Is Postpartum Depression Different From Depression Occurring Outside of the Perinatal Period? A Review of the Evidence

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Whether a major depressive episode occurring in the postpartum period (i.e., postpartum depression [PPD]) is sufficiently distinct from major depressive episodes occurring at other times (i.e., major depressive disorder) to warrant a separate diagnosis is a point of debate with substantial clinical significance. The evidence for and against diagnostic distinction for PPD is reviewed with respect to epidemiology, etiology, and treatment. Overall, evidence that PPD is distinct from major depressive disorder is mixed and is largely affected by how the postpartum period is defined. For depression occurring in the early postpartum period (variably defined, but typically with onset in the first 8 weeks), symptom severity, heritability, and epigenetic data suggest that PPD may be distinct, whereas depression occurring in the later postpartum period may be more similar to major depressive disorder occurring outside of the perinatal period. The clinical significance of this debate is considerable given that PPD, the most common complication of childbirth, is associated with immediate and enduring adverse effects on maternal and offspring morbidity and mortality. Future research investigating the distinctiveness of PPD from major depressive disorder in general should focus on the early postpartum period when the rapid decline in hormones contributes to a withdrawal state, requiring profound adjustments in central nervous system function.

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For more than 150 years, a debate has existed on whether depression occurring after a woman gives birth is significantly different from major depressive disorder such that it should be considered a distinct disorder (1). In the mid-1800s, medical case studies began describing a distinctive type of puerperal mental illness that differed from non-puerperal illnesses (1). Then, in the 1960s, a seminal article described a type of "nonclassical depression" that characterized the majority of depressions occurring after childbirth (2). By 1994, the *DSM-IV* included a postpartum specifier for major depressive disorder. This specifier referred to the distinct timing of a major depressive episode in the postpartum period; major depression "with postpartum onset" indicated a depressive episode that started within 4 weeks after birth (3). This specifier persists in the *DSM-5* but now includes episodes that begin in pregnancy, "with peripartum onset" (4).

Perinatal depression (PND) is a term sometimes used interchangeably with postpartum depression (PPD), but it typically refers to major or minor depression that starts during pregnancy or up to 12 months postpartum (5). To date, no definition considers PPD to be truly distinct from major depressive disorder other than the timing of the depressive episode onset (6). Moreover, the varying definitions of PPD and PND conflict on the duration of time that defines the postpartum period, ranging from starting in pregnancy up to 4 weeks postpartum (4) to starting after childbirth up to 6 weeks postpartum (7) or even up to 12 months postpartum (7). Thus, the debate regarding PPD as a distinct disorder is happening in the context of another debate: "what constitutes the postpartum period?" Throughout this review, major depressive disorder refers to a major depressive episode that occurs outside of the perinatal period (the period occurring before pregnancy or more than 12 months after childbirth); in studies focusing on PPD, the reference period is clarified with respect to number of weeks to months after childbirth when possible.

Other systematic limitations to discerning whether PPD is distinct from major depressive disorder include variability among screening tools used for measuring a major depressive episode as well as similarities between depressive symptoms and "normal" postpartum experiences (1, 8). Rather than being signs of depression, fatigue, disrupted sleep, and loss of appetite could come from the challenges of infant care (9). Efforts to create screening and diagnostic tools that consider the overlap between symptoms of depression and postpartum adjustment are hindered by the aforementioned lack of clarity and consistency in defining the time frame that is considered the postpartum period. The Edinburgh Postnatal Depression Scale (EPDS)

(10), the most widely used self-report screening tool for PPD, has lower sensitivity and specificity for detecting a major depressive episode in the postnatal period (variably defined) than a major depressive episode occurring at other times. In other words, the EPDS may be better at detecting major depressive disorder than PPD (for which it was designed) (1).

