Postpartum Psychiatric Disorders

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Acknowledgements

We would like to thank Dr. Alan Gemmill from Parent-Infant Research Institute and Holly Krohn from the University of North Carolina at Chapel Hill for their contributions to the preparation of this manuscript.

Competing interests

S.M-B. has received research grant support to The University of North Carolina at Chapel Hill from Sage Therapeutics and Janssen. L.M.H. is funded through a National Institute for Health Research (NIHR) Professorship in maternal mental health (NIHR-RP-R3-12-011). V.B. is supported by NWO (VENI 91616036 and Clinical Fellowship 90715620) and the EMC fellowship. IJ is a trustee of Action on Postpartum Psychosis and the Maternal Mental Health Alliance and is supported through the National Centre for Mental Health grant from Health and Care Research Wales. All other authors declare no competing interests.

Author contributions

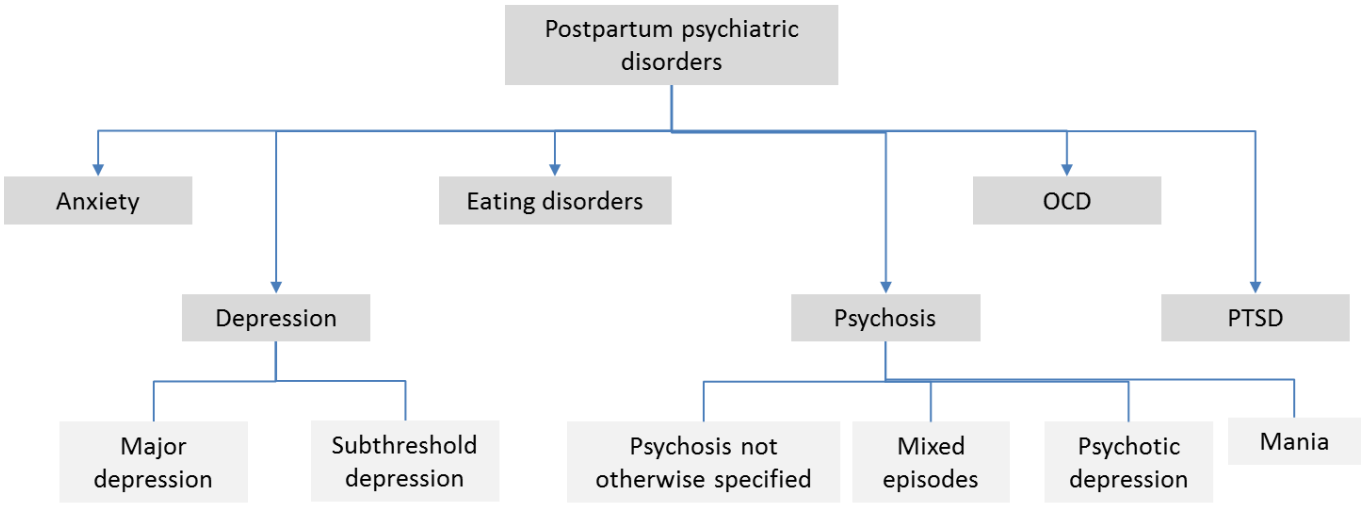
Introduction (S.M-B. and all co-authors); Epidemiology (T.M-O.); Mechanisms/pathophysiology (I.J. and S.M-B.); Diagnosis, screening and prevention (L.M.H., S.H. and J.M.); Management (S.V. and V.B.); Quality of life (J.M.); Outlook (All); Overview of Primer (S.M-B.).

Abstract

Pregnancy is a complex and vulnerable period that presents a number of challenges to women, including the development of postpartum psychiatric disorders (PPDs). These disorders can include postpartum depression and anxiety, which are relatively common, and the rare but more severe postpartum psychosis. In addition, other PPDs can include obsessive–compulsive disorder, post-traumatic stress disorder and eating disorders. The aetiology of PPDs is a complex interaction of psychological, social and biological factors, in addition to genetic and environmental factors. The goals of treating postpartum mental illness are reducing maternal symptoms and supporting maternal-child and family functioning. Women and their families should receive psychoeducation about the illness, including evidence-based discussions on risks and benefits of each treatment option. Developing effective strategies in global settings that allow the delivery of targeted therapies to women with different clinical phenotypes and severities of PPD is essential.

[H1] Introduction

Pregnancy and the first year after childbirth (which collectively can be referred to as the perinatal period) is arguably one of the most transformative times in a woman's life. This timeframe is also a complex and vulnerable period that presents a number of challenges for women. In particular, an increased risk for onset or worsening of psychiatric illness including mood disorders, anxiety disorders and psychosis exists during the first three months postpartum. All types of psychiatric disorders can occur during the postpartum period, with many chronic disorders starting before pregnancy and persisting throughout pregnancy into the postpartum period[1]. In this Primer, we focus specifically on the postpartum psychiatric disorders (PPDs). Collectively, the postpartum psychiatric disorders (PPDs) can include postpartum depression, which is relatively common; common anxiety disorders such as generalized anxiety disorder (GAD; which can include anxieties about the health of the baby); post-traumatic stress disorder (PTSD; which can occur due to a traumatic childbirth experience or can reflect pre-existing symptoms due to previous traumas before conception or during pregnancy); and the rarer, but usually severe presentation of postpartum psychosis. Other PPDs include eating disorders (which can worsen or recur postpartum, particularly when the infant is undergoing weaning), and obsessive–compulsive disorder (OCD)



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In pregnancy, depressive and anxiety disorders are common with recent population estimates of 11% for depressive disorders and 15% for anxiety disorders.[2] Further, antenatal anxiety and depression are one of the greatest risk factors for postpartum psychiatric disorders (PPD).[3] Inadequate social support and a history of adverse life events increases the risk for PPDs in all countries and levels of society[4, 5]. However, this risk is increased in poorer socioeconomic populations and lower income countries, due to poverty and limited access to health care.[6]

In recent years, awareness of the potentially serious adverse consequences in both the mother and the baby associated with untreated perinatal psychiatric illness has increased. Maternal suicide due to postpartum mood disorders (including unipolar and bipolar depressive disorders) is a leading cause of maternal mortality. [7, 8,9] In addition, perinatal mood disorders are associated with an increased risk for low birth weight and premature birth, impaired mother-infant attachment, and infant malnutrition during the first year of life[10, 11].

In this Primer, we focus on maternal PPDs, as they are common, morbid, and have a growing literature on the underlying pathophysiology. These disorders should not be confused with the so-called 'baby blues', which are usually described as transient mild mood and anxiety symptoms that often persist ≤2 weeks and usually resolve spontaneously with no sequelae.[12] If the symptoms of the 'baby blues' worsen and/or persist, they are considered PPDs. Herein we discuss the epidemiology of PPDs, and their underlying mechanisms and pathophysiology. We mainly focus on maternal PPDs, although paternal disorders are mentioned in some instances (Box 1). Importantly, we review the latest evidence on diagnosis, screening and prevention as well as management of PPDs. Lastly, we hope to put in context the public health impact of these disorders on mothers, their children and families to encourage wide scale adoption of strategies that make maternal mental health a global priority[13].

[H1] Epidemiology

Data on the incidence of postpartum depression are from studies conducted in countries across the world, and variable incidence and prevalence are reported between countries[14]. By comparison, studies estimating the incidence and prevalence of postpartum psychosis are primarily carried out in Europe[15], and demonstrate less variability in reported incidence and prevalence[16, 17]. Several methodological factors have influenced these differences. [18] For example, particularly for postpartum depression, the definition of the postpartum period is variable between studies, and has been defined as up to 4 weeks, 3 months, 6 months or 12 months postpartum[19]. Differences in study designs, such as using different tools to define case-groups and phenotypes can lead to variability in the reported number of cases. Data sources for postpartum depression and postpartum psychosis include self-reports and interviews, in addition to some population-based register data[16]. Moreover, the incomplete availability of longitudinal data that is needed to distinguish between first-time and recurrent psychiatric episodes might impede calculations of the true incidence and prevalence of PPDs. Consequently, a variation in reported incidence and prevalence could be explained by differences in methodologies between studies, which make direct comparisons difficult. In addition, the diverse symptoms of PPDs pose specific challenges to the estimation of prevalence and incidence of these disorders[20].

As the literature surrounding the epidemiology of PPDs continues to grow with well-designed studies, we will have a better understanding of if differences in the incidence and prevalence of postpartum depression and postpartum psychosis are due to local/regional and national differences, or if the differences are due to variable study designs and data sources. This knowledge will assist hypothesis generating that might provide clues for the aetiology of these disorders.

