Postpartum Depression

2

Alba Roca Lecumberri, Estel Gelabert Arbiol, and Lluïsa Garcia-Esteve

2.1 Introduction

Pregnancy, childbirth, and postpartum are periods of high vulnerability to the development or relapse of perinatal mental disorders. Many women may present postpartum "maternity blues" or "baby blues," a transient mood disturbance related to hormonal changes that occur after childbirth. Nevertheless, for some women this mood disturbance can persist and be more severe, developing a postpartum depression (PPD), one of the most common complications of childbearing [1]. Postpartum depression (PPD) is a significant public health problem associated with increased morbidity for both infants and mothers. The symptoms can range from mild to severe and an appropriate detection and treatment are imperative.

In this chapter we will conduct a brief review of the most relevant aspects of PPD.

2.1.1 Epidemiology of Postpartum Depression

Epidemiological data of postpartum depression are from studies conducted in countries across the world, and different incidence and prevalence values are reported between countries. The most recent systematic review and meta-analysis [2] found that the incidence of postpartum depression was 12% (95% CI 0.04–0.20) while the

A. R. Lecumberri (✉) · L. Garcia-Esteve
Perinatal Mental Health Unit CLINIC_BCN, Hospital Clínic de Barcelona, Insistut Clínic de Neurociències (ICN), Barcelona, Spain
e-mail: aroca1@clinic.cat; lesteve@clinic.cat

E. G. Arbiol
Department of Clinical and Health Psychology, Universitat Autònoma de Barcelona, Cerdanyola, Spain
e-mail: estel.gelabert@uab.cat

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overall prevalence of depression was 17% (95% CI 0.15–0.20) among healthy mothers without a prior history of depression. Prevalence was similar regardless of the type of diagnostic tool used; however, there were statistical differences in the prevalence between different geographical regions. There was no statistical difference in prevalence between different screening time points, but an increasing prevalence was observed beyond 6 months postpartum.

In low-income and middle-income countries (LAMIC) antepartum and postpartum depression is highly prevalent affecting about one in four and one in five women, respectively. Specifically, postpartum depression prevalence was estimated in 19.7% (16.9–22.8%) [3]. We must consider that these numbers may be an underestimate with the lower reports resulting from mental health stigma, cultural norms, and myths in relationship with maternity.

Data on whether there is an increased risk of depression in postpartum period than in another times in life are scarce. American study compared prevalence of psychiatric disorders in a pregnant women sample with nonpregnant women of childbearing age sample and found that pregnancy per se was not associated with an increased risk of new onset or recurrence of mental disorders; however, the risk of major depressive disorder was significantly higher in postpartum women (9.3%) than in nonpregnant women (8.1%) (OR 1.59, 95% CI = 1.15–2.20) [4]. Also, a study found that primiparous women had an increased risk of incident hospital admission through the first 3 months after childbirth, especially for women with affective disorders (bipolar and unipolar) [5].

The onset of postnatal depression is variable, and is not always in the first weeks following the birth; moreover, the perinatal vulnerability to depression begins before delivery and extends beyond 6 weeks postpartum. In a study of women with postpartum depression, 11.5% reported prenatal onset, 22.0% late postpartum onset (>6 weeks), and 66.5% early postpartum symptom onset (<6 weeks). Those reporting pregnancy onsets were more likely to be unmarried, and those with a late postpartum onset were less likely to report a history of postpartum depression [6].