Despite its potential limitations, in a systematic review of 16 depression scales validated for use among postpartum women, the EPDS was found to be the most favorable of the scales with regard to reliability, validity, sensitivity, specificity, brevity, and the diversity of populations in which the scale was validated (11). The ideal self-report tool for measuring PPD would capture potential unique symptoms of PPD that are missing from major depressive disorder screening instruments, limit the weight of symptoms that overlap with expected postpartum experiences, and have good content validity and reliability (1). Without more sensitive screening tools, PPD remains difficult to distinguish from the exceptionally common "baby blues" as well as from clinical diagnoses with symptom overlap, such as generalized anxiety disorder, obsessive-compulsive disorder, and postpartum psychosis (9). Thus, although the field of psychiatry is aiming for precision medicine, much imprecision still surrounds the methodologies of PPD research in important ways, such as in how the postpartum period is defined as well as in how PPD is measured.

Because psychiatric diagnoses before and during pregnancy are the strongest predictor of PPD (12, 13), it is possible that PPD is biologically and phenotypically distinct from major depressive disorder only in women for whom the index episode of clinical depression is their first and only psychiatric episode. Whether there is a "pure" PPD condition such that women will have a major depressive episode only in the perinatal period is debatable and perhaps less clinically relevant given that the vast majority (78%) of PPD cases are a relapse of major depressive disorder (8). Major depressive disorder is a highly recurrent disorder, and risk of PPD is 20-fold higher in women with a history of major depressive disorder before the birth of their first child (13). Moreover, a history of depression before pregnancy predicts a more severe postpartum depressive episode (14), suggesting that pure PPD, if it exists, may be a subtype with less severe depressive symptoms (9). Nevertheless, these findings suggest that it might be useful to subtype PPD depending on whether the PPD episode is unique (i.e., pure PPD) or whether it occurs in the context of a previous prepregnancy major depressive episode or other psychiatric diagnosis.

With these limitations and challenges in mind, we review recent evidence supporting or refuting the distinctiveness of PPD as a diagnosis, focusing on findings from the past 4 years in order to build on an excellent, previous review by Di Florio and Meltzer-Brody (15). The review we present compares and contrasts PPD and major depressive disorder in terms of epidemiologic and etiologic evidence and effective treatment options. We draw upon this evidence to weigh whether PPD should be considered a distinct disorder and make recommendations for future research.

EPIDEMIOLOGY

Prevalence

Similarities. To directly compare the prevalence rates of PPD and major depressive disorder, we draw on studies that measure both PPD and major depressive disorder within the same population. In general, studies using this approach suggest that the prevalence estimates of PPD and major depressive disorder are similar (16–18). For example, in a study using a nationally representative sample from the United States, the 12-month prevalence rate of major depression did not differ significantly between women who were 0–12 months postpartum and women of childbearing age who were outside of the peripartum period (10.2% vs. 13.1%, respectively) (16). Another study reported similar prevalence rates of PPD (measured 6 weeks after delivery) and major depressive disorder (8.9% vs. 13.6%). These rates did differ statistically (19). However, when this study adjusted for risk factors that were more common in the sample of nonpostpartum women, the risk of depression in the postpartum period actually became greater than the risk of depression outside of the perinatal window (the fluctuations in their findings might be explained by their relatively small sample size) (19). Taken together, these studies suggest that PPD and major depressive disorder are likely comparably prevalent.

Differences. Compared with estimating the prevalence of major depressive disorder, estimating the prevalence of PPD requires additional considerations, such as defining the window of time for the postpartum period and deciding whether to include women with a history of major depressive disorder and/or any other psychiatric disorders. Although focusing on subgroups precludes generalizations to the broader population of postpartum women, doing so can be informative for determining risk and developing targeted therapies. Relatively wide assessment windows (e.g., 12 months postpartum) may obscure whether individuals with a history of depression who experience depression during the postpartum period are experiencing an etiologically distinct major depressive episode unique to the postpartum period or a relapse of a preexisting depressive illness. When studies that define the length of the postpartum window in drastically different ways are grouped together, this may obscure meaningful etiologic differences between subtypes of PPD and mask the true prevalence of PPD triggered by the biological and hormonal events of birth (20).