[H2] Mood disorders and anxiety

Postpartum depression, comprising major depressive disorder and subthreshold depression, has an estimated point prevalence of 13% in high-income countries[11], and ~20% in low-income and middle-income countries, 3 months postpartum (Box 2)[21]. In women with a history of any eating disorder, the prevalence of postpartum depression has been estimated at 35%[22]. Studies of postpartum depression often rely on self-reported questionnaires, including the commonly used Edinburgh Postnatal Depression Scale (EPDS)[14, 23].

Although the prevalence estimates for postpartum mood disorders ranges between studies, guidelines are available that state that these disorders pose substantial public health risks and consequently, must be identified and treated[24,25]. Moreover, there is consensus that childbirth is a strong and potent risk factor for bipolar disorder. Indeed, the risk of underlying bipolarity in first-onset depression that occurs in the postpartum period is higher than in first-onset depression that occurs outside the perinatal period. In addition, women with bipolar disorder have a high risk of postpartum episodes, including depression, anxiety, mania and psychosis [26, 27].

The estimated prevalence of postpartum anxiety disorders is ~10%, with a prevalence of 6% for GAD [28]. Anxiety disorders have substantial comorbidity with postpartum depression and other disorders, including postpartum PTSD, eating disorders and the exacerbation of personality disorders[17].

[H2] Postpartum psychosis

The onset of a severe mental disorder requiring acute inpatient psychiatric treatment in the first postpartum months is ~1 per 1,000 births[29-32], and are considered some of the most severe forms of illness in psychiatry [18]. These severe psychiatric disorders that have an onset in the immediate postpartum period are often called postpartum psychosis, which is an umbrella term for disorders recorded as, for example, mania, mixed episodes, psychotic depression, or psychosis not otherwise specified[33]

http://journals.sagepub.com/doi/abs/10.1177/0004867414564698?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed&] . Women with bipolar disorder have the highest risk for postpartum psychosis than women with other psychiatric diagnosis, as the risk for postpartum relapse in women with bipolar disorder is on average 37%[18]. However, variations also occur within bipolar disorder, as the risk of a severe episode (ie postpartum psychosis) is greater for women with bipolar I disorder than women with bipolar II disorder[34]. Additionally, the risk of symptom recurrence is particularly high for women with bipolar disorder who are not receiving medication during pregnancy[18] .

Relapse of psychosis can also occur in women with other psychiatric disorders, such as women with schizophrenia, although this is less common[35] (~16% within the first 12 months postpartum) Yes—it has been added now. https://www.ncbi.nlm.nih.gov/pubmed/19188541] , and manifests differently from what is observed in women with bipolar disorder[16].

Despite the widespread use of the term postpartum psychosis, this diagnosis is not recognized in current classification systems, including both ICD-10 and DSM-5 [36]. However, it is clear that psychotic episodes are more prevalent during the postpartum period than in other periods in a woman's life, and evidence clearly suggests a particular vulnerability in women with bipolar disorder [29].

In women with severe postpartum psychiatric illness, maternal suicide is often a predominate concern. Although maternal suicide is a leading cause of maternal mortality[7], the rates of completed suicide in postpartum women are lower than those in age-matched women without children[37]. Nonetheless, the prevention of maternal suicide is paramount and requires careful monitoring during the postpartum period and possibly extending beyond the first year. For example, one study demonstrated that most postpartum suicides occurred between 9 and 12

months postpartum and that the perinatal suicides were by highly lethal means (such as via firearm), suggesting that limiting follow-up to 1, 3 or 6 months postpartum might be insufficient.[38]

[H1] Mechanisms/pathophysiology

As previously mentioned, childbirth is one of the most potent triggers of psychiatric illness. Given that postpartum mental health disorders are one of the few occurrences in psychiatry whereby a biological trigger occurs at a known time point, elucidating the pathophysiology of these disorders may shed light on the mechanisms of mood and psychiatric disorders more broadly, and is vital for developing new treatment approaches.

The aetiology of all psychiatric disorders, including PPDs, is a complex interaction of psychological, social and biological factors, including the effect of genetic and environmental influences on risk (Figure 1)[12]. The involvement of particular combinations of aetiological factors differs between specific PPDs[34]; for example, biological factors might have a greater role in the triggering of postpartum psychosis, whereas psychosocial factors might have an important contribution in postpartum depression.[34] These are areas of intense investigation and future research is needed to extend our understanding of the many ways that psychological and biological processes interface. Stopping or changing medications in women with a prior history of psychiatric disorders due to concerns about the safety of medication during pregnancy could be considered a simple explanation for the triggering of PPDs. However, continuing medication in pregnancy is protective against mood disorders in a subset of patients[39]. Similarly, discontinuation of medication does not guarantee that a woman will relapse[40]. However, there is much that is still not understood about PPDs and the onset of PPDs reflects the outcome of many different pathways that manifest in vulnerable women. Future research will need to disentangle the mechanisms of depression in women before, during and after pregnancy to increase our understanding of the similarities and differences between perinatal depression and depression occurring at other times in life. We will

next discuss current theories on psychosocial and biological contributions that increase risk for PPDs.

[H2] Psychosocial factors and comorbidities

Psychological and social stressors contribute to the development of maternal PPDs and are associated with poorer outcomes in the infants or children[41, 42]. In particular, adverse life events and a history of trauma have a greater prevalence in women that develop postpartum mood disorders, compared with mood disorders outside of the perinatal period [4, 43, 44]. A history of adverse early life experiences can substantially affect a mother's ability to have a strong attachment with her infant[45], and adverse parent–infant interactions and worse attachment are associated with development of PPDs [46-48].

Social support has a vital role in either contributing to or mitigating the impact of postpartum mood disorders on both the mother and child[49]. Indeed, social support, or the degree of tangible support provided from the social network of the mother and from the partner (such as financial support or assisting with infant care), have the greatest effects on postpartum depression [50].

Other psychosocial risk factors include a past history of a mood disorder, which is consistently associated with an increased risk of postpartum depression and postpartum psychosis[34]. In addition, although the strength of the association between risk factors and PPDs is variable between high-income countries and low-income and middle-income countries, one of the strongest psychosocial risk factors in both settings is domestic violence and previous abuse, including abuse during childhood. [4, 51] Other risk factors with a medium to strong association with PPDs include marital difficulties, migration status and antenatal depression or anxiety[17, 52]. In addition, poverty, young age (between 14 and 21 years of age), substance misuse, increased parity, multiple births, an unwanted pregnancy, neuroticism, pregnancy complications including obesity and comorbidities

(for example diabetes, hypertension and pre-eclampia) and neonatal problems are associated with PPDs[17].

[H2] Genetic factors

Data from twin and adoption studies have implicated genetic factors in the aetiology of psychiatric disorders outside of the perinatal period, including schizophrenia and mood disorders[53, 54]. However, only recently have genetic investigations, primarily of postpartum depression and postpartum psychosis, been conducted.

Genetic epidemiological and linkage studies for postpartum depression have demonstrated the involvement of genetic factors [55, 56, 57] and two studies have demonstrated the increased heritability of postpartum depression compared with depression outside of the perinatal period[58, 59]. To date, studies have suggested that episodes of postpartum psychosis are a marker for a more-familial form of bipolar disorder and that the puerperal triggering of bipolar illness is familial. [60, 61]. However, a genome-wide association study (GWAS) for either postpartum depression or postpartum psychosis using modern genomics methods has not yet been carried out. Future genetic studies of postpartum mood disorders using modern genomics methods will require international collaborations and consortia to include large number of patients; these studies are currently underway[62, 63].

Psychological stressors and early life adverse events have a lasting negative impact and can result in pathophysiological changes and altered gene expression due to increased allostatic load (the cumulative stress on the body that is a sum of lifetime exposure to stress)[64]. Potential mechanisms underlying how stressful life events change gene expression include epigenetic modification (such as DNA methylation and histone modification that change DNA accessibility and chromatin structure, subsequently regulating gene expression)[65], changes in transcriptional control of stress-responsive pathways[66], and shortened telomere length[67, 68] . Epigenetic alterations have been

reported in two genes, *HP1BP3* and *TTC9B*, which have different methylation patterns in women with postpartum depression, depending on whether the mood symptoms begin during pregnancy and continue into the postpartum period, compared with symptoms that develop postpartum only [69, 70]. These data indicate that different gene patterns might arise based on the timing of symptom onset. However, given the history of non-replication in many genetic studies, these findings require replication and overall, the mechanism of action in postpartum depression remains to be established.

[H2] Sleep Disruption

An almost universal feature of pregnancy and childbirth is disruption to sleep. In addition, sleep and circadian rhythm disruption can trigger the onset of psychiatric disorders, particularly episodes of mania in the postpartum period[71, 72]. Thus, that circadian rhythm disruption has not received more attention as a potential mechanism in PPDs is surprising.

