

- Live birth
- Stillbirth
- Termination
- Miscarriage

Q 3. Delivery modality

- Normal vaginal delivery
- Elective caesarean section
- Emergency caesarean section
- Forceps / Ventouse

Q. 4 Baby health status:

- Healthy
- Minor problem
- Major problem

Please give brief details of any problems:

Q 5. Has she suffered an episode of psychiatric illness in this pregnancy or post-partum period?

Yes No

If yes please give brief details:

Completed by:

Name

Position

Date

Address

E-mail address

Telephone number

Please send completed questionnaire in the pre-paid envelope provided

Thank you for your time

Appendix K: Postpartum psychiatrist questionnaire

STUDY ID _____ INITIALS _____ DOB _____

Pregnancy and Childbirth Questionnaire**Q1. Episodes of psychiatric illness during pregnancy****Did she experience an episode of depression during the pregnancy?**Yes No Unknown **Did she experience an episode of mania, hypomania or a mixed affective episode during the pregnancy?**Yes No Unknown **Did she experience another form of psychiatric episode during the pregnancy?**Yes No Unknown

If yes please give brief details:

--

If yes to any of the above, was the onset of the episode;

In the first trimester of pregnancy

Yes No

In the second trimester of pregnancy

Yes No

In the third trimester of pregnancy

Yes No

A continuation of an episode from before pregnancy

Yes No **Was she admitted to hospital?**Yes No

Q 2. Episodes of psychiatric illness in the postpartum period**Did she experience an episode of depression following this delivery?**Yes No **Did she experience an episode of mania, hypomania or a mixed affective episode following this delivery?**Yes No **Did she experience another form of psychiatric episode following this delivery?**Yes No

If yes please give brief details:

--

If yes to any of the above, was the onset of the episode:

the continuation of an episode from pregnancy

Yes No

an onset following delivery

Yes No **If a postpartum onset, when was the onset in relationship to delivery?**
 days **Or** weeks following delivery
Was she admitted to hospital?Yes No

Q 3. Medication in relationship to the pregnancy

What prescribed medication did she take in the 6 months before pregnancy?
(Please indicate daily doses and say when any changes were made)

What prescribed medication did she take during the pregnancy?
(Please indicate daily doses and say when any changes were made)

What prescribed medication did she take in the postpartum period?
(Please include daily doses and say when any changes made)

Completed by:

Name

Position

Date

Address

E-mail address

Telephone number

Please send completed form in the pre-paid envelope provided

Thank you for your time

Appendix L: Three month postpartum interview

PROSPECTIVE POSTNATAL INTERVIEW

TO BE COMPLETED VIA TELEPHONE 3 MONTHS POSTNATALLY AFTER LETTERS SENT TO GP AND PSYCHIATRIST

STUDY ID _____ **INITIALS** _____ **DOB** _____

Date of delivery _____

OUTCOME:		
1 Normal vaginal delivery	3 Stillbirth	5 Termination
2.1 Elective caesarean section	4 Miscarriage	6 Forceps/ Ventouse
2.2 Emergency caesarean section		
GESTATION: _____ wks		MATERNAL AGE AT DELIVERY: _____ yrs
SEX OF BABY:		
1 Male <input type="checkbox"/>	5 Twins – male & female <input type="checkbox"/>	
2 Female <input type="checkbox"/>	6 Other _____ <input type="checkbox"/>	
3 Twins – both male <input type="checkbox"/>	7 Unknown <input type="checkbox"/>	
4 Twins – both female <input type="checkbox"/>		
PREGNANCY:		
Any complications during pregnancy (maternal or baby medical condition severe enough to warrant treatment either as an out patients or hospital admission)? Y / N/UK If yes give details		
Pre-eclampsia diagnosis Y / N/UK		
Pre-eclampsia symptoms? Y / N/UK If yes give details of symptoms		
DELIVERY:		
Labour: Induction	Y / N	If yes, select method: IV <input type="checkbox"/> Pessary <input type="checkbox"/> Other _____
Augmentation	Y / N	If yes, select method: IV <input type="checkbox"/> Pessary <input type="checkbox"/> Other _____
Time contractions started _____ Time of delivery _____ Length of labour (hrs) _____		
Sleep loss during labour: Y / N/UK Total number of nights missed sleep _____		
Pain relief given: Epidural	<input type="checkbox"/>	Pain score: _____
Pethidine	<input type="checkbox"/>	(At worst during labour / delivery)
Gas & Air	<input type="checkbox"/>	1 = mild discomfort
TENS	<input type="checkbox"/>	10 = worst pain imaginable
Other	<input type="checkbox"/> _____	
Complications during delivery? (breech, distress, cord accidents): Y / N/UK If yes give details		
Any problems identified with the baby at birth or following birth? Y / N/UK If yes give details		
Birth weight (g) _____	Apgar score at birth _____	Apgar score at 5 mins _____
BREASTFEEDING: Y / N		Duration

During your pregnancy or following childbirth have you experienced any periods of depression, high, irritable or mixed mood? Yes No Unknown

Timeline details of all episodes during perinatal period i.e during pregnancy and following delivery (including time frames, treatments received, if admitted, any psychotic symptoms)

First period following delivery?
If yes, when?
Did this have any effect on mood? (e.g. trigger episode, improve/worsen symptoms?)

Worst episode during this pregnancy (RATE SCAN SYMPTOMS FOR THIS EPISODE):

0	No problems	5	“Baby blues”
1	Mania (including Mixed)	6	Cycloid
2	Hypomania	7	Other psychotic episode
3	Psychotic depression	8	Other perinatal episode
4	Non-psychotic depression	9	Unknown

If immediate or as soon as baby born rate 1 week unless day of onset

Onset: _____ wks clearly stated. 0.3 = 3 days. Use negative number for onset before term

e.g. – 8 weeks = 32 wks.

Use decimal place for days eg 0.3 = 3 days.

Duration: _____ wks Use 2nd decimal place for hours eg 0.03 = 3 hours.

If > 9 hours round up to one day.

Worst episode following delivery (RATE SCAN SYMPTOMS FOR THIS EPISODE):

0	No problems	5	“Baby blues”
1	Mania (including Mixed)	6	Cycloid
2	Hypomania	7	Other psychotic episode
3	Psychotic depression	8	Other perinatal episode
4	Non-psychotic depression	9	Unknown

If immediate or as soon as baby born rate 1 week unless day of onset

Onset: _____ wks clearly stated. 0.3 = 3 days. Use negative number for onset before term

e.g. – 8 weeks = 32 wks.

Use decimal place for days eg 0.3 = 3 days.

Duration: _____ wks Use 2nd decimal place for hours eg 0.03 = 3 hours.

If > 9 hours round up to one day.

Was the episode following delivery a continuation of the episode during pregnancy? Y, N UK, NA

SYMPTOMS EXPERIENCED DURING MOOD EPISODE

Rate SCAN items for worst episode: if worst episode is depression- start with depression section and then ask mania section for that episode also. If worst episode is a manic episode, ask the manic section first and then the depression section. Ask psychosis questions regardless of polarity

Ask following 3 items regardless of polarity

	Preg	Delivery
Did you feel particularly anxious, worried or uptight?	___	___
Did you feel scared?	___	___
During this episode did you feel confused? Did you have difficulty getting your thoughts in order?	___	___
Did you understand clearly what was going on?	___	___

DEPRESSION

Use 0,1, 2, 8, 9 unless where indicated

6.001 Depressed mood	___	___
How would you describe your mood during this period? Sad, gloomy, despairing, deeply depressed?		
7.004 Loss of interests	___	___
What were your interests before? Did you lose interest in work, recreation, appearance? To what extent- did you lose interest altogether?		
6.005 Capacity for enjoyment	___	___
Was there anything you enjoyed doing that lifted your spirits? Were you able to positively enjoy things, interests, hobbies? Or were you unable to find pleasure in things you would normally enjoy?		
6.012 Tedium vitae	___	___
Did you feel that life was not worth living, or you didn't care if you wake up? Ever wish you had a fatal disease? Recurrent death thoughts?		
Following 2 items not to be asked explicitly rate if mentioned		
6.011 Suicide or self-harm [0-5]	___	___
Thoughts of harming baby		___
6.009 Morning depression [0-1]	___	___
When did it feel worse? Any time less severe? 0= not worse early/ 1= worse early in day		
6.017 Loss of self-esteem	___	___
What was your opinion of yourself compared to others? Did you feel less competent than them? Inferior or worthless?		

- | | Preg | Delivery |
|---|------|----------|
| 6.013 Pathological guilt | — | — |
| Did you blame yourself for things you had done? Feel guilty or ashamed? What had you done? Would you feel the same now? Out of proportion. | | |
| 6.015 Loss of self confidence with other people | — | — |
| How confident did you feel in yourself- in talking to others and managing relationships with others? | | |
| 6.016 Social withdrawal | — | — |
| Did you want to stay away from other people? Would you answer the door or telephone? Did you try to avoid company of others? Refuse it when offered? | | |
| 7.002 Loss of concentration | — | — |
| Was your concentration as good as usual, did your attention wander? Could you complete tasks? | | |
| 7.003 Subjectively inefficient thinking | — | — |
| Were you able to think clearly? Or were simple decisions hard to make? Thoughts slower? Indecisive? To what extent, severe- hardly begin to think about a problem? | | |
| 7.005 Subjective feeling of retardation | — | — |
| Did you feel as though you were slowed down in your movements? Talk or move much more slower? Arms and legs feel like lead? Did everyone else seem faster? | | |
| 7.006 Loss of energy | — | — |
| Did you feel as though you had lost energy or vigour? Was everything too much trouble? Comparative loss of energy to normal functioning? | | |
| 4.001 General rating of anxiety (in the context of depression) | — | — |
| Now I would like to ask you about feelings of anxiety or panic during PERIOD. When people get anxious or panicky they often feel fearful. They may feel their heart beating fast, or they may start shaking or sweating, or feel they can't get their breath. Have you had feelings like that? Can you describe it? [0/1] | | |
| 3.006 Agitated anxiety (in the context of depression) | — | — |
| Were you so fidgety and restless that you couldn't sit still?
Did you have to keep pacing up and down?
[fidgety = mild; restlessness = moderate; pacing = severe] | | |
| Mixed episodes | | |
| During episodes of depression, did you ever also experience (even for brief periods) manic-type symptoms such as elevated mood, increased energy, racing thoughts and increased self esteem? | | |
| | — | — |

MANIA/HYPOMANIA

- | | Preg | Delivery |
|---|------|----------|
| 10.001 Expansive (elevated) mood | ___ | ___ |
| Did you feel intensely happy or elated without reason? So elated it was unnatural for you | | |
| 10.03 Irritable mood | ___ | ___ |
| During that time did you find that you were easily irritated, that any little thing provoked you? Did others comment you were too impatient? | | |
| 10.004 Pressing and racing thoughts | ___ | ___ |
| Did you find thoughts crowding and racing through your mind, speeding up and have too many compared to usual? Describe? How long did this last? | | |
| 10.005 Over-talkativeness | ___ | ___ |
| Did people say you talked too fast/ too much so you weren't understood? Could others understand you? Did you feel a pressure to keep talking? | | |
| 10.006 Distractibility | ___ | ___ |
| Could you concentrate or keep your attention on one thing so that you could complete the task or deal with something properly? Were you distracted by irrelevant things around you/ environmental surroundings? | | |
| 10.007 Self-reported overactivity | ___ | ___ |
| Were you more active than usual/normal? So active that others thought that there was something wrong? Did you have tremendous energy? Was it unnatural and out of character for you? | | |
| 10.010 Exaggerated self esteem | ___ | ___ |
| Did you seem especially efficient or really good at work or in your daily activities- as though you had super powers or talents? Superbly healthy, high intelligence, extraordinary abilities? How did you explain this? How did you opinion compare to others? | | |
| 10.012 Actions based on expansive mood | ___ | ___ |
| Did you do anything that you wouldn't have normally? Was it because of the mood, high spirits you were in? Spend money you didn't have/ gamble/ reckless driving? Do anything you regretted later or got you into trouble? Describe? | | |
| 10.013 Decreased need for sleep | ___ | ___ |
| Did you sleep less at night? Manage with far less sleep without getting tired? | | |
| 10.014 Socially embarrassing behaviour | ___ | ___ |
| Were you more sociable than usual? Was it inappropriate, over-familiar or interfering? Behaviour that was embarrassing? Foolish actions out of character? | | |

10.015 **Increased sexual drive or activity**

Did you find that your sex drive or activities changed? In what way? Increased sexual activity, increased flirting, sexual indiscretions? _____

Dysphoric Mania

During episodes of high mood, did you ever also experience (even for brief periods) depressive-type symptoms such as low mood, loss of energy, hopelessness or suicidal feelings? _____

HALLUCINATIONS, THOUGHT DISORDER, REPLACEMENT OF WILL & DELUSIONS

• **Probe question: Hearing noises/voices**

Have you ever heard noises or voices when there was nobody around and no ordinary explanation seemed possible?

IF YES brief description

During pregnancy
Following delivery

17.009 **Third person Auditory Hallucinations** Did you ever hear voices talking about you between themselves or did you ever hear a single voice talking about you?

IF YES brief description

During pregnancy
Following delivery

17.008 Voice(s) commenting on thoughts or actions Did a voice comment on your thoughts or actions?

IF YES brief description

<p>During pregnancy</p> <p>Following delivery</p>
--

• **Probe question: Visual Hallucinations**

Have you ever had visions or seen things other people couldn't see?

IF YES brief description

<p>During pregnancy</p> <p>Following delivery</p>
--

• **Other hallucinations (17.022, 17.026, 17.028)**

Have you ever noticed any unusual smells that you couldn't account for or any unusual sexual sensations or noticed any other strange or inexplicable sensations of touch, taste, or temperature, or pain, or floating? Or like a crawling sensation under the skin?

IF YES brief description

<p>During pregnancy</p> <p>Following delivery</p>
--

• Probe Question: Interference with thoughts

Have you ever felt some outside force or person was interfering with or controlling your thoughts or felt that your thoughts were being read? Have you ever experienced a thought in your mind repeating over, like an echo? Has it ever seemed that the thoughts in your mind were not your own, and they seemed to come from somewhere else? How did they get in your mind? Have you ever felt your thoughts were somehow public, not private, so that others know what your thinking? Did you feel the thoughts leaving? Have you ever experienced your thoughts actually been taken out or sent out of your mind

IF YES brief description

During pregnancy
Following delivery

• Probe Question: Experience of Replacement of Will Have you ever felt some outside force or person was controlling your actions?

IF YES brief description

During pregnancy
Following delivery

19.004 Delusions of reference

Have you ever felt the TV, radio or newspaper were talking about you? or giving messages to you? Have people ever seemed to drop hints meant for you, or say things with double meanings?

IF YES brief description

During pregnancy
Following delivery

Have people seemed to talk about you, check up on you, or follow you about, or record your movements?

IF YES brief description

<p>During pregnancy</p> <p>Following delivery</p>
--

19.007 Delusions of misidentification

Are there people about who are not what they seem? Perhaps in disguise? (strangers are people from the past, nursing staff are impostors/or police)

IF YES brief description

<p>During pregnancy</p> <p>Following delivery</p>
--

- **19.008 Familiar people impersonated (by strangers)**

Did you feel that the appearance of people you know well had changed in ways that suggested someone was impersonating them?

IF YES brief description

<p>During pregnancy</p> <p>Following delivery</p>
--

• **19.012 Delusions of persecution**

Have you ever experienced the feeling that someone or some organisation was trying to harm you?

IF YES brief description

<p>During pregnancy</p>
<p>Following delivery</p>

19.014 Delusional jealousy

Were you jealous of your friend or spouse? What did you do to convince yourself nothing was wrong?

IF YES brief description

<p>During pregnancy</p>
<p>Following delivery</p>

19.017 Delusional lover

Have you believed that someone important was in love with you, even though there was no evidence? Are you loved by someone who does not publicly acknowledge it? Who is it? What evidence do you have of these advances? Do you try to make contact?

IF YES brief description

<p>During pregnancy</p>
<p>Following delivery</p>

- **19.021 Religious delusions**

Have you ever been unusually preoccupied with religious ideas for example thoughts about God or the Devil?

IF YES brief description

<p>During pregnancy</p> <p>Following delivery</p>
--

-

- **10.016/19.029 Delusions of grandiose ability or 10.017/19.030 identity**

Have you ever felt that you or your baby have had special powers? or thought you were somebody special?

IF YES brief description

<p>During pregnancy</p> <p>Following delivery</p>
--

- **Delusions of guilt or worthlessness (6.018/19.025)**

Have you ever felt responsible for a crime, evil or harm to others?

IF YES brief description

<p>During pregnancy</p> <p>Following delivery</p>
--

- (OPCRIT item 57) **Delusions of poverty**

Have you ever believed that you have lost all of your money or property?

IF YES brief description

<p>During pregnancy</p> <p>Following delivery</p>
--

- (OPCRIT item 58) **Nihilistic delusions**

Have you ever felt that part of your body had disappeared or was rotting away or was affected by some devastating or malignant disorder or did you ever believe that you were dead?

IF YES brief description

<p>During pregnancy</p> <p>Following delivery</p>
--

General probe question

Have you ever had any other unusual or abnormal experiences when your mind has played tricks on you that looking back now seems strange or unusual?

IF YES brief description

<p>During pregnancy</p> <p>Following delivery</p>
--

SECTION 4: PANIC, ANXIETY AND PHOBIAS**4.001 General rating of anxiety in prospective pregnancy**

When people get anxious or panicky they often feel very fearful. They may feel their heart beating fast, or they may start shaking or sweating, or feel they can't get their breath.

___[0/1]

PANIC ATTACKS**4.020 Frequency of panic attacks with autonomic symptoms**

Have you had any attacks of panic, or sudden attacks of anxiety which very quickly become intolerable since we last spoke?

[number in a 4 week period]

Note symptoms in 4.003-4.019

4.021 *Enduring apprehension of having an attack- after an attack do you worry*

about its effects or about getting another attack ?

4.022 *Action to prevent or to end panic attack –do you have to do something to end an attack*

, like leaving a bus, or anything to prevent attacks?

0=absent, 1=action to prevent , 2=action to end, 3 prevent and end

ALL (0/1)

Panic

Generalised anxiety

4.003 *can't get breath and smothering feeling*

4.004 *heart pounding, missing beats, faster*

4.005 *dizzy, light-headed, faint, unsteady*

4.006 *tingly, numbness in face/fingers*

4.007 *tightness, discomfort or pain in chest*

4.008 *dry mouth not due to medication or dehydration*

4.009 *difficulty in swallowing, lump in throat,*

4.010 *sweating e.g. palms*

4.011 *trembling or shaking e.g. hands or limbs*

4.012 *hot or cold sweats or flushes*

4.013 *unreality, 'not really here' like an actor*

4.014 *churning stomach, nausea, butterflies*

4.015 *fear of dying*

4.016 *fear of choking*

4.17 *fear of going crazy, or fear of losing*

emotional control or passing out

4.018 *apprehension, jumpiness, or increased startle response*

4.019 *other e.g. increase urinary frequency*

Did panic attacks form a prominent part of the WE PN episode (Y, N , UK) ___

GENERALISED ANXIETY

4.023 Free floating anxiety

- Have you had anxiety periods for longer periods not just in attacks during pregnancy or following childbirth? (include only anxiety with no apparent reason) ___
0=none, 1=mild occasional anxiety, 2= moderately severe 3= severe anxiety

4.025 Duration of free floating anxiety – **number of months** ___

PERIOD RATED _____

***Note symptoms in 4.003-4.019* and also the following all rated (rating scale 1 0-3)**

3.001 Worrying – did you worry a great deal? did unpleasant thoughts go round and round in your mind, could you stop worrying by looking at the TV or reading or thinking about something you enjoy ___

3.002 Feeling of nervous tension- did you often felt on edge or keyed up or mentally strained, everyday problems get on top of you?. Did you Startle too easily? ___

3.003 General muscular tension- did you have difficulty relaxing, muscles feel tensed up? ___

3.005 Localised tension pains- did you have aches and pains, like headache, backache, aching muscles? Exclude migraine ___

3.006 Subjective describes restlessness- were you fidgety and restless? ___
fidgety=mild restless=moderate, pacing=restless

3.08 Fatigability and exhaustion- were you exhausted and worn out during the day even when you hadn't been working very hard ___

3.010 Irritability – were you more impatient or irritable than usual ___
1= mild irritability, brief domestic quarrels mood, 2= raised voice, anger, shouting, 3=pushing hitting, lost control

3.012 Depersonalisation and derealisation Did you feel that things around you or you yourself were unreal ___

7.002 Loss of concentration was your concentration as good as usual? ___

Did your sleep pattern alter during this episode of anxiety [0/1]

Did generalised anxiety form prominent part of the WE PN episode (Y, N , UK) _____

Questions about your feelings about your pregnancy and the support you received since we last spoke

Overall, was your pregnancy a positive experience for you? (please circle one)

1 2 3 4 5
Not at all Somewhat Very much

Did you feel you had people you could depend on for emotional support when you got home with your baby? (other than partner) (please circle one)

1 2 3 4 5
Not at all Somewhat Very much

Did you have you a partner in this pregnancy? (please tick one) Yes
No

If yes, was your relationship with your partner an emotionally supportive one? (please circle one)

1 2 3 4 5
Not at all Somewhat Very much

Question about your sleep during the third trimester of your pregnancy

1) In the third trimester, how would you rate your sleep quality overall?

Very good Fairly good Fairly bad Very bad

Baby's sleep over the two weeks

Please mark only **one (most appropriate choice)**, for answers with a few options.

1. Sleeping arrangement:

- Infant crib in a separate room Infant crib in parents' room
 In parents' bed Infant crib in room with sibling
 Other, Specify: _____

2. In what position does your child sleep most of the time?

- On his/her belly On his/her side On his/her back

3. How much time does your child spend in sleep during the **NIGHT** (between 7 in the evening and 7 in the morning)? Hours: _____ Minutes: _____

4. How much time does your child spend in sleep during the **DAY** (between 7 in the morning and 7 in the evening)? Hours: _____ Minutes: _____

5. Average number of night wakings per night: _____

6. How much time during the night does your child spend in wakefulness (from 10 in the evening to 6 in the morning)? Hours: _____ Minutes: _____

7. How long does it take to put your baby to sleep in the evening? _____

8. How does your baby fall asleep?

- While feeding Being rocked Being held
 In bed alone In bed near parent

9. When does your baby usually fall asleep for the night? _____

10. Do you consider your child's sleep as a problem?

- A very serious problem A small problem Not a problem at all

Questions about smoking, drugs and alcohol in pregnancy

Depending on answer to antenatal questionnaire: Since we last spoke did you continue to smoke/start smoking cigarettes during your pregnancy?

Yes No

If YES, on average, how many cigarettes a day have you smoked since we last spoke?

Depending on answer to antenatal questionnaire: Since we last spoke did you continue to drink alcohol regularly/start drinking alcohol regularly during your pregnancy?

Yes No

If YES, how many units of alcohol have you consumed on average per week since we last spoke? (1 unit of alcohol is equal to one small glass of wine, a single measure of spirits or half a pint of beer/lager/cider)

Depending on answer to antenatal questionnaire: Since we last spoke did you continue use any of the following substances/start any of the following substances when they have not been prescribed by a doctor during your pregnancy?

- Sedatives Yes No
- Cannabis Yes No
- Speed Yes No
- Ecstasy Yes No
- Glue Yes No
- Solvents Yes No
- Cocaine Yes No
- Heroin Yes No
- Methadone Yes No
- Other non prescription/over the counter drugs Yes No

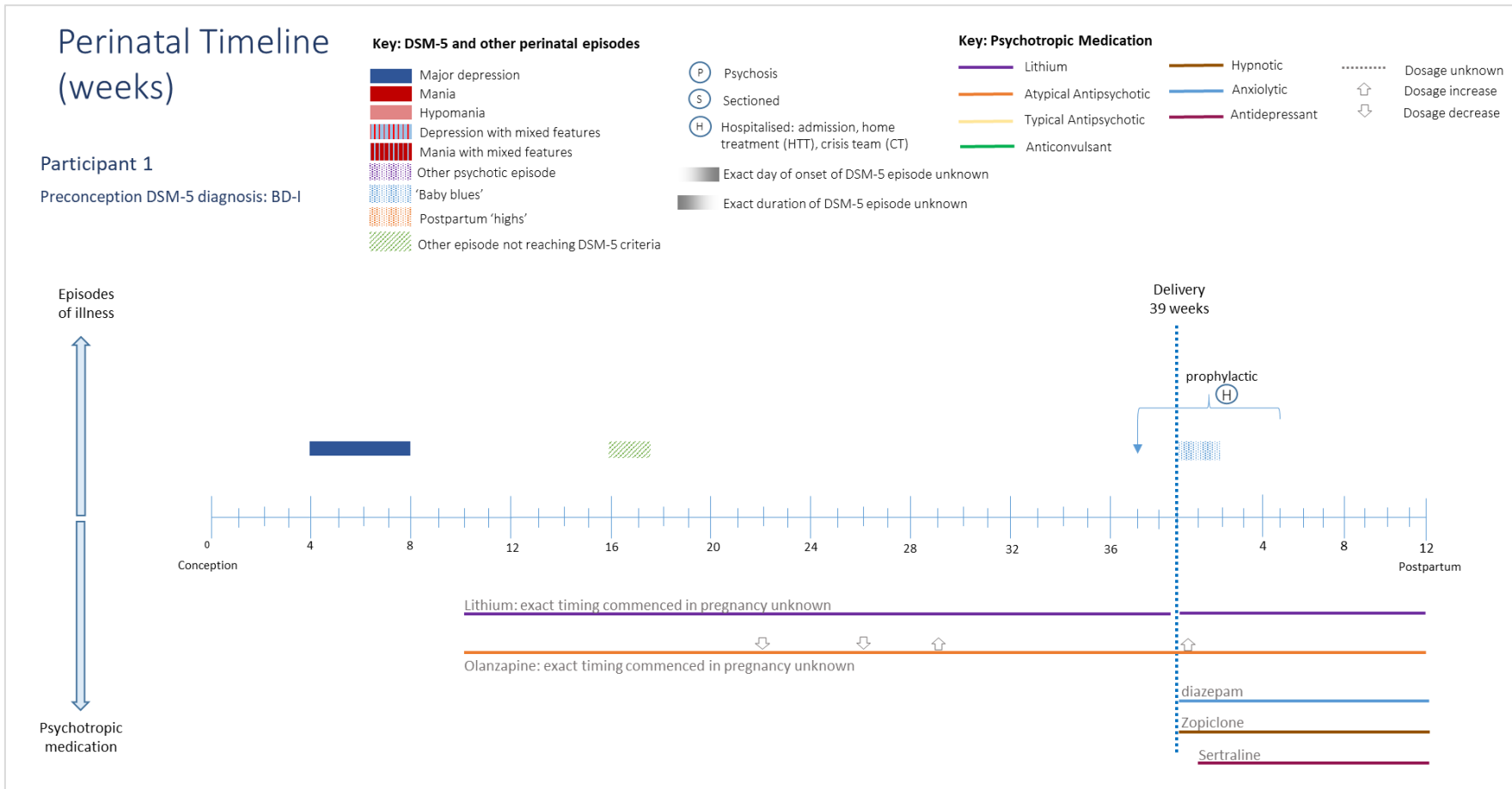
If yes please give brief details

BLEQ (since last interview)

1. In the last 6 months, did you suffer from a serious illness, injury or an assault?
Yes No
If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
2. In the last 6 months, did a serious illness, injury or assault happen to a close relative?
Yes No
If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
3. In the last 6 months, did a parent, spouse (or partner), child, brother or sister of yours die?
Yes No
If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
4. In the last 6 months did a close family friend or relative die, such as an aunt, cousin or grandparent?
Yes No
If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
5. In the last 6 months, did you have a separation due to marital difficulties or break off a steady relationship?
Yes No
If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
6. In the last 6 months, did you have a serious problem with a close friend, neighbour or relatives?
Yes No
If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
7. In the last 6 months were you made redundant or sacked from your job?
Yes No
If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
8. In the last 6 months were you seeking work without success for more than one month?
Yes No
If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
9. In the last 6 months did you have a major financial crisis such as losing the equivalent of three months income?
Yes No
If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
10. In the 6 months, did you have problems with the police involving a court appearance?
Yes No
If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
11. In the 6 months, was something you valued lost or stolen?
Yes No
If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad
12. In the last 6 months other than being pregnancy any other significant event happened in your life?
Yes No

If yes, what was it? _____

Appendix M: Perinatal timelines



Perinatal Timeline (weeks)

Participant 2

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

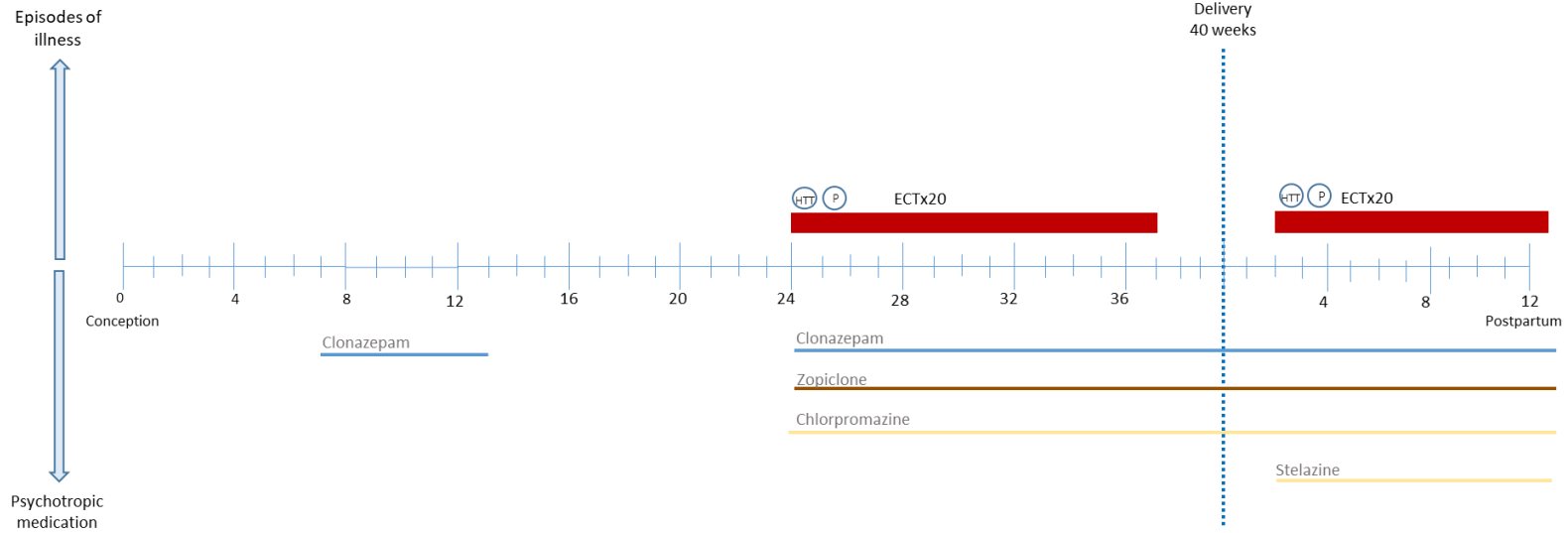
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 3

Preconception DSM-5 diagnosis: BD-I

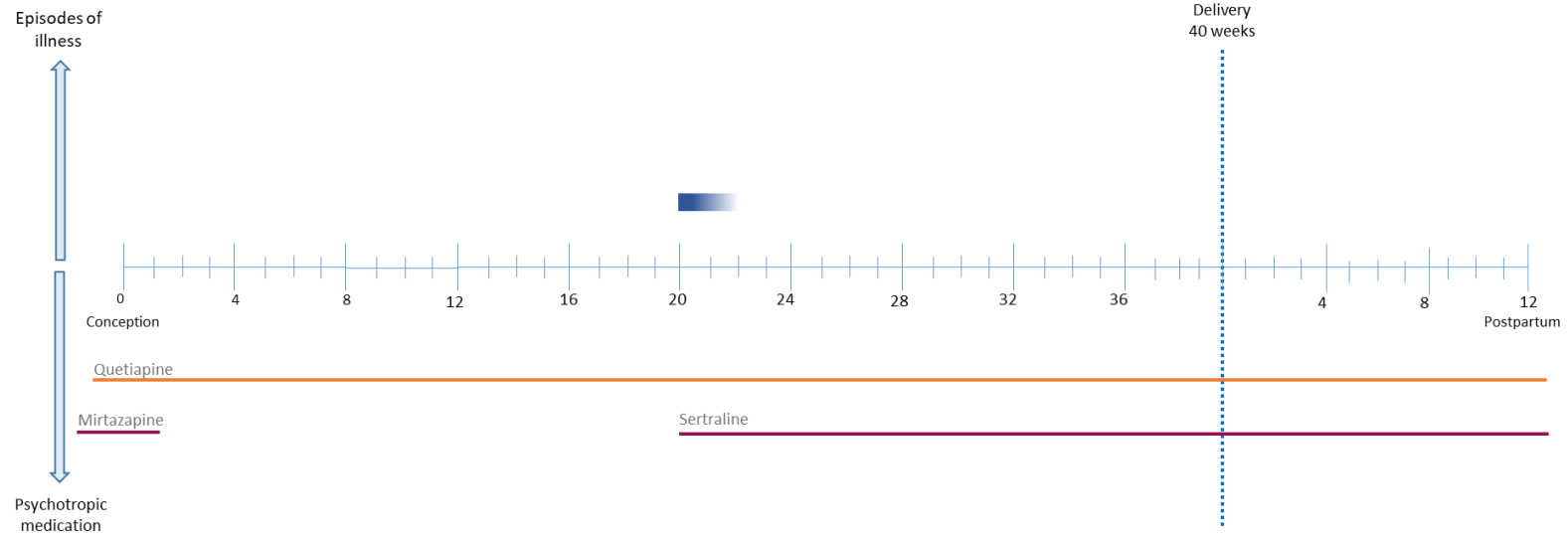
Key: DSM-5 and other perinatal episodes

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- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 4

Preconception DSM-5 diagnosis: BD-I

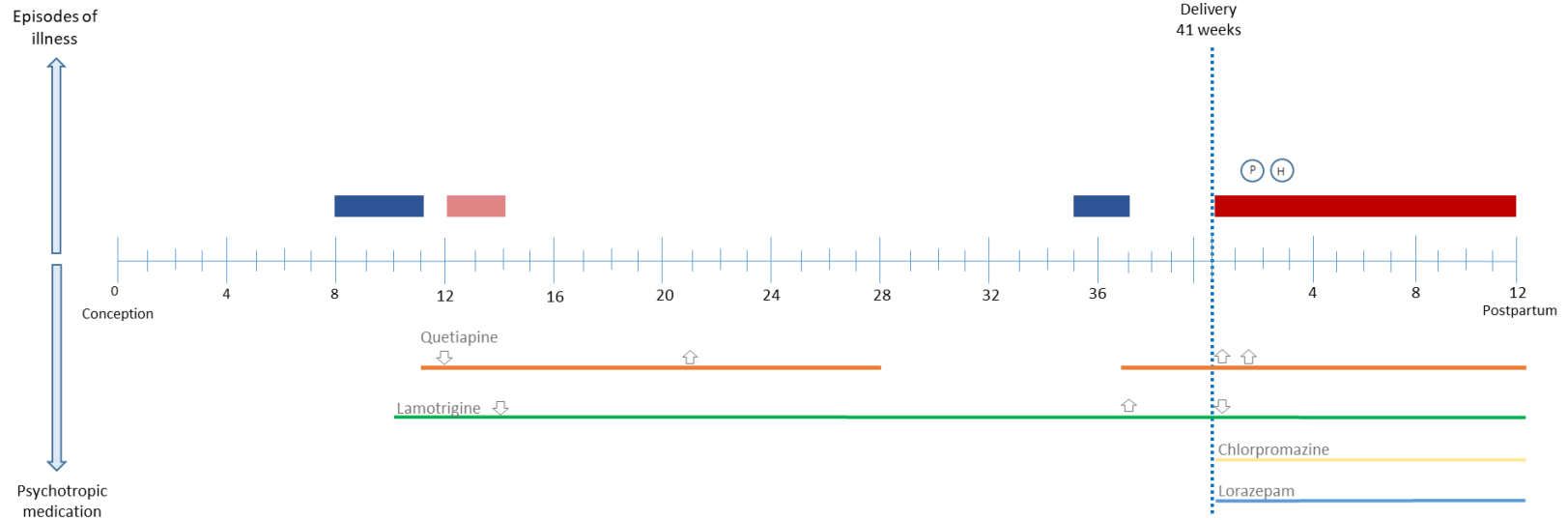
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 5

Preconception DSM-5 diagnosis: BD-I

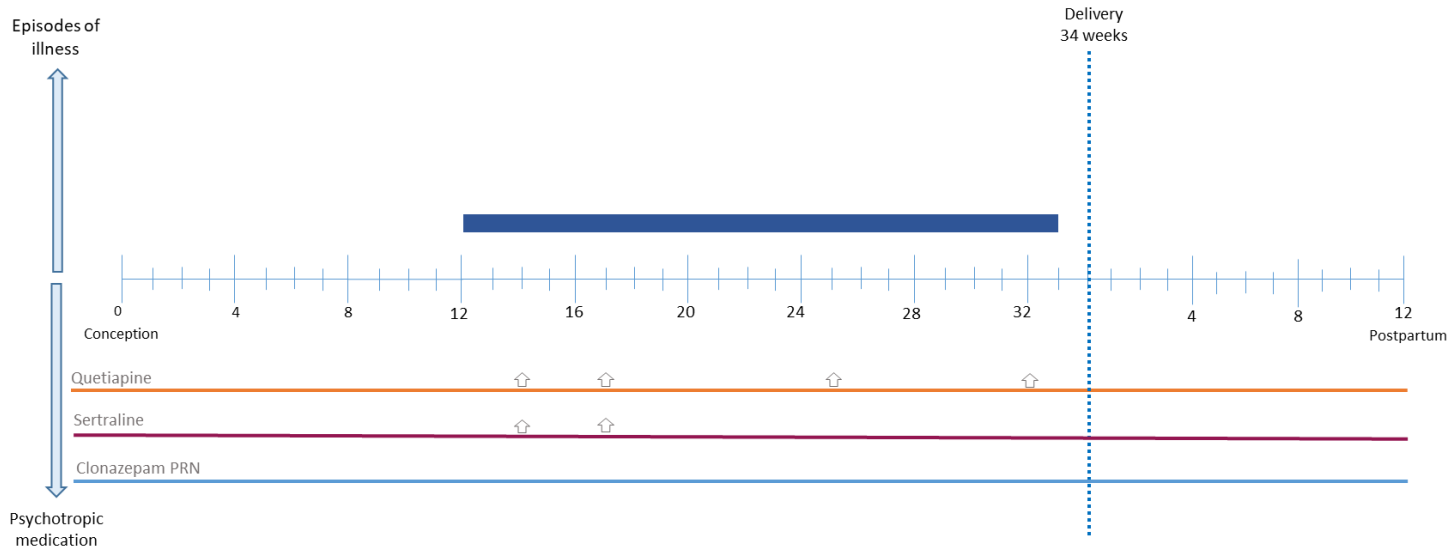
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

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- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 6