Symptomatology

Similarities. PPD and major depressive disorder are both heterogeneous disorders, with symptoms presenting in some depression cases but not others (21, 22). Studies comparing

TABLE 1. Similarities and differences in prevalence and symptomatology between PPD and major depressive disorder[a]

Variable	Similarities	Differences
Prevalence	There is no significant difference in 12-month prevalence of depression among postpartum versus nonpostpartum women of childbearing age (16).	For PPD, the prevalence depends on how the postpartum window is defined.
Symptomatology	Both are heterogeneous disorders (21, 22). Both have similar symptom endorsement (16).	Symptom presentations vary by time of onset within perinatal period; anxious, anhedonia depression subtype is more common in the immediate postpartum (23).

[a] PPD, postpartum depression.

PPD and major depressive disorder indicate that some symptoms are either more common or more severe among women with PPD, such as anxiety (postpartum period defined as up to 6 weeks after delivery) (23), aggressive obsessional thoughts (postpartum period not clearly defined) (24), restlessness and agitation (postpartum period defined as up to 3 months after delivery) (25), and impaired concentration and decision making (postpartum period defined as up to 3 months after delivery) (25). In contrast, a study that applied item-response theory to a large, nationally representative sample found that PPD (occurring within 12 months postpartum) and major depressive disorder tend to not differ in their clinical presentation of depressive symptoms (with the exception of psychomotor disturbances, which were more prevalent in major depressive disorder) (16).

Differences. The clinical presentation of depressive symptoms varies depending on the timing of depression onset within the peripartum period (26). Notably, women who experienced depression onset within 8 weeks postpartum were almost four times more likely to present with severe depression compared with women who experienced depression onset during pregnancy. These women with onset of depression within 8 weeks postpartum were also more likely to present with an anxious anhedonia subtype of depression compared with women who experienced depression onset during pregnancy or 8–12 weeks postpartum (26). Although not a direct comparison between PPD and major depressive disorder, this study indicates that unique symptomatic features may characterize PPD with onset in the early postpartum period.

Key Points

Depression is common for women in both the peripartum and nonperipartum periods. Estimating the prevalence rates of PPD is challenging given variability in measurement methods (self-report questionnaires vs. clinician-administered interviews), postpartum period definitions, instruments used to diagnose PPD, and risk factors considered (e.g., previous history of depression). However, most studies comparing prevalence rates of PPD and major depressive disorder show that depression occurs at similar rates. In addition, although some studies have reported that certain symptoms are more prevalent depending on the timing of depression onset, overall, the symptoms for both PPD and major depressive disorder are similar. In the future, epidemiology studies should examine the prevalence and symptomatology of PPD with onset in the early postpartum (i.e., within 8 weeks postpartum) compared with PPD with onset in the later postpartum as well as with major depressive disorder. A summary of key similarities and differences in the epidemiology of PPD and major depressive disorder can be found in Table 1.

ETIOLOGY

PPD and major depressive disorder arise from biological factors (e.g., genetic, neural, and hormonal), psychosocial factors (e.g., stressors), and their interaction (e.g., epigenetics). PPD is unique from major depressive disorder in its timing (following birth), type of psychosocial stressors (e.g., parenting a new infant, relationship adjustments), and potential physiological underpinnings (the drastic elevation of gonadal hormones followed by rapid withdrawal associated with pregnancy and birth, respectively). PPD and major depressive disorder also share many of the same risk factors. In this section, we highlight the ways that PPD and major depressive disorder are similar and different in terms of their genetic, hormonal, neural, psychosocial, and epigenetic risk factors.

Genetic Factors

Similarities. Most research indicates that PPD and major depressive disorder have similar genetic underpinnings. One systematic review posited that the substantial overlap between PPD and major depressive disorder in terms of genetic risk factors (e.g., monoamine oxidase [MAO], catechol-*O*-methyltransferase [COMT], and 5HTT) may indicate that they are essentially the same disorder with a temporal variant (27). Even genes involved in reproductive and stress hormone pathways (e.g., estrogen and glucocorticoid receptor genes) predict both PPD and major depressive disorder (28–31). Overall, PND and non-PND share two thirds of their genetic variance (32).