Numerous studies have demonstrated profound changes in maternal sleep patterns during the perinatal period. Pregnant women experience poorer subjective sleep quality, increased waking, and more sleep-wake transitions than women who are not pregnant[73]. In the postpartum period, new mothers have frequent night waking, decreased night-time sleep, increased daytime napping, and a more irregular sleep-wake schedule, which is speculated to increase the risk of PPDs[74]. The mechanisms underlying the reported disrupted maternal sleep patterns in the perinatal period have been reported in two cross-sectional studies. The first study demonstrated a blunted melatonin amplitude is in postpartum women, compared with non-pregnant women,[75] and the second study demonstrated differences in circadian rhythms between perinatal women with depression and perinatal women without depression; indeed, in the second study, women with depression had clinically-significant circadian rhythm phase shifts.[74] Further research is needed to better

understand the mechanisms of sleep disruption that might trigger PPDs and potential interventions that target the circadian rhythm disruptions during the perinatal period[76].

[H2] Reproductive Hormones

One important hypothesis for the aetiology of PPDs is based on the temporal onset of these disorders immediately after childbirth, which is a time of major physiological change for women, including alterations in hormonal systems. Multiple lines of evidence have demonstrated that fluctuations in reproductive hormones (such as oestrogen and progesterone) during the perinatal period are substantial contributors to the development of postpartum mood disorders in vulnerable women. Gonadal steroid hormones (such as oestrogen and progesterone) are produced at very high levels during pregnancy, but rapidly decrease to pre-pregnancy levels after childbirth. One study simulated this pattern of hormone expression and demonstrated substantial mood symptoms (such as sadness, anhedonia and anxiety) during the withdrawal period in five of eight women with a history of postpartum depression, but in none of the eight women with no history of postpartum depression[77]. Thus, women who are vulnerable to postpartum psychiatric episodes might not have gross abnormalities in endocrine physiology (such as no differences in the absolute levels of hormones), but might have an abnormal response to the hormonal fluctuations of pregnancy and childbirth.

Reproductive hormones have important functions in the central nervous system. Oestrogen and progesterone receptors are expressed throughout the brain and can modulate neurotransmission and neuroplasticity via both genomic and non-genomic mechanisms. For example, rodent studies have shown that ovariectomy reduces and estradiol administration increases brain-derived neurotrophic factor (BDNF) levels in the hippocampus and the forebrain[78]; BDNF levels are decreased by stress and depressive symptoms and are increased following treatment with antidepressants[79]. The rapid fall in oestrogen levels in the postpartum period might, therefore,

reduce BDNF levels and increase susceptibility to PPDs in women who are vulnerable. Similarly, progesterone has an important role in regulating neurotransmitter synthesis, release and transport [80] and, has been shown to up-regulate BDNF expression in the hippocampus and cerebral cortex in rodent models[81].

The neurosteroid, allopregnanolone, which is a major metabolite of progesterone, might also have an important role in the aetiology and, potentially, in the treatment of postpartum depression[82, 83]. Allopregnolone is a positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors[84, 85] and animal models have demonstrated that intravenous allopregnolone administration significantly reduces anxiety and depressive symptoms[86]. Allopregnanolone concentrations reach peak physiological levels during the third trimester of pregnancy and rapidly decrease following childbirth[87, 88]. The failure of $GABA_A$ receptors to adapt to the rapid fluctuations in allopregnanolone levels at childbirth is hypothesized to be a trigger for postpartum depression[89, 90]. This line of inquiry is being further explored by the development of brexanolone (a proprietary formulation of allopregnanolone) as a treatment for postpartum depression[91,92].

Oxytocin is a neuroactive hormone that supports childbirth, lactation, maternal behavior, and social bonding[93]. Some studies have demonstrated an inverse association between circulating oxytocin levels and postpartum depression[94] although other studies have not found this[95] .The alterations in the oxytocin system that occur during pregnancy and childbirth do not occur in isolation, and the role of oxytocin in postpartum depression is likely to be complex and not accounted for by absolute levels, similar to the roles of other neuroactive hormones [83].

Further, recent neuroimaging data increases our understanding of the neurobiological basis underlying perinatal mood disorders and the development of maternal behavior. Indeed, one study demonstrated that the effects of a polymorphism in *BDNF* (*BDNF* Val[66]Met) on hippocampal function are selectively modulated by estradiol[96]. This work lends further data to the importance of the role of sex steroids on the regulation of behavioural functions associated with psychiatric

disorders, such as emotional processing, arousal, cognition, and motivation. Thus, it follows the involvement of sex steroids of brain function could be revealed using neuroimaging. Indeed, multiple cortical and subcortical brain regions have altered activity observed using functional MRI or PET (such as, measurement of brain MAO-A[97]) in mothers with depression, in response to infant and non-infant emotional cues[98, 99]. These alterations might impact important neuronal networks that are associated with learned reward, reaction to stimuli, stress, motivation and executive functioning. In addition, recent research from functional MRI studies shows distinct neurobiological patterns that distinguish anxiety and depression occurring in the perinatal period, compared with other times of a woman's life, and these patterns may have significant impact on the mother-infant relationship[100].

[H2] Other factors

[H3] Stress axis. The postpartum period is a time of great flux for the HPA stress axis[101]. Indeed, alterations in the hypothalamic–pituitary–adrenal (HPA) axis occur during pregnancy, such as corticotropin-releasing hormone (CRH) production by the placenta, resulting in significantly increased levels during pregnancy, which abruptly decline postpartum[102], and rising levels of gonadal steroids that contribute to puerperal hypertrophy of the pituitary and adrenal glands, leading to increases in ACTH and cortisol levels[103]. CRH fluctuations during the perinatal period might trigger HPA axis dysregulation and contribute to the onset of depressive and anxiety symptoms in a subset of vulnerable women [104]; however, inconsistent findings have been reported[105, 106].

[H3] Thyroid hormones. Thyroid hormones have been implicated in the development of postpartum mood disorders. Thyroid binding globulin (TBG, which transports thyroid hormones in the blood) concentrations increase during pregnancy and might be an index of sensitivity to

368 elevated oestrogen levels. Some data also suggest that decreased **[Au:OK? YES]** TBG levels are
369 a predictor of perinatal depression[107]. In addition, first-onset postpartum autoimmune thyroid
370 disorders often co-occur with postpartum mood disorders [108]. The occurrence of both disorders
371 coincides with the postpartum rebound phenomena of the maternal immune system, suggesting an
372 overlap in aetiology[109]. Supporting this hypothesis, women with increased thyroid peroxidase
373 antibodies during pregnancy have an increased risk for postpartum psychiatric episodes[109, 110].
374 Accordingly, the assessment of thyroid function (such as measurement of thyroid-stimulating
375 hormone levels, tri-iodothyronine (T3) and tetraiodothyronine (T4)) is an essential part of diagnostic
376 evaluations in women with postpartum psychiatric episodes.

377

378 **[H3] Neuroimmune pathways.** Neuroimmune pathways might also have a role in the
379 pathophysiology of postpartum mood disorders[101, 111-113]. The transition from pregnancy into the
380 postpartum period is characterized by an accelerated immune response (mediated through both
381 pro-inflammatory and anti-inflammatory mediators for healing and involution) during labor that
382 continues into the early postpartum period [114]. Consequently, immune changes at the end of
383 pregnancy might predict postpartum depression. IL-6 levels are increased in women with
384 postpartum depression compared with postpartum women who do not have depression in some,
385 but not all studies. [112,115] However, leptin (a protein hormone made by adipose cells that regulates
386 energy and has inflammatory functions might also be associated with postpartum depression.
387 Indeed, decreased maternal serum leptin levels during delivery are associated with a higher risk for
388 postpartum depression, and might potentially serve as a biomarker for postpartum depression[115].
389 Lower levels of Clara cell protein (CC16, an endogenous anti-inflammatory compound) are
390 associated with PPD a few weeks later[116, 117]. Furthermore, decreased levels of ω3
391 polyunsaturated fatty acids (PUFAs) at the end of the third trimester are suggested to associate
392 with increased risk of PPD in the early postpartum period[118]. The underlying mechanism is
393 hypothesized to be increased peripheral inflammation[118] owing to the anti-inflammatory effects of

ω3 PUFAs. In summary, dysregulation of the crosstalk between the immune system and the HPA-stress axis is hypothesized to be associated with the onset of postpartum depression[101, 119]

Interestingly, first pregnancies are more often followed by psychiatric episodes than subsequent pregnancies, which may illustrate the dysregulation of psychoneuroimmune systems. This effect is hypothesized to be due to the biological differences between first and subsequent pregnancies, and has raised the possibility of an aetiological link with other medical conditions that have a similar increase in prevalence in first pregnancies such as pre-eclampsia[120]. Intriguingly, pre-eclampsia and postpartum psychosis are both associated with immune dysregulation, for example the increased rates of postpartum autoimmune thyroiditis[108, 109] and alterations in immune biomarkers (such as, CNS autoantibodies) in women with postpartum psychosis[121]. In addition, abnormalities in monocyte and T cell function and tryptophan breakdown has been demonstrated in patients with postpartum psychosis or mania, compared with postpartum women without any psychiatric symptoms.[122] Patients with postpartum psychosis had monocytosis and failed to demonstrate the physiological T- cell increase that is normally observed during the postpartum period. These findings support the notion that immune system dysregulation contributes to affective instability and severe postpartum episodes[122].