2.2 Causes of PPD.

The exact causes of PPD are unknown, but it is considered that there are different vulnerabilities that can precipitate it and included within the general stress-vulnerability model. This model considers giving birth as a neurohormonal and immunological stress factor, and the transition to motherhood as a psychosocial stress factor. Both factors demand an adaptive effort in order to respond to the demands of motherhood. The depression may be a result of the different types of bio-psycho-social vulnerabilities [7]:

(a) *Genetic vulnerability*. For depression occurring in the early postpartum period (onset in the first 8 weeks), symptom severity, heritability, and epigenetic data suggest that PPD may be distinct to major depressive disorder occurring outside

of the perinatal period, whereas depression occurring in the later postpartum period may be more similar [8]. In one of the more recent studies of heritability of PPD, the authors investigated the relative importance of genetic and environmental influences on perinatal depression, and the genetic overlap between perinatal depression and nonperinatal depression in a sample of twins and a sample of sisters [9]. The heritability of perinatal depression was estimated at 54% and 44%, respectively, in separate samples, and the heritability of nonperinatal depression at 32%. The authors suggest that perinatal depression constitutes a subset of depression that could be prioritized and future genetic studies using genomic methods will require international collaborations to include a large number of patients.

Moreover we must considered mechanisms like epigenetic modifications. Epigenetic alterations have been demonstrated in two genes; TTC9B and HP1BP3 DNA methylation at early antenatal time points showed moderate evidence for association to the change in estradiol and allopregnanolone over the course of pregnancy, that may be important for mediating hormonal sensitivity [10]. Specifically, antenatal TTC9B and HP1BP3 gene DNA methylation is prospectively predictive of postpartum depression (PPD) with ~80% accuracy [10, 11].

Other genes like serotonin transporter gen (5-htt) have been implicated to greater vulnerability for depressive symptoms after childbirth with controversial results [12, 13].

(b) *Neurohormonal vulnerability.* The sudden decrease in estrogens during birth and the immediate postnatal period bring about a sharp decrease in brain neurotransmitters, which contribute to the presence of the depressive symptoms in the postnatal period. One experimental study [14] investigated the possible role of changes in gonadal steroid levels in postpartum depression by simulating two hormonal conditions related to pregnancy and parturition in euthymic women with and without a history of postpartum depression. Overall, 63% of women with a history of PPD and none of the women in the comparison group developed significant mood symptoms during the withdrawal period suggesting that women with a history of postpartum depression are differentially sensitive to mood-destabilizing effects of gonadal steroids. Author's hypotheses that gonadal steroids function as major neuromodulators, profoundly altering the activity of central nervous system neurotransmitter systems implicated in mood regulation and mood disorders (serotonin, norepinephrine, MAO, GABA, BDNF). Latest studies have shown that peripartum changes in allopregnanolone, a major progesterone metabolite, may play a critical role in PPD through gamma aminobutyric acid (GABA) receptors [15]. Allopregnanolone is a positive allosteric modulator of synaptic and extrasynaptic γ-aminobutyric acid type A (GABAA). The failure of GABAA receptors to adapt to the rapid fluctuations in allopregnanolone levels at childbirth is hypothesized to be a trigger for postpartum depression [16]. Postpartum period is characterized by an accelerated immune response mediated by pro-inflammatory and anti-inflammatory changes that may play a role in the vulnerability

to mood disorders during the peripartum period. However, few studies have directly investigated the role of the immune system in postpartum depression with controversial results [17].

(c) *Cognitive vulnerability*. The impact of perinatal experiences is different depending on personality traits, cognitive style, and the coping strategies used and family, social, and logistic support. Moreover, high perfectionism and particularly high concern over mistakes is a personality dimension associated with major postpartum depression [18]. Also, neuroticism has been described as a predictor for postpartum suicidal ideation [19].

(d) *Psychosocial vulnerability*. The changes in the transition and in the combining of roles together with other psychosocial factors can affect the mood during this period: physical changes and self-image, loss of occupational status, penalization of professional or working life, loneliness or social isolation, and lack of time.

2.3 Course and Recurrence of Postpartum Depression

2.3.1 Course of PPD

Available data on the course of PPD show how that this can be a chronic, non-benign disease. A review of 23 prospective studies about course of PPD (depressive symptoms or clinical diagnosis) described that about 30% of mothers from community samples, diagnosed with PPD, and 50% of mothers with PPD from clinical samples still meet criteria for depression during the first postnatal year and thereafter [20]. Recent study [21] measures the course of postpartum major depressive episode with survival analysis. Results showed that the mean time to achieve partial remission was 28.2 weeks, while the mean time to achieve total remission was 49.4 weeks, almost a year.