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

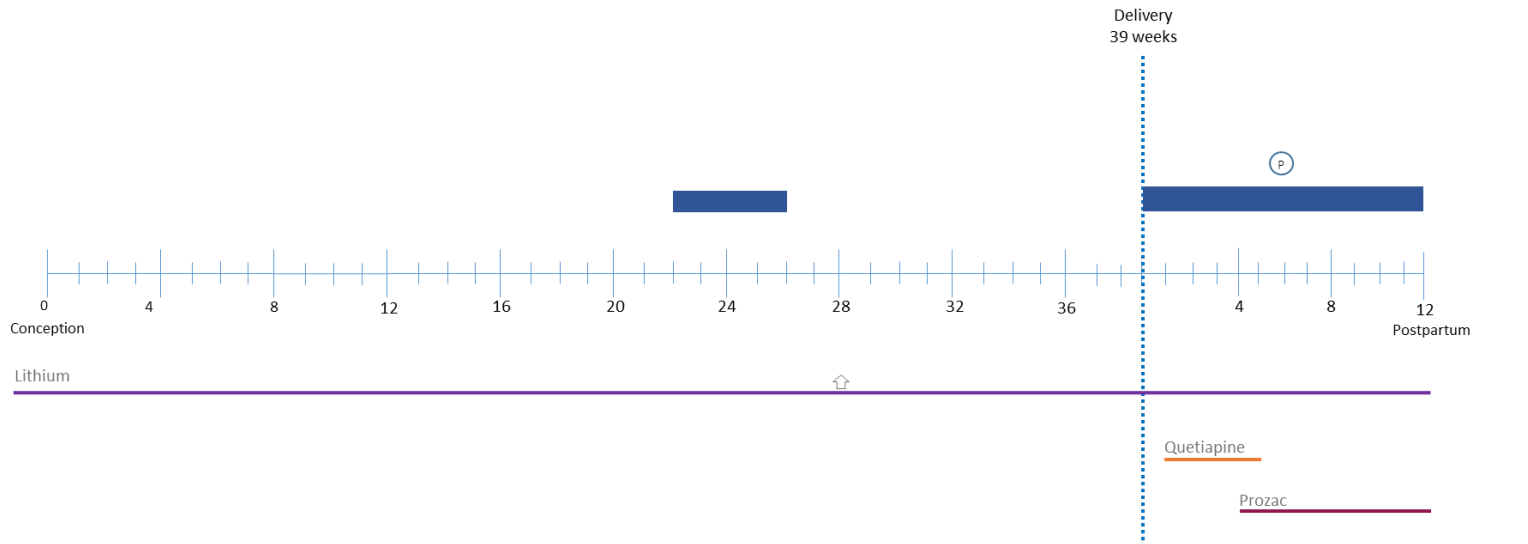
- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness

Psychotropic medication



Perinatal Timeline (weeks)

Participant 7

Preconception DSM-5 diagnosis: SA-BD

Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

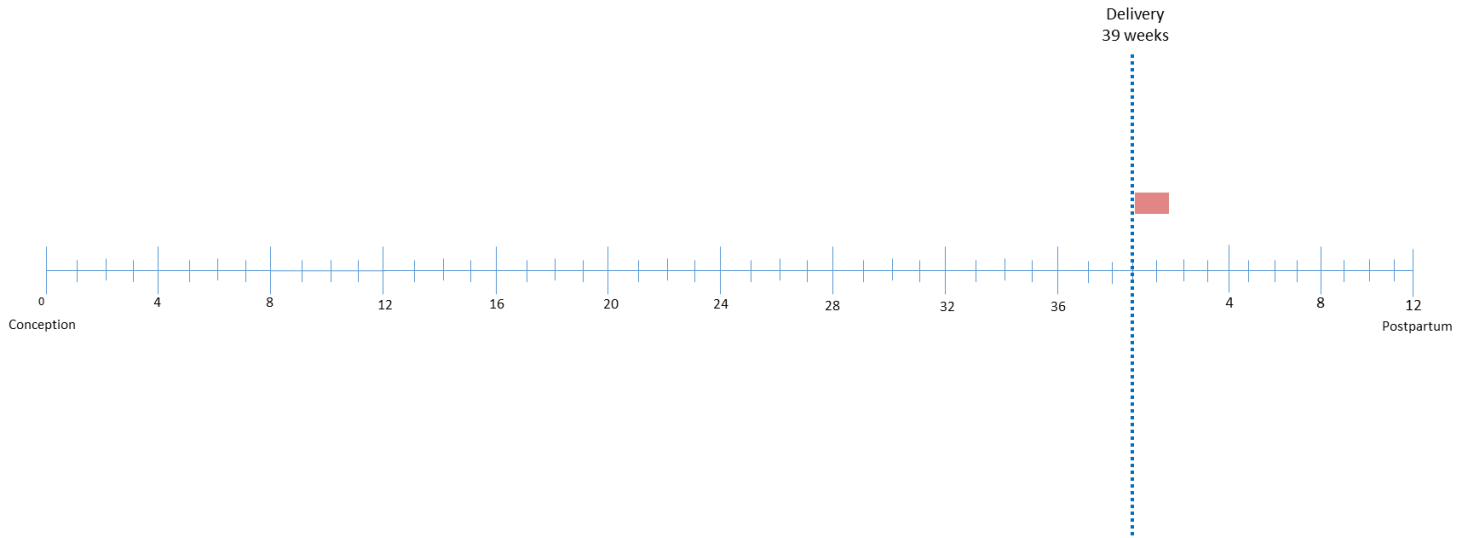
- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant

- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness



Psychotropic medication



Perinatal Timeline (weeks)

Participant 8

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

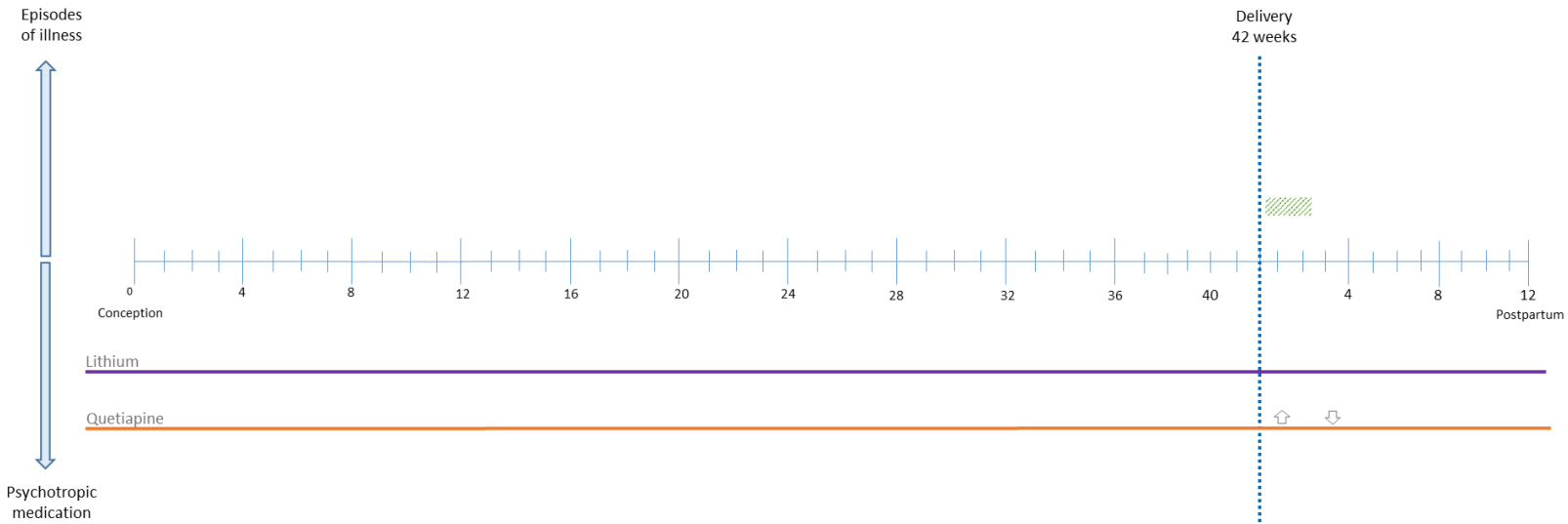
- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant

- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 9
Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

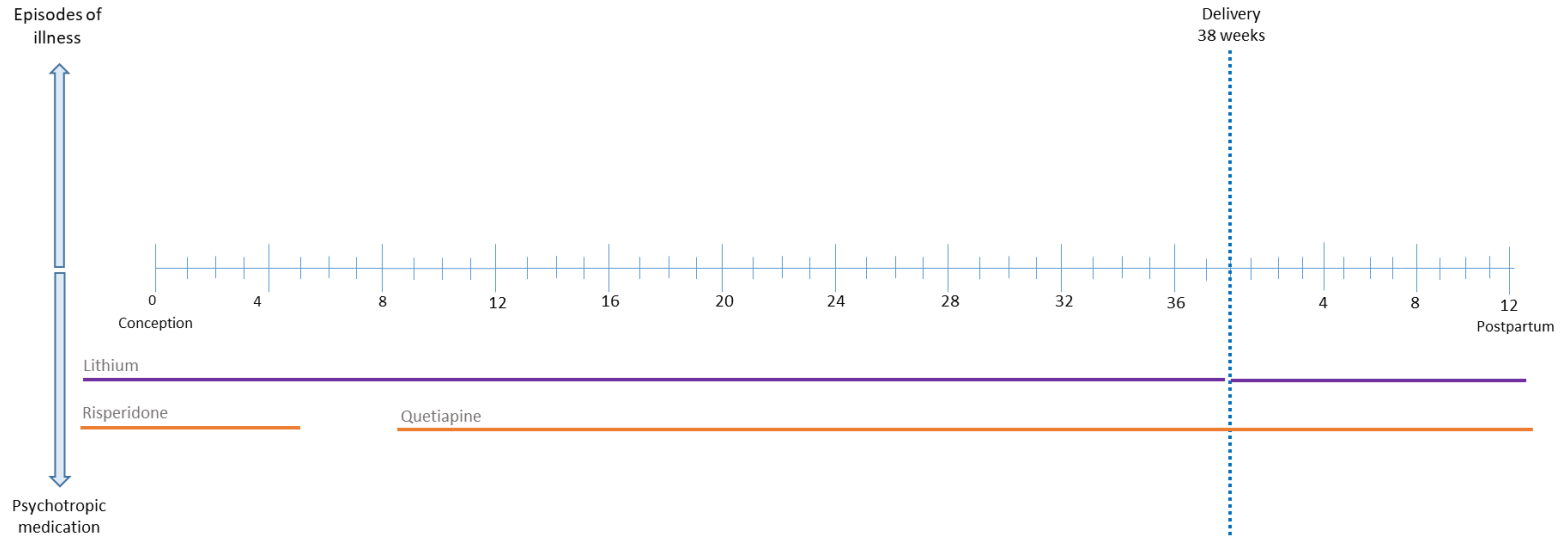
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- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 10

Preconception DSM-5 diagnosis: BD-I

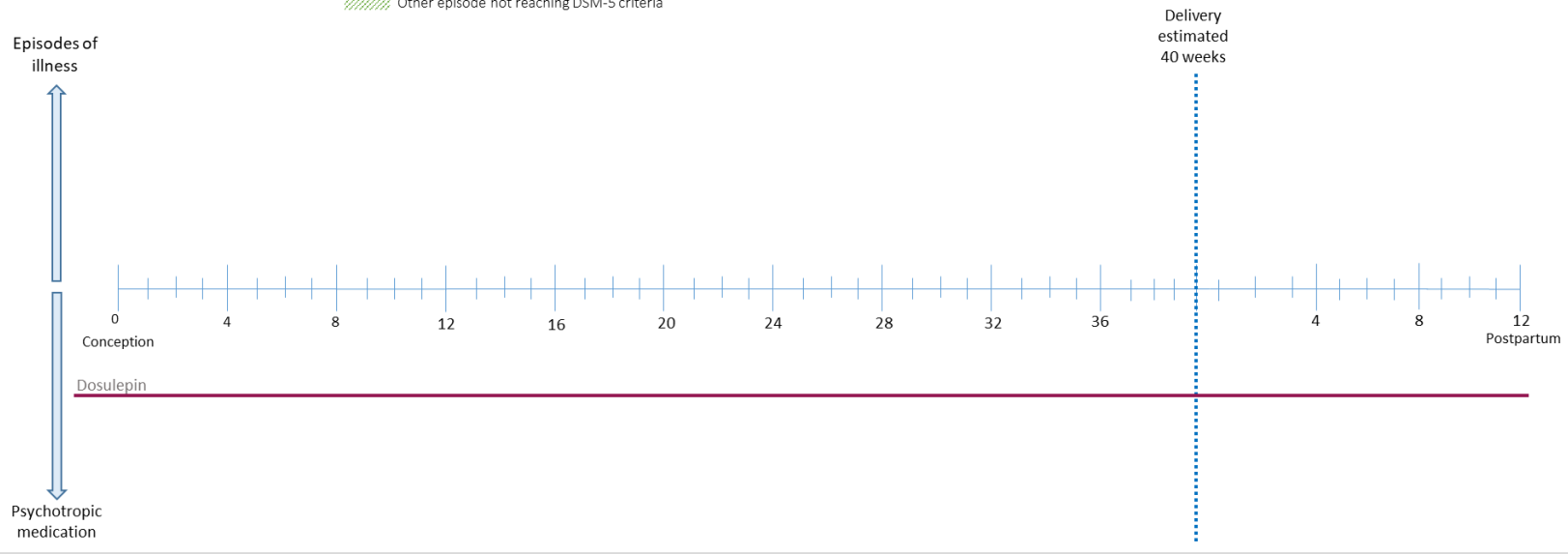
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 11

Preconception DSM-5 diagnosis: SA-BD

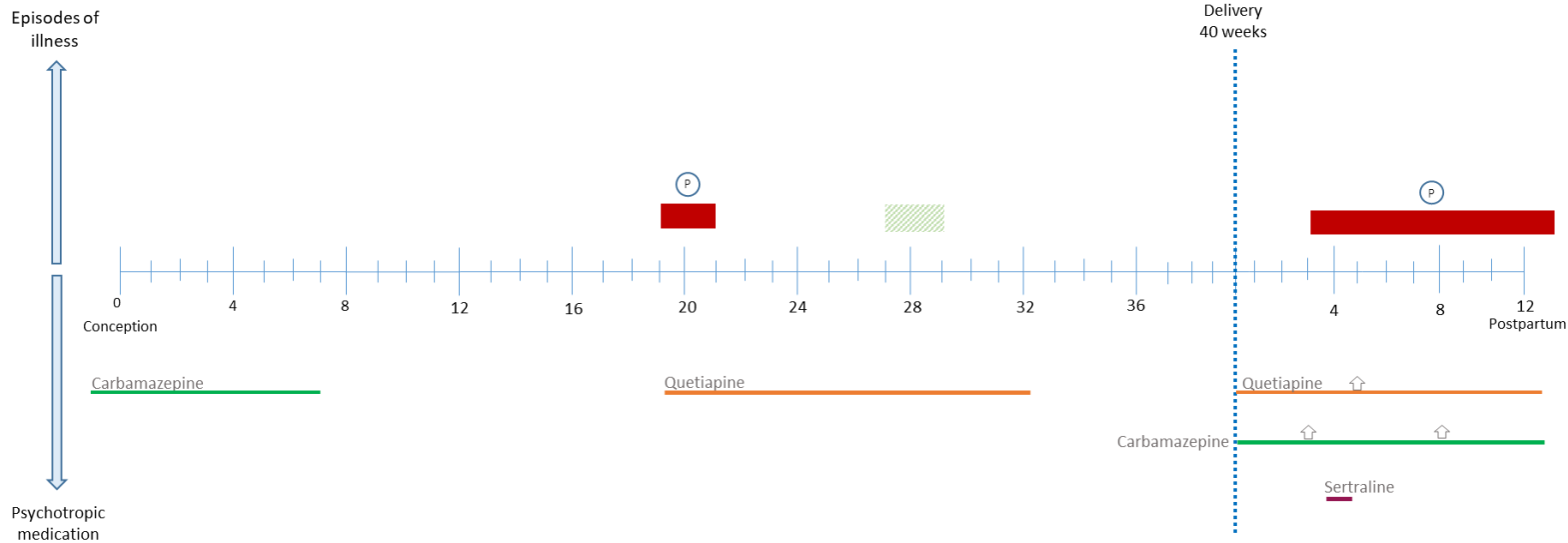
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 12

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

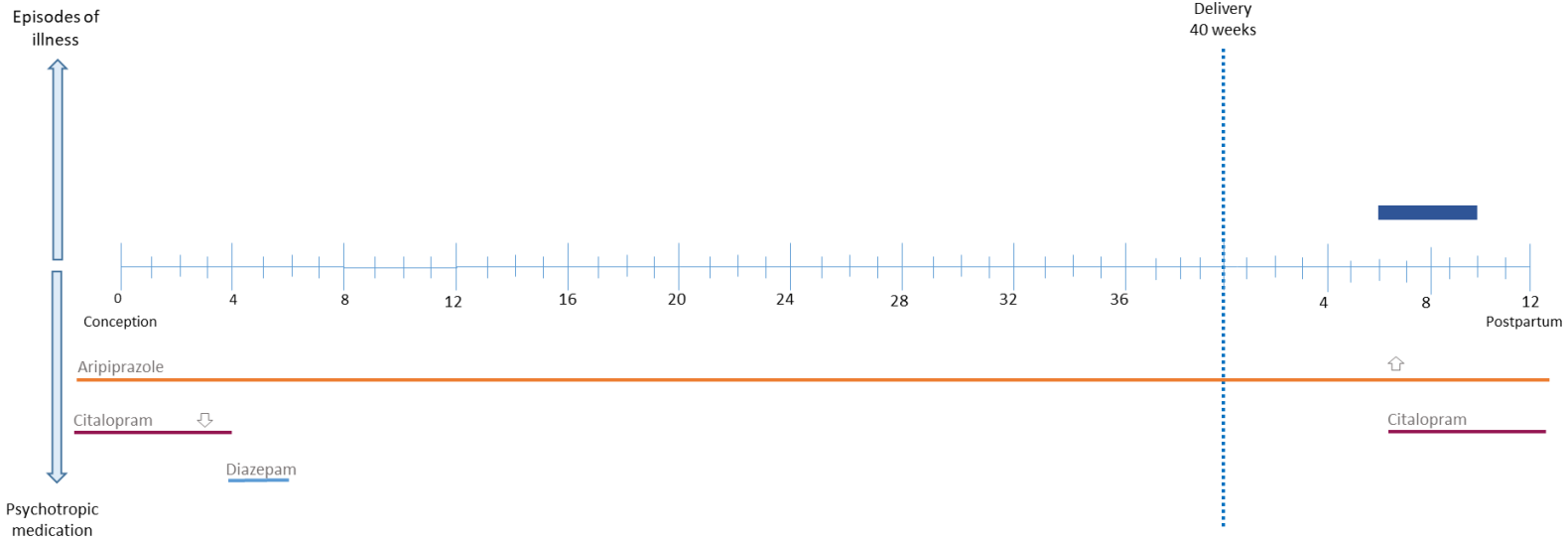
- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant

- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 13

Preconception DSM-5 diagnosis: BD-II

Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

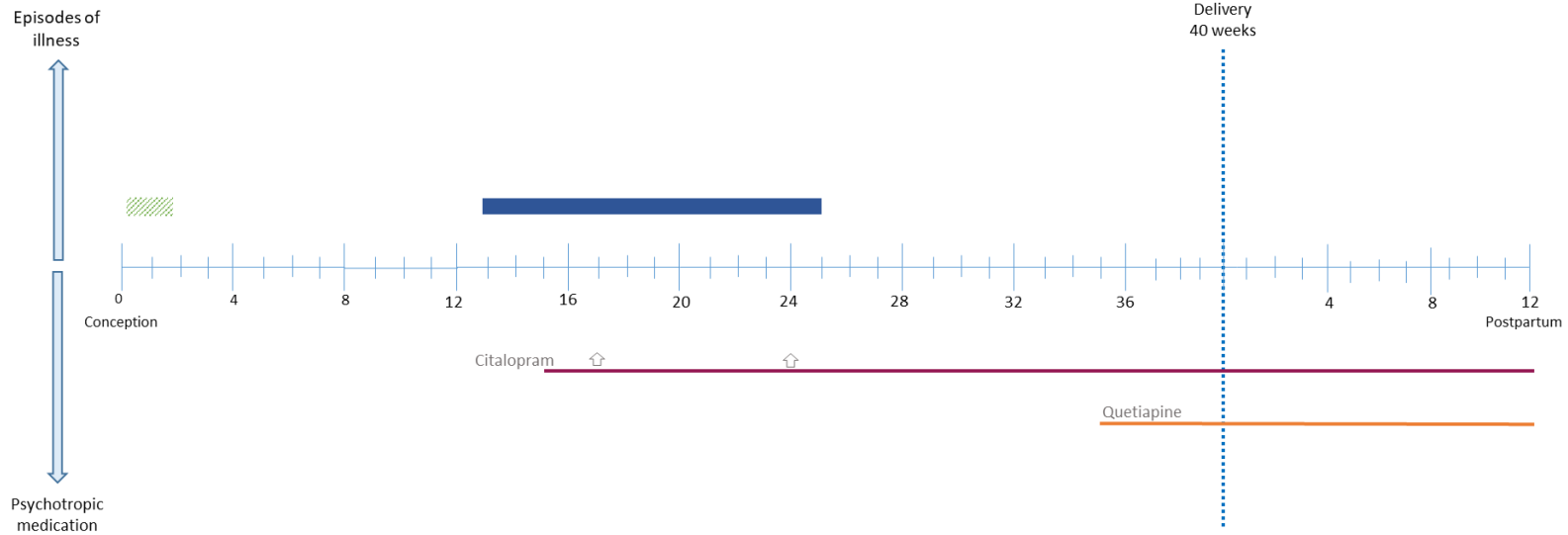
- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant

- Dosage unknown
- ↑ Dosage increase
- ↓ Dosage decrease



Perinatal Timeline (weeks)

Participant 14

Preconception DSM-5 diagnosis: BD-I

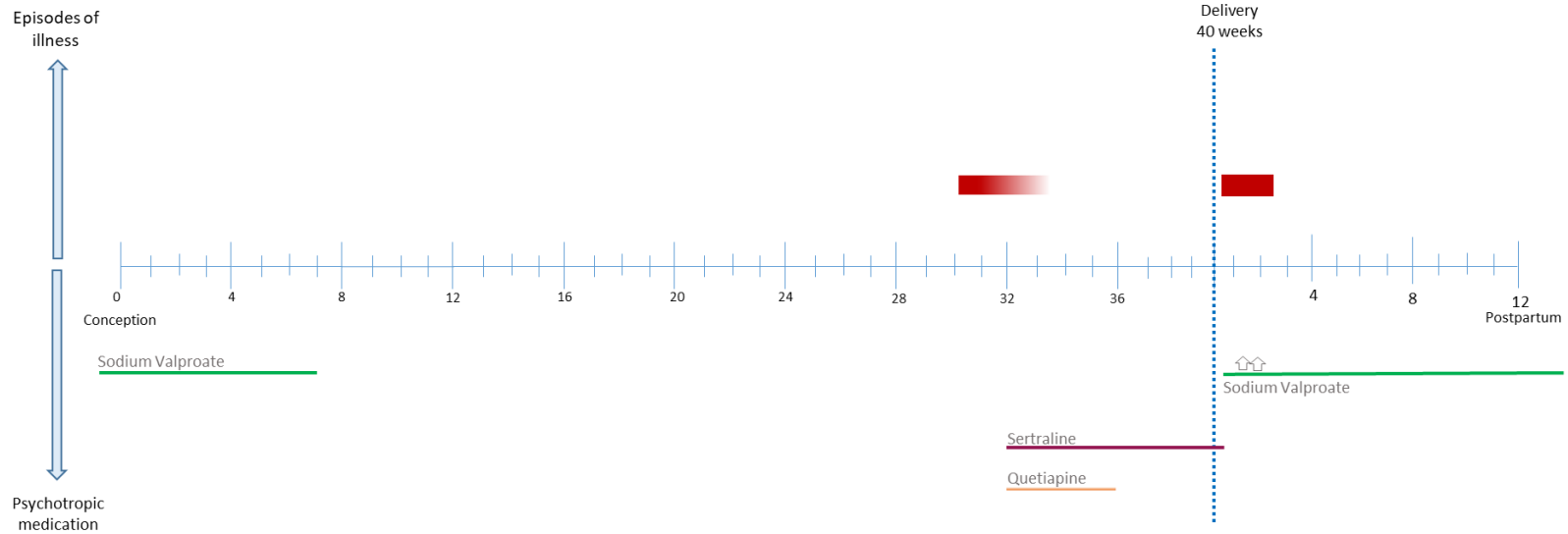
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 15

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

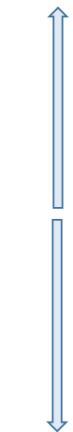
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

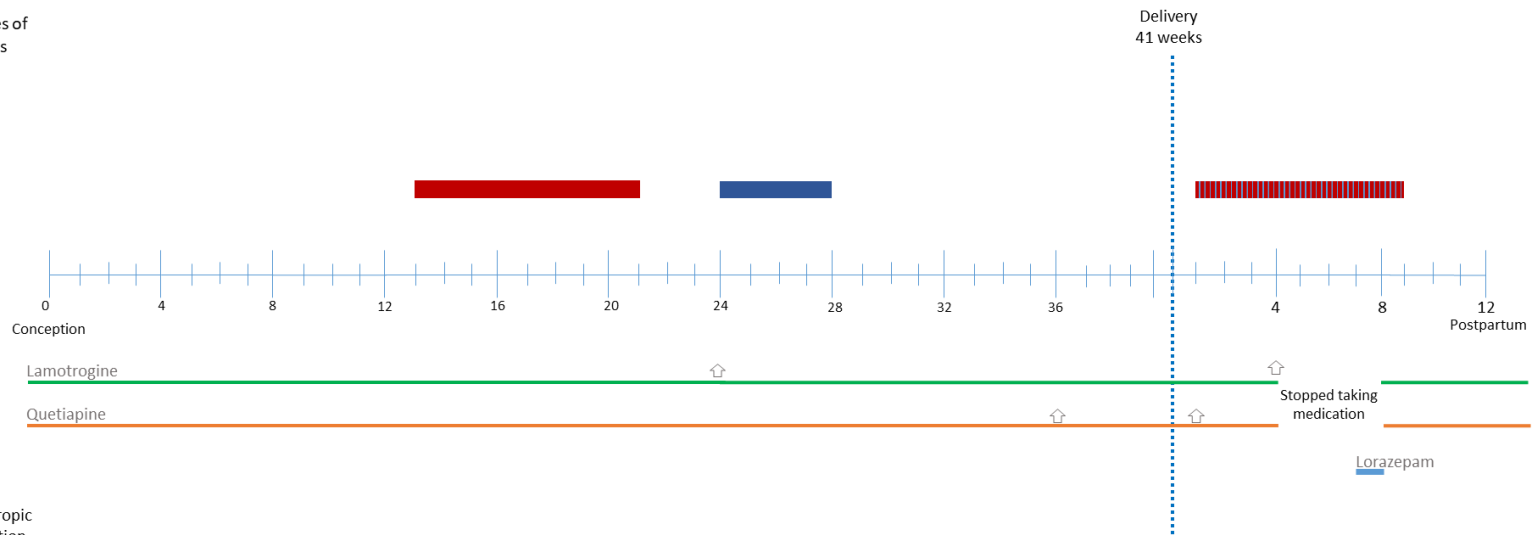
Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness



Psychotropic medication



Perinatal Timeline (weeks)

Participant 16

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

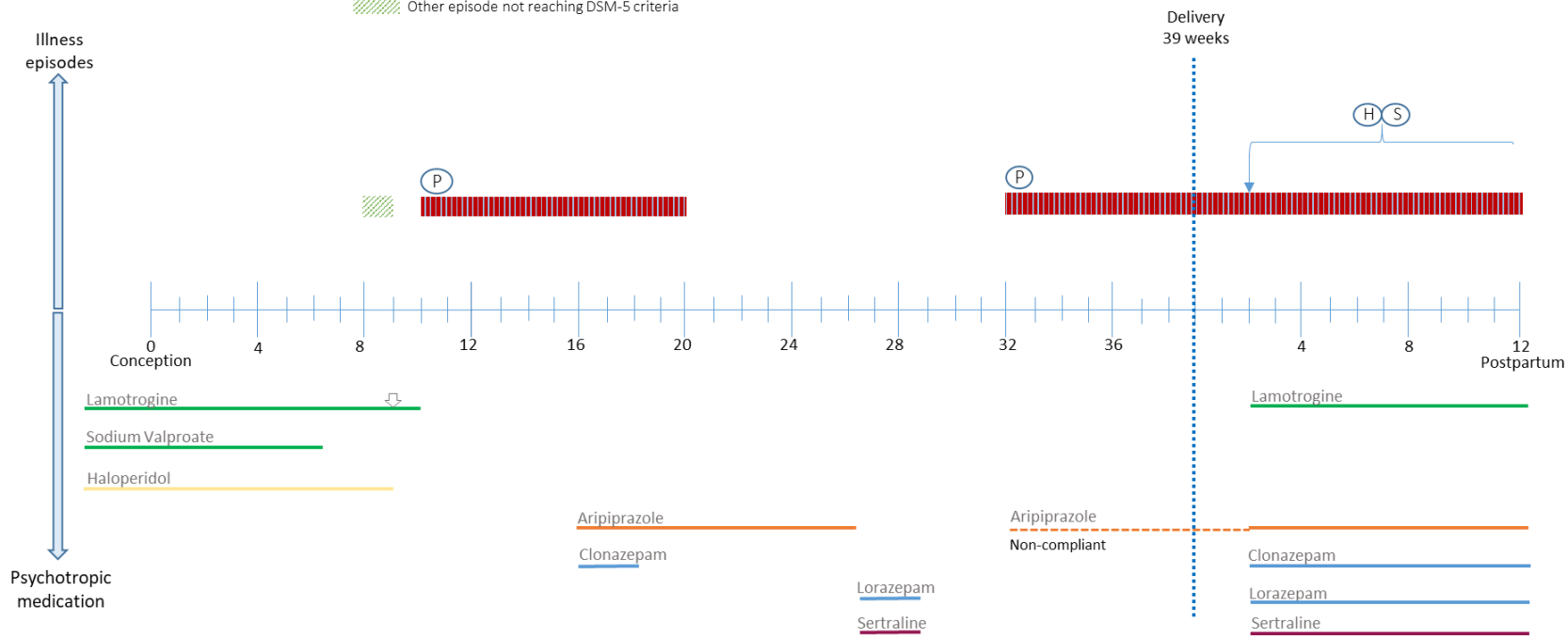
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- ↑ Dosage increase
- ↓ Dosage decrease



Perinatal Timeline (weeks)

Participant 17

Preconception DSM-5 diagnosis: BD-I (PP only prior episode)

Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

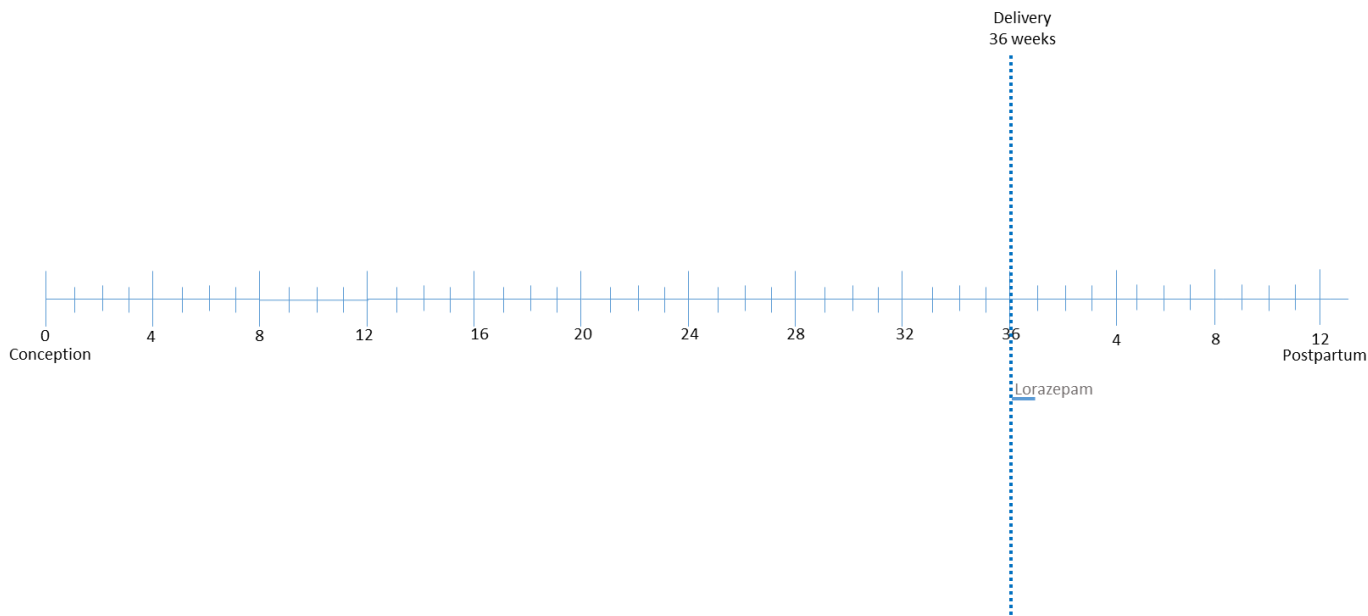
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Illness episodes

Psychotropic medication



Perinatal Timeline (weeks)

Participant 18

Preconception DSM-5 diagnosis: BD-I

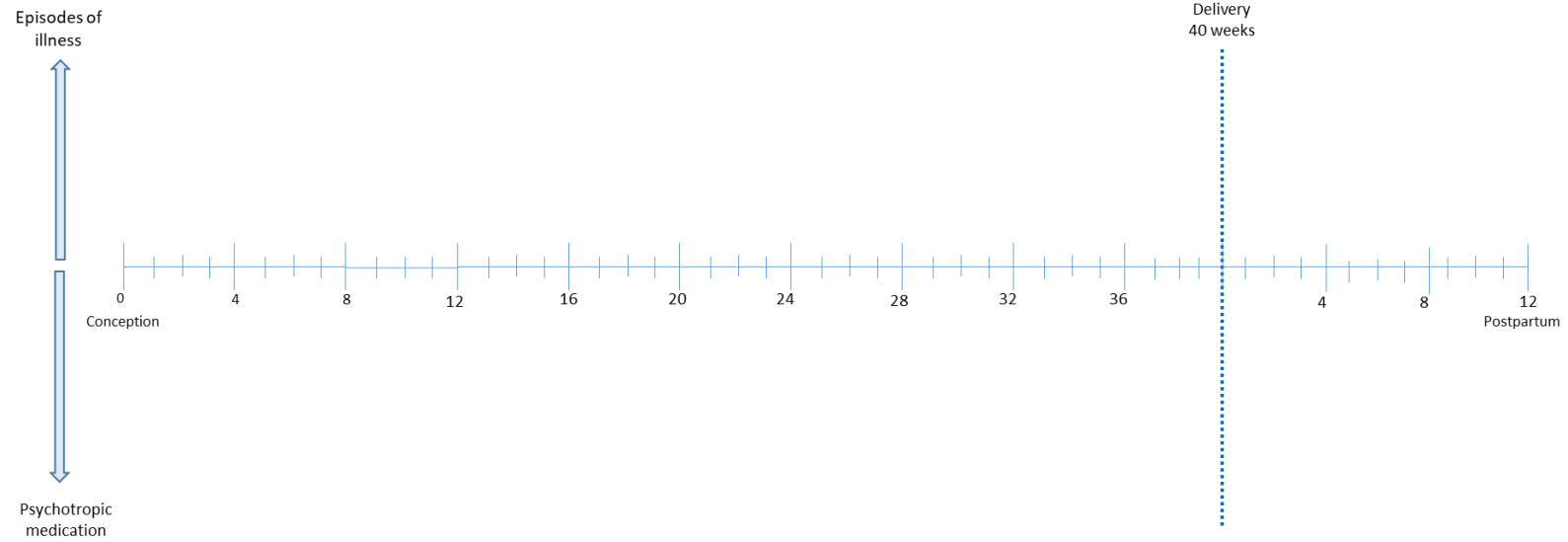
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 19

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

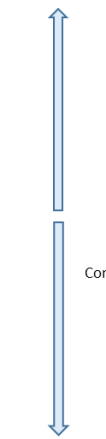
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

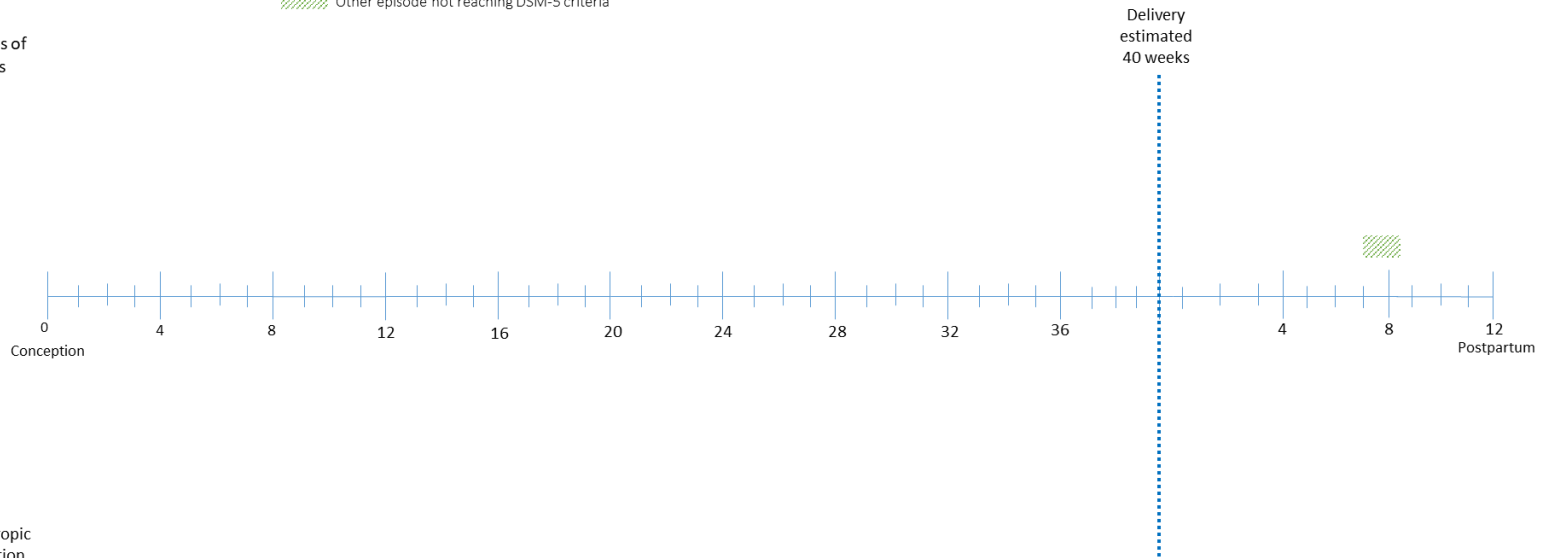
Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness



Psychotropic medication



Perinatal Timeline (weeks)

Participant 20

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

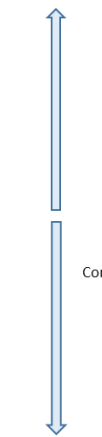
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