Future studies are needed to extend our understanding of the ways in which psychological and biological processes interact in PPDs. For example, social support might exert a stress-buffering effect via the downregulation of stress responses, including inflammatory reactivity to stressors and dampened sympathetic and hypothalamic-pituitary-adrenal (HPA) axis activity [123, 124].

[H1] Diagnosis, Screening and Prevention

As with all psychiatric disorders, the diagnosis of postpartum depression is reached by a comprehensive clinical interview and diagnostic criteria that provide an operationalised definition of the disorder, using classification systems such as the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[125] or International Classification of Diseases, Tenth Edition

(ICD10)[126]. Diagnostic criteria are similar across the DSM-5 and ICD-10, which are the two most common classification systems; however, the DSM-5 uses the term 'depression with peripartum onset' to refer to the onset of depression during pregnancy and into the first month postpartum, whereas ICD10 does not use a primary code referring to the perinatal period, although a second code denoting postpartum onset is available (which is not used in practice) . However, the diagnosis of psychiatric disorders is more than a list of symptoms and the impact on symptoms of functioning; diagnosis should also include an understanding of predisposing aetiological factors, triggers and maintenance factors, which are elicited by a comprehensive biopsychosocial assessment[24].

Postpartum depression is one of the most common postpartum psychiatric disorders, and can be mild and relatively self-limiting lasting only a few weeks, or can be more severe, with severe episodes potentially including psychotic symptoms[17]. Some symptoms of depression such as fatigue, sleep disturbance and appetite disturbance need careful enquiry, as a woman with a baby will be more tired than usual and have disrupted sleep (due to the baby needing a feed), although appetite might not be affected as breastfeeding will stimulate appetite despite a low mood. Checking whether the mother is able to sleep when the baby is asleep, whether the fatigue persists after rest and the interest in food will help establish whether the symptoms are pathological and if they are indicative of postpartum depression. Notably, anxiety might be a prominent symptom in postpartum depression[63], or can be a symptom of a comorbid anxiety disorder[127]. Diagnostic assessment should evaluate a history of manic or hypomanic symptoms, as first-onset postpartum depression can indicate underlying bipolar disorder[26]. Diagnostic challenges include barriers to disclosing symptoms due to stigma[128] and variations in the manifestation of symptoms, which might reflect cultural or educational differences[129]. In addition, it is important to ensure symptoms are not due to an underlying medical condition such as thyroid disease or an early presentation of first episode psychosis.

Although postpartum psychosis is not included as a primary diagnosis in the DSM-5 or ICD-10, this disorder is still recognised clinically and is usually considered to be a severe mood disorder.[16] Women with postpartum psychosis often have a history of bipolar disorder.[16] Most women have prodromal symptoms before the overt onset of postpartum psychosis; however, some women have acute onset of severe symptoms [130, 131]. Evaluation of women with postpartum psychosis includes assessment of manic, depressed, anxious and psychotic symptoms, and the assessment of the risk of causing harm to herself or her baby. Women with postpartum psychosis can present with either low or high mood (both elation and irritability), or frequently can present with a mixed state, including symptoms of both mania and ; a minority of women have an atypical symptom profile with disorientation and/or disturbance of consciousness [132]. Symptoms can also manifest as delusions, hallucinations, and particularly confusion and perplexity and patients can also have severe mood swings, insomnia, agitation and rapid deterioration. Postpartum psychosis is usually a rapid onset severe psychosis, typically starting within the first 2-4 weeks after birth, and is considered a psychiatric emergency as a lack of self-care and an inability to care for the infant can lead to suicide and/or, in rare cases, infanticide[16]. Accordingly, assessment should be carried out quickly (for example, The National Institute for Health and Care Excellence (NICE) recommend assessment within 4 hours of clinical presentation; in clinical practice this means within 24 hours of the acute onset of severe psychiatric symptoms) to ensure the woman can be cared for safely and appropriately. Excluding other medical disorders, such as cerebral space occupying lesions, thyroid disorders or infections is important as part of the diagnostic work-up. In many cases the mother's partner or family ask for psychiatric evaluation when the mother is irritated or agitated and not aware that she is seriously ill.

Anxiety disorders (such as GAD and panic disorder), OCD and PTSD can all manifest in the postpartum period. OCD is characterised obsessive thoughts. Obsessions are intrusive, repetitive thoughts, images or impulses that are unacceptable and/or unwanted and give rise to subjective

resistance. By contrast, delusions that occur in psychotic disorders are fixed, false beliefs[133] that need appropriate psychological intervention[17]. Postpartum OCD poses a particular diagnostic challenge, as intrusive thoughts about harm befalling the infant (such as, what if I drop my infant or I accidently cut the infant with a knife when I'm cooking) might be perceived as delusional and could lead to concerns about the safety of the infant. However, these thoughts are not associated with actual direct harm and the obsessions remain very ego-dystonic and highly distressing to the patient. Traumatic childbirth experiences can trigger PTSD, particularly in women with prior histories of trauma[134]. Differentiating the exacerbation of PTSD symptoms in women with past trauma and new onset PTSD owing to traumatic childbirth is important[135]. Past trauma history should include assessment of prior childhood abuse, adult interpersonal or other violence, among other forms of trauma. In addition, many women with PTSD or OCD present with symptoms of anxiety and mood symptoms, making the diagnosis of any one particular disorder a challenge[63, 136].

Women with a previous history of psychiatric disorders will often experience a worsening of symptoms during the postpartum period, although few studies have examined strategies to mitigate this exacerbation of symptoms[39]. For women without a prior history of psychiatric disorders, the acute onset of psychiatric symptoms in the postpartum period is often highly distressing. However, whether the first onset of psychiatric symptoms in the postpartum period indicates the beginning of a more persistent and chronic mood disorder, or is a condition that will be restricted only to the postpartum period is unclear. This is an important area for future study.

[H2] Screening

Screening for postpartum depression has attracted widespread interest from researchers, clinicians and policy makers due to the high prevalence and associated sequelae in terms of maternal morbidity and adverse child outcomes. In many countries, screening for postpartum depression

during routine obstetrical care, including care by health visitors, is inconsistent, and this strategy has become an area of focus in many countries. In addition, up to 60% of perinatal women with depression do not seek help [137]. However, given the availability of screening instruments and effective treatments [138], Clinical Practice Guidelines and recommendations are increasingly supportive of routine screening[139, 140]. More generally, international guidelines reflect a consensus that improved identification of PPDs is vitally important [141,142]. Accordingly, several national campaign to increase awareness of PPDs are underway, such as the Maternal Mental Health Alliance[143] in the UK. This alliance is a coalition of organizations that are dedicated to achieving consistent, accessible and quality mental health care in the first year after giving birth. In addition, state mandates for perinatal depression screening are increasing in the United States, including the US Preventive Services Task Force recommendation[140]. However, although this task force has concluded that the evidence base that is sufficient to recommend screening for perinatal depression when combined with adequate support systems[25, 140] this conclusion has also been criticised by others[144].

The most widely researched and used screening tool for postpartum depression is the brief 10-item Edinburgh Postnatal Depression Scale (EPDS[145]), which was designed to exclude symptoms that can be normal features of the perinatal period, such as poor sleep, but that are often included in other self-report measures. A cut-off score of 13 is most commonly used to recommend further diagnostic assessment[146, 147]. In addition, the EPDS includes question about thoughts of self-harm, which can help to mobilise risk assessment and can predict suicidal intent[148]. The EPDS has been used prenatally and validated in a number of languages, its properties are relatively well-understood [147] and it appears to be highly acceptable in the target population [149,150]. High EPDS scores can reflect several psychiatric diagnoses. For example, among the 826 screen-positive women out of a sample of 10,000 women, the most common primary diagnosis was unipolar depressive disorder (found in 68.5% of women), but almost two-thirds of women had co-morbid anxiety disorder and 22.6% had a bipolar disorder [151]. These data highlight another potential

benefit of the EPDS: that most women with a false-negative result for unipolar depression have another diagnosable, and potentially treatable, psychiatric condition.