Various studies identified the factors associated with chronic course of postpartum depression. The most frequent reported are poor social or partner support, the onset of the episode before or during pregnancy [21] and having a previous history of treated depressive episodes [21]. Principal factors associated with chronic course of PPD are poor social or partner support, childhood sexual abuse [20], having financial problems [21], and previous psychiatric history (especially previous depressive episodes) [20, 21]. Also, onset of symptoms during pregnancy has been identified as a risk factor for most severely and chronic postpartum depression symptoms [20, 22, 23], suggesting that timing of symptom onset could be a useful indicator of prognosis of PPD, with more chronic and/or severe trajectories of postpartum depression in women with high prenatal depressive symptoms. The risk factors associated with prognosis would give us clues for an early intervention in the event of pregnancy symptoms being detected, as well as for the implementation of specific interventions for mothers with PPD at risk of becoming chronic.

2.3.2 Recurrence of PPD

Major depressive disorder is a highly recurrent illness. The risk of the recurrence of major depressive disorder progressively increases with each successive episode and decreases as the duration of recovery increases [24]. Few studies examined recurrence rates of PPD in a follow-up studies of interventions. Our team research conducted a 2-year follow-up study of a cohort of mothers with a major depressive episode in the postpartum period and found a total of 16.5% relapses/recurrences during the 2-year follow-up (6.4% relapses and 10.1% recurrences, a rate that rose to 11.3% considering only mothers who achieved complete remission). Factors that have independently shown an association with relapses/recurrences were the onset of depression before pregnancy and emotional abuse in childhood [25].

Furthermore, women who have suffered from one episode of postpartum-onset major depression experience increased risk for recurrence in the year following another birth, with a recurrence rate of 41% (a quarter in a first 2 postpartum weeks [26]). This risk is higher for women with early-onset PPD (47%) than for women with late-onset PPD (22%) [27].

2.4 Detection and Diagnosis of Postpartum Depression

There is international consensus on the need for screening of postpartum depression. NICE Guideline, one of the principal resources for perinatal mental health disorders, recommends Whooley questions at the first contact of pregnant women with primary care and the early postnatal period [28]:

1. During the past month, have you often been bothered by feeling down, depressed, or hopeless?
2. During the past month, have you often been bothered by little interest or pleasure in doing things?

A positive response to the two-item instrument had a sensitivity of 96% (95% CI 90–99%) and a specificity of 57% (95% CI 53–62%) [29]. If a woman responds positively to one of the questions, it is recommended using the Edinburgh Postnatal Depression Scale (EPDS) as part of a full assessment for perinatal depression. EPDS is the most widely researched and used screening tool for postpartum depression [30]. This brief ten-item tool has been translated and validated into more than 20 languages with different cut-off points (a cut-off score of 13 is most commonly used). In case of positive screening for depression, we must take into account that a clinical evaluation is the gold standard for determining a diagnosis.

The diagnosis of PPD is made by a clinical interview with the patient. So far, there are no imaging or laboratory tests that can help to provide a reliable diagnosis of this disorder. The last version of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [31] classified PPD as “Major Depressive Disorder,

with peripartum onset." This specifier can be applied if onset of mood symptoms occurs during pregnancy or in the 4 weeks following delivery. This definition has caused controversy because it potentially excludes depressive episodes with later onset. In addition, the diagnostic criteria for a major depressive episode do not differ from other periods, and include at least 2 weeks of persistent low mood or anhedonia, as well as at least five of the following: depressed mood, diminished interest or pleasure, changes in appetite, a slowing down of thought and a reduction of physical movement, fatigue or loss of energy, sleep disturbance, feelings of worthlessness or guilt, diminished ability to think or concentrate, indecisiveness, thoughts of death, or suicidal ideation. This classification can lead to underdiagnosis of PPD because some of these symptoms, such as sleep disturbance and appetite disturbance, fatigue, or concentration difficulties need careful inquiry, could be underestimated in a mother with a baby. In addition, postpartum depression is characterized by the presence of prominent anxiety symptoms and restlessness that can lead to diagnostic confusion. It is also essential to assess the presence of suicidal ideation but also infanticide thoughts, and not to confuse infanticide ideas with intrusive thoughts of infant-related harm. Thoughts of harming the infant are described in 41% of depressed mothers and could cause difficulties in mother–baby relationship like fear of being alone with the infant and/or inability to care for the infant [32].