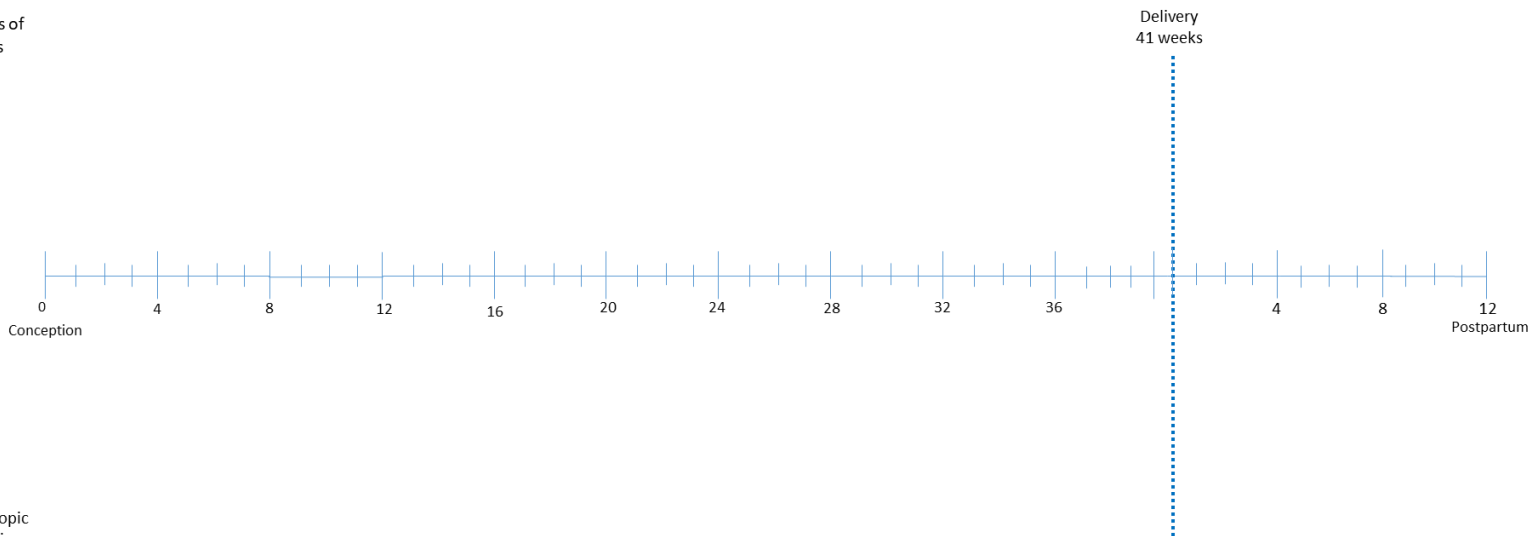
Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness



Psychotropic medication



Perinatal Timeline (weeks)

Participant 21

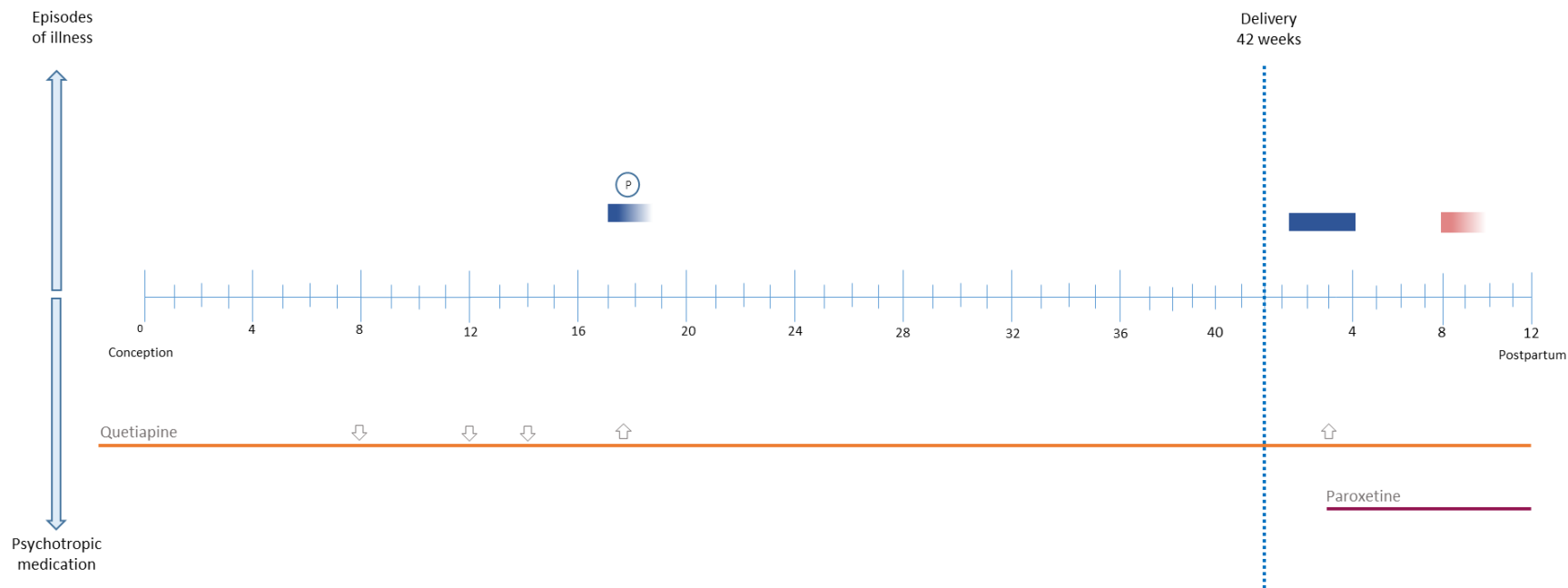
Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

- Major depression
 - Mania
 - Hypomania
 - Depression with mixed features
 - Mania with mixed features
 - Other psychotic episode
 - 'Baby blues'
 - Postpartum 'highs'
 - Other episode not reaching DSM-5 criteria
- P Psychosis
 - S Sectioned
 - H Hospitalised: admission, home treatment (HTT), crisis team (CT)
 - Exact day of onset of DSM-5 episode unknown
 - Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- ↑ Dosage increase
- ↓ Dosage decrease



Perinatal Timeline (weeks)

Participant 22

Preconception DSM-5 diagnosis: BD-I

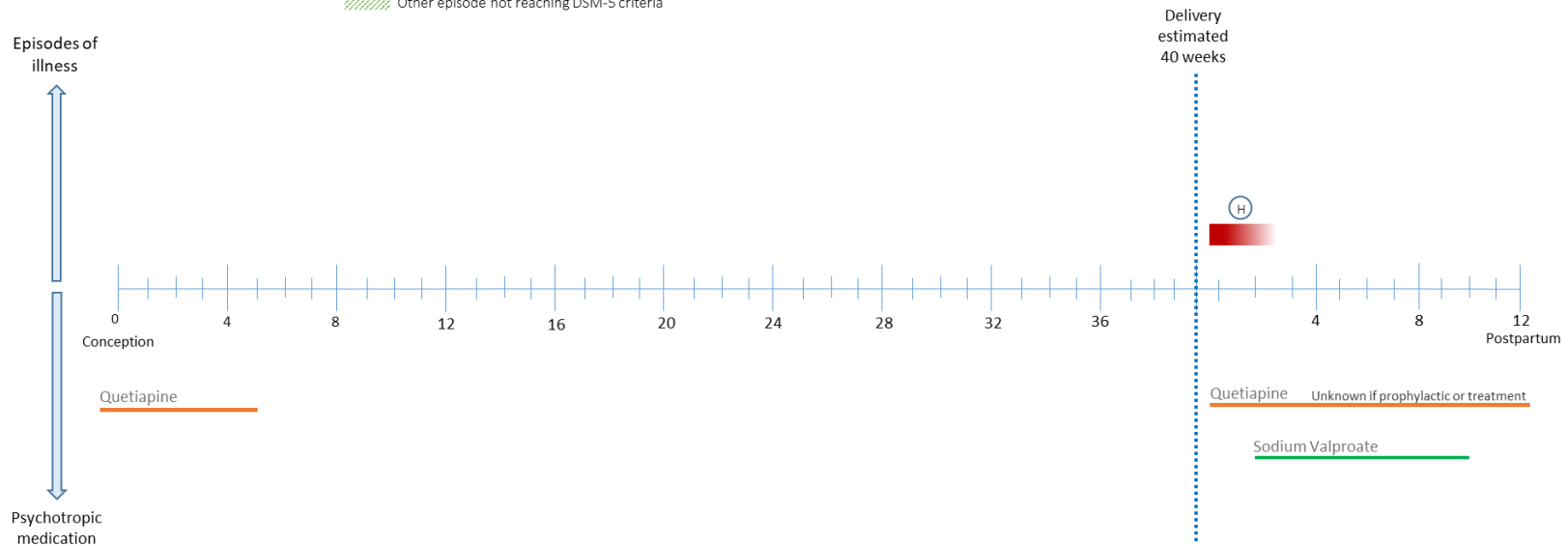
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 23

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

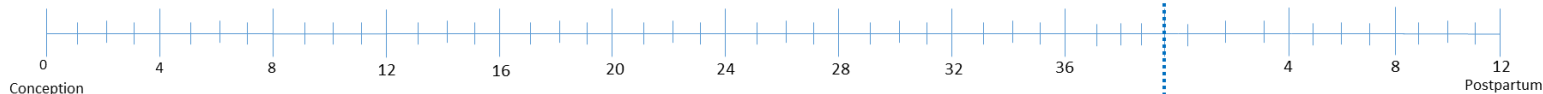
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness



Psychotropic medication

Perinatal Timeline (weeks)

Participant 24

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

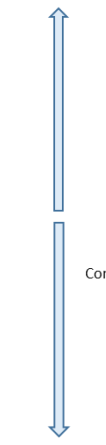
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

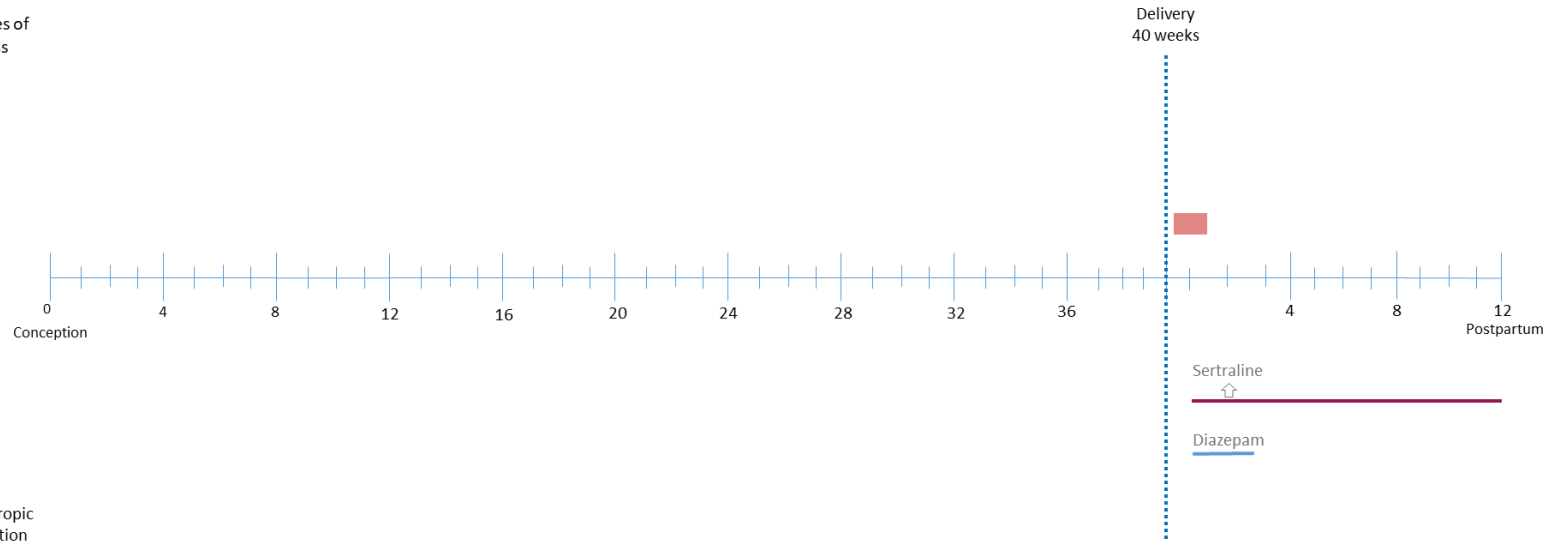
Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness



Psychotropic medication



Perinatal Timeline (weeks)

Participant 25

Preconception DSM-5 diagnosis: BD-I

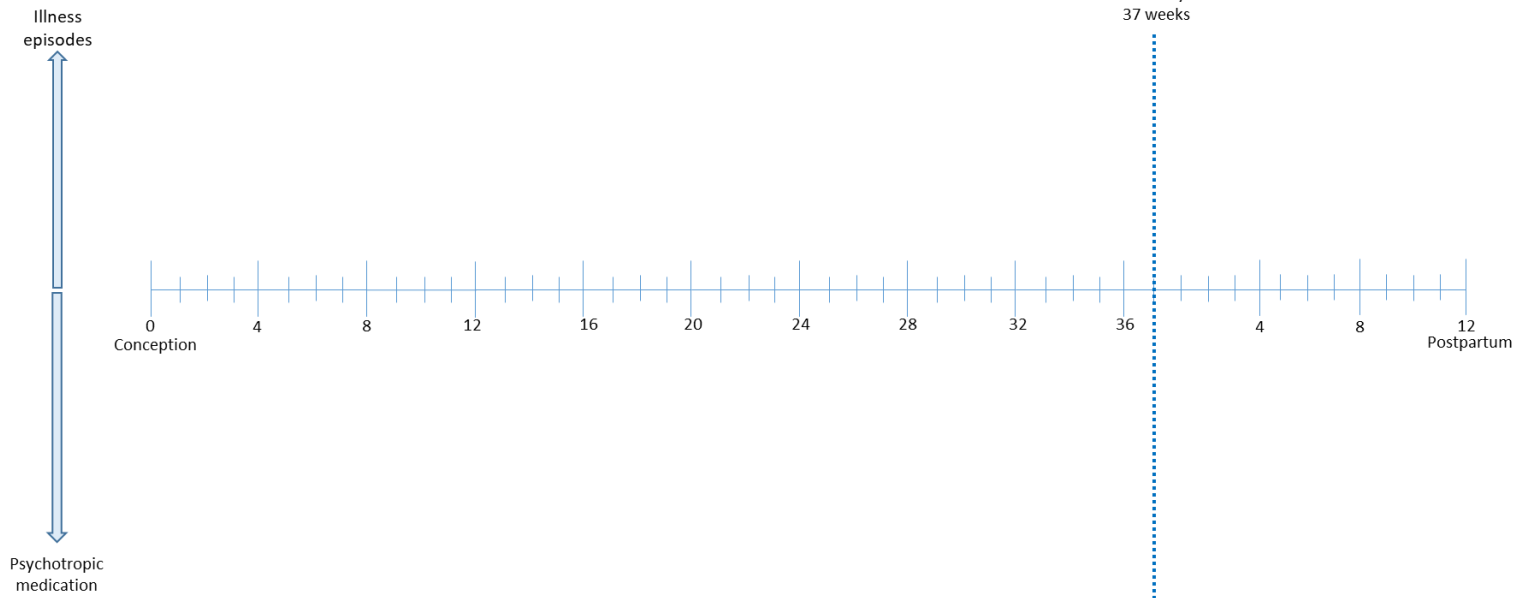
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 26

Preconception DSM-5 diagnosis: BD-I

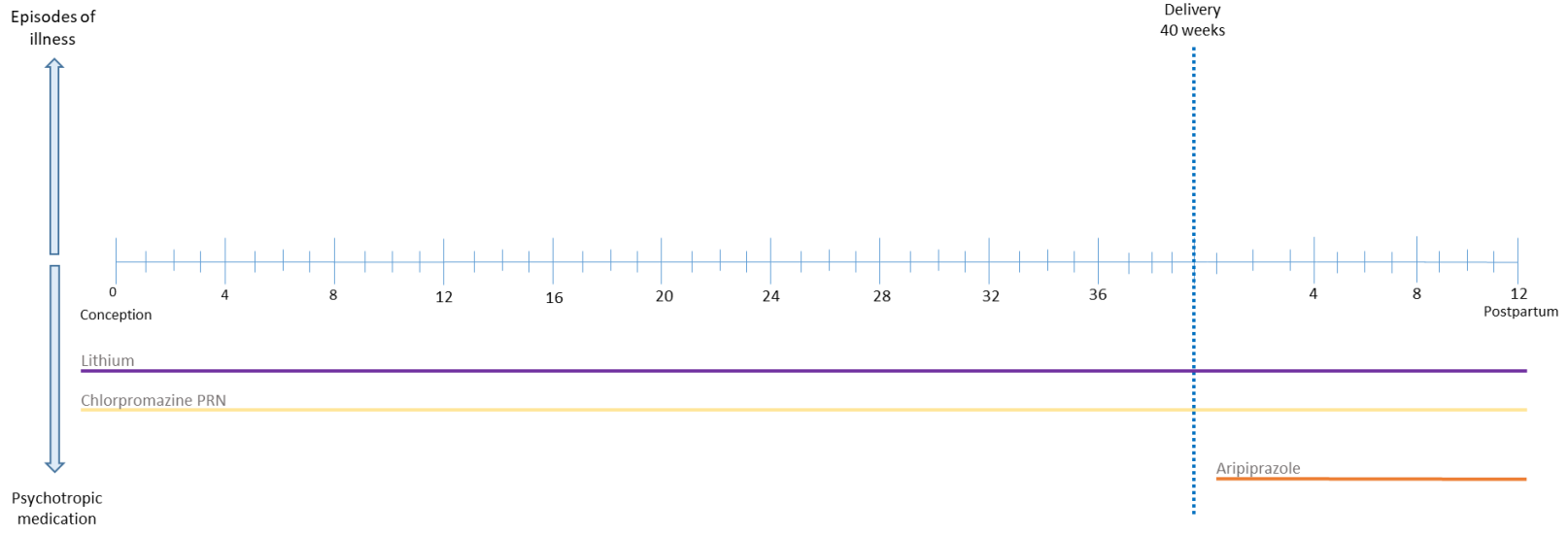
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 27

Preconception DSM-5 diagnosis: BD-I

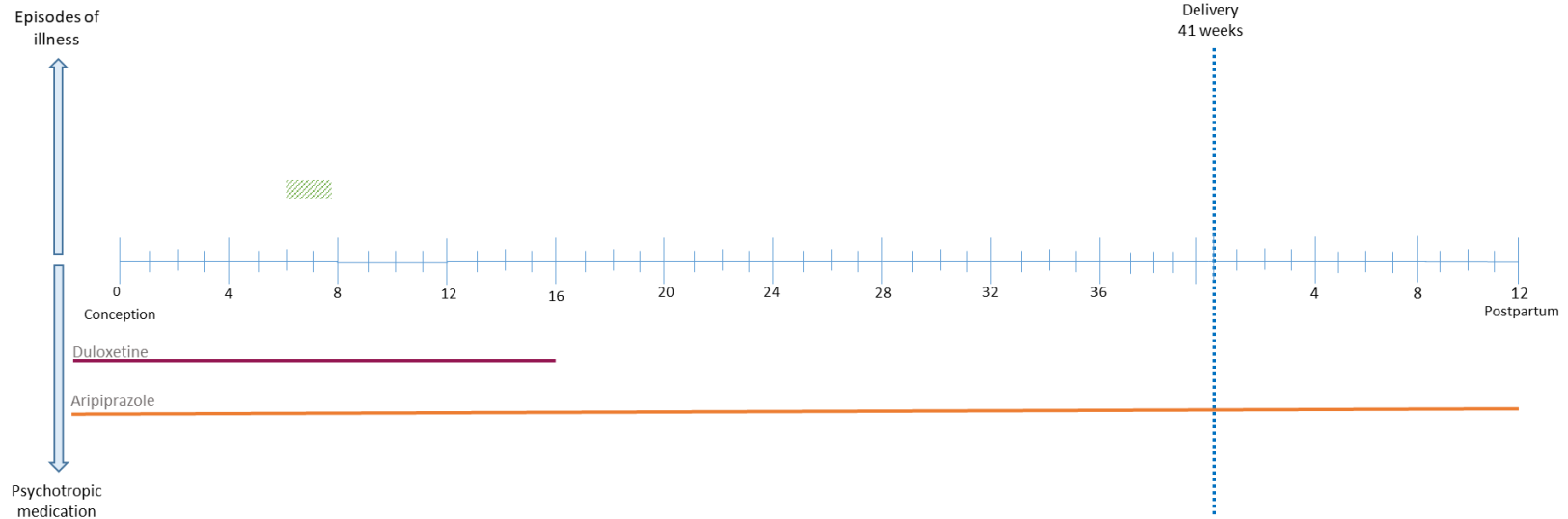
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 28

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

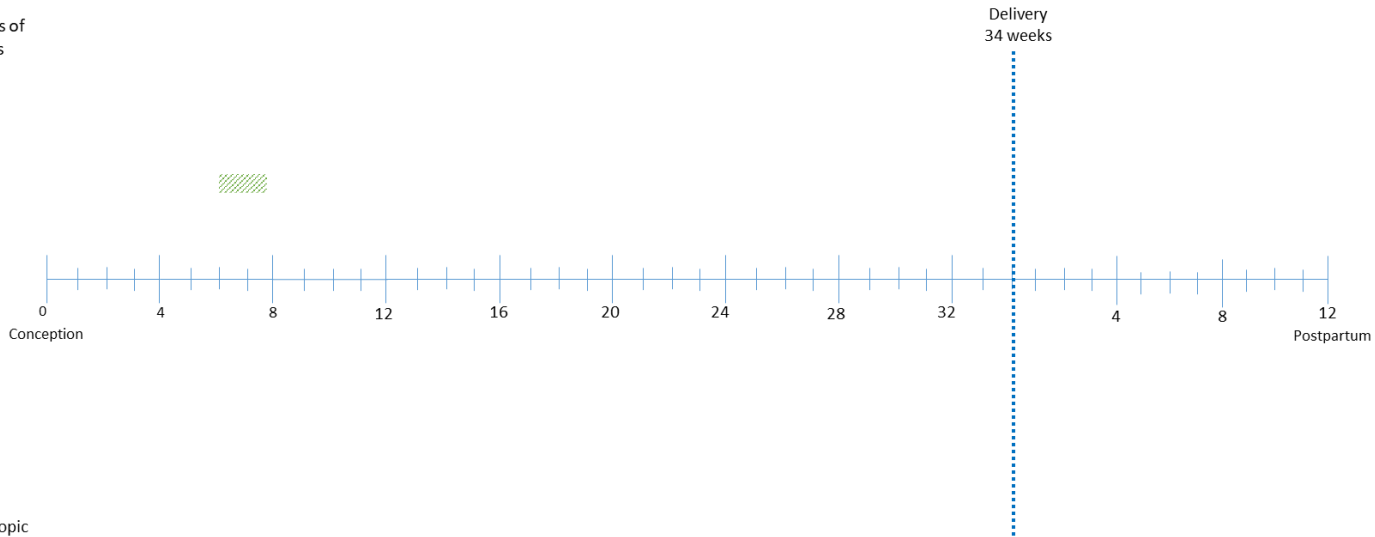
Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant

- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness

Psychotropic medication



Perinatal Timeline (weeks)

Participant 29

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

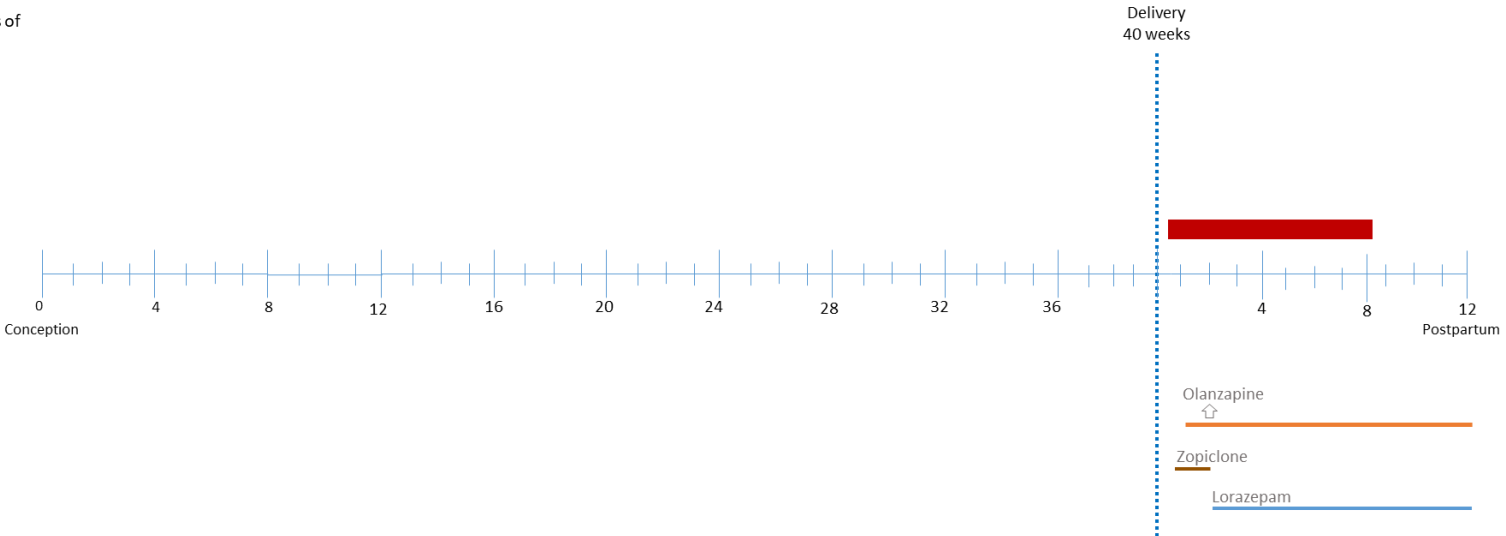
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness



Perinatal Timeline (weeks)

Participant 30

Preconception DSM-5 diagnosis: BD-II

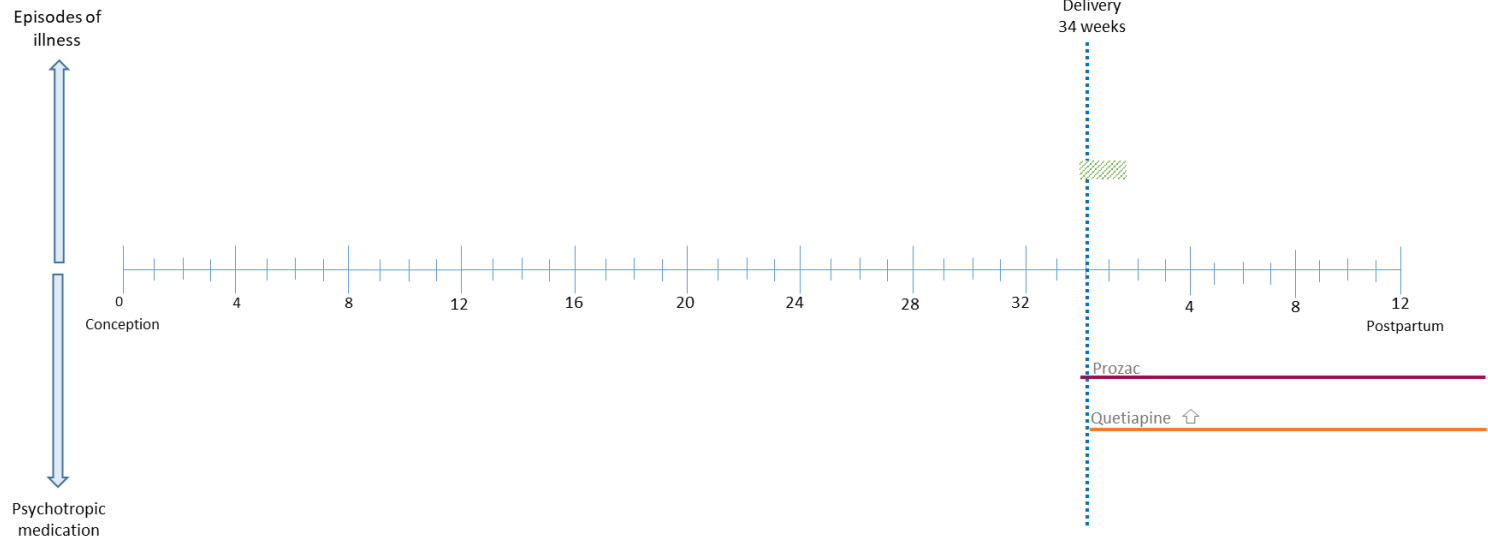
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 31

Preconception DSM-5 diagnosis: BD-II

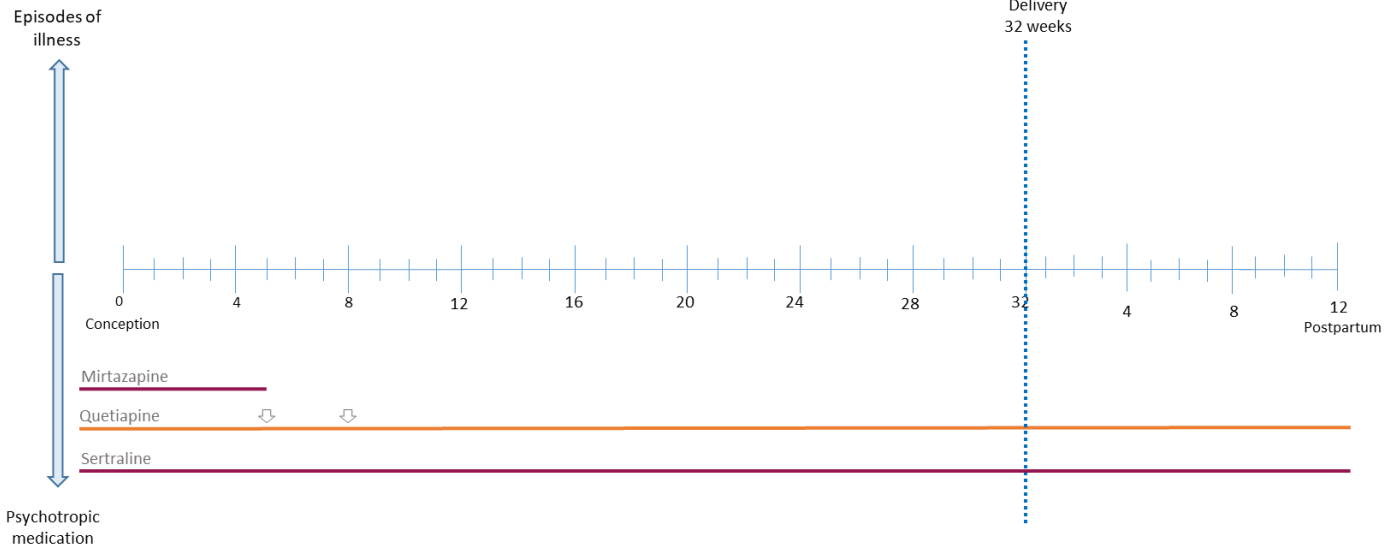
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 32

Preconception DSM-5 diagnosis: BDNOS (PP only prior episode)

Episodes of illness

Psychotropic medication

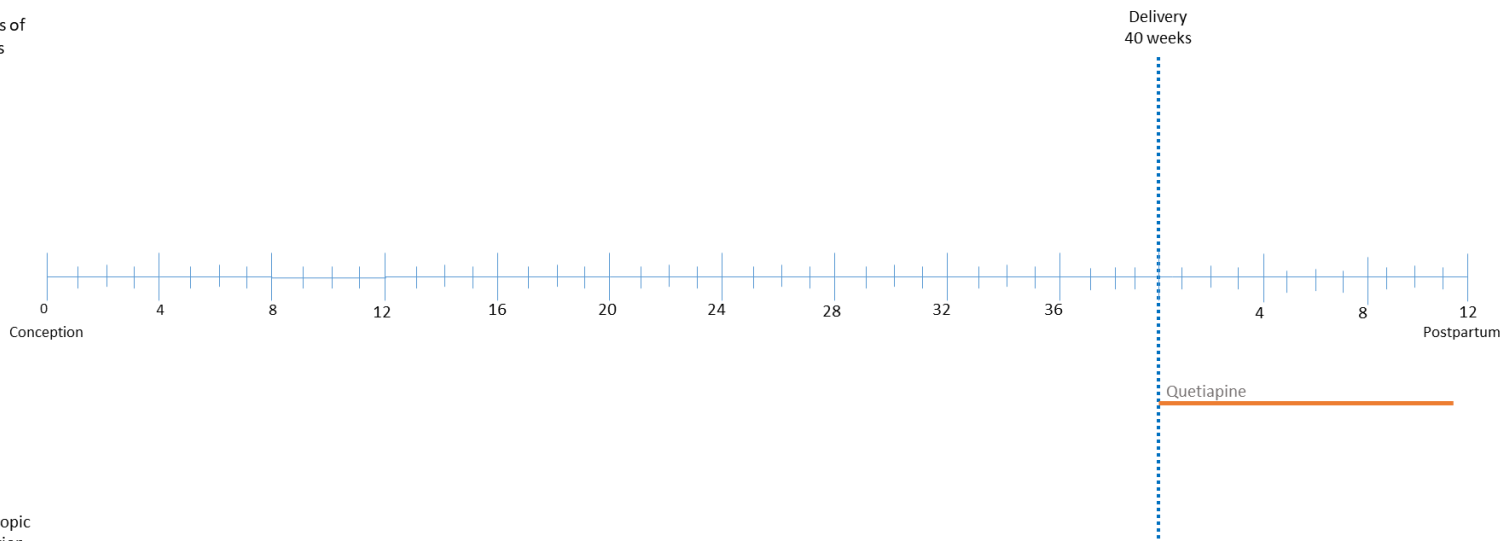
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 33

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

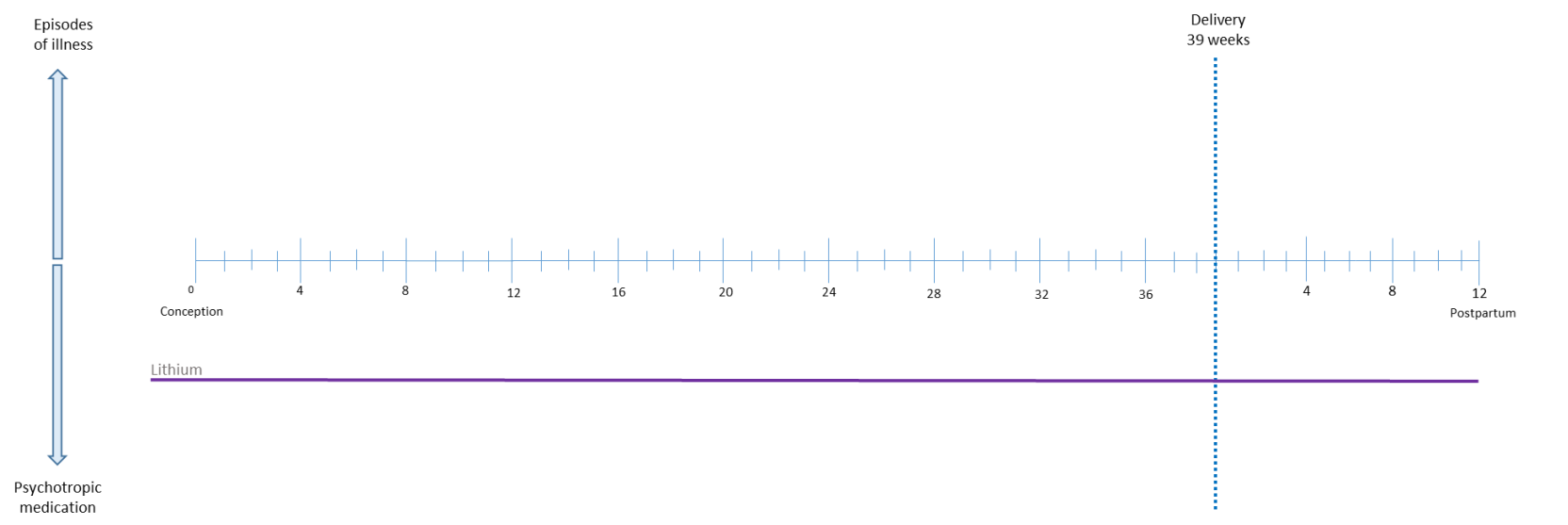
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 34

Preconception DSM-5 diagnosis: BD-II

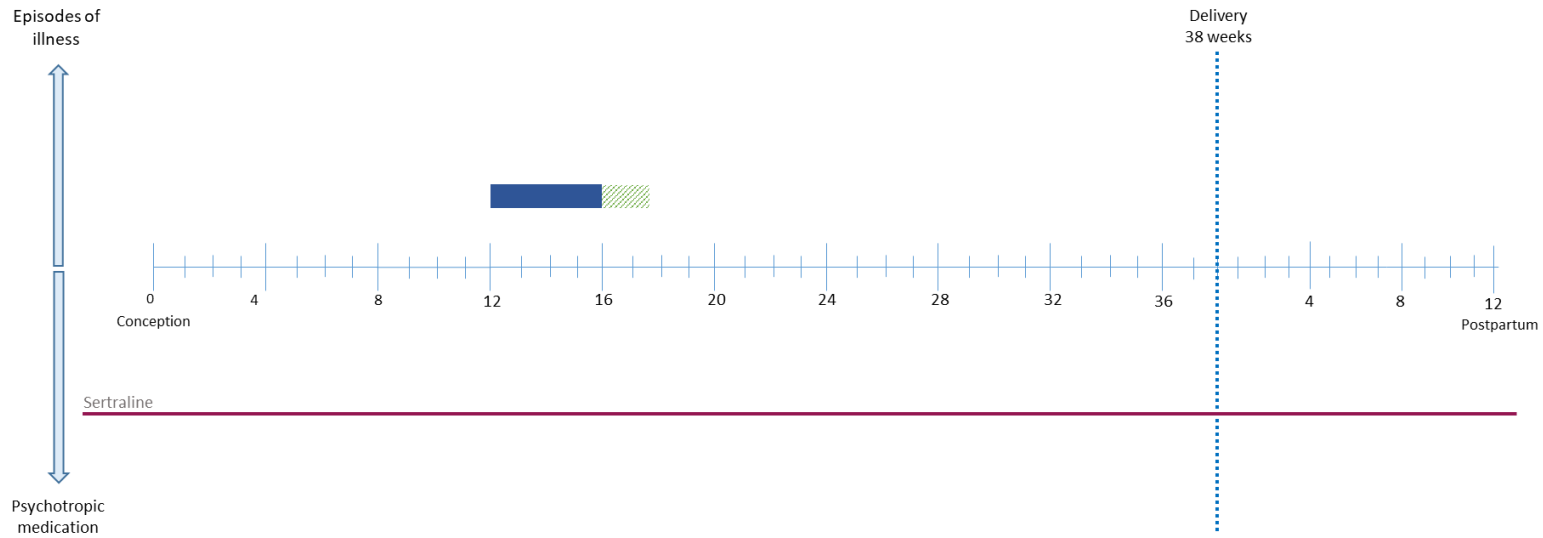
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- ↑ Dosage increase
- ↓ Dosage decrease



Perinatal Timeline (weeks)

Participant 35

Preconception DSM-5 diagnosis: BD-I

Episodes of illness

Psychotropic medication

Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

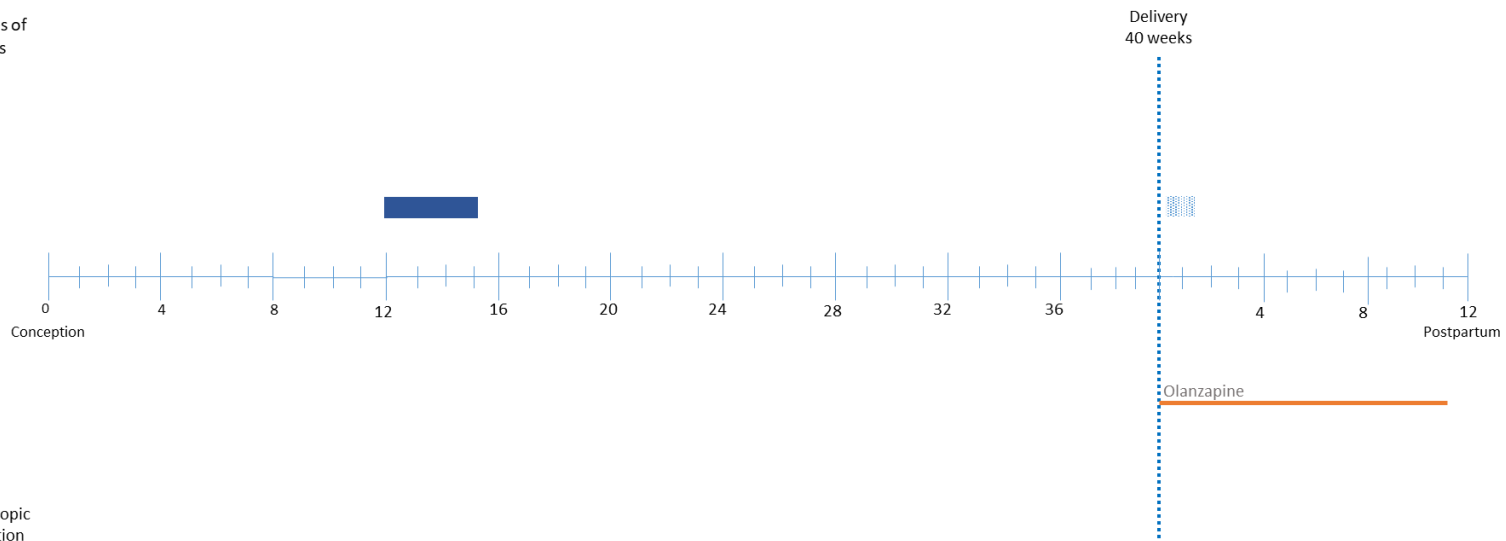
- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant

- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 36

Preconception DSM-5 diagnosis: BD-II

Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

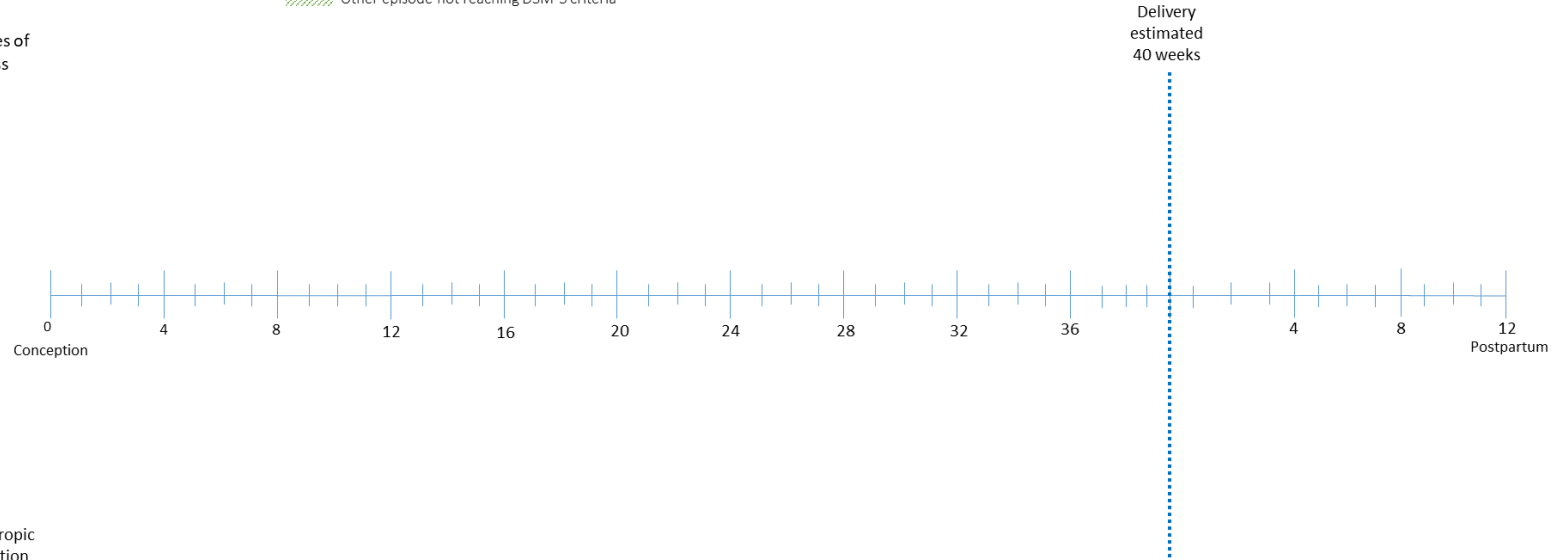
- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant

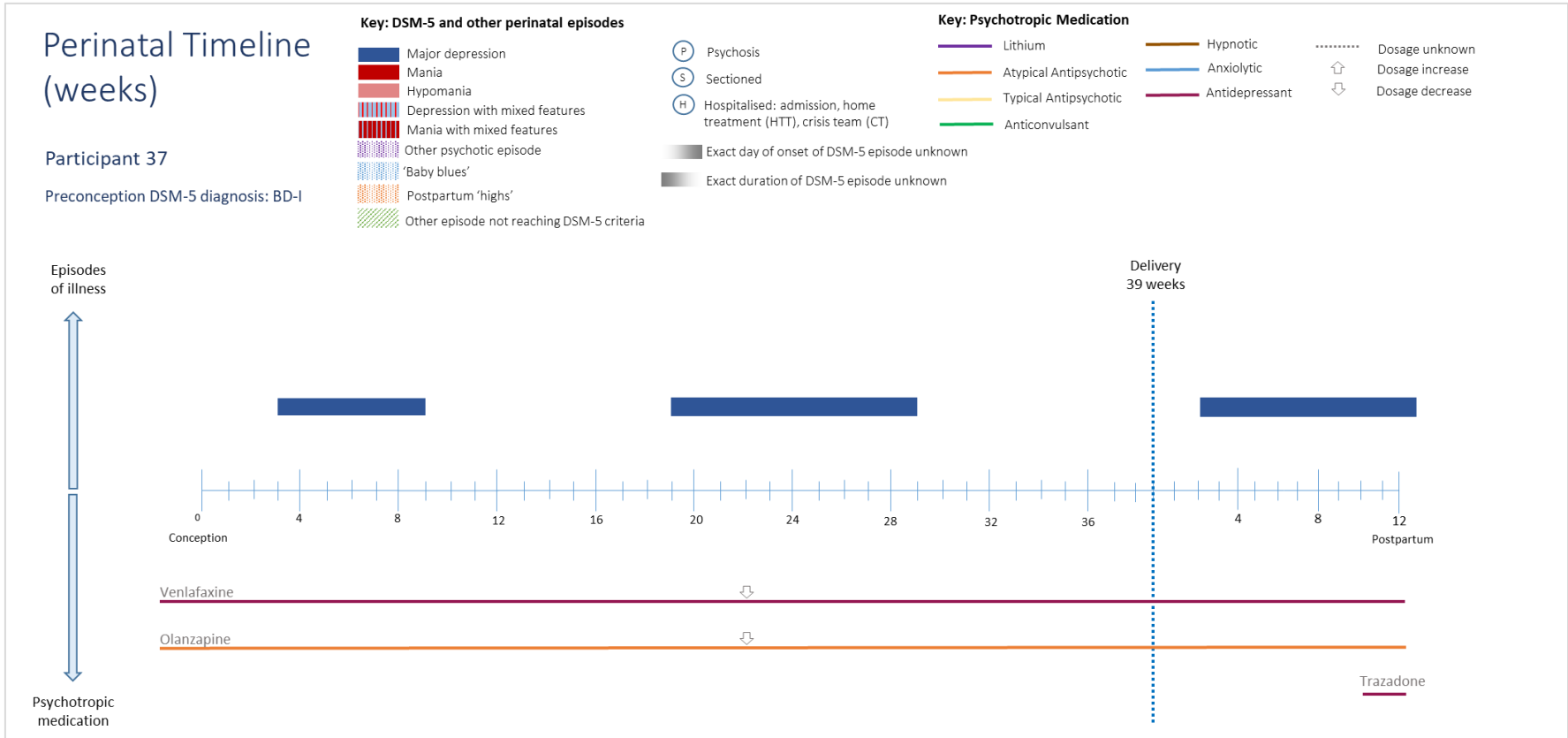
- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness



Psychotropic medication





Perinatal Timeline (weeks)

Participant 38

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

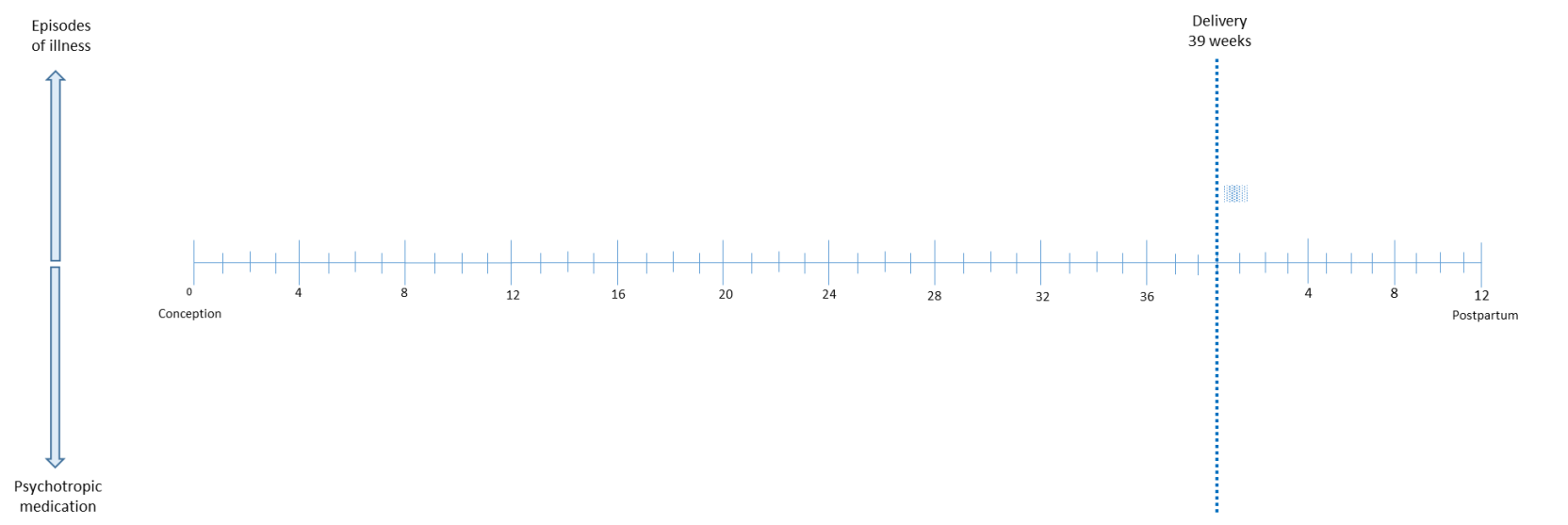
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 39

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

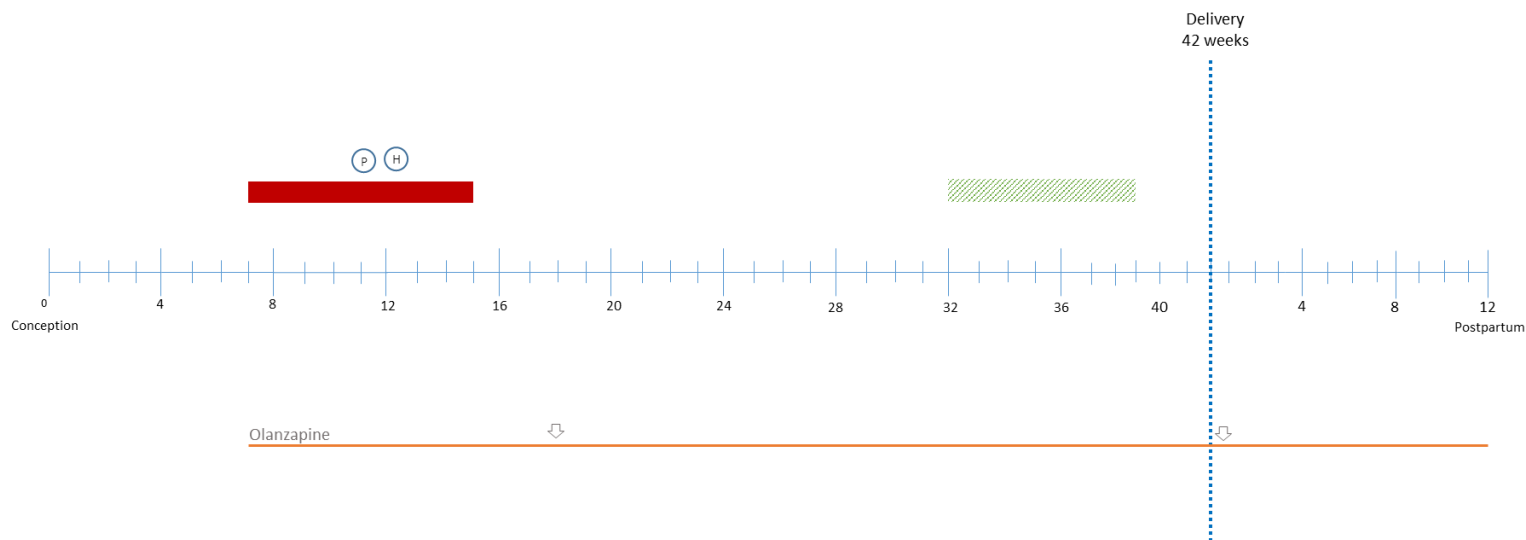
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness



Perinatal Timeline (weeks)

Participant 40

Preconception DSM-5 diagnosis: BD-I

Episodes of illness

Psychotropic medication

Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

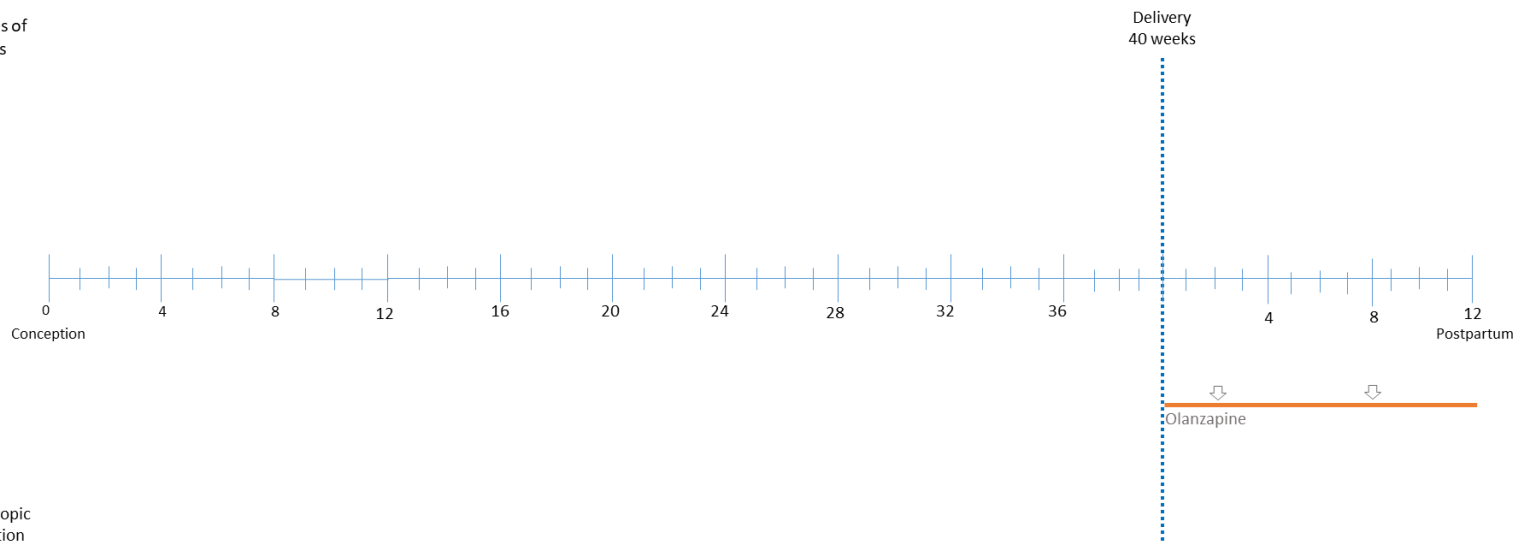
- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant

- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 41

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

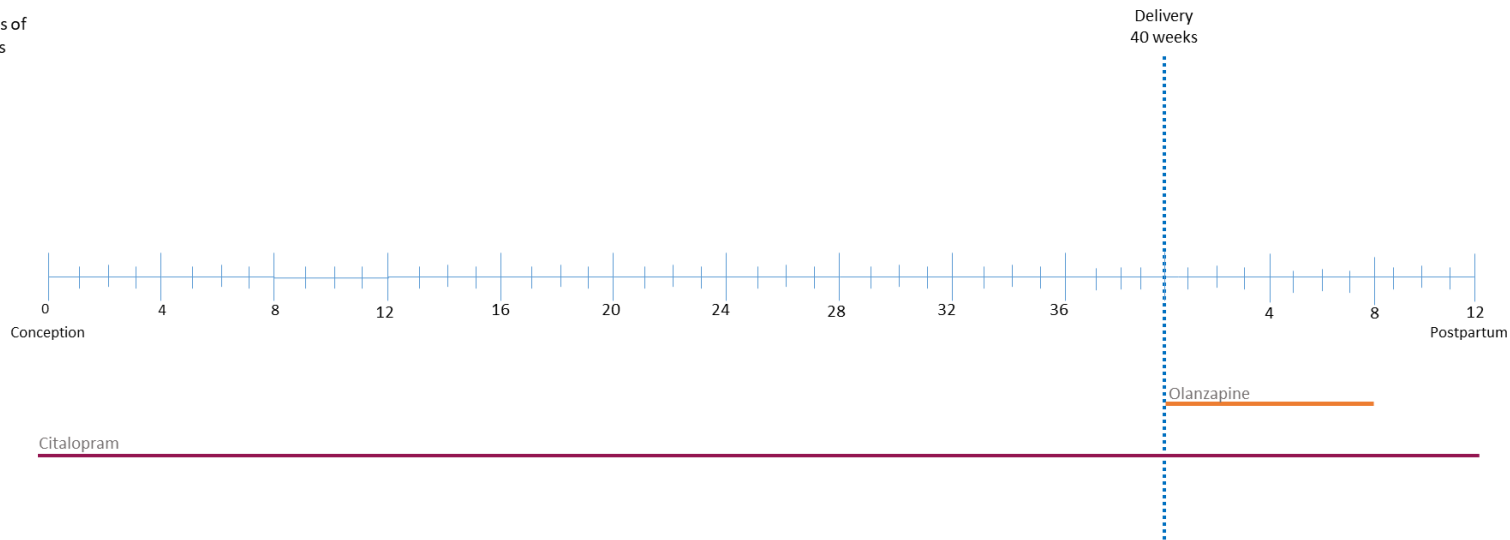
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness



Perinatal Timeline (weeks)

Participant 42

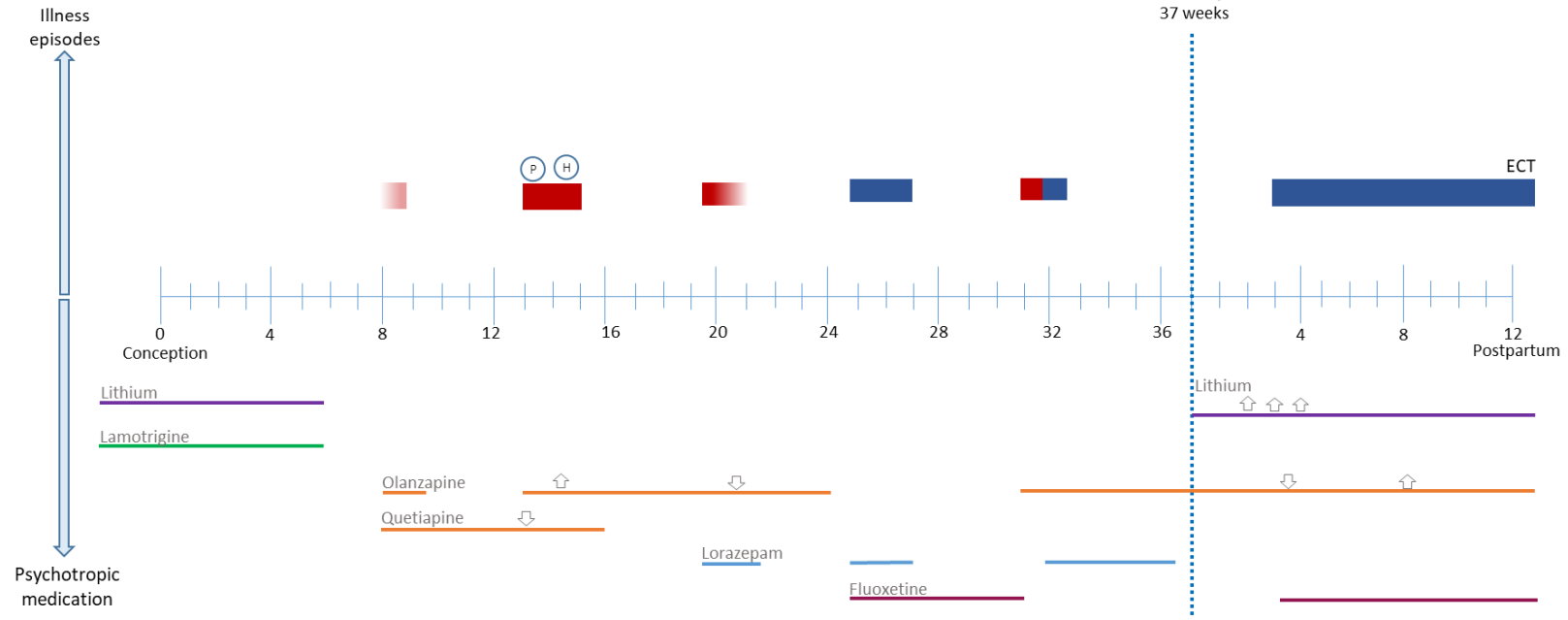
Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

- Major depression
 - Mania
 - Hypomania
 - Depression with mixed features
 - Mania with mixed features
 - Other psychotic episode
 - 'Baby blues'
 - Postpartum 'highs'
 - Other episode not reaching DSM-5 criteria
- P Psychosis
 - S Sectioned
 - H Hospitalised: admission, home treatment (HTT), crisis team (CT)
 - Exact day of onset of DSM-5 episode unknown
 - Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- ⬆ Dosage increase
- ⬇ Dosage decrease



Perinatal Timeline (weeks)

Participant 43

Preconception DSM-5 diagnosis: BD-I (PP only prior episode)

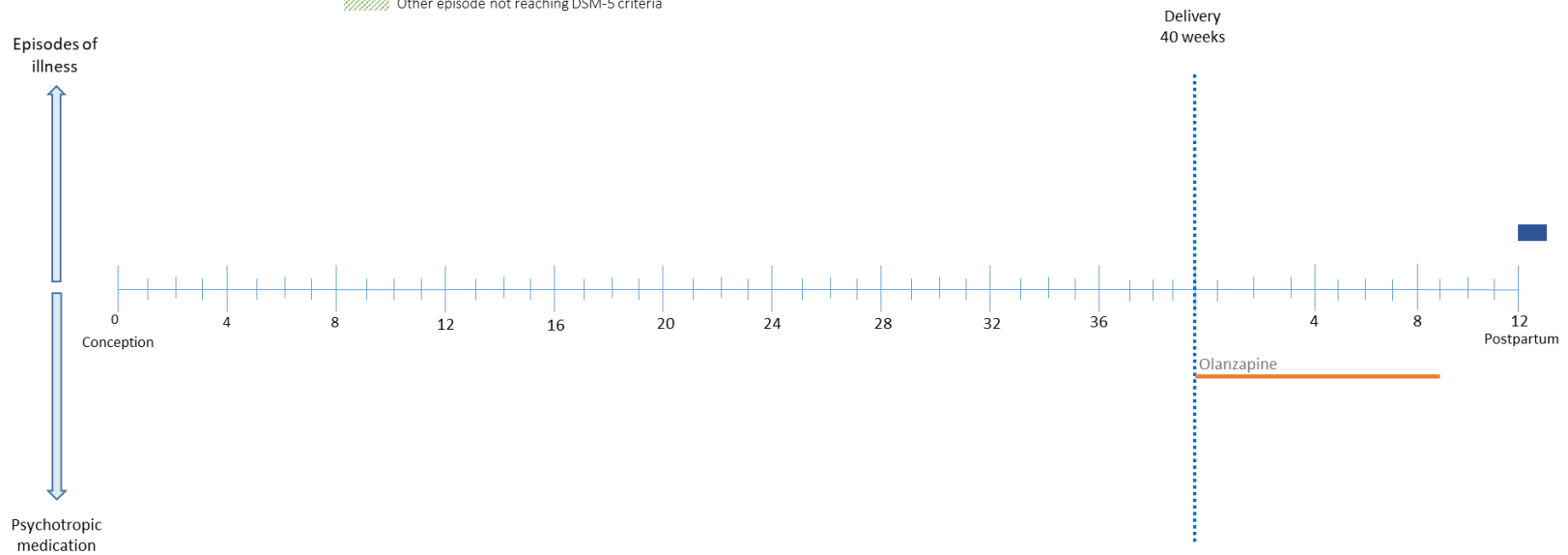
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 44

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

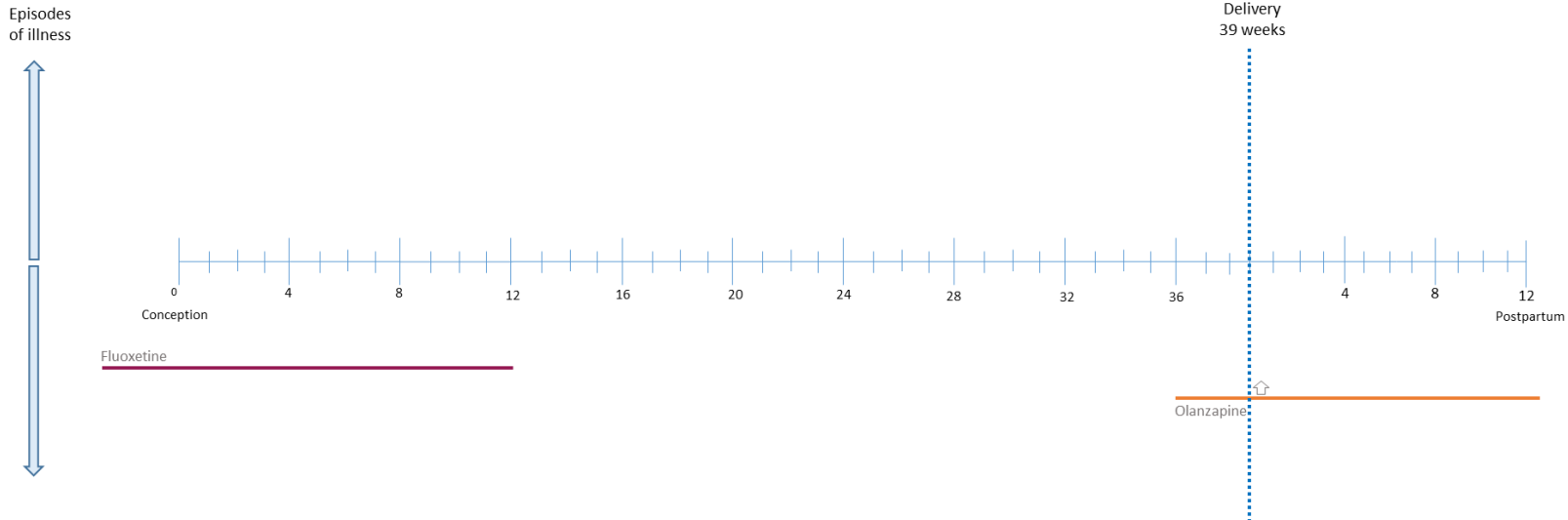
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

Exact day of onset of DSM-5 episode unknown
 Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 45

Preconception DSM-5 diagnosis: BD-I

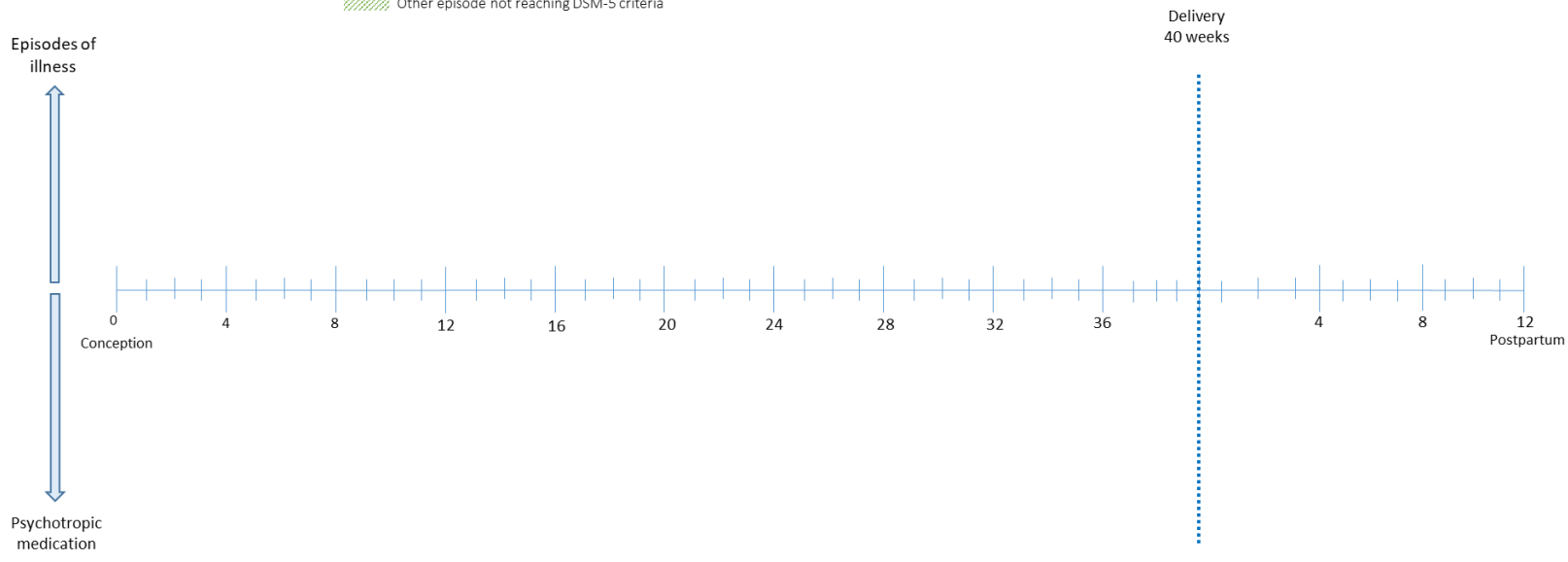
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 46

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

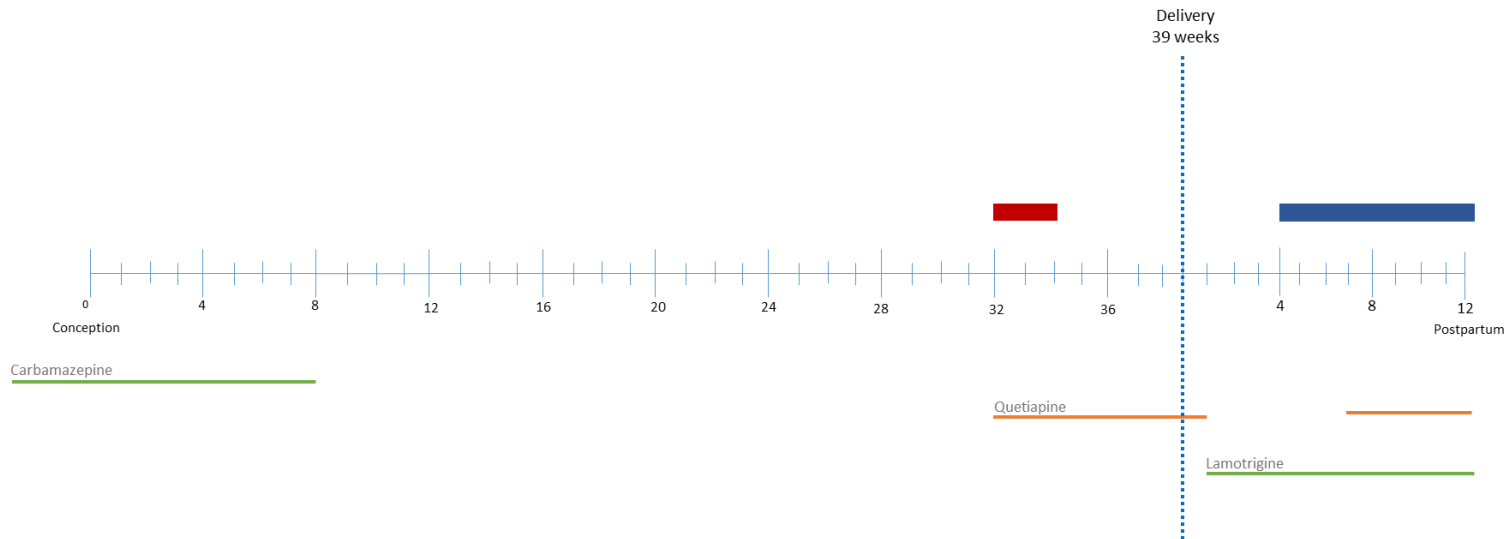
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness



Perinatal Timeline (weeks)

Participant 47

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

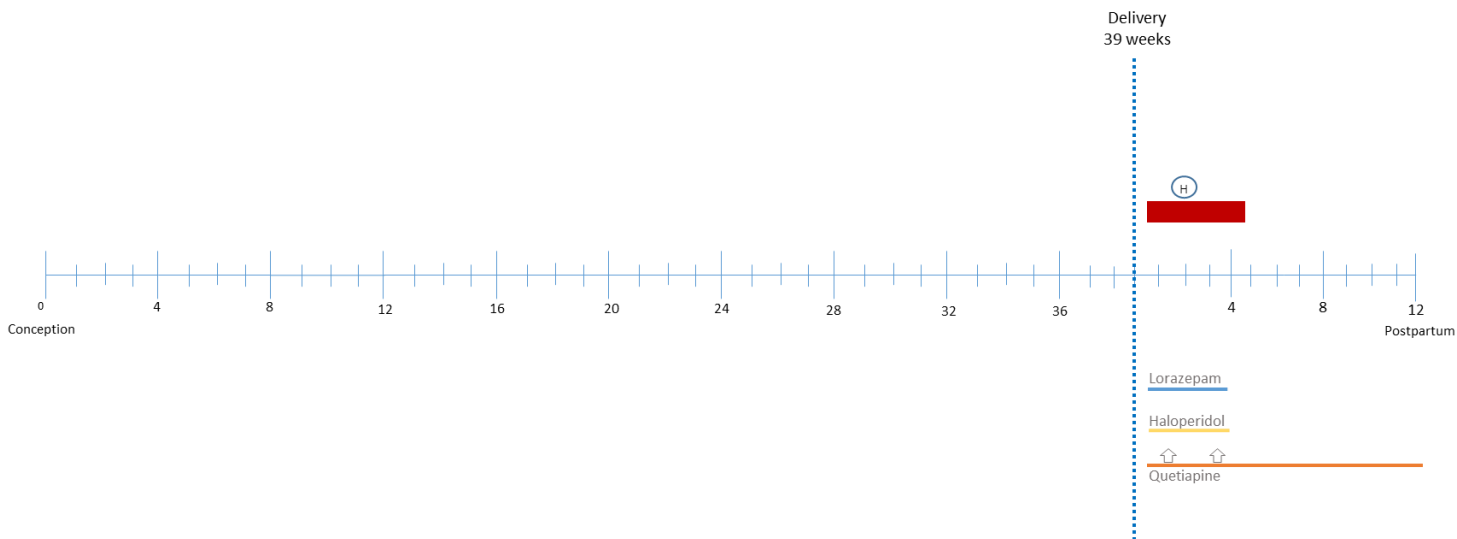
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness



Perinatal Timeline (weeks)

Participant 48

Preconception DSM-5 diagnosis: BD-I (PP only prior episode)

Key: DSM-5 and other perinatal episodes

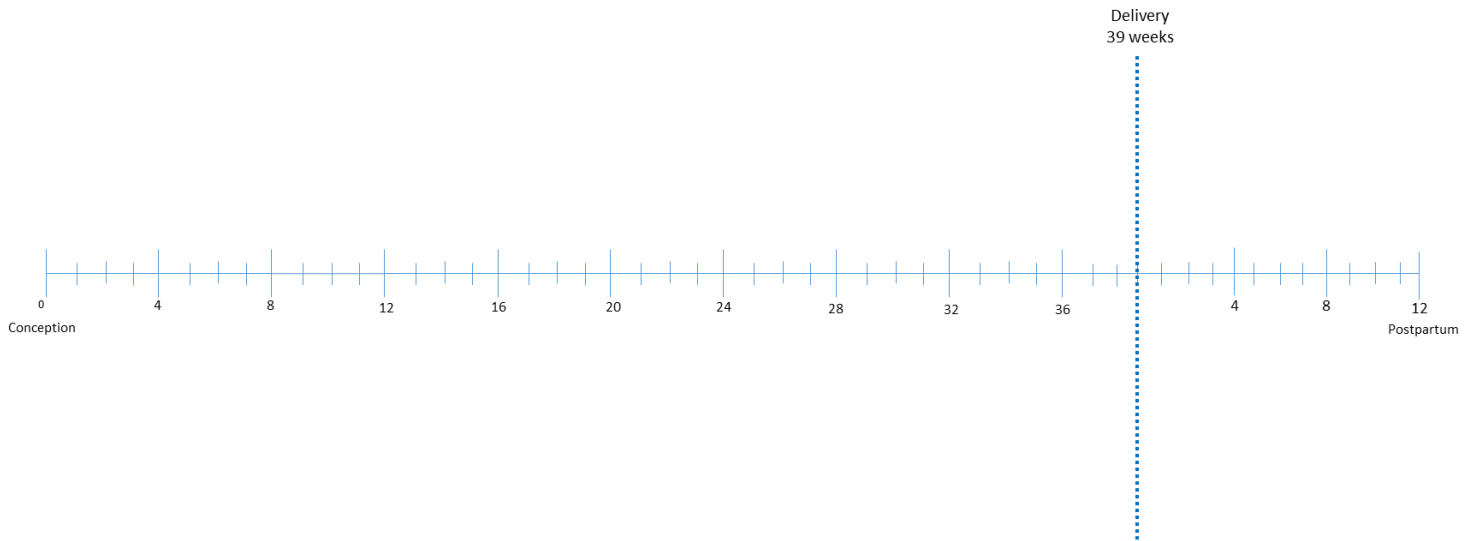
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness



Perinatal Timeline (weeks)

Participant 49

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

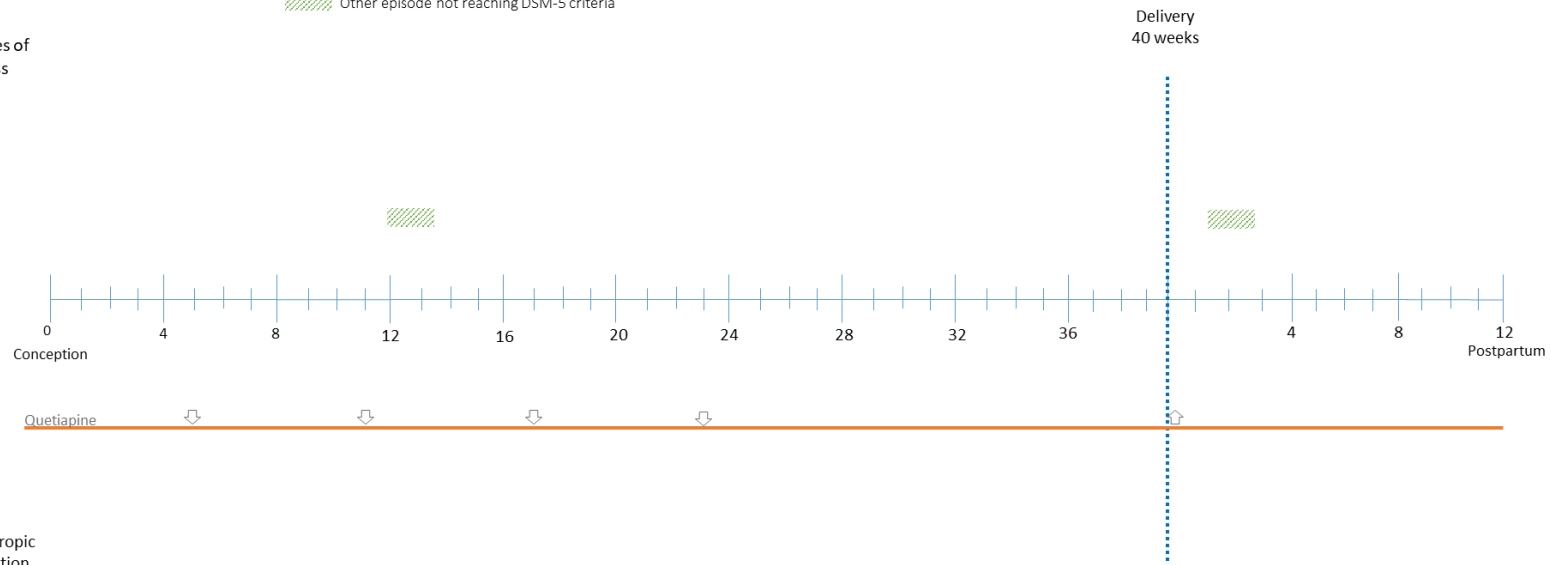
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness



Psychotropic medication

Perinatal Timeline (weeks)

Participant 50

Preconception DSM-5 diagnosis: BD-I

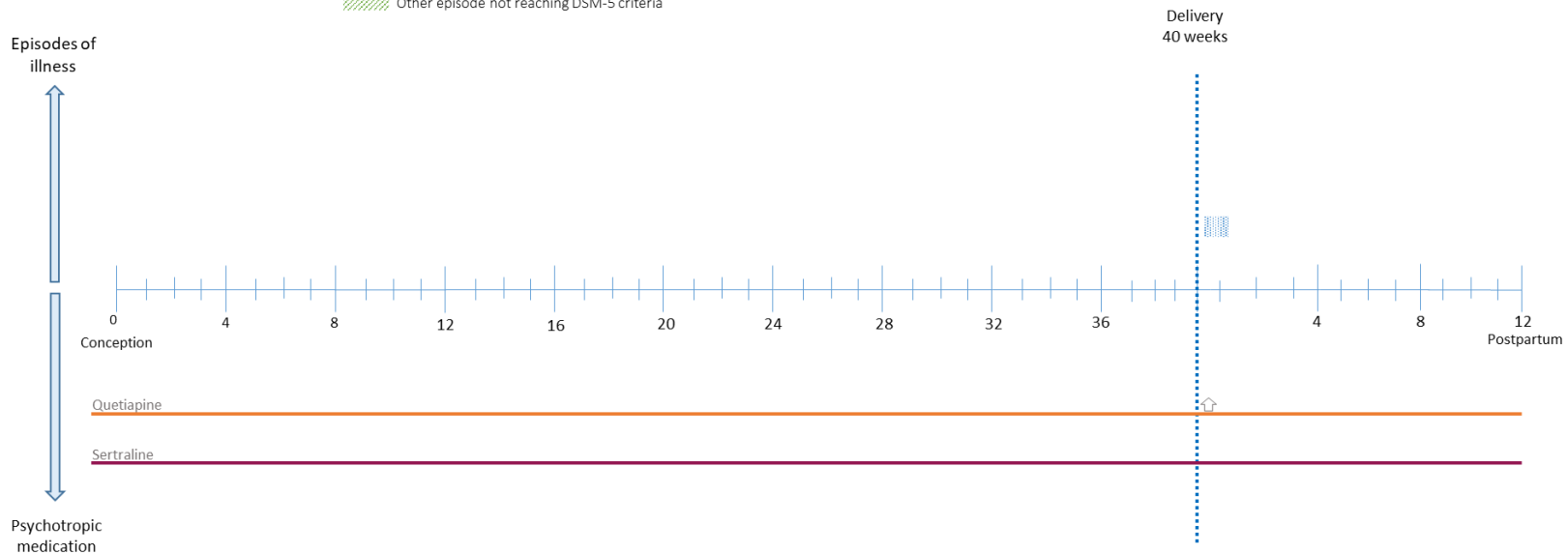
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 51

Preconception DSM-5 diagnosis: BD-I

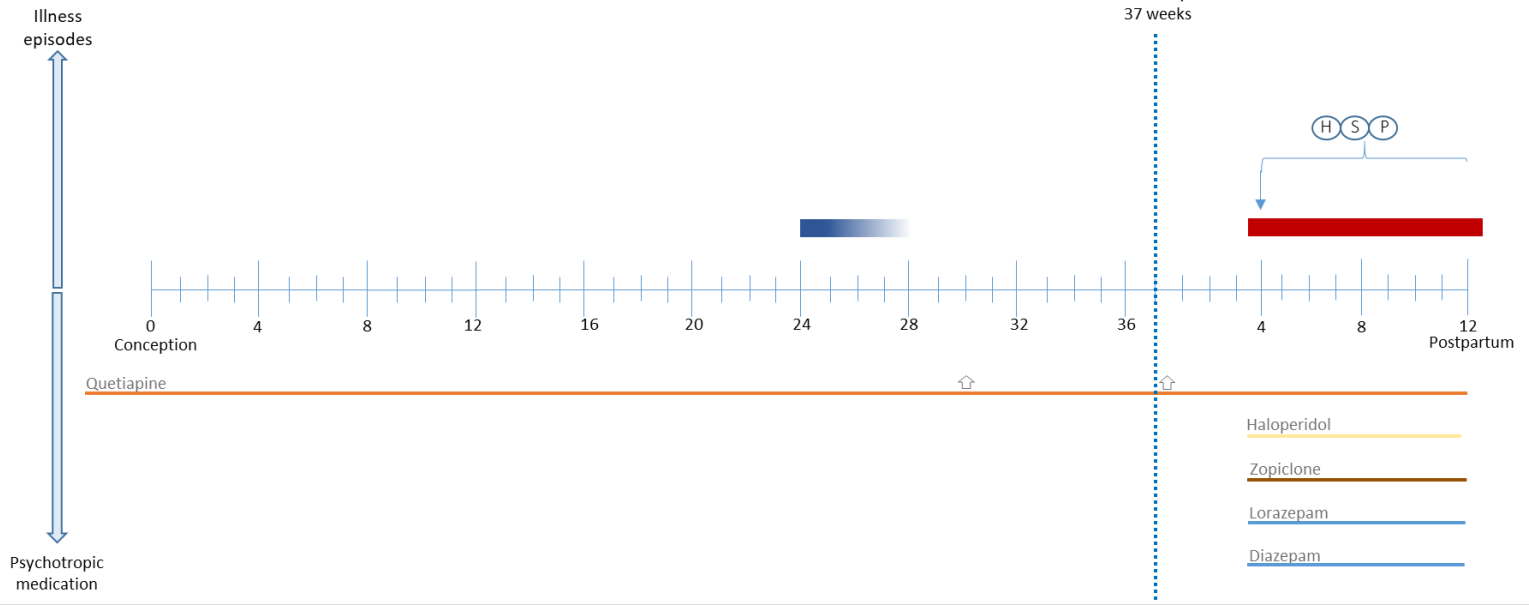
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- ↑ Dosage increase
- ↓ Dosage decrease



Perinatal Timeline (weeks)

Participant 52

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

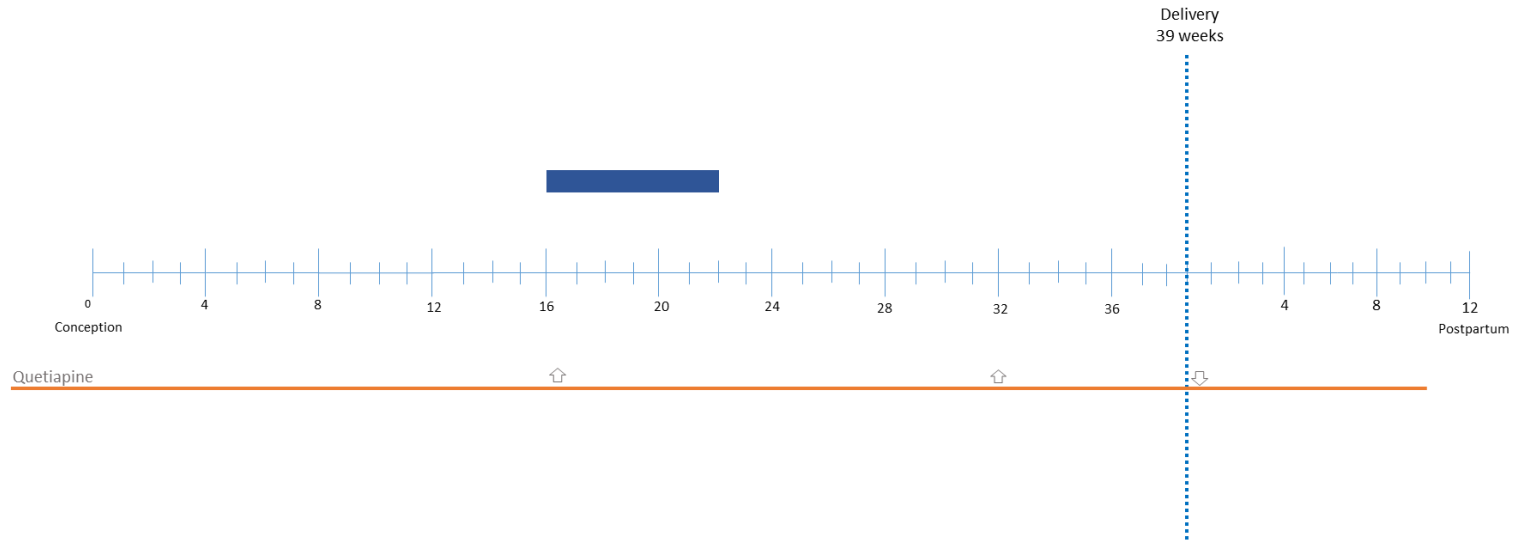
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness



Perinatal Timeline (weeks)

Participant 53

Preconception DSM-5 diagnosis: BD-II

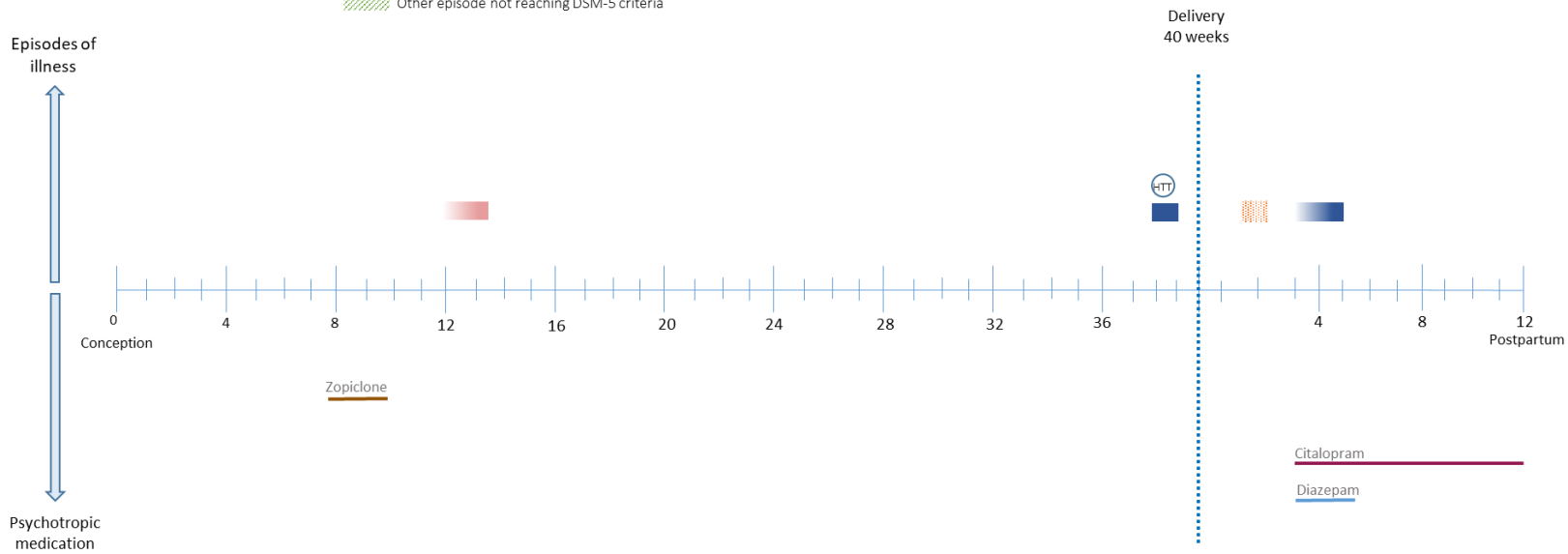
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 54

Preconception DSM-5 diagnosis: BD-II

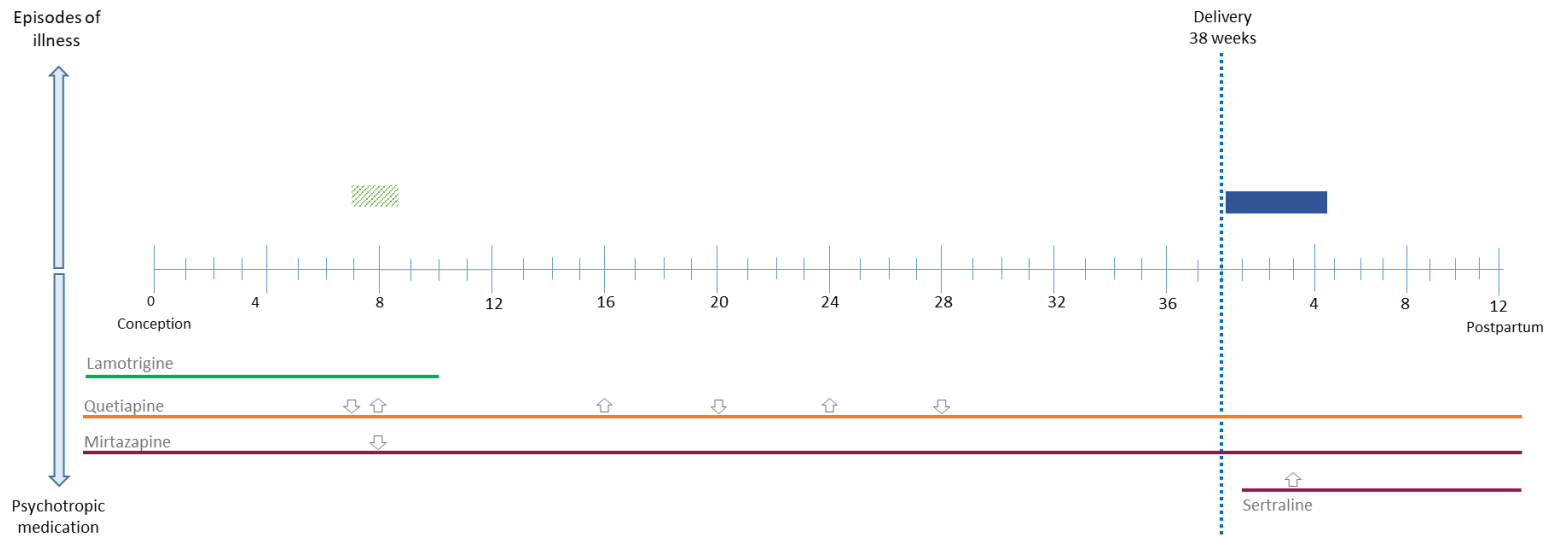
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 55

Preconception DSM-5 diagnosis: BD-I

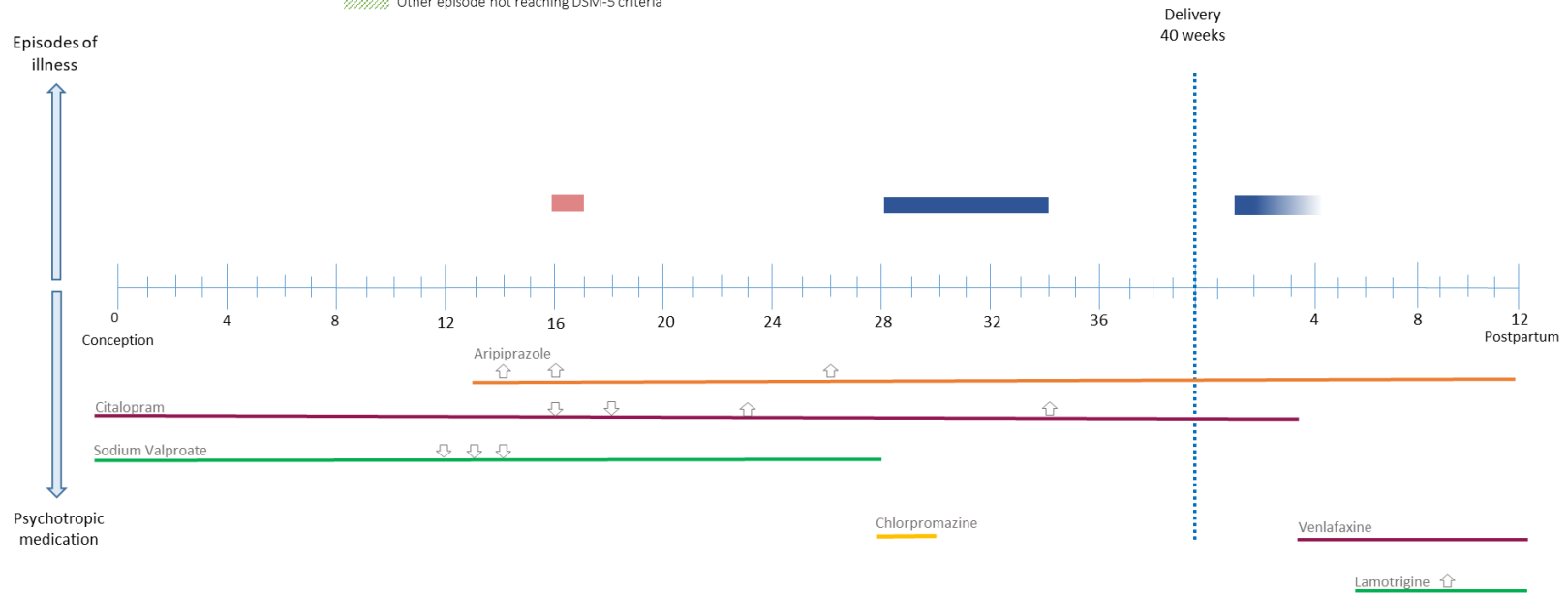
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 56

Preconception DSM-5 diagnosis: BD-I

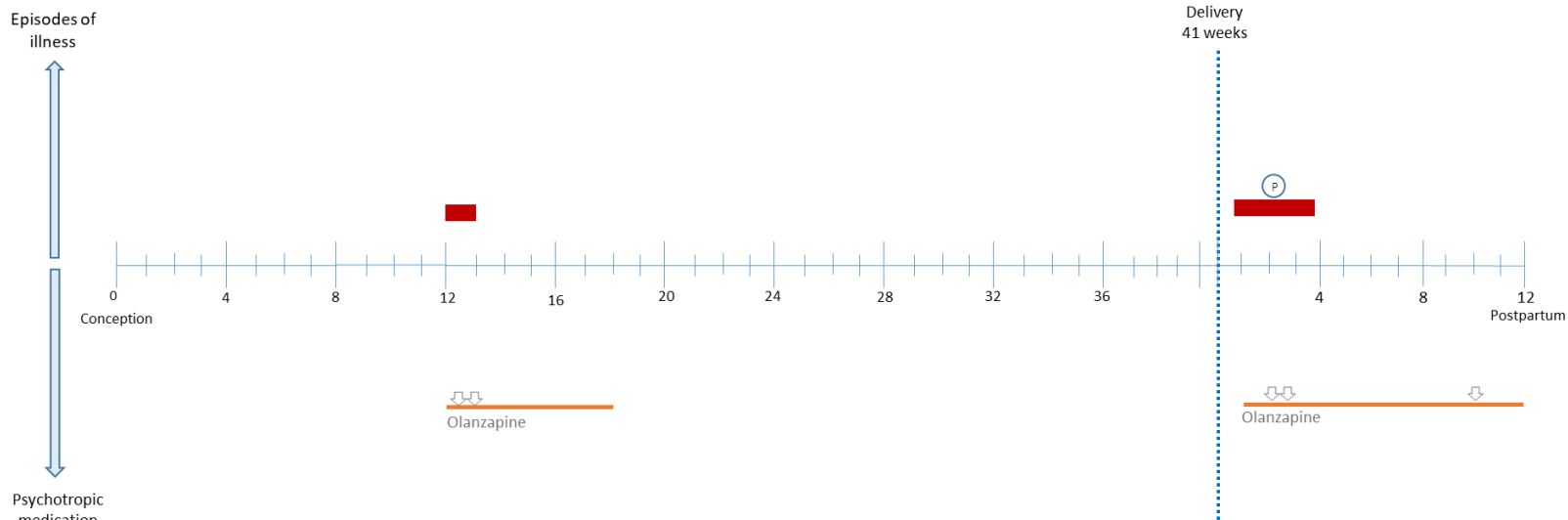
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 57

Preconception DSM-5 diagnosis: BD-I

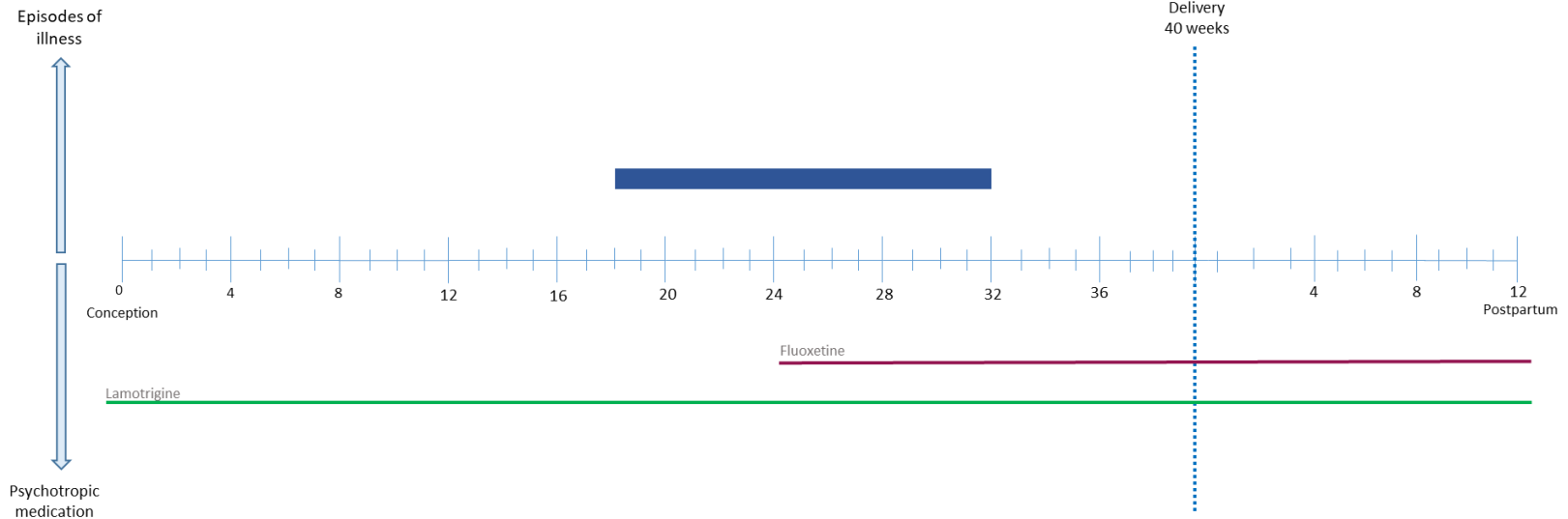
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- ↑ Dosage increase
- ↓ Dosage decrease



Perinatal Timeline (weeks)

Participant 58

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

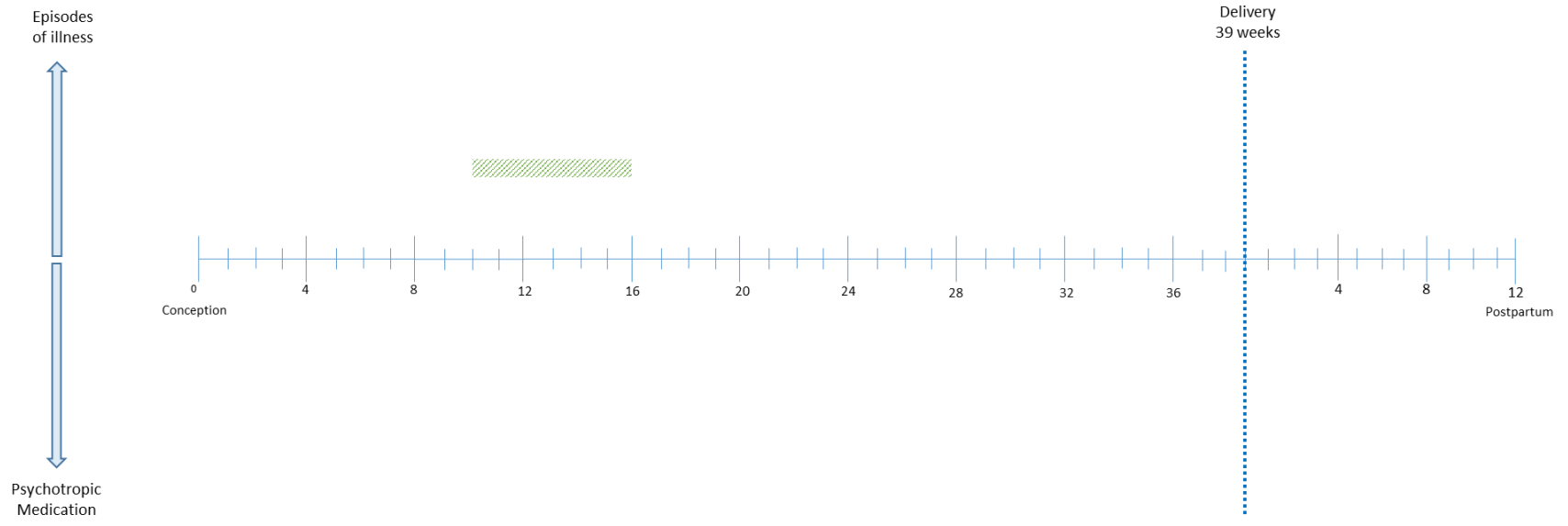
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- ↑ Dosage increase
- ↓ Dosage decrease



Perinatal Timeline (weeks)

Participant 59

Preconception DSM-5 diagnosis: BD-II

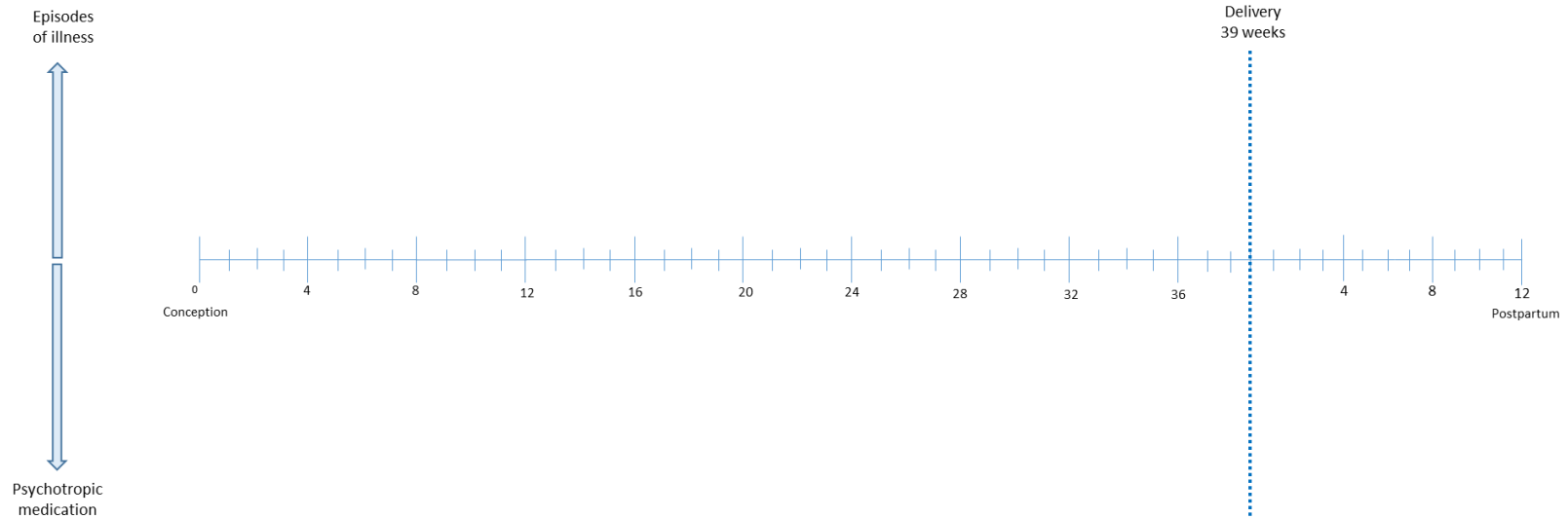
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 60

Preconception DSM-5 diagnosis: BD-I

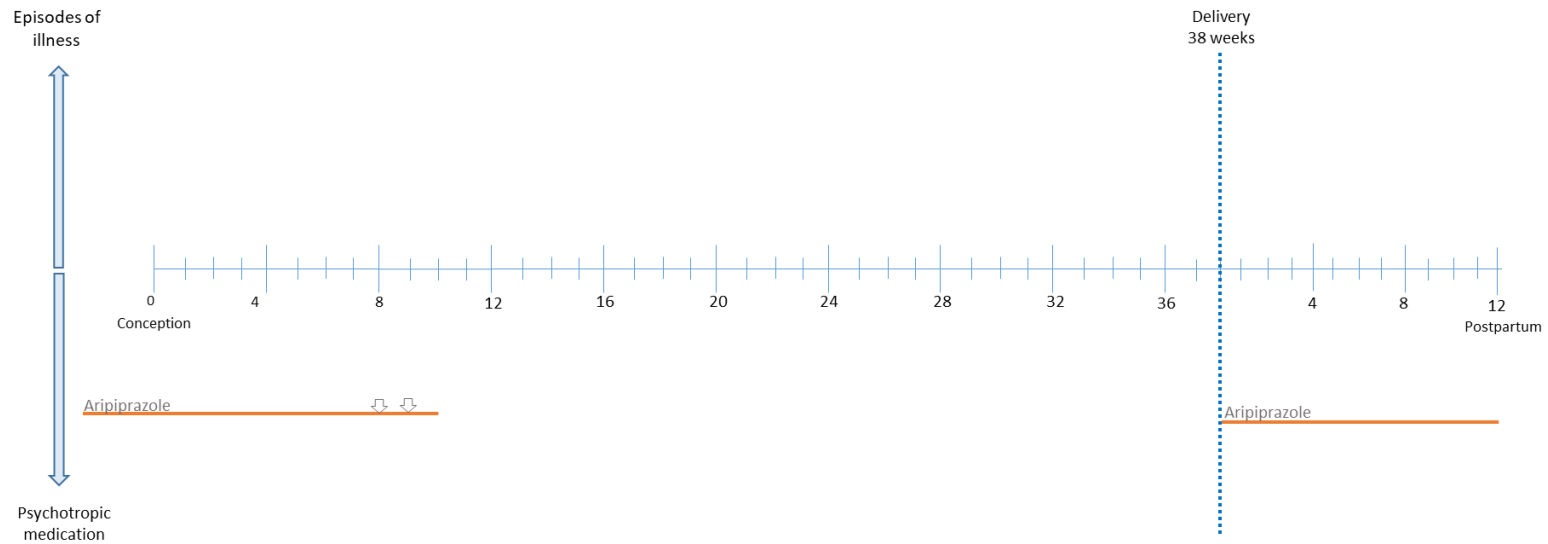
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 61

Preconception DSM-5 diagnosis: BD-I

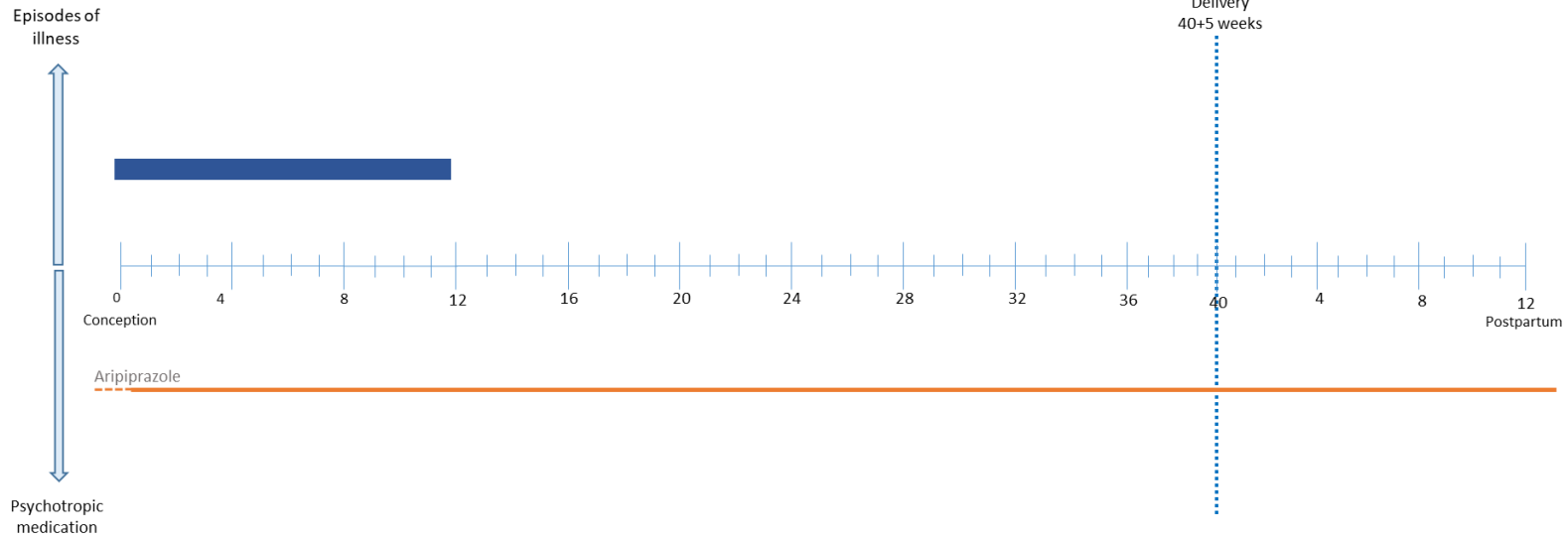
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 62

Preconception DSM-5 diagnosis: BD-I

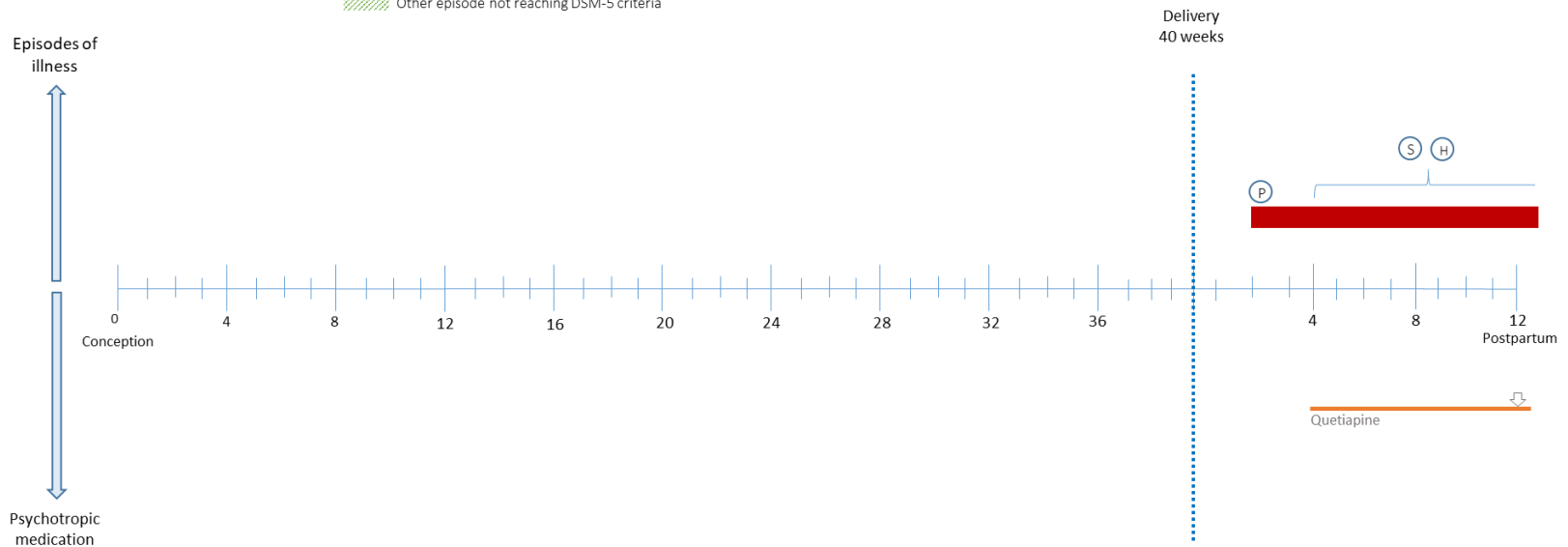
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 63

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

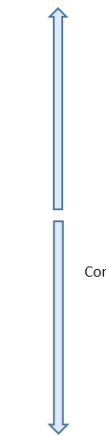
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

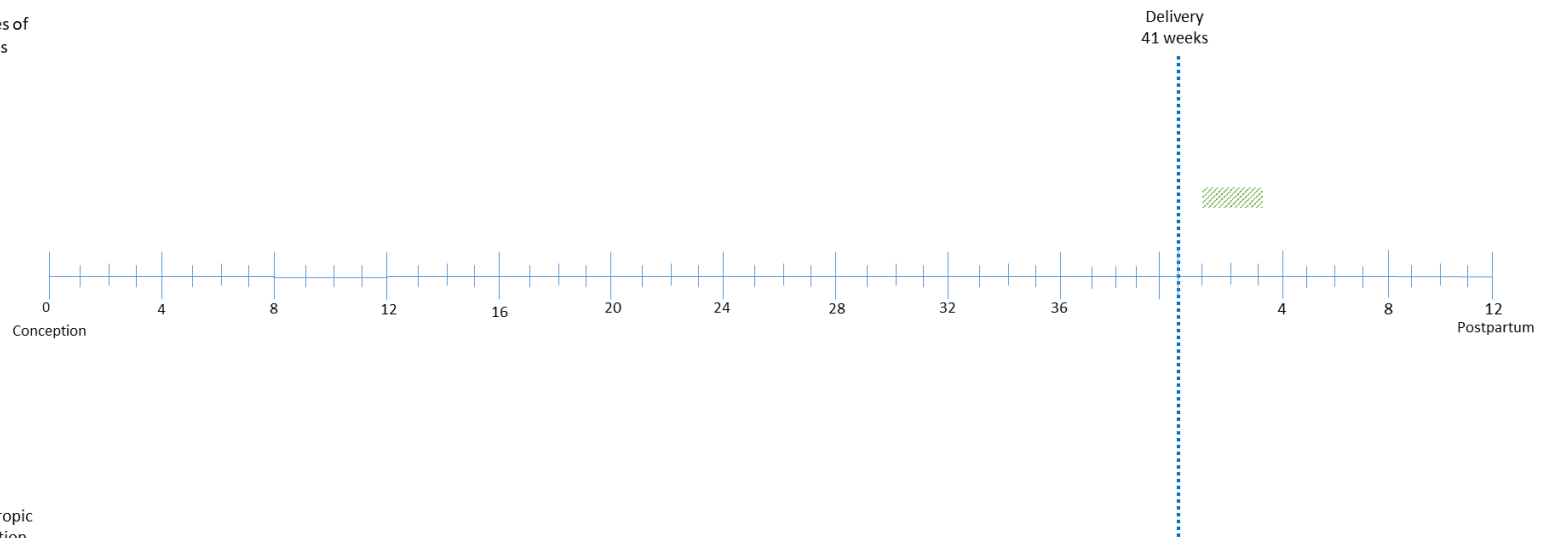
Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness



Psychotropic medication



Perinatal Timeline (weeks)

Participant 64

Preconception DSM-5 diagnosis: BD-I

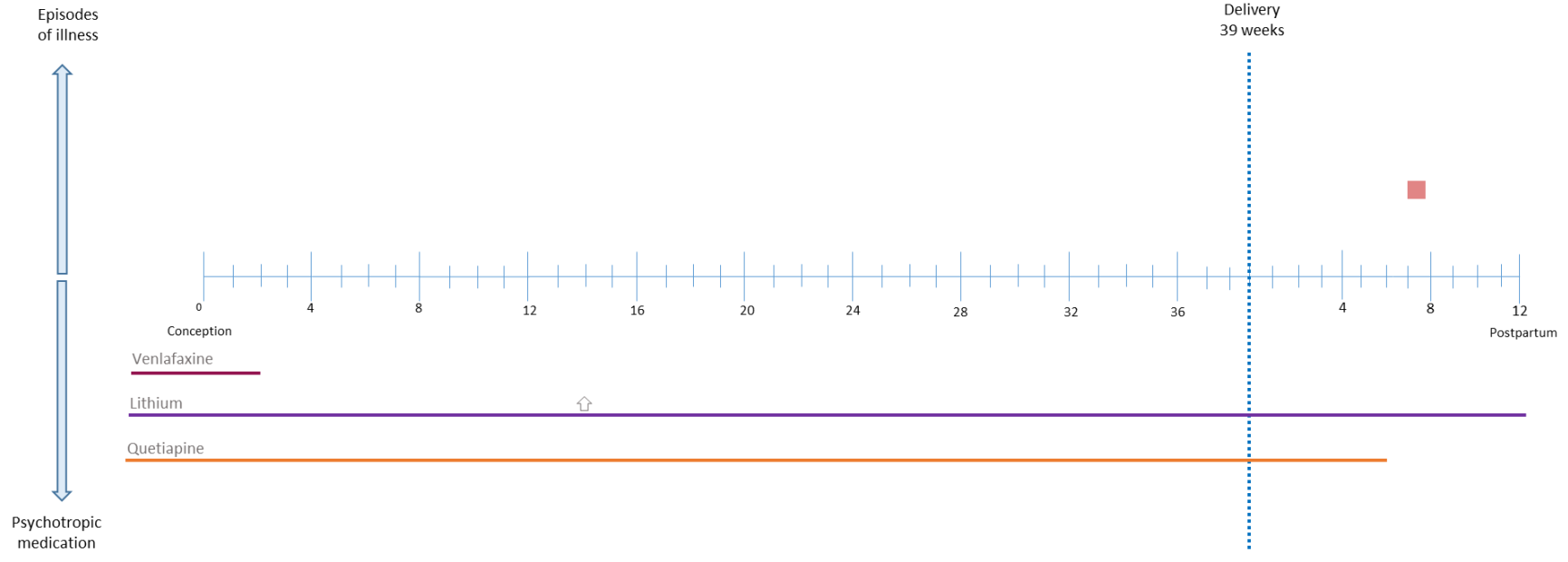
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 65

Preconception DSM-5 diagnosis: BD-I

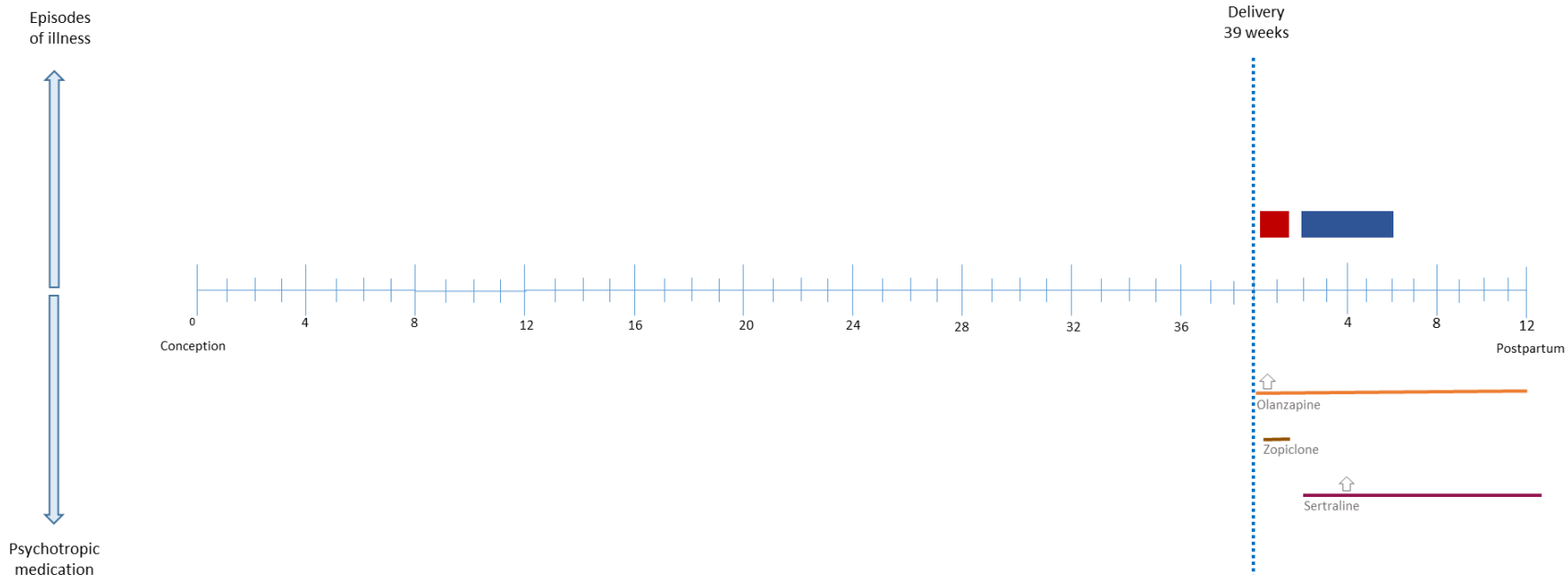
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 66

Preconception DSM-5 diagnosis: BD-I

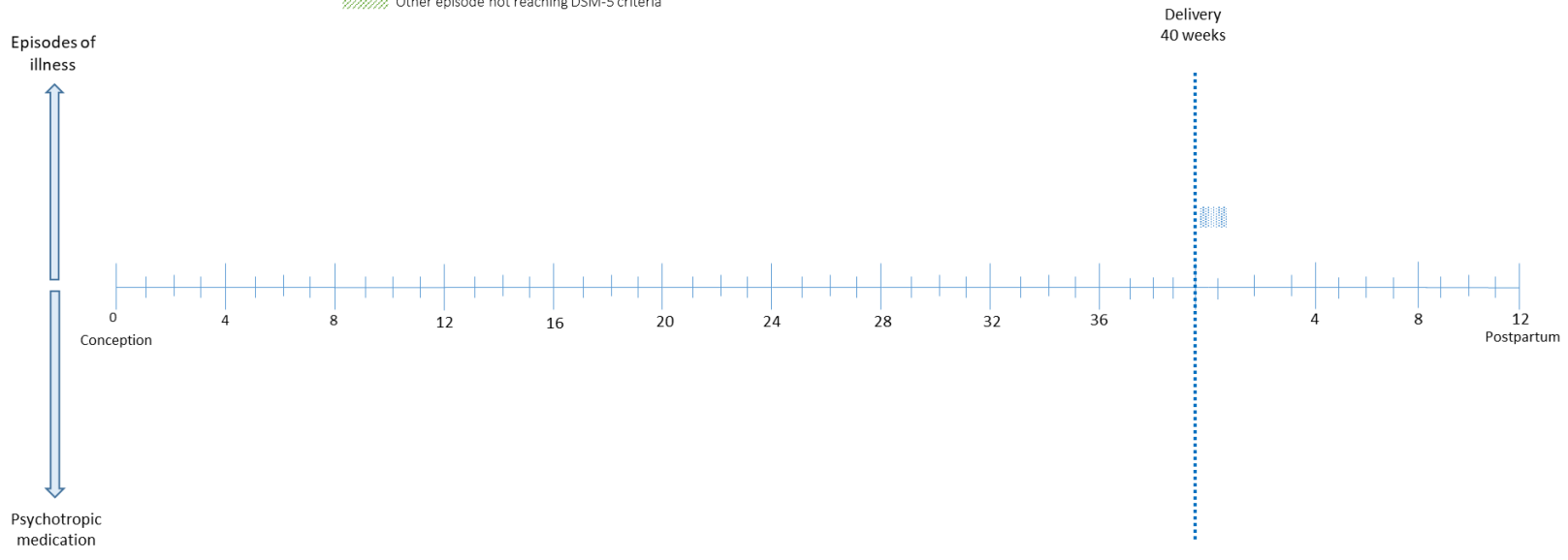
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 67

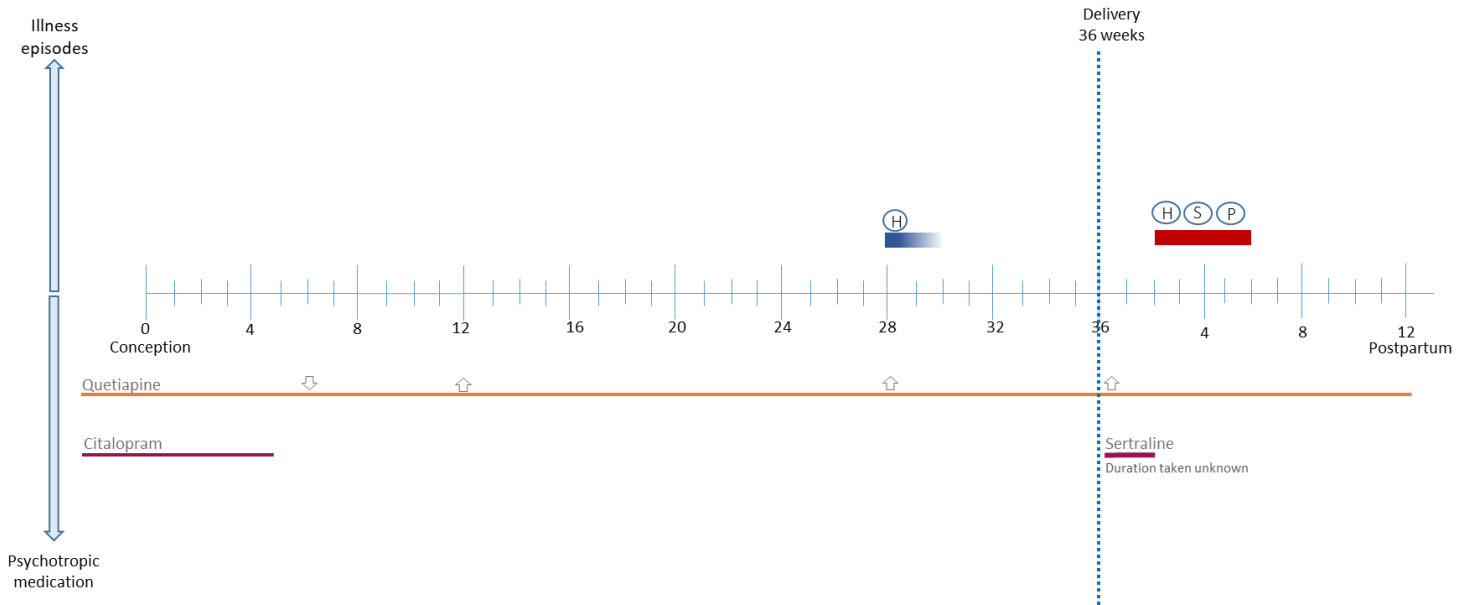
Preconception DSM-5 diagnosis: BD-I
(PP only prior episode)

Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

Key: Psychotropic Medication

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown
- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- ↑ Dosage increase
- ↓ Dosage decrease



Perinatal Timeline (weeks)

Participant 68

Preconception DSM-5 diagnosis: BD-II

Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

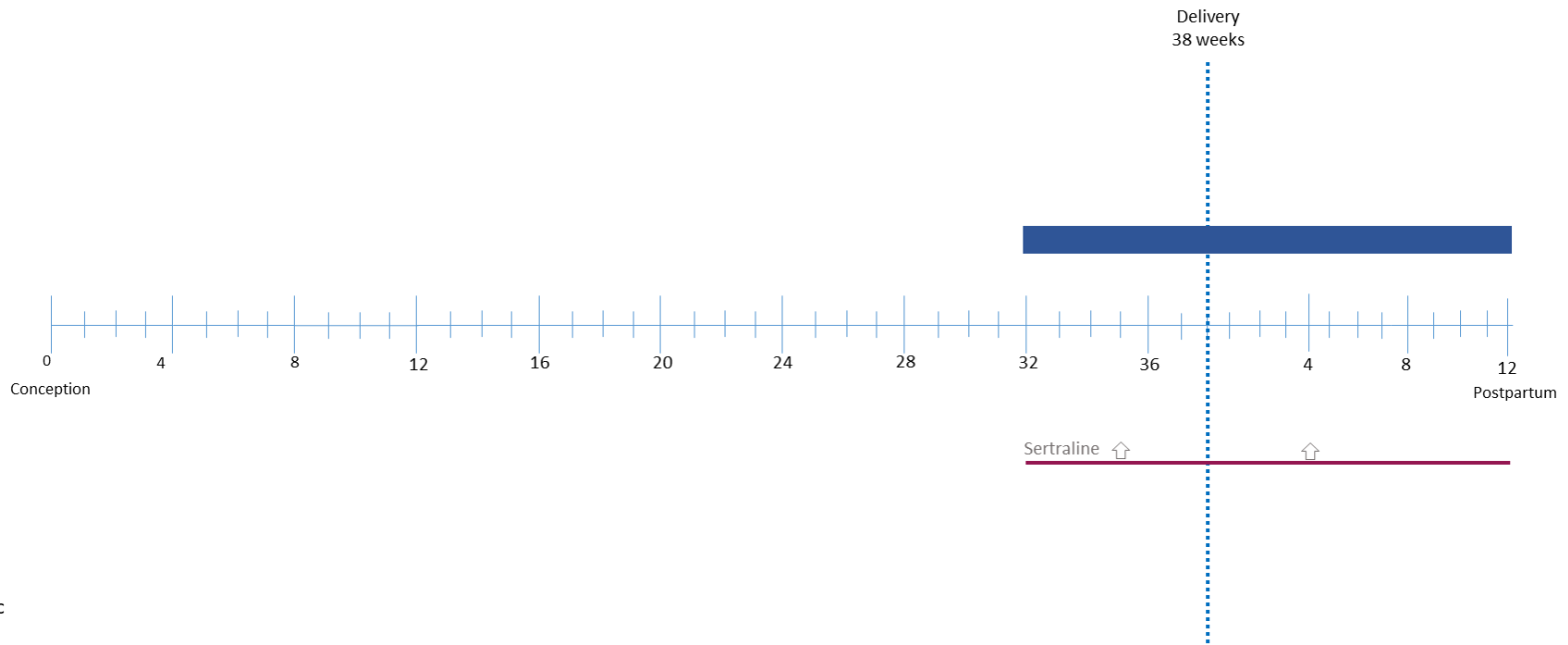
Key: Psychotropic Medication

- Lithium
- Hypnotic
- Atypical Antipsychotic
- Anxiolytic
- Typical Antipsychotic
- Antidepressant
- Anticonvulsant
- Dosage unknown
- ↑ Dosage increase
- ↓ Dosage decrease

Episodes of illness



Psychotropic Medication



Perinatal Timeline (weeks)

Participant 69

Preconception DSM-5 diagnosis: BD-I

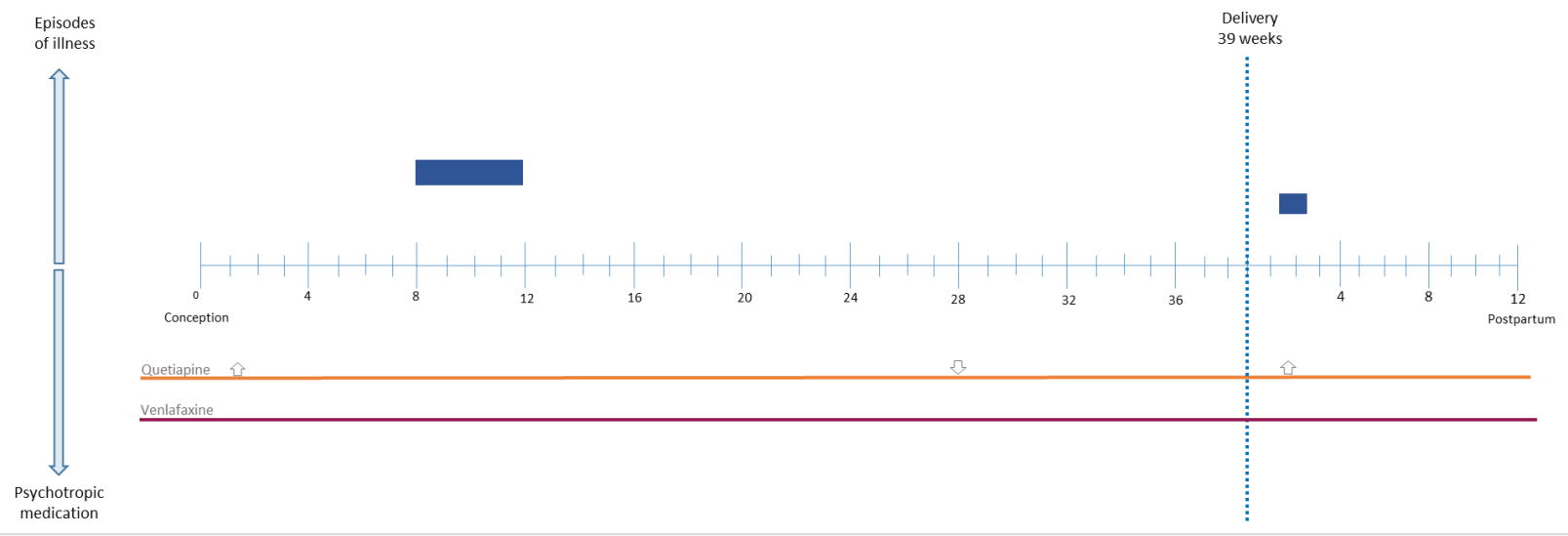
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 70

Preconception DSM-5 diagnosis: BD-I

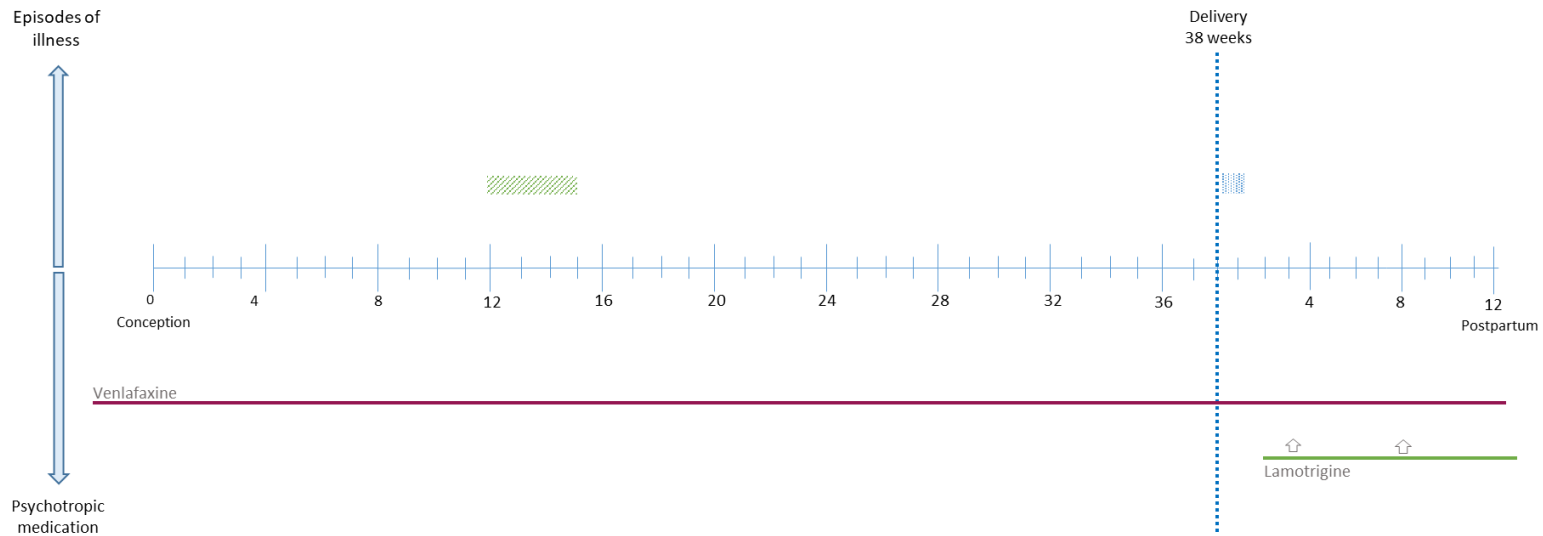
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 71

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

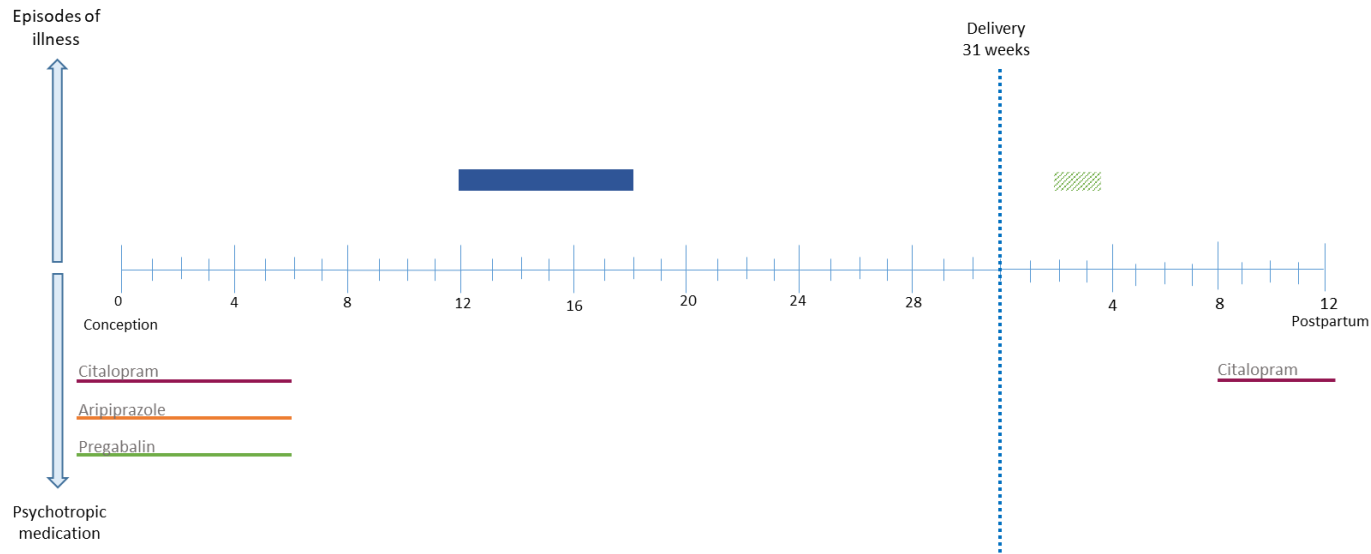
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 72

Preconception DSM-5 diagnosis: BD-I

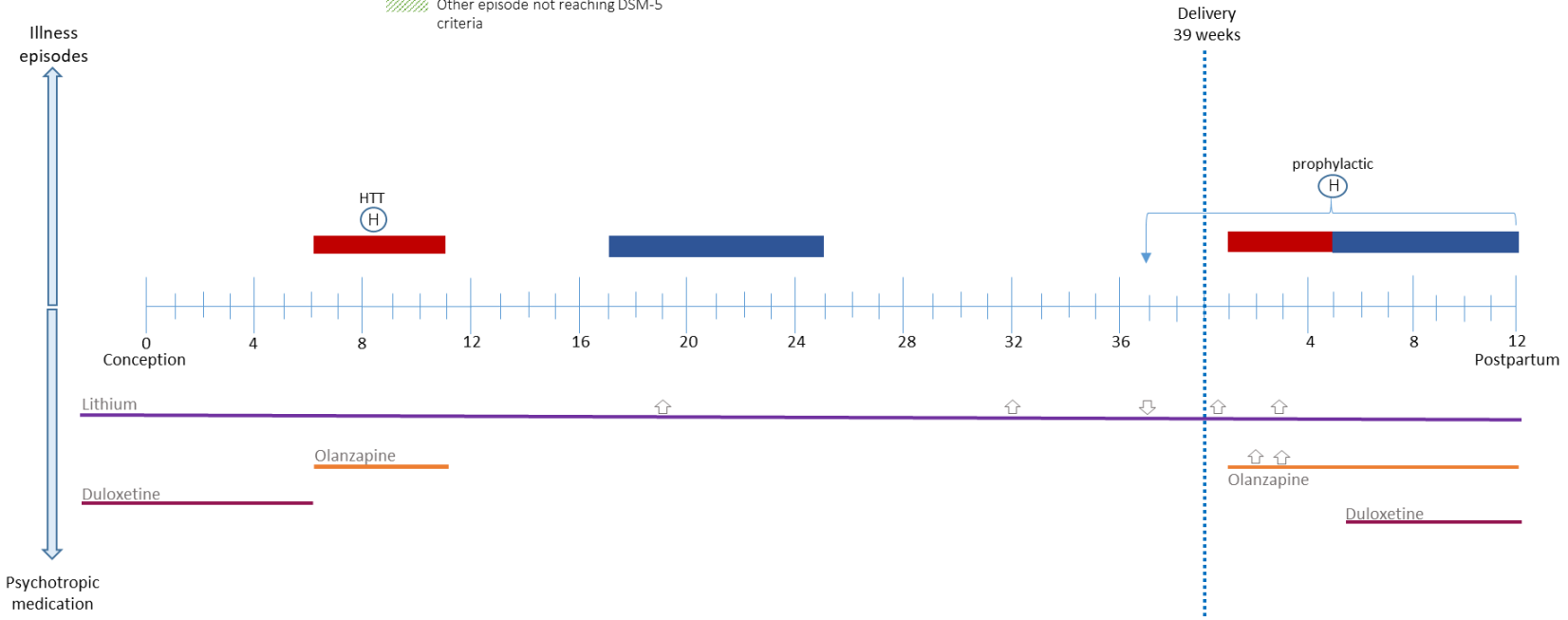
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- ↑ Dosage increase
- ↓ Dosage decrease



Perinatal Timeline (weeks)

Participant 73

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

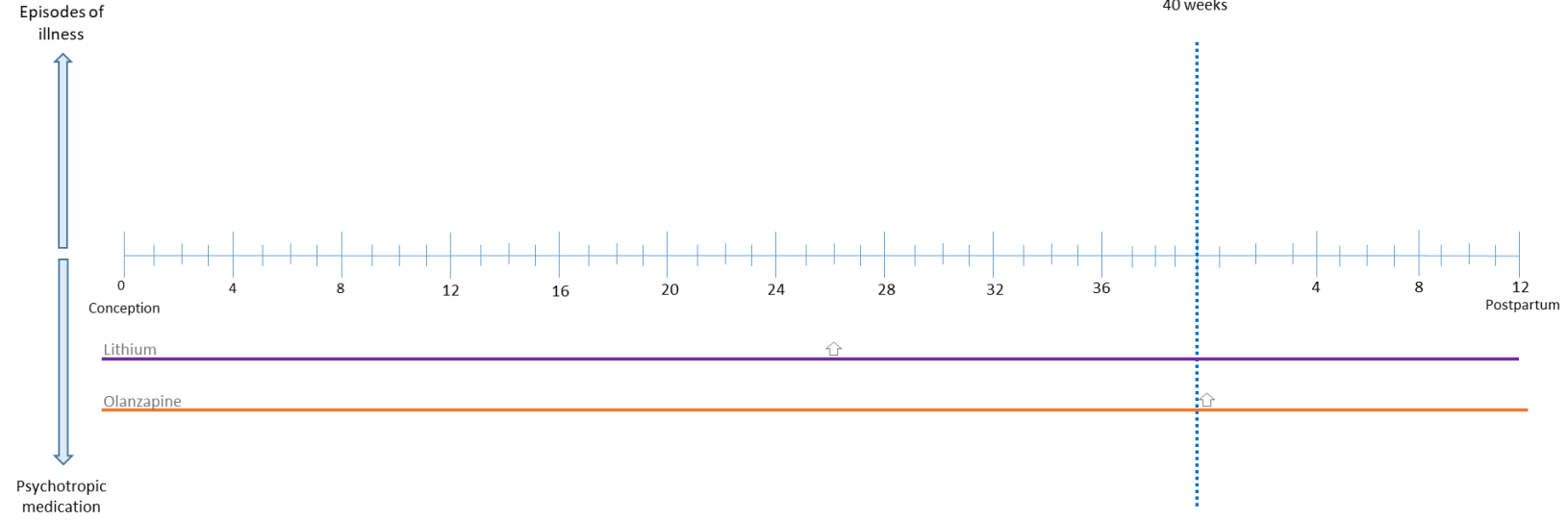
- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant

- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 74

Preconception DSM-5 diagnosis: BD-NOS

Key: DSM-5 and other perinatal episodes

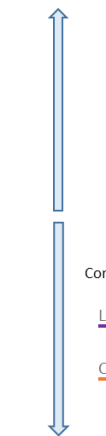
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

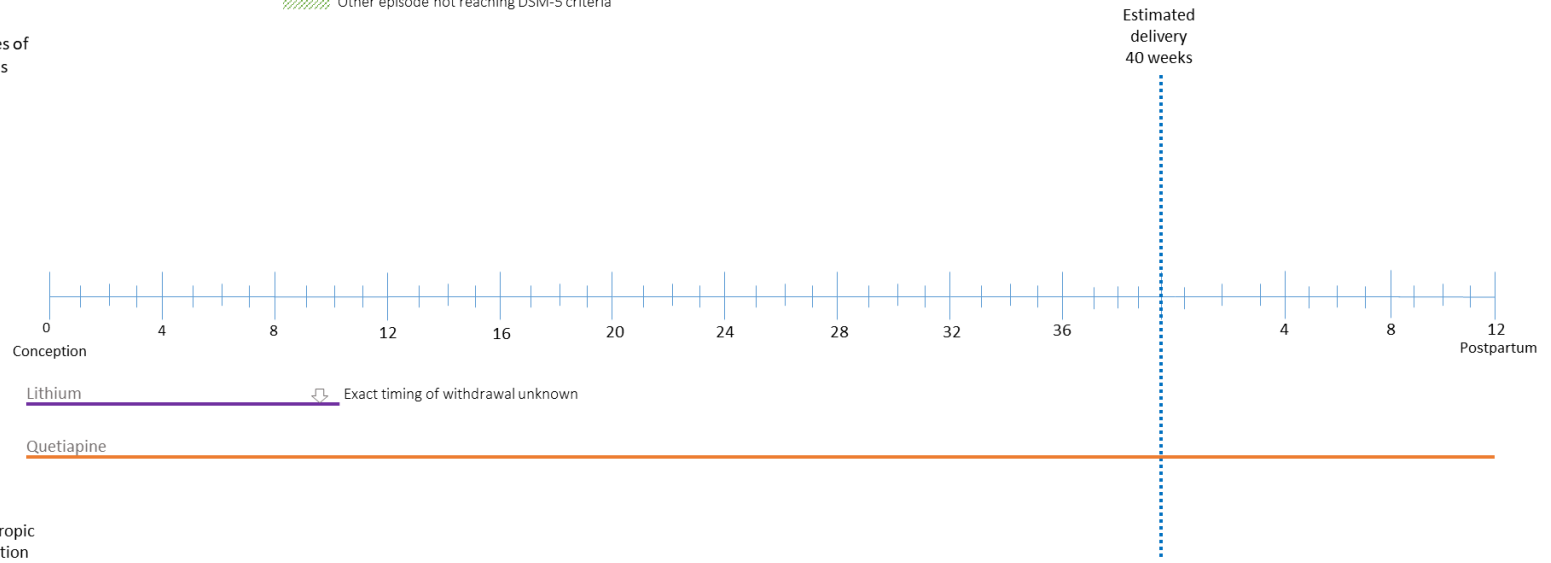
Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness



Psychotropic medication



Perinatal Timeline (weeks)

Participant 75

Preconception DSM-5 diagnosis: BD-II

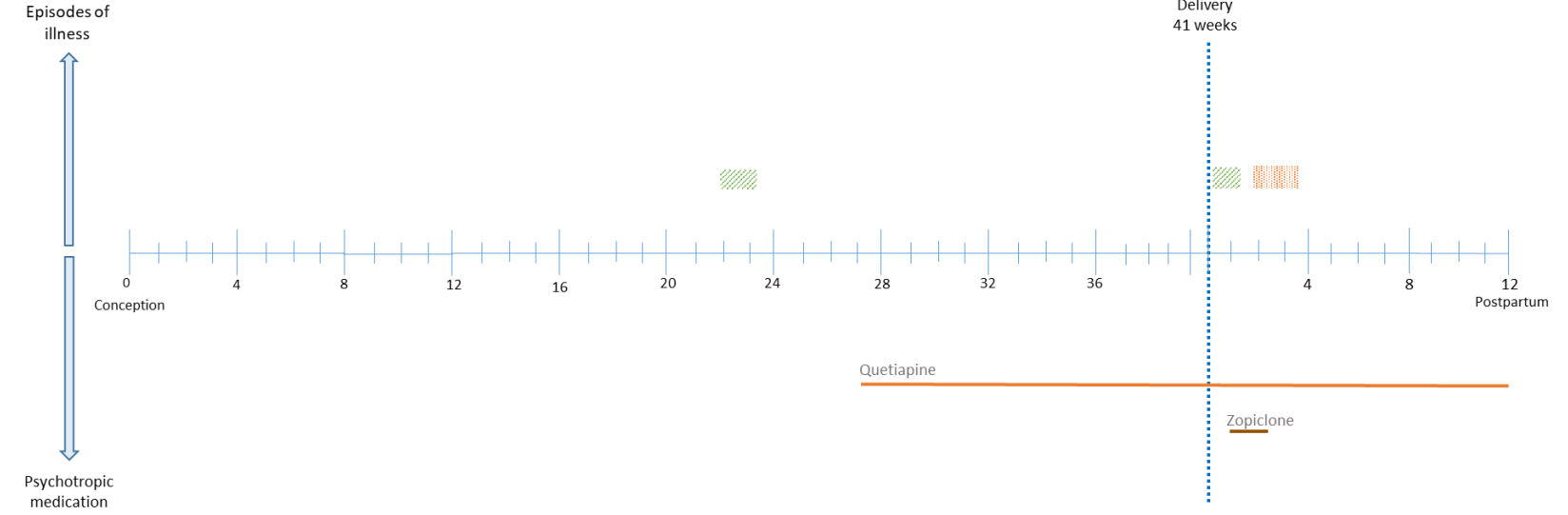
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 76

Preconception DSM-5 diagnosis: BD-I

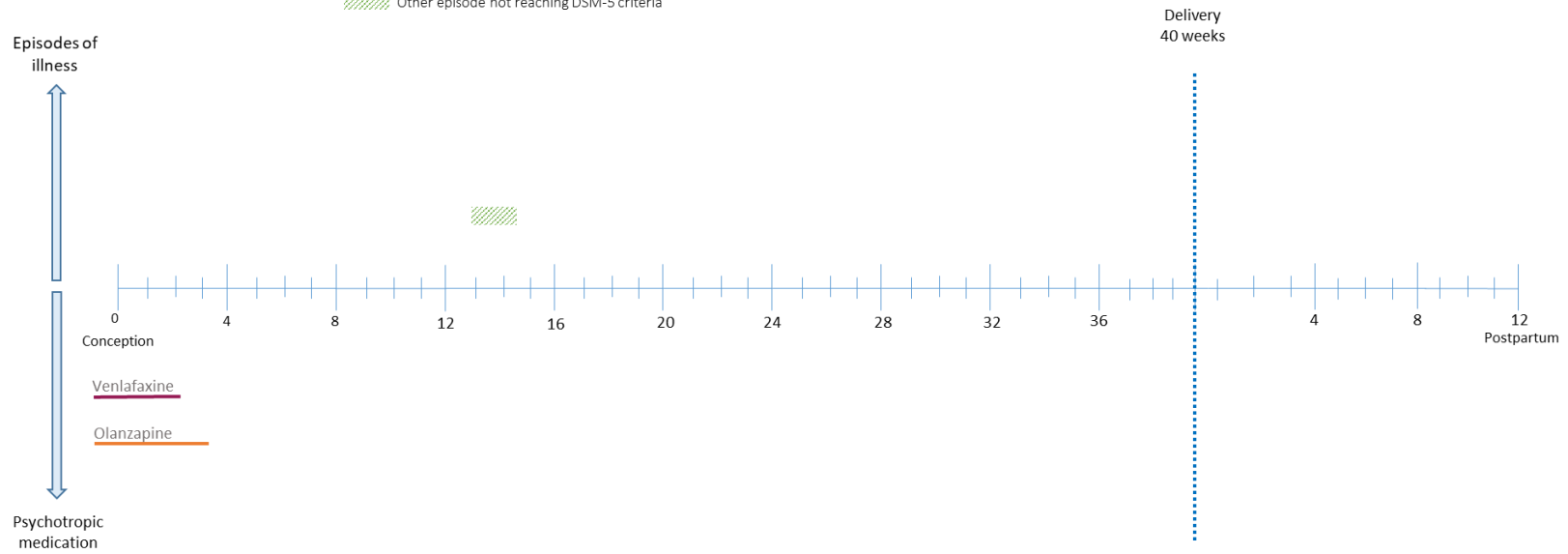
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 77

Preconception DSM-5 diagnosis: BD-I

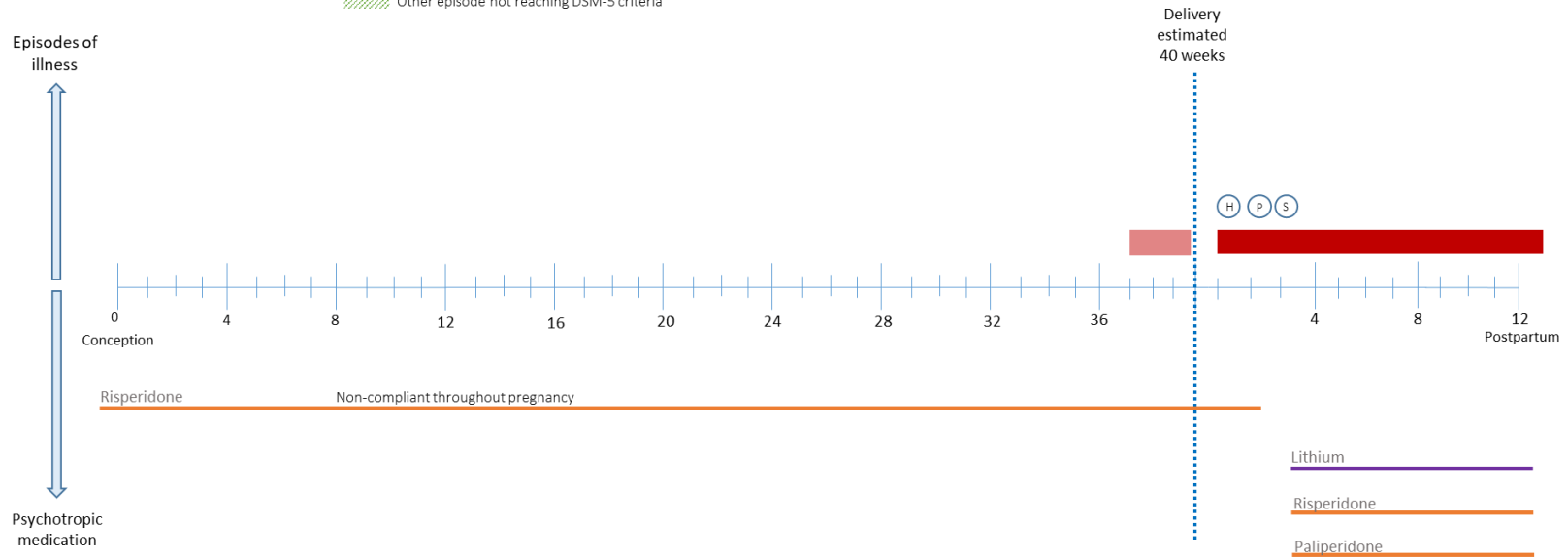
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 78