Other generic or perinatal-specific depression measures have been used to identify perinatal depression, but are not as well validated in perinatal women as the EPDS. Other measures include the Postpartum Depression Screening Scale[152], the Beck Depression Inventory-II[153] and the Patient Health Questionnaire-9[154,155]. Alternatively, two case finding questions (the so-called Whooley questions [141, 156, 157]) can be asked to women to determine whether further mental health assessment should be carried out, and the use of these questions is recommended by NICE guidelines in the United Kingdom. The Whooley questions can also be used to detect any psychiatric disorder, and are not limited to depression[2].

As previously mentioned, postpartum depression are frequently co-morbid with anxiety (in 4.3% of women). As anxiety substantially impacts maternal functioning and fetal and infant development[28, 158 159], this has spurred efforts to screen for postpartum anxiety. Three sub-items of the EPDS (the so-called EPDS-3A) can be used to identify perinatal anxiety disorders and sub-syndromal anxiety[160]. Other screening instruments for anxiety disorders include the Perinatal Anxiety Screening Scale (PASS)[161] and the generalized anxiety disorder scale (GAD-7)[162]. Screening tools for perinatal OCD and PTSD are also available, such as the specific perinatal OCD screening scale (The POCS),[163] and a short screening scale for PTSD (SPAN), respectively.[164].

The utility of routine screening for postpartum psychosis, hypomanic and manic symptoms and bipolar disorder faces several barriers including a lack of evidence base of effectiveness and the reduced predictive value of screening for a relatively rare condition. Despite steady progress in this area[165, 166] a consensus test with well-known precision and an agreed cut-off has not been identified[167,168]. However, the Mood Disorder Questionnaire (MDQ) has shown solid psychometric properties for assessing bipolar disorder and is increasingly used [169]. Taking a full personal and family history might help to identify vulnerability to bipolar disorders which could trigger further

546 diagnostic assessment, given the strong association between bipolar disorder and increased risk
547 for PPDs[141, 142].

548 In general, screening programs in the postpartum period should include a clear pathway from
549 screening, to diagnostic assessment and treatment[170]. Best practice guidelines agree that all
550 women who have a positive screen need subsequent assessment, during which, co-morbidities
551 and the woman's wider psychosocial context can be explored. Currently, only such well-resourced,
552 integrated management programs have provided evidence that perinatal mental health is improved
553 by depression screening [171, 172]. In this regard, e-screening and e-treatments to facilitate integrated,
554 cost-effective care might be useful[173]. Few well-understood, validated screening approaches for
555 PPDs that can ultimately improve morbidity and mortality are available. Indeed, further building of
556 the evidence-base for screening, including the cost-effectiveness of perinatal depression screening
557 as a policy direction is required[142, 174].

558

559 **[H2] Prevention**

560 Interventions for the prevention of postpartum depression or postpartum anxiety are intended to
561 prevent the onset, duration, or recurrence of these disorders. Prevention can reduce the mental
562 health, physical health and socio-economic burden associated with postpartum depression for
563 mothers, their offspring and families, as well as for health systems. The effectiveness of prevention
564 of postpartum depression is facilitated by the fact that pregnant women are motivated to address
565 factors that will affect their baby[175]. The assessment of risk factors for PPDs helps with diagnosis
566 and formulation, but is also important for identifying potentially modifiable targets for prevention
567 and treatment (Box 3)[176]. Thus, it is a requirement for both symptom screening and risk
568 assessment that systems exist for adequate follow-up and support. Furthermore, women and
569 clinicians should be informed that the established risk factors might have limited predictive value

570 for individual patients and, therefore, do not guarantee which women will develop or not develop
571 postpartum depression.

572 Some psychosocial and psychological interventions have reduced the risk of women developing
573 postpartum depression, although no single intervention type or modality appears superior to
574 others. Data from trials included in a Cochrane review[176] as well as randomized controlled trials
575 included in a qualitative review,[175] point towards particularly positive impacts when interventions
576 target at-risk groups (such as women with a previous episode of depression or a recent life
577 stressor), or include interpersonal therapy (IPT). As relationship challenges and lack of social
578 support constitute strong risk factor for PPD, the interpersonal focus of the IPT intervention,
579 therefore aims to address this causative or aggravating factor. Interventions with the most promise
580 include interventions targeting at-risk groups (such as women with a previous episode of
581 depression or a recent life stressor).

582 Trials included in these reviews were conducted among high risk women, based on various factors,
583 as well as women enrolled from the general perinatal population. Trials assessing the use of
584 interpersonal therapy, cognitive behavioural therapy, peer support, parental preparedness, and
585 person-centred approaches for prevention of postpartum depression have demonstrated
586 significantly positive results, whereas trials assessing the use of cognitive behavioural therapy for
587 postpartum depression have demonstrated mixed results. These results, disaggregated for
588 universal, selective or indicated prevention strategies are summarized in a more recent systematic
589 review and meta-analysis[177]. The interventions were delivered using several modalities, including
590 home visits and telephone support, provision by professional and lay practitioners, individual and
591 group-based sessions, through multiple contact sessions and at postpartum initiation[176].

592 There is conflicting evidence for the treatment of vulnerable women with antidepressants for the
593 prevention of depressive episodes or anxiety symptoms during the perinatal period as well as
594 anxiety symptoms has conflicting evidence [178]. One of the earliest studies demonstrated a

595 reduction in recurrence of postpartum major depression with prophylactic antidepressant treatment
596 [179]. Small but emerging literature has suggested hormonal therapies, light therapy and other forms
597 of circadian manipulation might be promising therapies for prevention of depression[180]. There is no
598 strong evidence for the use of hormonal therapies, acupuncture, supplementation with omega-3
599 polyunsaturated fatty acids, light therapy and other forms of circadian manipulation for prevention
600 of postpartum depression. [177,180]

601 Interventions for the prevention of postpartum psychosis include careful monitoring for symptom
602 development in women at high risk and adjustments of prophylactic medication, especially in
603 women with bipolar disorder[18, 24]. Prophylactic treatment during pregnancy might reduce the rate of
604 postpartum relapse in women with bipolar disorder, although no evidence from randomized
605 controlled trials for this is available. For women with previous postpartum psychosis, prophylactic
606 treatment with lithium or antipsychotics immediately postpartum might reduce relapse[18].

607

608 **[H1] Management**

609 The goals of treating mental illness in the postpartum period are to reduce maternal psychiatric
610 symptoms and to support maternal-child and family functioning. All women and their families
611 should receive education about the illness and the potential treatment options, including the
612 potential benefits and harms of each treatment option. Social support should be optimized and
613 physical and psychiatric comorbidities should be addressed. In addition, strategies to assist women
614 in obtaining sleep and a stable circadian rhythm are helpful, given that sleep deprivation is
615 common during the postpartum period. In many cases, the symptoms of PPDs influence maternal–
616 child interactions, which should be observed and discussed in a non-judgmental way.

617 Although specific recommended treatments depend on the underlying diagnosis, in general, a
618 stepped care approach is advocated, in which the intensity of the intervention matches the severity
619 and acuity of the clinical presentation. For example, women with mild symptoms of depressive,

anxiety, obsessive–compulsive and/or trauma or stressor-related disorders should first be offered the lowest-intensity interventions such as peer support and guided self-help, whereas women who do not respond to these treatments might require formal psychotherapeutic interventions, such as psychological therapies. For women with severe symptoms, who do not respond to non-pharmacological treatment, or who have bipolar disorder or psychosis, pharmacological interventions are likely to be introduced as a first-line treatment, used alone or in combination with a lower-intensity intervention. In such cases, the well-established benefits of breastfeeding on the infant must be considered in the context of maternal mental wellbeing, the passage of psychotropic medication into breast-milk and the infant, and the potential effects of medications on the neonate. Indeed, when breast-feeding is challenging, and/or when frequent nighttime feedings leads to sleep disruption, symptoms of depression or anxiety might be precipitated or exacerbated. In these cases, the benefits of breastfeeding must be weighed against the risk of ongoing maternal mental illness, and formula feeding is a viable and often recommended alternative. Other somatic treatments, such as electroconvulsive therapy (ECT), can be considered in women with treatment-refractory disorders. Throughout, monitoring progress to determine when or if to move to a higher-intensity intervention, and to ensure safety for mother and child is important. In the initial assessment and during treatment the patient and her family should be asked if thoughts of suicide or infanticide have occurred. Safety concerns and/or evidence of active psychosis are medical emergencies that require specialist consultation, emergency hospitalization and treatment.