Some of the symptoms we advise should be considered are summarized in Table 2.1 [33].

Table 2.1 Symptoms to consider in women with postpartum depression

Depressive mood for most of the day	"Looking at my baby I can't stop crying." "I see a black future." "I feel I am in an endless tunnel." "I will never be like I was before"
Decrease in interest or ability to enjoy	This difficulty can include enjoying the newborn baby: "I don't feel like being with my baby or I can't be alone with it" or, on the contrary: "To be with my baby, is the only thing that soothes me"
Changes in appetite and weight	Loss of appetite and weight or on the contrary an increase in appetite with anxiety due to eating, and an increase in weight
Changes in sleep pattern	Insomnia unrelated to the waking up of the baby. There can also be excessive sleepiness during the day (hypersomnia)
Feeling of tiredness and loss of energy	
Anxiety and persistent feeling of fear and uneasiness	"I am continuously suffering." "I don't stop thinking that my baby is ill or has a serious illness"
Feelings of blame and/or uselessness	"I am not a good mother." "I don't know how to give him a bath, or change him." "I can't soothe him when he cries." "I would prefer someone to look after him"
Decrease in the ability to concentrate	There can be difficulties to make decisions as regards the nurturing and basic care of the baby. "I go periods without dressing him because I don't know if have to put on a short- or long-sleeved shirt"
Thoughts of harm baby	
Difficulties in bonding with the newborn baby	"I look at him and I feel that it is not my child, I would prefer that someone will look after him"

Postpartum depression should not be confused with the "postpartum/maternity blues," defined as low mood and mild depressive symptoms that are transient and self-limited. The depressive symptoms include sadness, crying, exhaustion, irritability, anxiety, decreased sleep, decreased concentration, and labile mood. These symptoms typically develop within 2–3 days of childbirth, peak over the next few days, and resolve by themselves within 2 weeks of their onset [34]. Postpartum blues are extremely common and are estimated to occur in about 50% or more of women within the first few weeks after delivery [1]. Postpartum blues can be distinguished from a depressive episode by the severity and persistence of the latter. For example, severe obsessional preoccupations, ideas of guilt, and suicidality are not usually present with the blues. If symptoms of "postpartum blues" persist or worsen, it is advisable to consult a specialist for to rule out postnatal depression or other perinatal mental health disorder.

Furthermore, diagnostic assessment should evaluate for a history of manic or hypomanic symptoms, as first-onset postpartum depression can indicate underlying bipolar disorder. A register-based cohort study showed that the risk of bipolar disorder among women with a nonpsychotic postpartum affective episode was higher than that in women with an affective episode outside the postpartum period [35]. Our team conducted a prospective longitudinal study with an 8-year follow-up in a cohort of women diagnosed with postpartum major depressive episode (DSM-IV-TR criteria) at 6 weeks postpartum (index episode). Approximately 12% of women diagnosed with postpartum major depressive episode meet diagnostic criteria of Bipolar Disorder Type II at 8-years of follow-up [36].