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

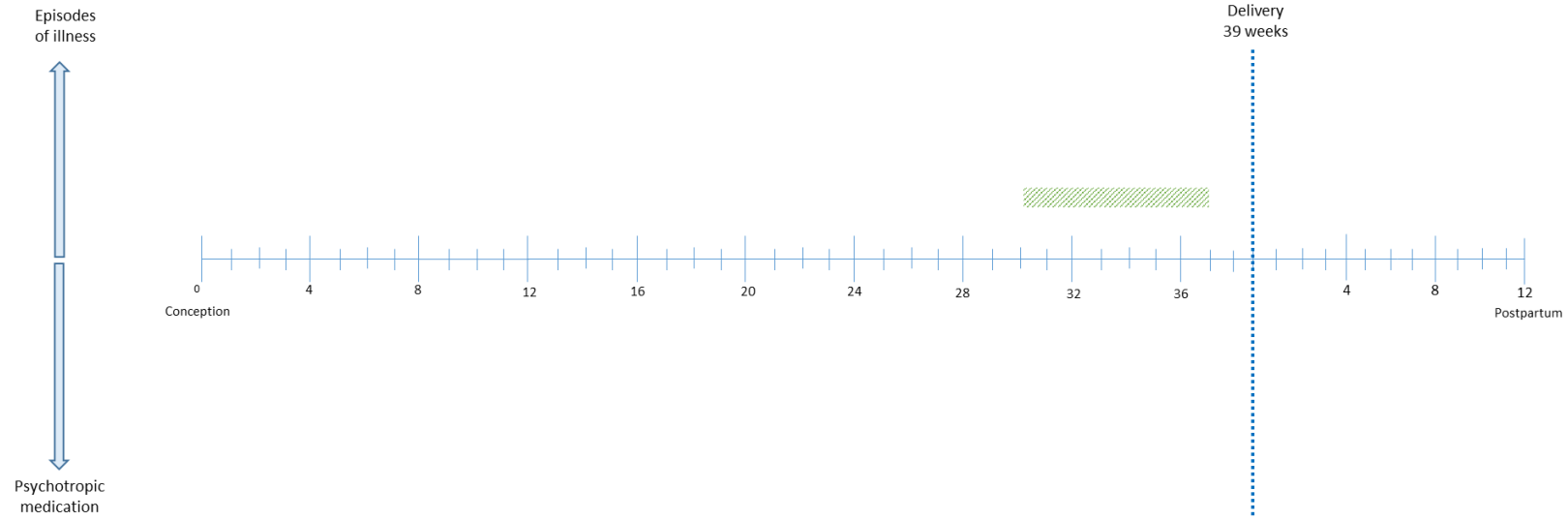
- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant

- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 79

Preconception DSM-5 diagnosis: BD-I

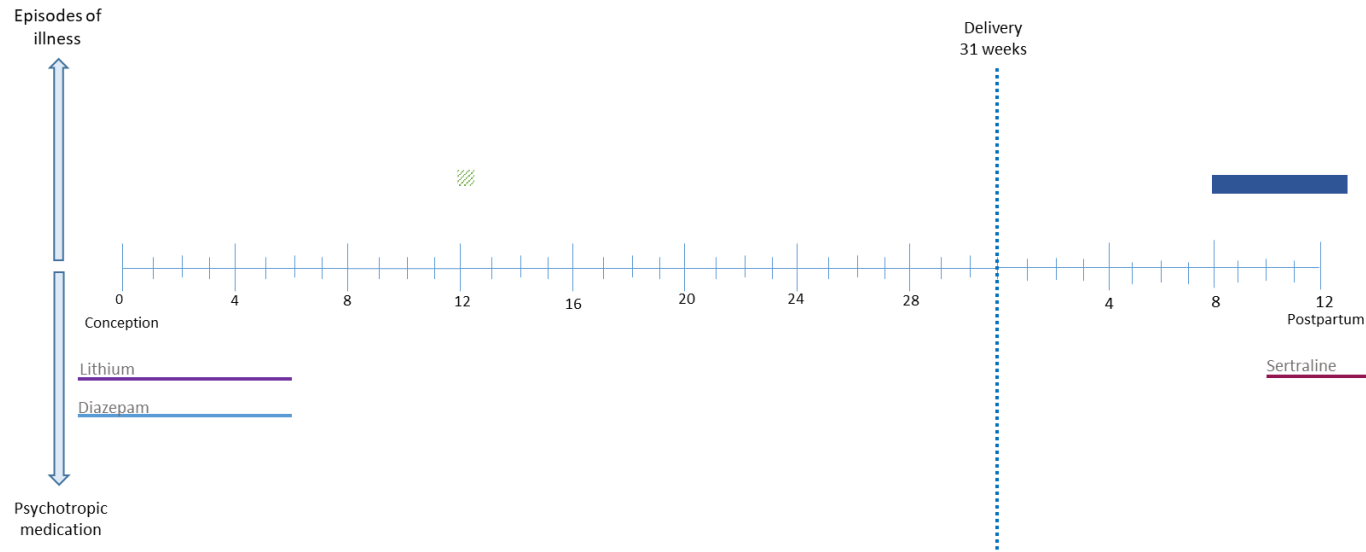
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- ↑
Dosage increase
- ↓
Dosage decrease



Perinatal Timeline (weeks)

Participant 80

Preconception DSM-5 diagnosis: BD-I
(PP only prior episode)

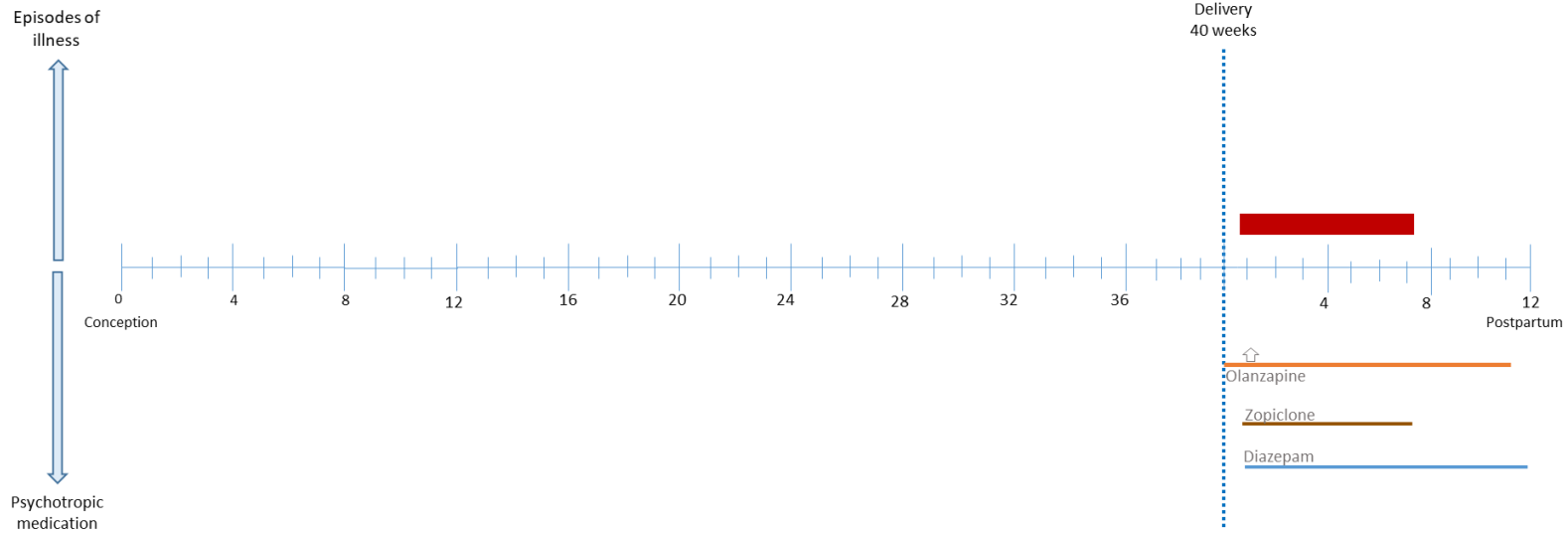
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 81

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

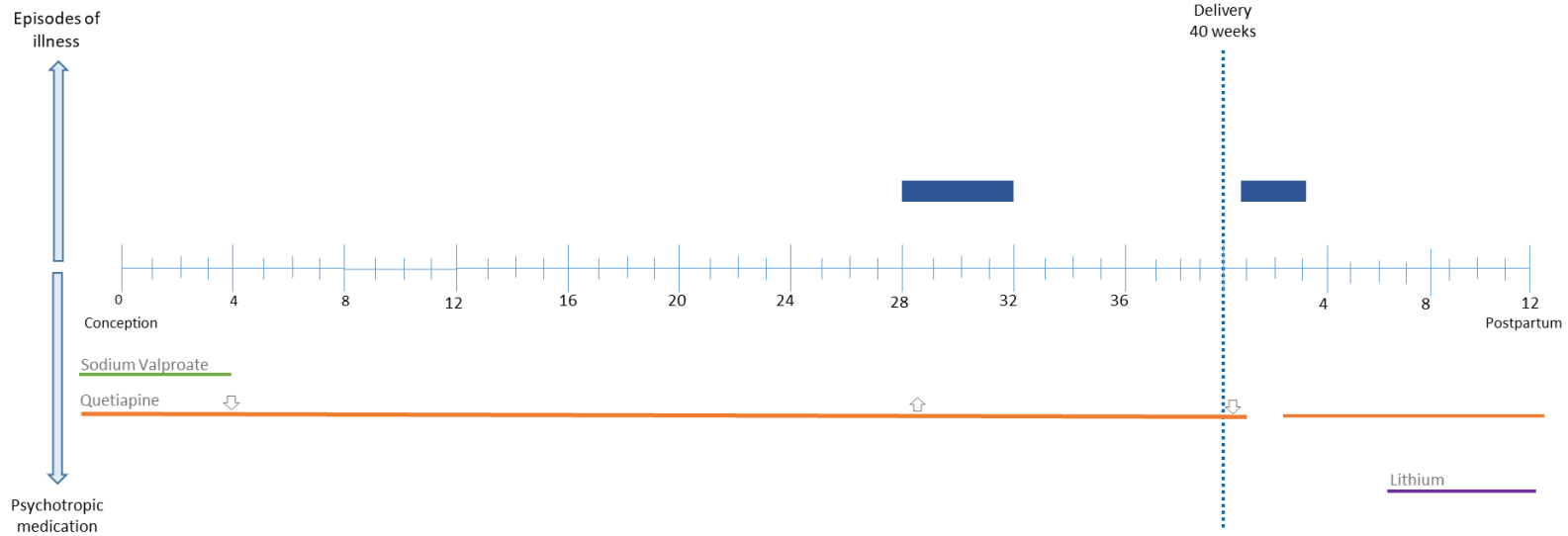
- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant

- Dosage unknown
- ↑ Dosage increase
- ↓ Dosage decrease



Perinatal Timeline (weeks)

Participant 82

Preconception DSM-5 diagnosis: BD-I

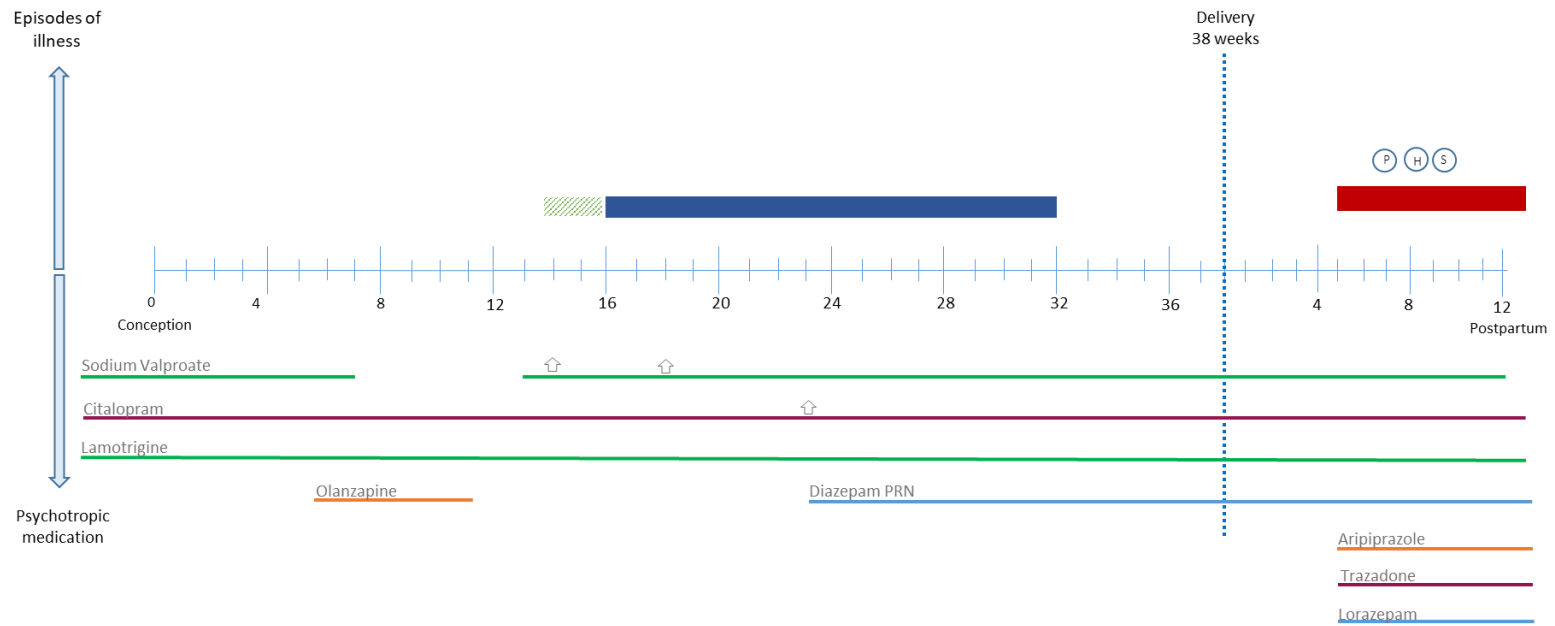
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 83

Preconception DSM-5 diagnosis: BD-I

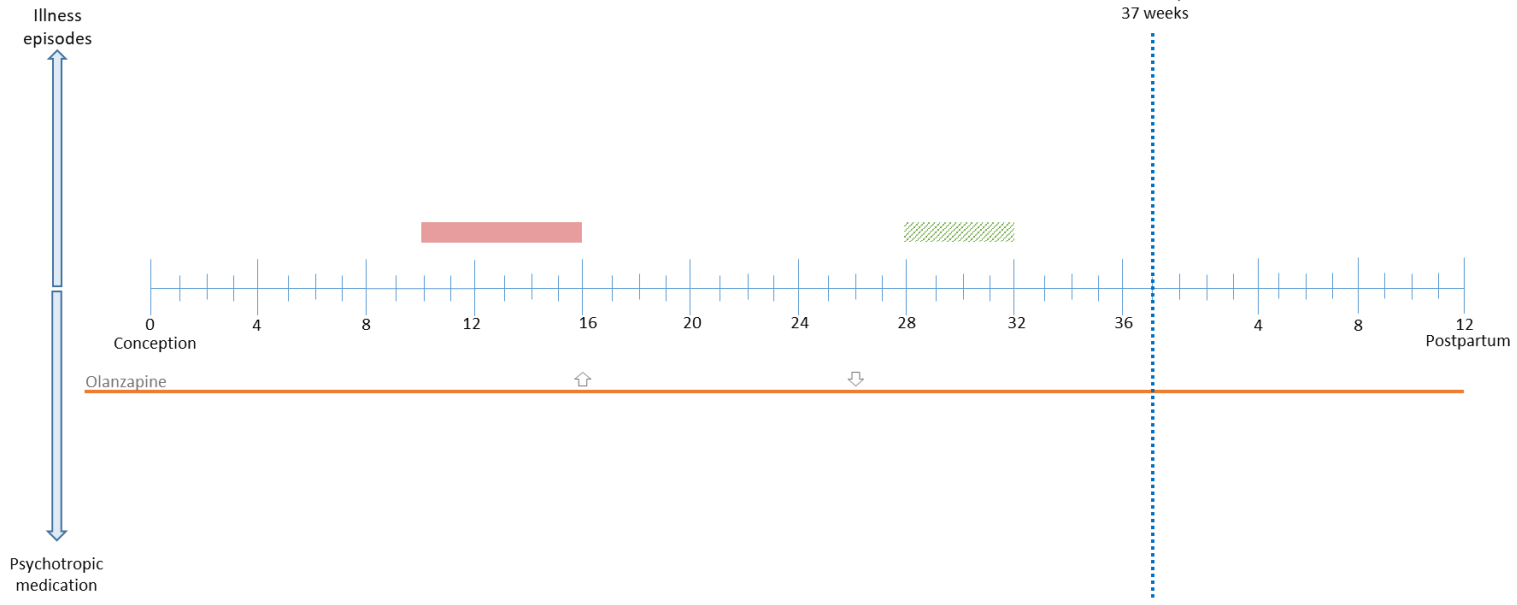
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 84

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

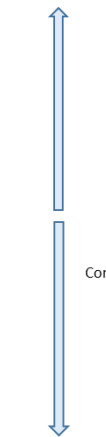
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

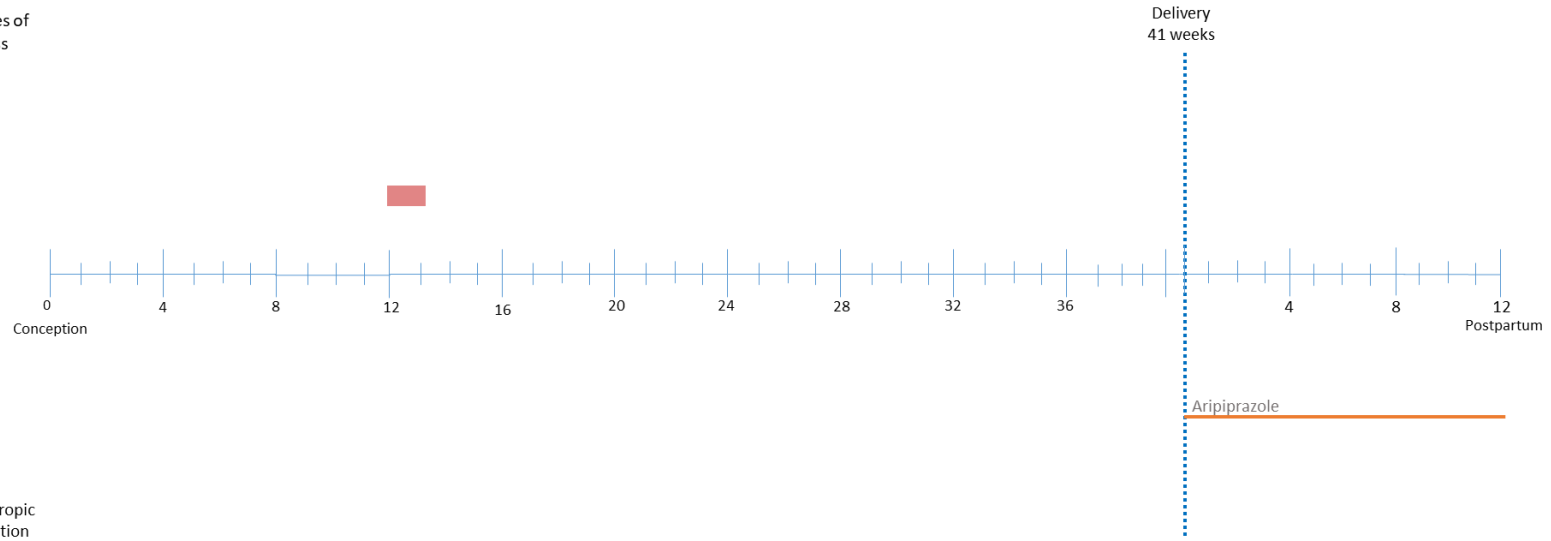
Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness



Psychotropic medication



Perinatal Timeline (weeks)

Participant 85

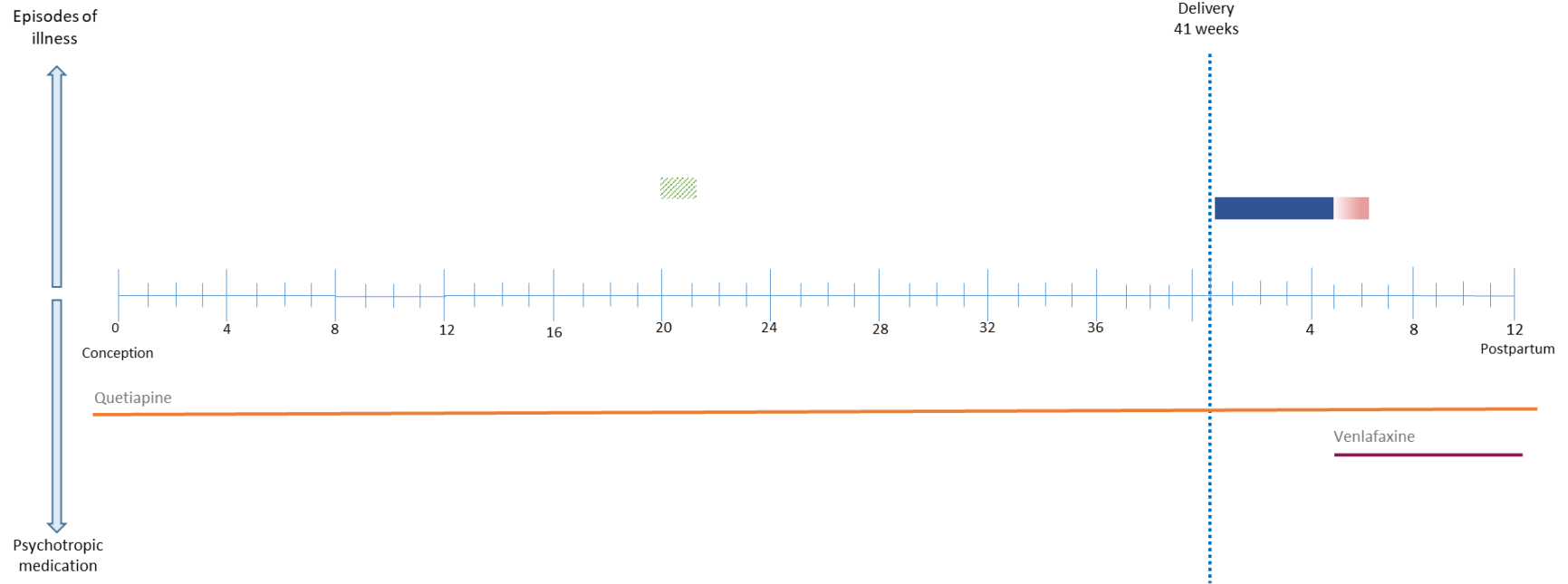
Preconception DSM-5 diagnosis: BD-II

Key: DSM-5 and other perinatal episodes

- Major depression
 - Mania
 - Hypomania
 - Depression with mixed features
 - Mania with mixed features
 - Other psychotic episode
 - 'Baby blues'
 - Postpartum 'highs'
 - Other episode not reaching DSM-5 criteria
- P Psychosis
 - S Sectioned
 - H Hospitalised: admission, home treatment (HTT), crisis team (CT)
 - Exact day of onset of DSM-5 episode unknown
 - Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 86

Preconception DSM-5 diagnosis: BD-I

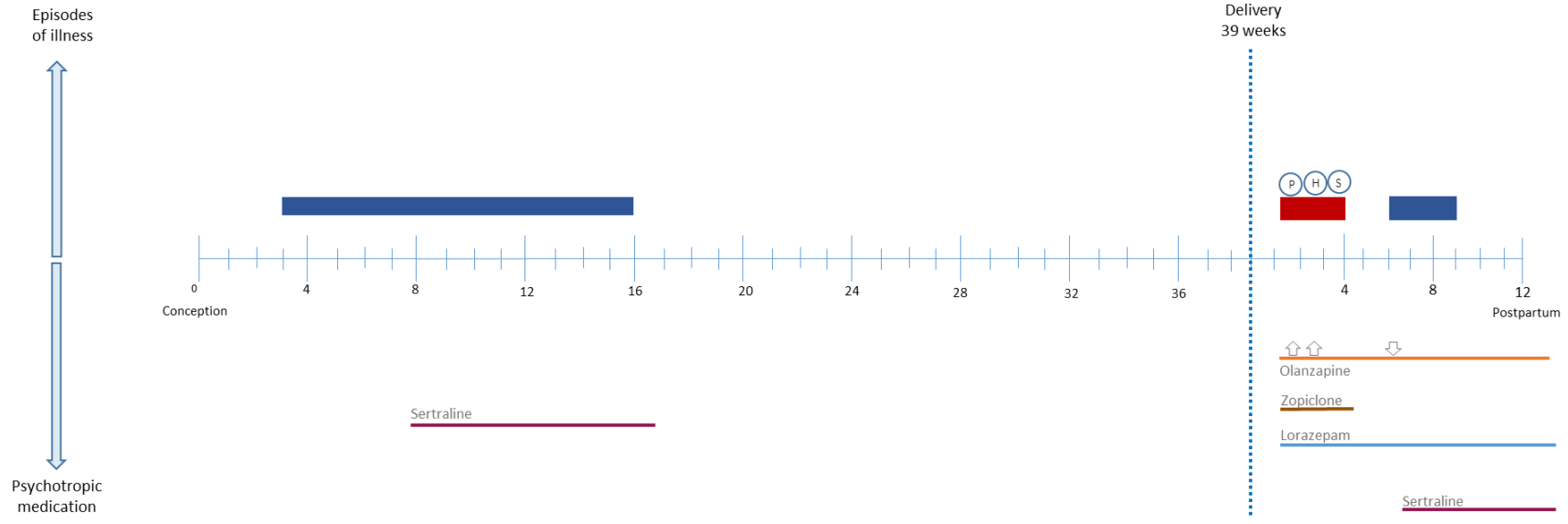
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 87

Preconception DSM-5 diagnosis: BD-I

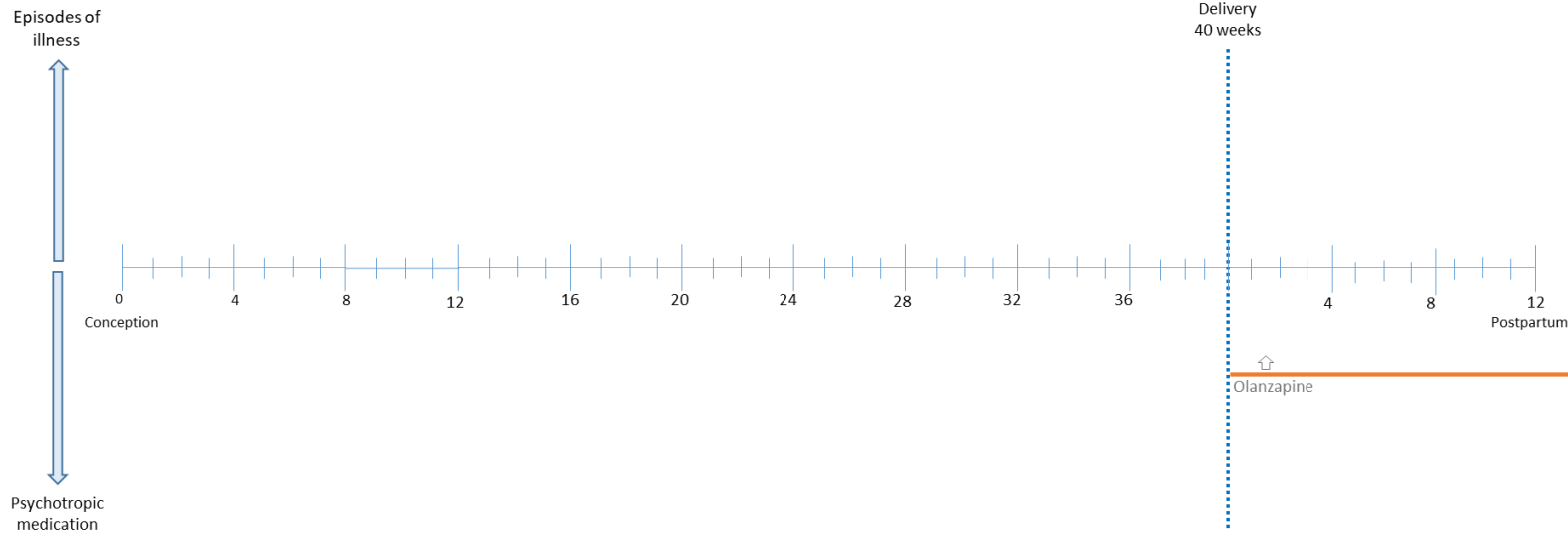
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

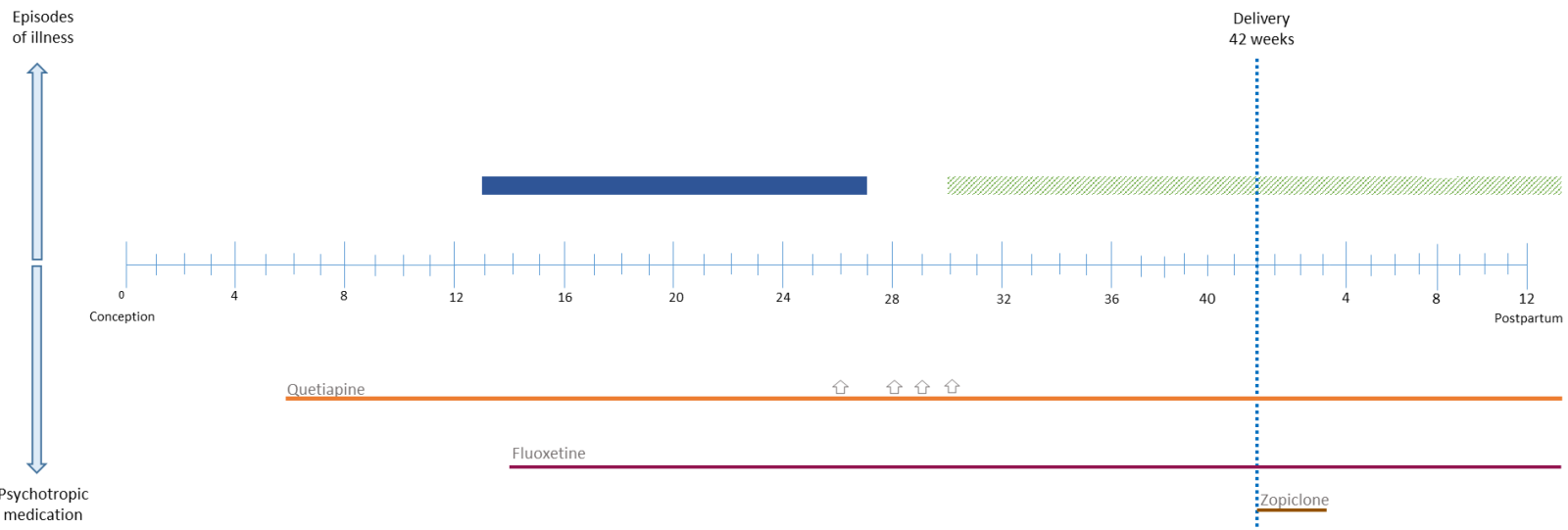
- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 88
Preconception DSM-5 diagnosis: BD-I

- Key: DSM-5 and other perinatal episodes**
- Major depression
 - Mania
 - Hypomania
 - Depression with mixed features
 - Mania with mixed features
 - Other psychotic episode
 - 'Baby blues'
 - Postpartum 'highs'
 - Other episode not reaching DSM-5 criteria
- Key: Psychotropic Medication**
- Lithium
 - Atypical Antipsychotic
 - Typical Antipsychotic
 - Anticonvulsant
 - Hypnotic
 - Anxiolytic
 - Antidepressant
 - Dosage unknown
 - Dosage increase
 - Dosage decrease
- Key: Hospitalisation**
- Psychosis (P)
 - Sectioned (S)
 - Hospitalised: admission, home treatment (HTT), crisis team (CT) (H)
 - Exact day of onset of DSM-5 episode unknown
 - Exact duration of DSM-5 episode unknown



Perinatal Timeline (weeks)

Participant 89

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

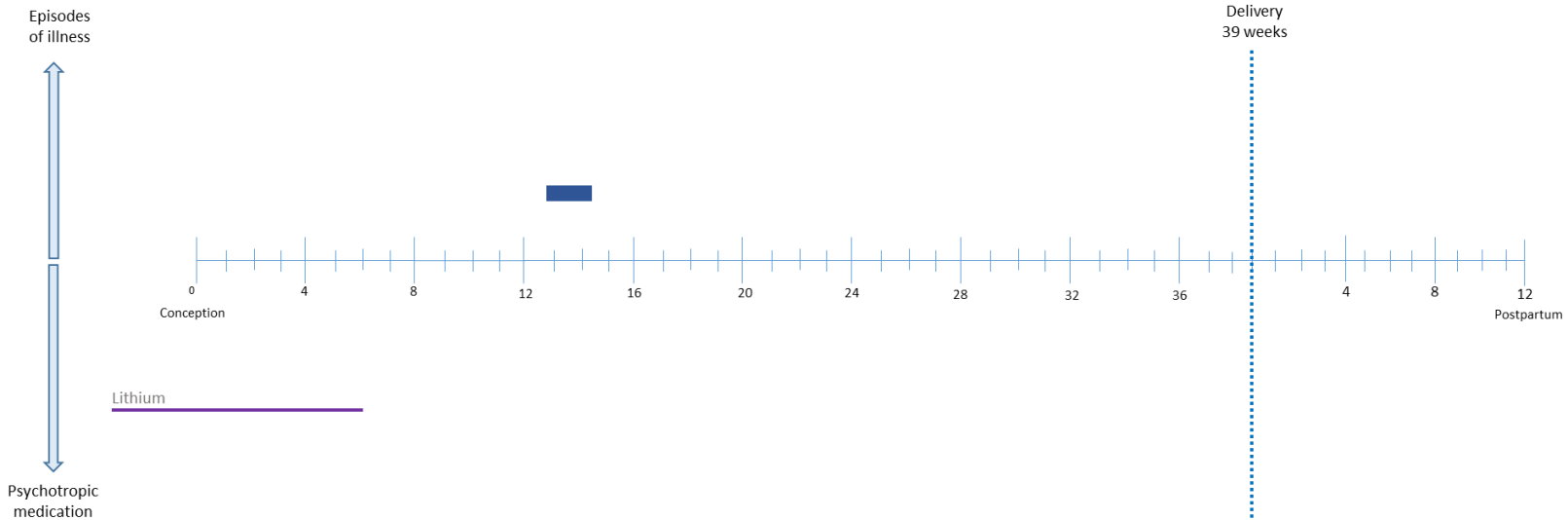
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 90

Preconception DSM-5 diagnosis: BD-II

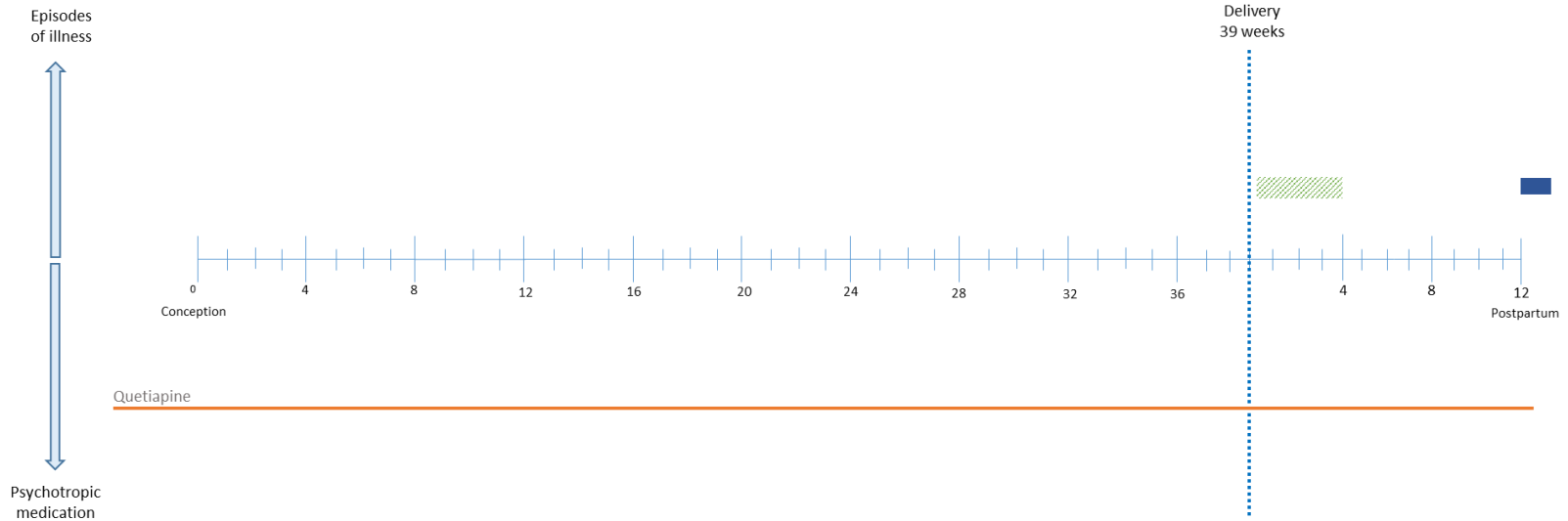
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 91