[H2] Mood disorders and anxiety

Treatment of postpartum depression and other non-psychotic mental disorders (such as anxiety, OCD and trauma and stressor-related disorders; Box 4) depends on the severity of the initial presentation and the level of functional impairment, including the effect on the maternal–child interaction.[128] For women with a past history of mental illness, the previous treatment response and the time to response of previous episodes should be considered. The patient's treatment

preference, in addition to as access to care and utilization of care should also be considered in all women, as patients who receive their preferred treatment are most likely to benefit from this treatment than other treatments.[181] Most women with non-psychotic mental disorders often prefer psychotherapy over pharmacological treatments, although the uptake and effectiveness of this therapy can be limited due to barriers in attending appointments, such as unpredictable infant schedules and competing childcare responsibilities.[182] Similarly, fathers also prefer psychological treatments to pharmacological therapy.[183] However, some women prefer pharmacological treatment alone, so individualizing treatments based on patient preferences is important. Treating maternal postpartum depression might not always improve the maternal–infant relationship, and additional interventions aimed at the mother–infant dyad or the family as a whole might be required.[184]

[H3] Psychological Interventions. Most trials for postpartum depression have focused on non-pharmacological treatments. For women with mild postpartum depression, psychosocial treatments including peer support, guided self-help, and supportive counseling by trained professions such as public health nurses (at home, or in support groups) can improve symptoms. For example, one systematic review of 5 trials demonstrated a 1 year remission rate of 68% in women with postpartum depression who received psychosocial treatments compared with a remission rate of 54% in women treated with standard primary care.[185] For women with moderate symptoms of depression, or women who do not responded to psychosocial strategies, psychotherapies such as cognitive-behaviour therapy (CBT) and interpersonal therapy (IPT) that specifically address the psychological and related challenges of transitioning to parenthood are effective when delivered in individual, group, and partner-assisted formats, and either in-person, by telephone, or online.[186] A systematic review of 4 CBT and 1 IPT trials demonstrated a pooled remission rate of 60.3% for these interventions, compared with a rate of 48.1% for usual care.[185]

In addition, a CBT-based program was demonstrated to reduce worry and depressive symptoms in women with postpartum anxiety disorders, including GAD, social phobia and OCD, compared with symptoms at baseline.[187] The effectiveness of CBT for postnatal OCD symptoms was confirmed in a small RCT.[188]. Although additional research is required, CBT-based interventions for postpartum anxiety disorders, and specifically interventions such as eye movement desensitization and reprocessing (EMDR) and trauma-focused CBT for trauma and stressor related disorders, can be used, although the latter two interventions have not been specifically evaluated in postpartum women [189].

The increasing use of internet-based CBT and the development of mobile apps that use this treatment modality demonstrates the power of digital health, which is often more accessible than traditional psychotherapy, and extends to individuals who can't participate in psychotherapy. A good example of this is MumMoodBooster, which was developed in Australia[173].

[H3] Drug therapies. Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are the mainstay of pharmacological treatment for postpartum anxiety and depressive disorders. These therapies can be used alone or in combination with psychosocial or psychological treatments. In a systematic review, the pooled remission rate was significantly higher in patients receiving SSRIs (46.0%) compared with those receiving placebo (25.7%).[190] Although pharmacological therapies can be used alone or in combination with psychosocial or psychological treatments, whether combinatorial therapy is superior to either one alone has not been evaluated in postpartum women. However, combinatorial treatment does not lead to further improvements in functional outcomes compared with medication alone, in non-perinatal populations.[191, 192] To our knowledge, there are no drug treatment trials in maternal anxiety disorders, or in paternal postpartum depression or anxiety. However, SSRI and SNRI medications are first line pharmacological treatments for anxiety and depression outside the postpartum period. The duration of antidepressant therapy required for new-onset postpartum

depression, anxiety or a related disorder has not been studied, but clinicians are recommended to follow guidelines for these disorders in the general population. For depression, the initial treatment should be continued for 6 months to 1 year after remission; longer durations are required for severe and/or recurrent illness.[193]

Many women and their partners are concerned about the safety of using antidepressant drugs during breastfeeding. However, the use of antidepressants during the postpartum period is not a contraindication to breastfeeding, and indeed, the avoidance of medication when needed for severe illness is associated with maternal suicides[194]. The passage of SSRIs and SNRIs into breast-milk is variable between drugs, but most pass into the breast-milk at <10% of the maternal dose, which is compatible with breast-feeding.[195] As such, changing the antidepressant drug or the dose during the perinatal period to switch to a drug with lower breast-milk passage is generally not recommended. For new-onset postpartum depression, sertraline is often recommended as a first-line pharmacological treatment due to very minimal passage into breast-milk (Figure 2). However, in patients with a prior history of psychiatric disorders, therapies that have previously demonstrated efficacy should be considered, even those that have less data regarding safety during breastfeeding. Other SSRIs, SNRIs or mirtazapine (an atypical antidepressant) also have minimal passage into breast-milk, so these drugs are unlikely to be a cause for concern. Buproprion is generally not given to lactating women due to case reports of infant seizures associated with exposure to this drug.[196] In cases of severe depression and/or anxiety (with or without psychotic features), older antidepressants, other therapies such as benzodiazepines or antipsychotics might be indicated.

[H3] Other treatments. Given the likely role of hormonal fluctuations in the aetiology of postpartum depression, hormonal treatments have been evaluated. Transdermal oestrogen therapy reduced the symptoms of postpartum depression in one small study, but further trial are required. Progestin

724 therapy worsens postpartum depressive symptoms.[197] One trial of demonstrated the superiority of
725 allopregnenalone to placebo in improving depressive symptoms in 21 women with severe
726 postpartum depression,[92] although this requires further investigation. Complementary and
727 alternative medicine treatments (for example, folate, s-adenosylmethionine, massage and
728 acupuncture) are not well-supported by evidence.[198] However, using aerobic exercise for
729 postpartum depression was recently examined in a systematic review and has good supporting
730 evidence for mild symptomatology [199]. ECT can be considered in severe or treatment-refractory
731 cases of depression.

732

733 **[H2] Postpartum psychosis**

734 Fluctuations in symptoms are common in women with postpartum psychosis, and thoughts of
735 infanticide or suicide are often well hidden. Thus, outpatient treatment is not safe and psychiatric
736 hospitalization is recommended for diagnostic evaluation and treatment [15]. The preferred treatment
737 setting is a mother–baby joint admission unit, but these units are not available worldwide [200, 201].
738 Alternatives are the admission of the mother only to a hospital with expertise in perinatal
739 psychiatric care or women's mental health, or, if these facilities are unavailable, admission to a
740 standard mental health inpatient setting, or based on a careful assessment of the safety of both the
741 mother and the infant, intensive home treatment where available and with appropriate
742 supervision[16]. The effect of these approaches on long term outcomes of the mother and baby are
743 being investigated[15].

744 The management of postpartum psychosis is dependent on psychiatric history. For women with
745 known severe psychiatric illness with non-perinatal episodes, reviewing the nature and
746 effectiveness of past treatments and restarting previous effective treatment is important.
747 Management of women without a history of bipolar disorder or other severe psychiatric disorder are
748 summarized in Figure 2. The main treatment goals for women without a prior history of bipolar

749 disorder, psychosis or other severe psychiatric disorder include the limitation of the current episode
750 and the prevention of a bipolar disease course with multiple episodes. Accordingly, management in
751 the first year postpartum should focus on full recovery (that is, complete symptom remission and
752 social and vocational functioning). In the absence of guidelines and controlled trials, treatment
753 recommendations are based on results from naturalistic cohort studies and expert consensus
754 groups[24, 202]. The largest study (consisting of 68 patients) demonstrated the efficacy of a stepwise
755 sequence of short-term benzodiazepines, antipsychotics and lithium, and showed high remission
756 rates (remission in 98.4% of women) in the acute phase [203]. Moreover, this study demonstrated
757 that lithium monotherapy is protective against relapse of psychosis, depression and mania within
758 one year. The second largest study described successful ECT treatment in 34 patients with
759 postpartum psychosis of whom many had symptoms of catatonia[204]. The effectiveness of lithium
760 and ECT is supported by case reports [205]. Successful treatment with antipsychotics has been
761 described in case reports [206, 207], but antipsychotic monotherapy did not show efficacy in a cohort
762 study [203]. Together, lithium monotherapy might be the preferred initial intervention for postpartum
763 psychosis but adjunctive treatment with benzodiazepines or antipsychotics is useful for the acute
764 treatment of agitation, mania and psychotic symptoms, given the well documented effectiveness in
765 non-perinatal populations. Several antipsychotics are used for the treatment of severe PPDs
766 including risperidone, quetiapine and olanzapine[208]. ECT is the primary treatment for patients with
767 severe catatonic or depressed psychotic features, or if patient's prefer this therapy [15].