2.5 Risk Factors for Postpartum Depression

Significant risk factors for PPD include a history of depression prior to or during pregnancy, anxiety during pregnancy, poor marital relationship, stressful life events, negative attitude toward pregnancy, and lack of social support are significant contributors to postpartum depression. Factors that have shown a stronger association are as follows:

- *Previous psychiatric history*. The current greatest predictor of PPD is the assessment of psychiatric disorders both prior to and during pregnancy, specially previous depressive episodes. Women with history of depressive disorder had high risk for recurrence (43%), especially if discontinued their medication during pregnancy (68%) [37]. It's imperative to ask about previous psychiatric history and consider that women with histories of depression who are euthymic in the context of ongoing antidepressant therapy should be aware of the association of depressive relapse during pregnancy and postpartum with antidepressant discontinuation.
- *Premenstrual syndrome (PMS).* Women with this syndrome are vulnerable to present depressive symptoms due to the changes in the reproductive hormones that are produced in the postnatal period. Current evidence supports a significant

association between history of PMS and development of PPD (OR: 2.20, 95% CI: 1.81–2.68) [38].

- *Stressful life events*. During the pregnancy like, for example, an illness, death, or suffering of a loved one; a difficult or emergency delivery; unplanned pregnancy; to have contradictory feelings; or chronic stressful situations, such as a lack of social support (considered an independent predictor of PPD), financial problems, or low income [39].
- *Situations of abuse or violence*. Women who experience any violence events are at a higher risk of developing PPD (OR 2.04; 95% CI 1.72–2.41). Different types of violence events such as sexual (OR = 1.56; 95% CI: 1.35–1.81), emotional (OR = 1.75; 95% CI: 1.61–1.89), and physical violence (OR = 1.90; 95% CI: 1.36–2.67), as well as domestic (OR = 2.05; 95% CI: 1.50–2.80) or childhood violence (OR = 1.59; 95% CI: 1.34–1.88) also increased the risk of developing PPD [40].

2.6 Consequences of Postpartum Depression

Untreated maternal depression is associated with serious morbidity for the mother, the infant, the mother–baby bonding, and the family system. Recent systematic review evaluate both the infant and the maternal consequences of untreated maternal postpartum depression [41]. The main results are summarized below.

- *Impact on mother:*
  - Poor physical health (physical functioning, bodily pain, and general health perceptions).
  - More consultations to healthcare professionals or emergencies.
  - Lower scores on quality of life.
  - Greater perceived stress, more negative life events, more financial problems, and more illness among close relatives.
  - Lower levels of household functioning (household care).
  - More likely to be at risk for homelessness.
  - More relationship difficulties and therefore lower social function.
  - Poor relationship with partner.
  - More sexual dysfunction during the first year after childbirth.
  - More tobacco use.
  - Increased prevalence of suicidal ideation and thoughts of self-harm.
  - Higher risk of suicide and infanticide.
- *Impact on baby.*
  - Gained less weight (controversial results).
  - Physical health concerns and a greater proportion of childhood illnesses.
  - More diarrheal episodes per year.
  - Greater overall pain in the infants and a stronger infant pain response during routine vaccinations.
  - Febrile disease.

  - Reduced probability of receiving age-appropriate vaccinations or age-appropriate well-child visits.
  - Threefold increased risk of mortality in infants up to 6 months of age, with an approximately twofold increased risk of mortality up to 12 months of age.
  - Increased incidence of infant night-time awakenings.
  - More problematic infant sleep patterns.
  - Higher risk of sleep disorders in children whose mothers had severe and/or chronic depressive symptoms.
  - Impaired motor development in infants at different times of evaluation (6–8 months, 12 months, and 18 months of age. Some studies did not found association.
  - Significant and negative association between maternal postpartum depressive symptoms and cognitive development in children.
  - Infants of depressed mothers also had a significantly higher fear score and higher degrees of emotional disorders, including anxiety disorders.
  - Child behavioral problems at age 2 years, more mood disorders and a more difficult temperament, more internalizing of problems, lower scores on the Communication and Symbolic Behavior Scales Developmental Profile, less mature regulatory behaviors, and higher fear scores that increased behavioral inhibition.
- *Impact on mother–baby interactions.*
  - Poor mother-to-infant bonding.
  - Less closeness, warmth, and sensitivity.
  - More difficulties in their relationships with their child during the first year.
  - More negative perceptions of their relationship with their infant.
  - Chronically depressed mothers were more likely to be insecurely attached.
  - Attachment insecurity or disorganization at 14 months.
  - Discontinue breastfeeding (early interruption of exclusive breastfeeding in the first months).
  - Engage in less-healthy feeding practices with their infant.
  - Less-healthy practices with infant (place their infant in the back-to-sleep position, to use a car seat).
  - Less participation in positive enrichment activities with the child.
  - Lower perception of their competence.
  - Risk of maltreatments (for example spanking their child).