Preconception DSM-5 diagnosis: BD-I

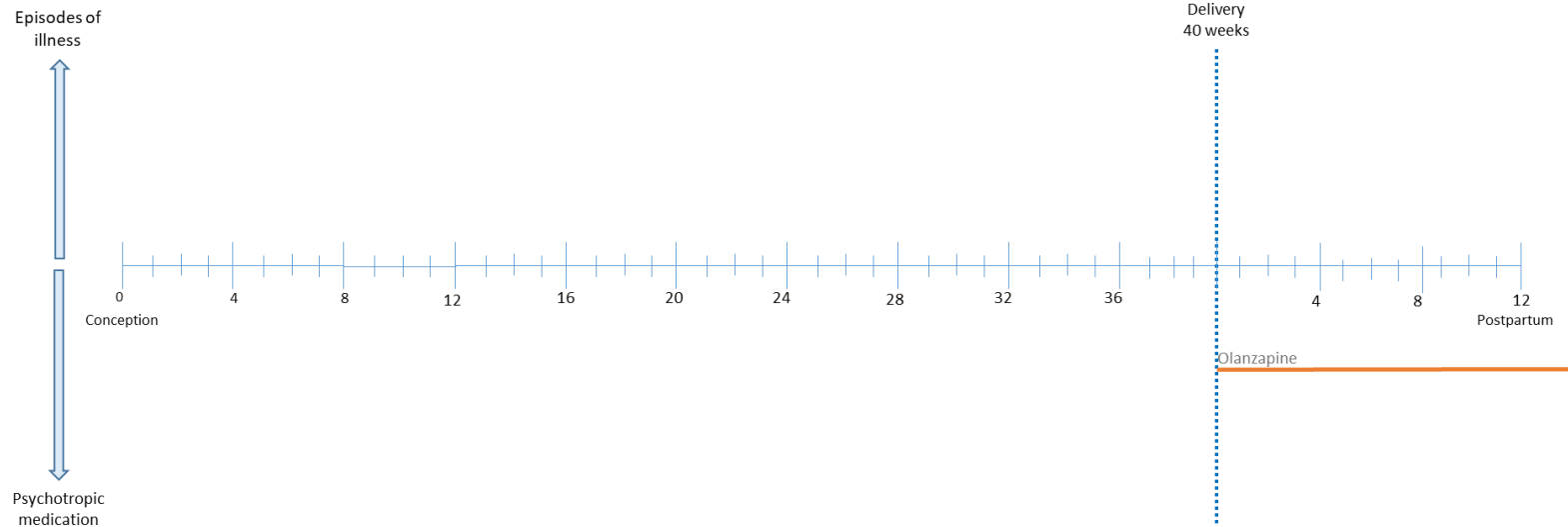
Key: DSM-5 and other perinatal episodes

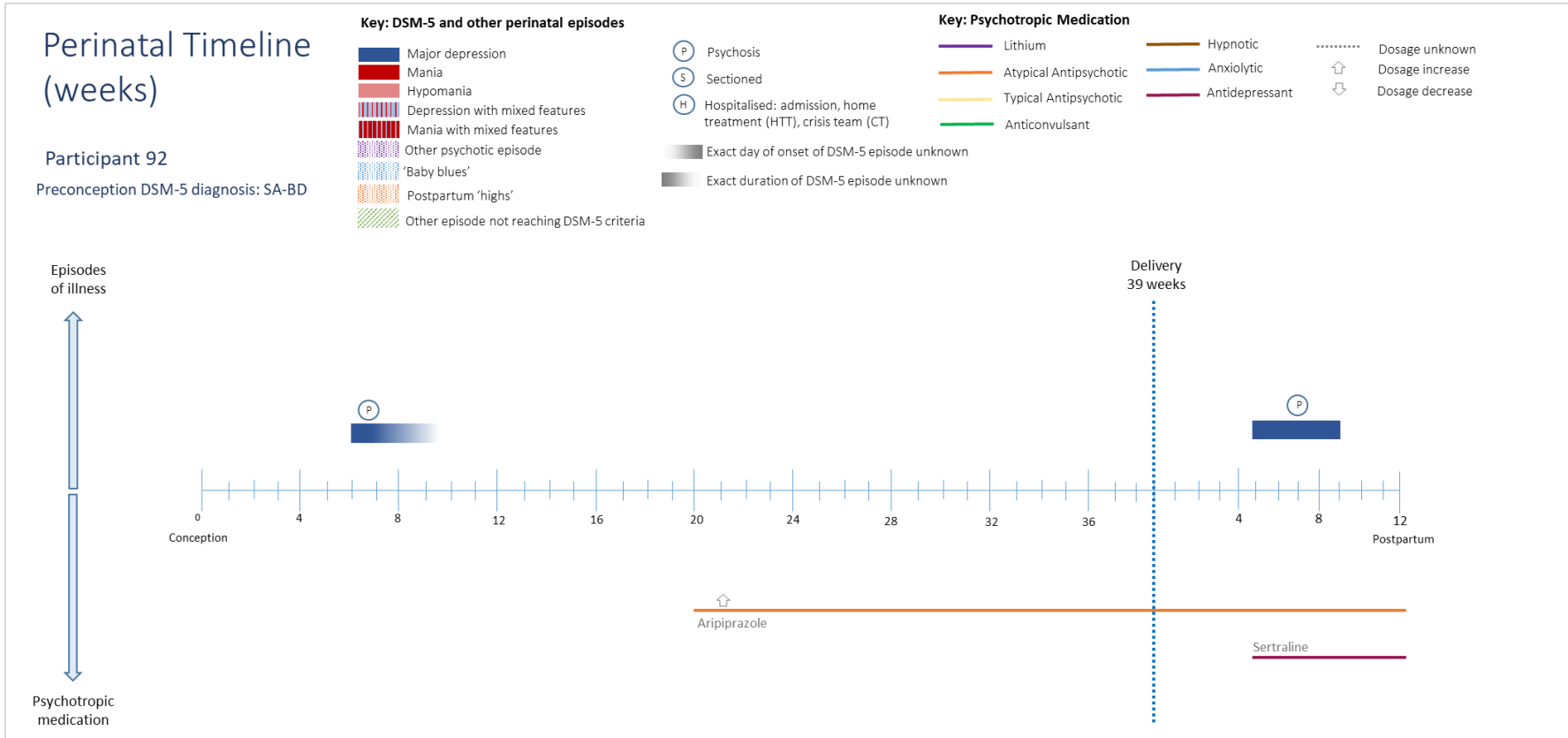
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease





Perinatal Timeline (weeks)

Participant 93

Preconception DSM-5 diagnosis: BD-II

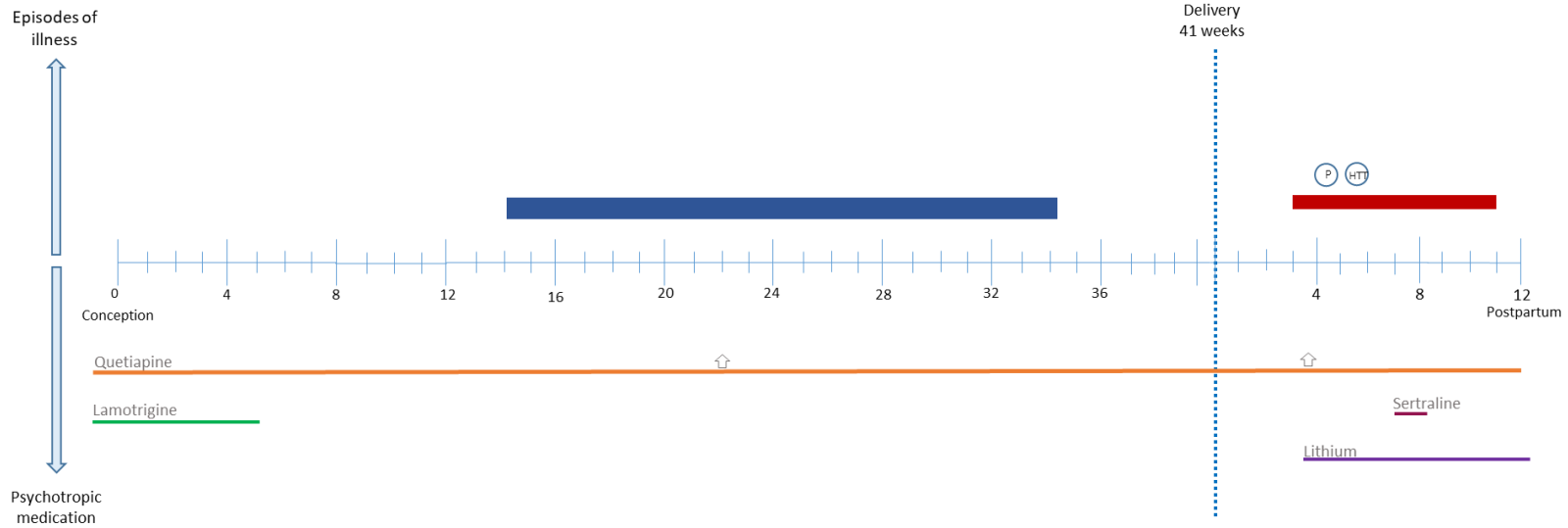
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
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- Lithium
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- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 94

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

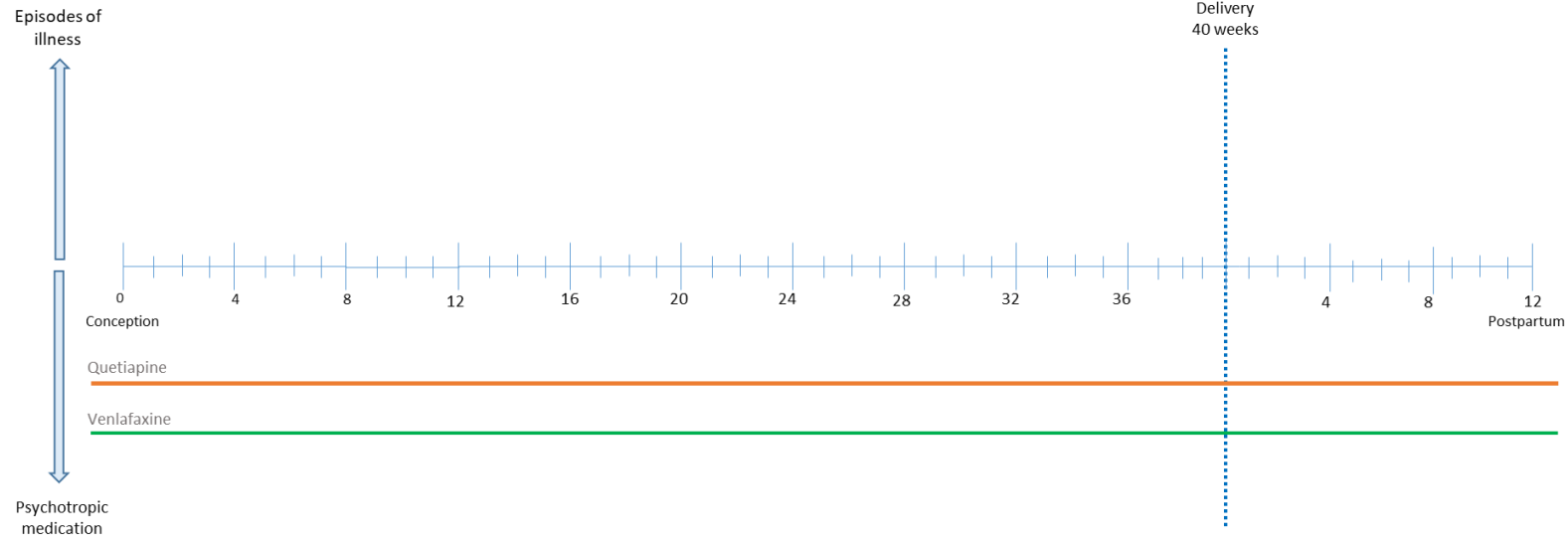
- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant

- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 95

Preconception DSM-5 diagnosis: BD-II

Key: DSM-5 and other perinatal episodes

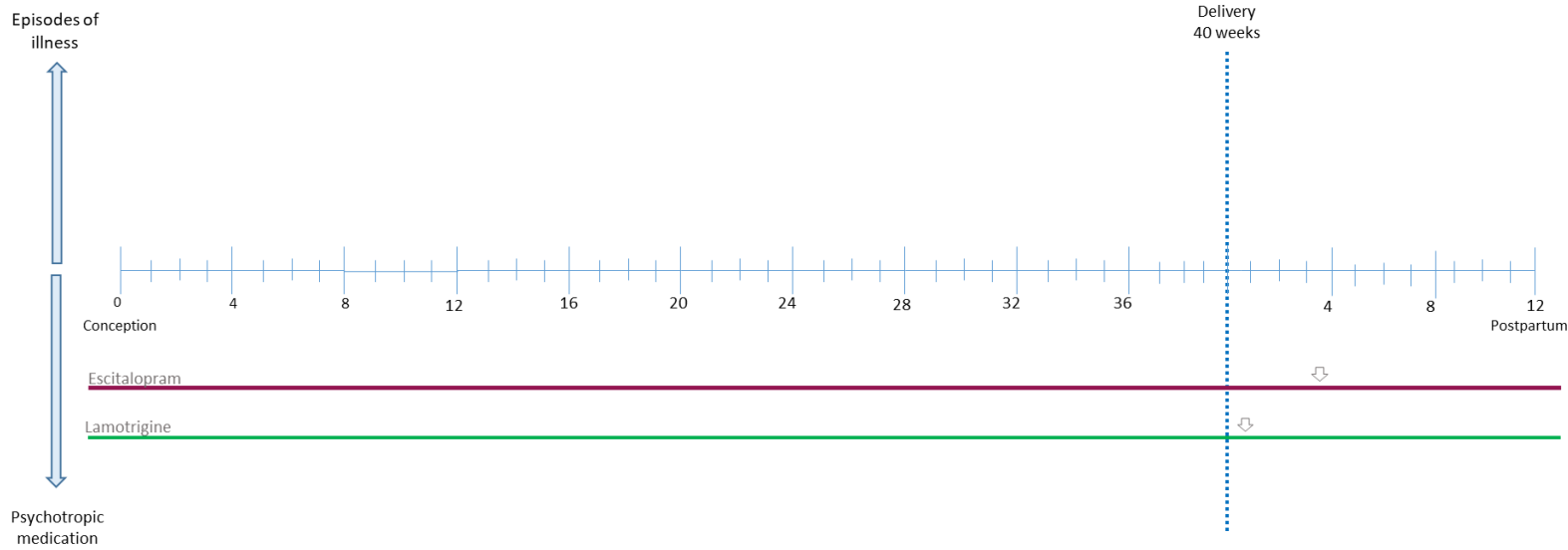
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 96

Preconception DSM-5 diagnosis: BD-I

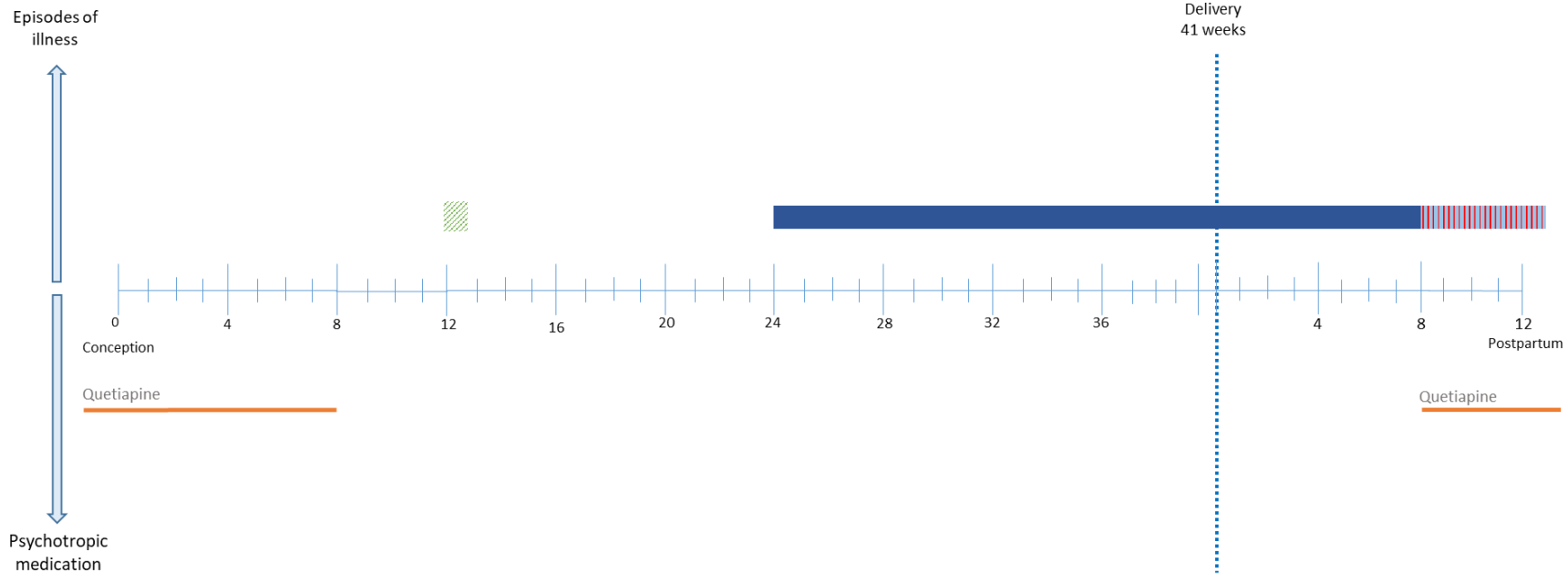
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
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- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 97

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

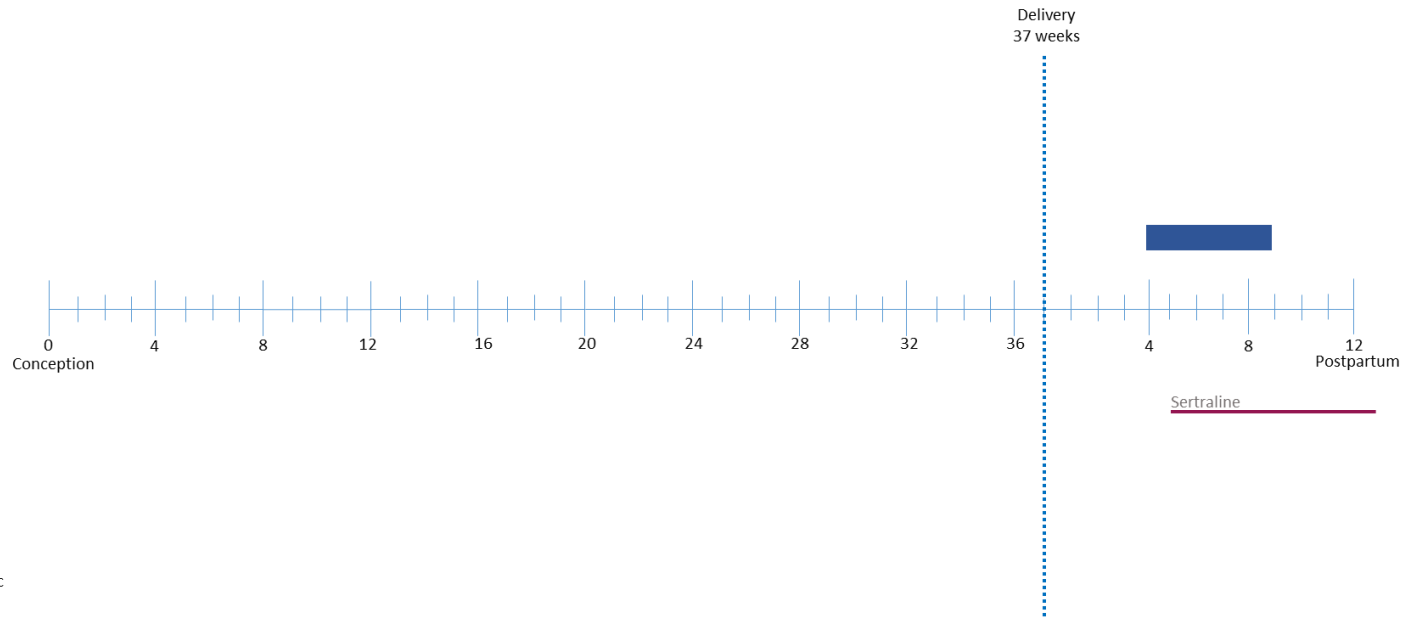
- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Illness episodes

Psychotropic medication



Perinatal Timeline (weeks)

Participant 98

Preconception DSM-5 diagnosis: BD-I

Key: DSM-5 and other perinatal episodes

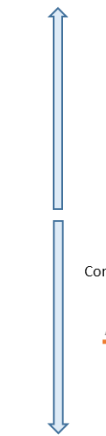
- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
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- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

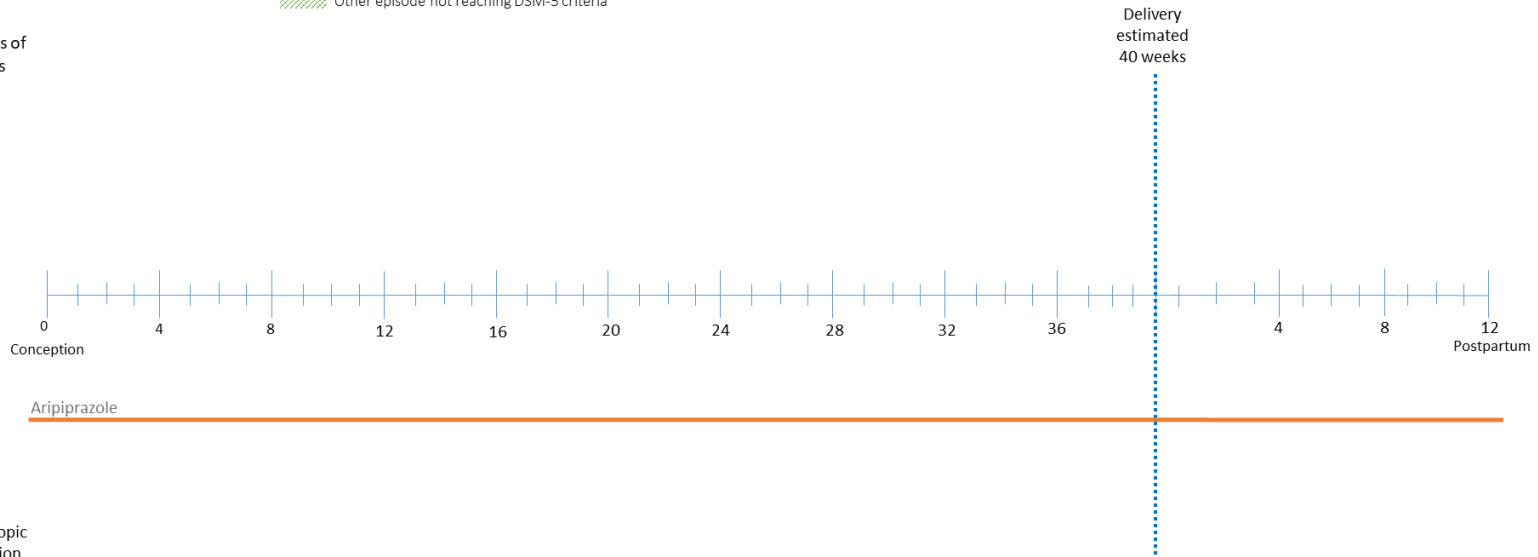
Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Episodes of illness



Psychotropic medication



Perinatal Timeline (weeks)

Participant 99

Preconception DSM-5 diagnosis: BD-II

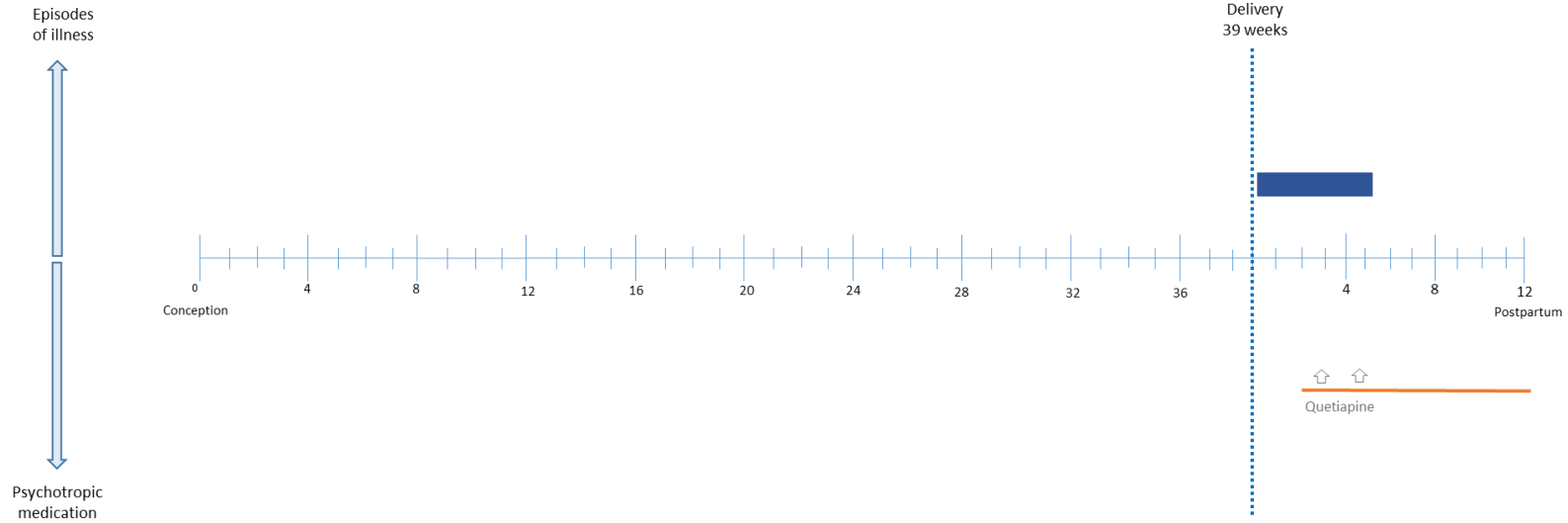
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- Psychosis
- Sectioned
- Hospitalised: admission, home treatment (HTT), crisis team (CT)
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 100

Preconception DSM-5 diagnosis: BD-I

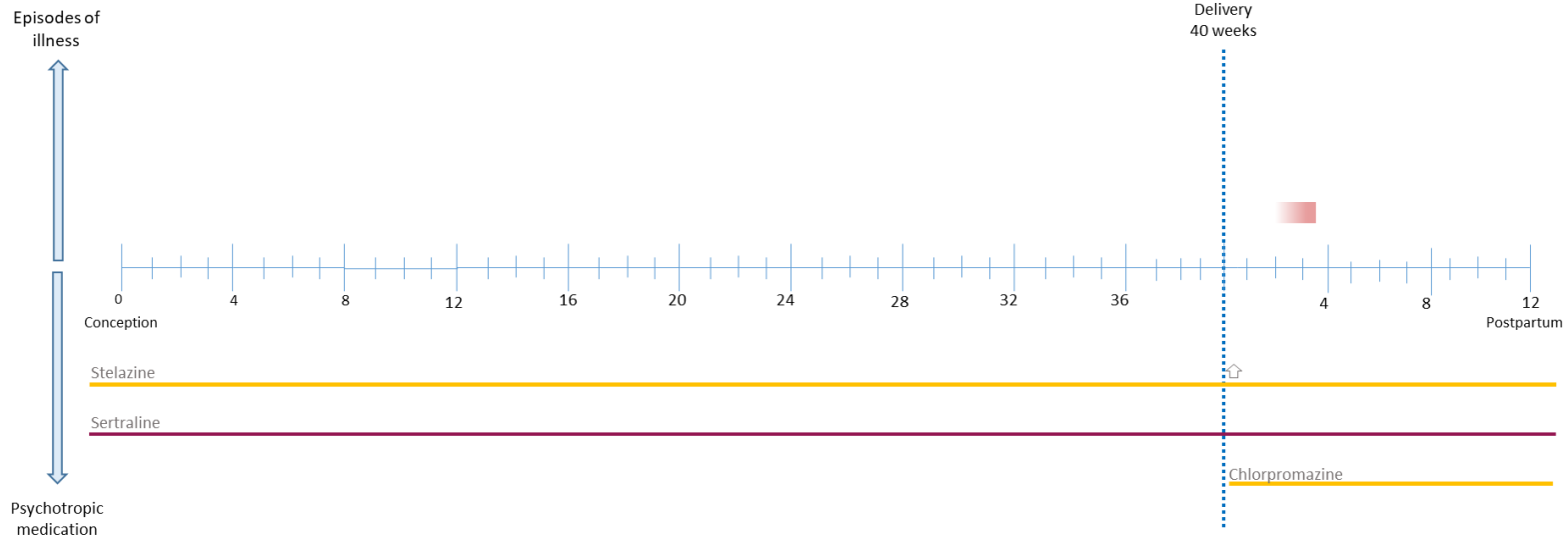
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
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- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

ID: Participant 101

Preconception DSM-5 diagnosis: BD-I

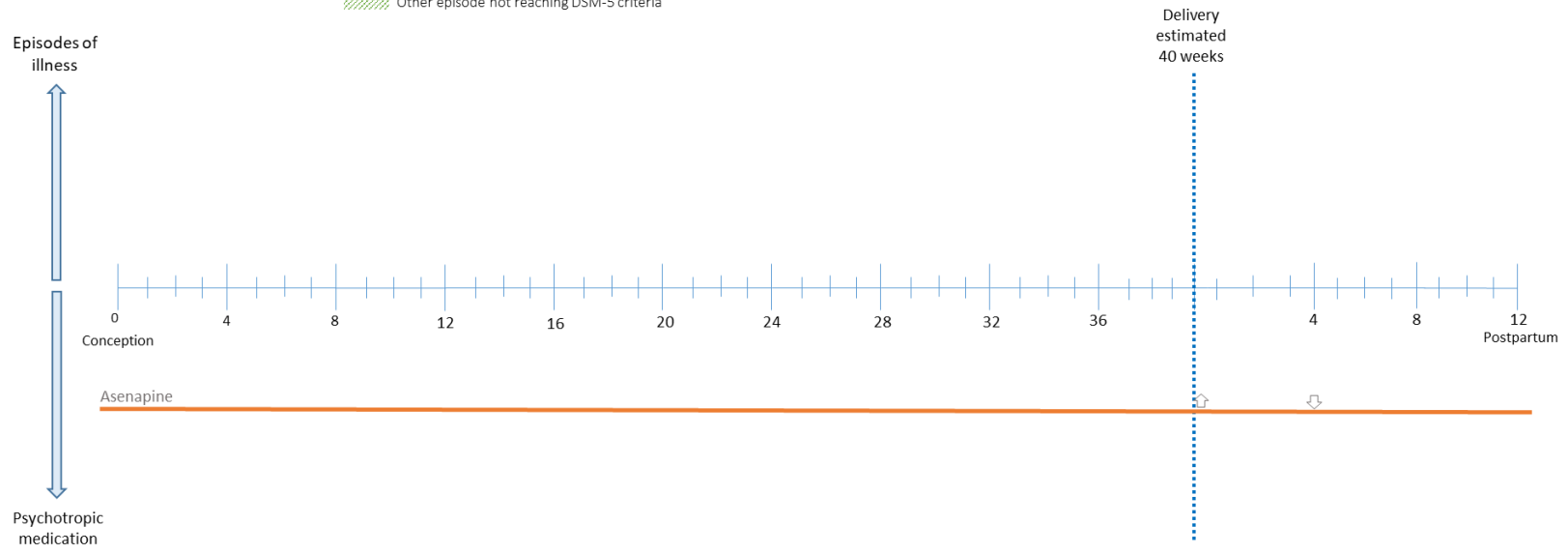
Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
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- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)
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- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Perinatal Timeline (weeks)

Participant 102

Preconception DSM-5 diagnosis: BD-II

Key: DSM-5 and other perinatal episodes

- Major depression
- Mania
- Hypomania
- Depression with mixed features
- Mania with mixed features
- Other psychotic episode
- 'Baby blues'
- Postpartum 'highs'
- Other episode not reaching DSM-5 criteria

- P Psychosis
- S Sectioned
- H Hospitalised: admission, home treatment (HTT), crisis team (CT)

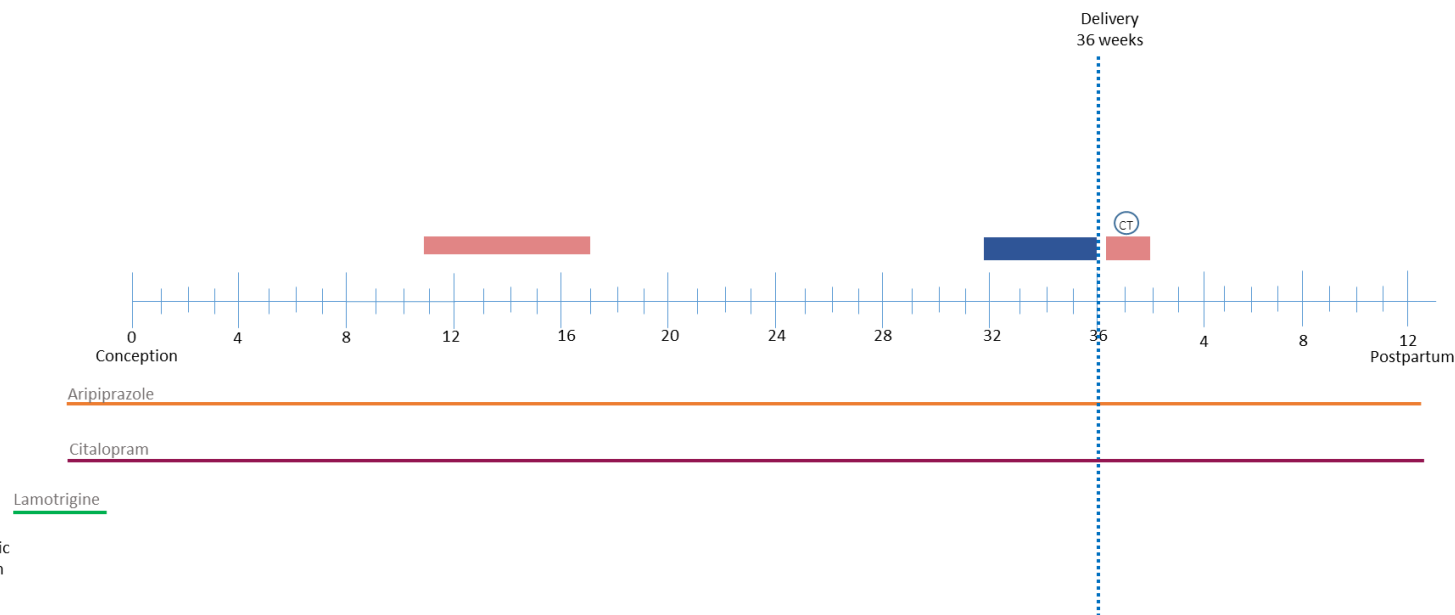
- Exact day of onset of DSM-5 episode unknown
- Exact duration of DSM-5 episode unknown

Key: Psychotropic Medication

- Lithium
- Atypical Antipsychotic
- Typical Antipsychotic
- Anticonvulsant
- Hypnotic
- Anxiolytic
- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease

Illness episodes

Psychotropic medication



Perinatal Timeline (weeks)

Participant 103

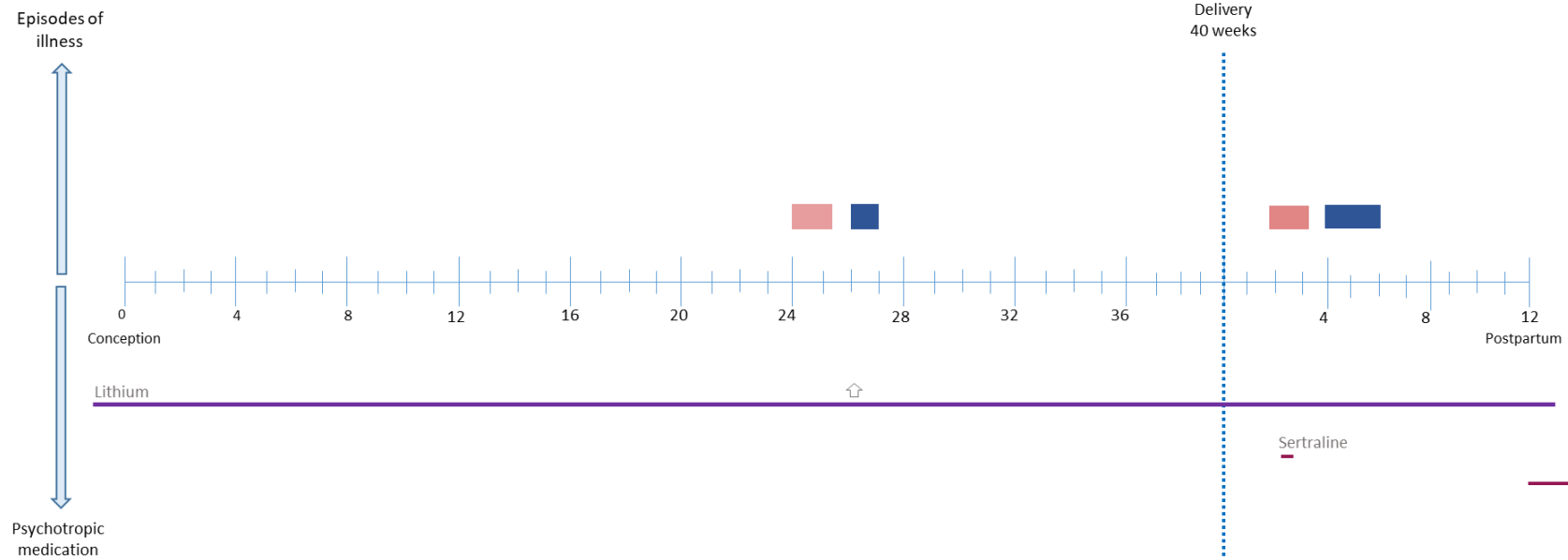
Preconception DSM-5 diagnosis: BD-II

Key: DSM-5 and other perinatal episodes

- Major depression
 - Mania
 - Hypomania
 - Depression with mixed features
 - Mania with mixed features
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- Atypical Antipsychotic
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- Antidepressant
- Dosage unknown
- Dosage increase
- Dosage decrease



Appendix N: Preconception lifetime psychiatric features according to use of prophylactic mood stabilising medication in the postpartum period in BD-I/SA-BD women in the BDRN pregnancy sample

To examine whether preconception severity of BD illness was associated with the use of prophylactic mood stabilising medication in the postpartum period (potentially confounding the relationship between use of prophylactic mood stabilising medication and reduced risk of PP), several key clinical characteristics of BD were compared between women who did and did not use prophylactic mood stabilising medication in the postpartum period.

Table I: Preconception lifetime clinical characteristics according to use of prophylactic mood stabilising medication in the postpartum period in BD-I women in the BDRN pregnancy sample

	Mood stabilising medication (n=28)	No mood stabilising medication (n=52)	Test statistic ^a	p- value
Age at onset of impairment of BD				
Median (IQR)	20 (8)	20 (11)	U= 595.000	0.637
Range	11-35	11-36	Z = -.471	
Preconception lifetime number of episodes of mania per illness year				
Median (IQR)	0.37 (0.38)	0.33 (0.65)	U= 591.500,	0.921
Range	0.05-7.37	0.08-1.68	Z = -.099	
Preconception lifetime number of episodes of depression per illness year				
Median (IQR)	0.49 (0.56)	0.41 (0.65)	U= 501.000,	0.370
Range	0.00-4.34	0-2.64	Z = -.896	
Preconception lifetime number of psychiatric hospital admissions				
Median (IQR)	1 (3)	1.5 (3)	U= 701.000,	0.891
Range	0-9	0-5	Z = -.137	
Preconception lifetime history of psychotic symptoms				
Yes	40 (76.9%)	21 (75.0%)	χ^2 (1) .037	0.847
No	12 (23.1%)	7 (25.0%)		
Preconception lifetime history of postpartum psychosis (<6 weeks)				
Yes	13 (25.0%)	8 (28.6%)	χ^2 (1) .120	0.729
No	39 (75.0%)	20 (71.4%)		

IQR: Interquartile range. ^a p-values calculated via Mann-Whitney U test for continuous variables. p-values for categorical variables calculated by Chi-Square tests.

As shown in **Table I**, there were no significant differences between women in the medication and no medication groups with regards to age at onset of impairment of BD (median age 20 years within both groups, $p=0.637$), preconception lifetime number of episodes of mania (median number of 0.37 and 0.33 respectively, $p=0.921$) or depression per illness year (median number of 0.49 and 0.41 respectively, $p=0.370$) or the number of preconception lifetime number of admissions (median number of 1 and 1.5 respectively, $p=0.891$). Furthermore, compared to women not using prophylactic mood stabilising medication in the postpartum period, women who did were not significantly more likely to have a preconception lifetime history of psychotic symptoms (75.0% vs 76.9%, $p=0.847$) or of PP within 6 weeks of a past delivery (28.6% vs 25.0%, $p=0.729$).

Appendix O: Use of prophylactic mood stabilising medication in the postpartum period according to method of recruitment in BD-I/SA-BD women in the BDRN pregnancy sample

As shown in **Table II**, women who were recruited to the BDRN Pregnancy Study by systematic methods were not significantly more likely to use prophylactic mood stabilising medication in the postpartum period compared to women who were recruited to the study non-systematically (60.5% and 69% respectively, $p=0.425$).

Table II: Method of recruitment according to use of prophylactic mood stabilising medication in the postpartum period in BD-I women in the BDRN pregnancy sample

	Systematic recruitment (n=38)	Non-systematic recruitment (n=42)	Test statistic ^a	p- value
Prophylactic mood stabilising medication postpartum				
Yes	23 (60.5%)	29 (69.0%)	$\chi^2 (1)$.637	0.425
No	15 (39.5%)	13 (31.0%)		

^a p-value calculated by Chi-Square test.