768 Anticonvulsants (that is, antiepileptic medications) are also used less frequently as mood
769 stabilizers in the treatment of bipolar disorder because of concerns of teratogenicity. However,
770 valproate use during pregnancy and lactation is associated with neural tube defects and
771 neurocognitive developmental delays in the offspring[24, 209]. Thus, valproate use is not advised
772 during the perinatal period, unless the risk/benefit assessment determines a prior efficacy in
773 particular women. By contrast, lamotrigine is used for the treatment of bipolar–depression (not
774 bipolar–mania) and is not associated with an increased risk of congenital malformations in

offspring. [210]. A review of recent studies demonstrated that lamotrigine had no adverse outcomes on infant IQ or neurodevelopment.[211]

The management of a breastfeeding woman with a severe psychiatric episode is challenging due to concerns about the exposure of breastmilk to pharmacological therapies and the need for sleep preservation in the mother[15]. The use of lactation inhibitors should be avoided. In some countries, the mother is recommended to breastfeed only if extensive psychiatric support and access to a pediatric professional that can monitor the infant are available. Moreover, the mother and her partner should be educated about the risks of breastfeeding with pharmacotherapy. In other countries, a more individualized approach (for example, NICE guidelines) based on previous responses to medication, preferences regarding breastfeeding and psychopathology[24], other than avoidance of breastfeeding if lithium (rather than an antipsychotic) is used. Small case series have provided information regarding the safety of lithium in lactation[212, 213]. When possible, level of lithium in the infants serum should be closely monitored; on average, the serum level of lithium is 25% of the maternal levels, but the range can vary and dehydration can lead to toxic levels [15,213]. No adverse effects were reported in ten infants of breastfeeding mothers who received ECT[204].

[H1] Quality of life

The symptoms and morbidity of postpartum depression are often reported in the academic literature, but this offers only a rather constricted view of the quality of life (QOL) of women with PPDs. [125,214 *215*] Nevertheless, the classic core symptoms of a depressive disorder would be expected to decrease the subjective quality of both an individual's inner life experience (anhedonia, sadness, hopelessness, thoughts of death), and their functioning (psychomotor retardation or agitation, disturbed sleep). Anxiety is frequently co-morbid and this further influences quality of life with persistent worry symptoms.

Definitions vary, but QoL is a broader multidimensional construct which commonly incorporates two central aspects: emotional well-being (including, frequency and intensity of joy, sadness, affection) and life evaluation (how satisfied one is with one's life, for example, housing, employment). Health, and the ability to function, as an essential component of QoL is referred to as health-related quality of life (HRQoL). Maternal QoL during the postpartum period also affects her infant's current and future quality of life. Many mothers with postpartum depression have difficulty interacting with their infants in a positive way[216], such as making less eye contact, showing less synchronous responsiveness, being uninvolved and showing restricted affect during mother-infant interactions.[217-219] Infant attachment security is a key predictor of child outcomes, including neurological, psychological and social outcomes over the course of development[220]. In addition, children of mothers with perinatal depression might have poorer psychological outcomes when they reach 18 years of age[221]. Some women have an intrusive engagement style that might lead to long-term difficulties in child social, cognitive and behavioural domains[222]. Women with postpartum psychosis face even more many parenting challenges often including disrupted attachment, which impact on the quality of life for mother and child.[223]

One of the most widely used generic measures of QOL is the 36 item short-form (SF-36)[224, 225], which has eight health domains that measure limitations in physical or usual role activities due to health issues, limitations in usual role or social activities due to emotional issues, pain, mental health, vitality, and general health perceptions. The SF-36 has been used in over 1,000 publications and for over 130 disorders including those that occur during the postpartum period, and both the full and short versions of this scale have been validated by numerous studies[225, 226]. However, few measures of QOL have been developed specifically for use in the postpartum period[227] . Only [228] three instruments for use during the postpartum period were reported in one systematic review: The Mother-Generated Index (MGI)[229], the Maternal Postpartum Quality of Life Questionnaire (MAPP-QOL)[230] and the Rural Postpartum QOL scale (RPQoL)[231]. The MGI requires women to specify domains of their life that have been affected by the birth of their baby, either

825 positive or negative, and to then score these out of 10. [232] The most common changes reported
826 were tiredness, less personal time, less time with partner or other family members, a worse
827 relationship with partner or other family members, physical complaints, low self-esteem, financial
828 worries, negative feelings towards the baby, more housework, poor sex life, decreased pleasure
829 from baby, less sense of happiness or fulfilment [229].

830 Not surprisingly, people with depressive illness in general report lower scores on generic QoL and
831 HRQoL measures, as do women experiencing postpartum depressed mood. [233] [234] Small studies in
832 postpartum women also suggest QoL is amenable to intervention. Improvements in QOL are not
833 fully explained by improvements in the severity of depressive symptom suggesting that
834 interventions should go beyond the mere reduction of symptom severity and consider other factors
835 that contribute to QoL as targets for intervention. . Maternal-specific measures of QOL could be
836 integrated into postpartum depression screening programs or routine postnatal care[235, 236]. Indeed,
837 QoL measures that allow a women to identify which areas of her life are most important to her,
838 could be used to allow women to indicate where she would like to see improvements.[229] Emerging
839 studies have highlighted the beneficial effect of social support on QOL[237], in addition to risk factors
840 for reduced QOL such as younger age and lower socio-economic status in women with postpartum
841 depression [238].

842 PPDs have economic considerations and can affect quality-adjusted life years (QALY)[142]. QALY
843 takes into account how treatment affects quality and quantity of life, and accordingly, QoL
844 measurement is necessary for studies of cost-effectiveness of treatments. Compelling data from
845 the London School of Economics[239] demonstrated the high economic costs of PPDs and the need
846 to address the loss of QALYs of women and their children, by treatment and prevention of these
847 disorders. This finding is particularly pertinent given the short and long-term effects of postpartum
848 depression. Indeed, as most women recover from postpartum mood disorders, these disorders can
849 become chronic in a subgroup of women[240]. One study demonstrated that, for each one-year

cohort of births, perinatal depression, anxiety and psychosis cost the UK around £8.1 billion in the long-term.[239]

[H1] Outlook

The postpartum period is a vulnerable time for onset of psychiatric illness. Indeed, postpartum mood and anxiety are heterogeneous and might be triggered by biopsychosocial factors including a vulnerability to the robust endocrine and immune-related changes that occur at childbirth. The heterogeneity of these disorders requires a thoughtful approach to assessment and treatment planning that includes the clinical presentation, family and personal psychiatric history, other psychosocial risk factors (including history of trauma), and awareness of potential biological or genetic contributions that might influence risk and vulnerability.

The precise vulnerability that leads to some women developing PPDs is currently unknown and novel research approaches are needed to identify the underlying pathophysiology of both prepartum and postpartum anxiety, depression and psychosis. This will require a multi-faceted approach in preclinical, clinical and translational research, to determine the mechanisms behind the neurobiology and physiological correlates of PPDs, and the observed peripartum mood and mothering behaviors. Additionally, these strategies must address the differences in the timing of symptom onset and the diverse types of symptoms.

Given the morbidity and mortality of postpartum psychosis, episodes of psychosis might be best considered to represent women with a bipolar disorder diathesis with a puerperal trigger. Understanding this trigger will be beneficial and should allow the development of new treatments and, ultimately, enable the prevention of psychosis or prevent unfavourable outcomes in women at high risk. Effective evidence based treatment approaches are available for psychosis and depression, including psychopharmacology, psychotherapy and ECT and circadian manipulation. However, postpartum depression and postpartum psychosis require different and targeted

875 treatment approaches and therefore, bipolarity must be considered in the evaluation and
876 management of all women with postpartum mood and anxiety disorders. In addition, primary
877 treatment goals should include the limitation of the current episode and the prevention of future
878 episodes (including unipolar or bipolar disease with multiple episodes, and chronic anxiety).
879 Whether there a continuum of severity between postpartum depression and postpartum psychosis,
880 or whether these disorders represent different conditions with different aetiological factors requires
881 further study.

882 A potential barrier to the engagement and retention of women in the treatment of postpartum mood
883 disorders is stigma. Understand this stigma and the fear that women have regarding postpartum
884 mood disorders is essential. The voices of women with postpartum mood disorders must be
885 incorporated into the development of services to ensure the needs of women, their infants and
886 families are met[241, 242].