2.7 Treatment of Postpartum Depression

Treatment of PPD should include not only pharmacological and/or psychological interventions of depressive episodes, but also maternal interaction intervention and accurate assessment of potential social vulnerabilities. Likewise, the management of depression and other mental health problems during pregnancy and the postnatal period differs from at other times because of the potential impact of any difficulties and treatments on the woman and the baby. As we have previously described there

are difficulties on the one hand because of the impact of untreated depression on mother and baby, and on the other hand for the risks associated with taking psychotropic medication during pregnancy and breastfeeding.

Clinical guidelines suggest that nonpharmacological treatments such as cognitive behavioral therapy or interpersonal psychotherapy are first-line treatment for mild or moderate depression during perinatal period (pregnant or lactating mother). However, for women with severe depressive episode or women that do not respond to psychotherapy we must considered pharmacological options. Concerns related to pharmacologic treatment of PPD include exposure to medication in breast milk, the effect of treatment on the ability of the mother to care for the baby (e.g., for sedative effects), and the perceived stigma of mother. The optimal way to treat depression during pregnancy and postpartum period remains uncertain. Antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs), are frequently used as a first-line treatment for depressive disorders. These treatments can be used in combination with psychological interventions. Recent publication in *Nature* about postpartum psychiatric disorders [42] developed an algorithm for management of postpartum psychiatric disorders and recommend:

- For mild mood and/or anxiety disorders: Psychological support interventions.
- For severe mood and/or anxiety disorders: Evidence-based psychological treatment (if available) and/or pharmacological therapy. If women are breastfeeding, they recommend the use of sertraline. If women are not breastfeeding, they recommend following evidence-based pharmacotherapeutic guidelines for the treatment of non-postpartum depression or anxiety. Sertraline is often recommended as a first-line pharmacological treatment in breastfeeding women because of its very minimal passage into breast milk. However, in patients with a prior psychiatric history we should consider previous response to other treatment, even those that have less data regarding safety during breastfeeding. Most antidepressant treatments also have minimal passage into breast milk and, therefore, can be used in women with poor response to sertraline or previous response to these drugs.

Other treatments that we must consider during perinatal period are electroconvulsive therapy, especially in case of severe depression and psychotic symptoms, and transcranial magnetic stimulation (TMS). Current evidence of randomized controlled trials showed that TMS could improve depression symptoms and cognitive function in patients with PPD.

Finally, in the latest studies, various randomized placebo-controlled studies were conducted with brexanolone for severe postpartum depression. All studies found a significant improve on depressive symptoms for group treated with allopregnanolone at hour 60 [43]. Since 2019, brexanolone become the first FDA-approved medication for the treatment of PPD. More data is needed, especially its compatibility with breastfeeding and the durability of the antidepressant effect. Recently, Sage Therapeutics has developed an allopregnanolone analog [44] that is in the clinical trial phase and may be a next oral treatment for PPD.

2.8 Conclusions

Postpartum depression is the most common perinatal mental disorder, and it can affect more than 1 in 10 women. The symptoms can be mild, but in some cases the symptoms and the evolution are serious, requiring combined interventions (psychotherapy and psychopharmacology) and even hospital admission in severe cases. The consequences of postpartum depression do not only involve maternal health but also the baby health and mother–baby relationship, which requires a multidisciplinary intervention with a holistic evaluation. We can minimize the risks with an early diagnosis and intervention. For this reason, screening for depression is recommended at all stages of the perinatal period. More research is needed on possible prevention interventions, study of course and impact, and possible therapeutic targets.

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