887 To date, the amount of research provides an important road map for PPDs in general, and
888 guidelines for screening or identification and treatment for perinatal depression in many countries
889 gives a strong mandate to improve mental health care for all women in the perinatal period. Thus,
890 developing effective strategies in low, middle and high income countries that allow the delivery of
891 targeted therapies to women with different clinical phenotypes and severity of PPDs is imperative.
892 In addition, whether the current ICD-10 and DSM-5 classification systems are adequate for
893 detecting specific phenotypes or diagnostic groups of patients should be evaluated. We should
894 also consider that PPDs might be phenotypically different than psychiatric disorders that begin
895 during pregnancy. Indeed, disorders that occur postpartum might have unique characteristics in
896 epidemiology, pathophysiology, psychosocial contributions, prevention and management than
897 disorders that occur during pregnancy.

898 In summary, PPDs are morbid and costly disorders. Advocating for early identification and
899 screening that begins in pregnancy to identify women at risk, in addition to timely and effective

900 treatments of PPDs is essential. Given the recent advances in knowledge, this an incredibly
901 exciting time for research in perinatal mood disorders. New approaches might allow the
902 identification of the underlying causes of postpartum mood disorders, which could lead efforts to
903 identify women at risk and personalize treatment. Although genetic, biological and hormonal
904 signals likely have an important role in risk of these disorders, psychosocial contributions including
905 the current impact of lifetime stressors must be part of comprehensive work-up and treatment plan.
906 The social determinants of postpartum mood disorders, such as poverty, domestic violence, poor
907 housing, and insecure migrant status, should also be assessed as part of routine practice of
908 maternal health care for all women. Finally, we must recognize that maternal mental health is
909 necessary for the physical and mental health of mothers, infants and families[17] and advocating and
910 protecting this population is our obligation.
911
912

Display items

Box 1. Paternal postpartum depression.

Fathers can also experience depression after the birth of a child. Indeed, in men, the prevalence of depression after the birth of a child is greater than at other times during life[243]. Although the literature of paternal depression is much smaller than that for maternal depression, the available literature demonstrates that paternal depression increases the risk for long-term adverse outcomes in the child due to potential impairments in parenting[244, 245]. In addition, a strong link between maternal depression and paternal depression has been reported. Pregnant women who had partners with depression during their pregnancy had worse depression symptom severity during the first six months postpartum[246]. Thus, including fathers in health assessments during the postpartum period and screening fathers for postpartum psychiatric disorders at similar time intervals as maternal screening is important. Efforts aiming to improve the overall health and functioning of the family unit will lead to best outcomes for the child[243, 245].

Box 2. Postpartum mental illness in low-income and middle-income countries

In resource-poor settings, women of reproductive age typically have socio-economic and health challenges that interplay in mutually reinforcing ways.[247, 248] For example, low levels of education, low gender status, food insecurity, domestic abuse and lack of access to social and health services leave women and girls vulnerable to maternal mortality and chronic morbidities, including common mental health disorders.[249, 250] Indeed, the prevalence of common perinatal mental disorders in low- and lower-middle-income countries is higher than in high-income countries. One systematic review and meta-analysis[21] demonstrated a weighted mean prevalence of 15.6% in pregnant women and 19.8% in women after childbirth. The most strongly associated factors for perinatal mental disorders are socio-economic disadvantage, unintended pregnancy, younger age, unmarried status, lacking intimate partner empathy and support, hostile inlaws, partner violence, insufficient emotional and practical support, a history of mental health problems and in certain settings, a female infant. [21]

[H1] Considerations for management

Mental health prevention and treatment investments in high-income countries is more than US$50 per year per person, compared with less than US$2 in most LMIC,[251] resulting in a profound paucity of mental health providers in these settings. The intervention coverage for common mental disorders (including those that occur during the perinatal period) ranges from 7% to 28% in LMICs.[252] The low monetary allocation represents, in part, poor appreciation by decision makers of the effect of mental illness on population disability and socio-economic development, low levels of political will and capacity, and competing health and development priorities.[253] Interventions that are most likely to succeed in LMICs would, therefore, need to adopt a systems strengthening, integrated and low-cost approach. Examples showing promise have integrated mental health into primary care, maternal and child health services or into the routine community based delivery of

health services (carried out by trained lay workers, or primary care healthworkers, using a task-sharing approach)[254]. Emerging evidence supports the benefit of including poverty alleviation strategies in to mental health interventions.[255]

[H1] Types of interventions

A systematic review and meta-analysis of evidence of common perinatal mental disorder trials from LMIC, reported similar relative risk outcomes in studies carried out in high-income countries[256]. For the 13 trials selected, the pooled effect size for maternal depression was −0.38. In this review, trials that demonstrated positive results used several culturally adapted treatment paradigms, either singly or in combination. The Thinking Health Program in Pakistan was a cognitive behaviour therapy (CBT) intervention delivered in homes in a semi-rural setting by Lady Health Workers. [257] Uptake of the intervention leveraged the belief, within multi-generational households, that the intervention with the mother would improve the infant's well-being . In an urban, deprived setting in Chile, midwives and nurses were trained to deliver eight weekly structured psychoeducational group sessions. These sessions included information about symptoms and treatments, some problem solving strategies, behavioural activation strategies (such as scheduling pleasurable activities) and some cognitive techniques using postnatal examples [258] .

Subsequently, a trial in Zimbabwe [259] used peer counsellors to deliver six weeks of group problem solving therapy adapted for the local setting to postnatal women with depression. In this study, family members were co-opted to support the mothers through strategies identified in the problem solving and a specific treatment element that explored community resources and support systems was included. Six weeks after the intervention, the drop in mean EPDS score was greater in the PST group than the control group who received antidepressant therapy. No difference in outcomes between women with or without HIV was reported.

Box 3. Targeting risk factors for postpartum depression.

Assessing the common psychosocial risk factors for postpartum depression might have the following functions:

- Assisting in the initiation of targeted interventions or determining rational management decisions to mitigate the risks across several global settings through
    - risk reduction interventions (for example, referring women for social grants, to domestic violence support groups or to a women's shelter and provision of integrated interventions for the mood disorder, which also addresses domestic violence [260]
    - activation of protective factors, (such as interpersonal therapy for relationship difficulties or activating social support networks)[175, 260].
- Assisting in screening of women who have an increased risk of postpartum depression but do not currently have the disorder.
- Assisting in timely referral for support in women with suspected postpartum depression and complicated psychosocial risk factors who are reluctant to endorse symptoms during screening due to stigma and poor contextual validity of the screening tool in some global settings, among other reasons[261]. This approach acknowledges that there may be several contextual factors contributing to false negative mental health screening results.

Box 4. General management guidelines for non-psychotic psychiatric disorders

1. Identify somatic comorbidities and optimize their management.
2. Check the mode of delivery, if complications were present and if delivery was experienced as traumatic. In the case of post-traumatic stress symptoms, consider specific treatments.
3. Assess for suicidal thoughts and intrusive thoughts of harm toward the baby. Consider the safety of the baby and whether the mother can provide care for the baby if she is alone or if other adult supervision is required.
4. Ask the mother of her attitude towards her baby and observe maternal-child interactions. Consider specific treatments with signs of problematic interactions or bonding.
5. Review the feeding pattern of the baby. Address problems with breast or bottle-feeding.
6. Provide strategies to preserve sleep, such as finding another person to feed the infant at night.
7. Assess psychiatric history before delivery. Review the nature and effectiveness of past treatments, and restart previous effective treatment when appropriate.

Figure 1, Mechanisms of postpartum psychiatric disorders.

Several factors have been implicated in the aetiology of postpartum psychiatric disorders, including both postpartum depression and postpartum psychosis. These factors include psycho-social factors and biological factors that are specific to pregnancy and the postpartum period, such as drastic alterations in gonadal sex steroids and impaired mother-infant interactions. Whether the aetiology of psychiatric disorders occurring in prenatally, during pregnancy or during the postpartum period is different requires future study.

Figure 2. Management of first onset postpartum psychiatric disorders.

Management of postpartum psychiatric disorders should take into account the diagnosis (such as psychosis, anxiety or depression), symptom severity and, with regards to mood and anxiety disorders, whether the mother is breastfeeding.

Bibliography: [Au: There are 5 pairs of duplicated references, can you please fix these using your reference manager:-- YES, this has been fixed. Thanks for letting me know!

- **27 and 147-- corrected**
- **16 and 19-- corrected**
- **30 and 162-- corrected**
- **11 and 22—corrected.**
- **20 and 56] --corrected**

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