Differences. A study of twins and nontwin siblings indicated that PPD has a higher heritability than major depressive disorder (32). In particular, the sibling study resulted in an estimated heritability of 40% for postnatal depression

(defined as depression in the year following birth) and 32% for non-PND (32). Because PPD occurs around the time of childbirth, the authors speculated that PPD may have greater homogeneity with respect to putative triggers and therefore higher heritability than depression occurring outside of the perinatal period (32). Heritability studies, however, have had methodological weaknesses that make heritability comparisons less informative. For example, previous studies have compared those who reported at least one PPD episode (who may or may not have had additional major depressive episodes) with those who reported only major depressive episodes outside of the perinatal period (32, 33). This method means that comparisons have been between women who mostly reported a mix of postpartum and nonperipartum major depressive episodes with women who reported only nonperipartum major depressive episodes. A stronger test would include a comparison of the shared genetics between pure PPD and major depressive disorder.

Timing of onset of a major depressive episode in the postpartum period affects how strongly genetics predict PPD. According to two systematic reviews, genetics contribute more to PPD in the early postpartum period (within 6–8 weeks postpartum) than in the late postpartum period (20, 34). For example, the short allele of the serotonin transporter gene predicts PPD in the early (weeks 1–8) but not late (weeks 9–24) postpartum (35), the genetic variants of the glucocorticoid receptor and corticotropin-releasing hormone receptor 1 increase risk for PPD in weeks 2–8 postpartum (28) but not in months 6–8 postpartum (36), and the low activity variants of MAO-A and COMT predict greater depressive symptoms at 6 weeks but not 12 weeks postpartum (37). In one study that correlated the timing of onset with heritability estimates, depressive symptoms that emerged between 6 and 8 weeks postpartum had the highest heritability of PPD (38).

Hormonal Factors

Similarities. Acute and chronic stress commonly triggers major depressive episodes (39, 40). However, depending on the developmental timing, type, and chronicity of stress exposures, these exposures can have an enduring impact on hypothalamic-pituitary-adrenal (HPA) axis function and contribute more broadly to risk for depression (41). Likewise, sex, gonadal steroids, and reproductive status affect stress responsiveness across the life span (41). Patients with PPD and patients with major depressive disorder both present with dysregulated HPA axis function, and this dysregulation is thought to play a role in the pathogenesis of depression (42–45).

Differences. A risk factor unique to PPD involves the hormonal changes specific to the transition from pregnancy to postpartum. Although hormonal fluctuations could serve as a trigger for PPD, PPD has not been consistently associated with hormone levels: measured either as absolute levels or relative levels (e.g., change in hormone from pregnancy to postpartum or ratio of one hormone to another) (46). Instead, empirical evidence suggests that a subset of women show particular sensitivity to the dramatic hormonal fluctuations that occur across the perinatal period (47, 48).

In one study (designed to mimic the hormonal changes associated with pregnancy and postpartum), five out of eight women with a history of PPD developed depressive symptoms when progesterone and estradiol were exogenously elevated and then rapidly withdrawn (49). In contrast, the control group (which only included women who did not have a history of PPD) did not experience increases in depressive symptoms despite undergoing the same hormonal manipulation and achieving similar peripheral hormone levels. Women who are prone to PPD are also more likely to experience depressive symptoms during other times of hormonal perturbations, such as during the premenstrual phase, during menopause, and when taking oral contraceptives (47, 48, 50). These findings suggest that PPD may be prevalent in a subset of women who are particularly sensitive to the mood-destabilizing effects of reproductive hormone exposures and fluctuations, and this subset may be biologically distinct from those prone to only nonperinatal major depressive episodes.

Neural Factors

Similarities. Some of the same neural regions involved in major depressive disorder are also implicated in PPD. For example, PPD (51) and major depressive disorder (52, 53) are both associated with decreased activation in reward-related brain regions (e.g., ventral striatum) in response to positive cues (that are noninfant related). Women with PPD even show reduced activation in reward-related regions in response to cues of their own infant (54, 55), and the extent to which this response is dampened corresponds to PPD severity (54). Given that reward responsivity to the infant is thought to be important for mother-infant attachment (56), reduced responsivity in reward-related regions may explain the mechanism for how PPD can affect the ability to bond with the infant.

Furthermore, similar neurotransmitter systems have been implicated in PPD and major depressive disorder, namely, the serotonergic and gamma-aminobutyric acid (GABAergic) systems. For the serotonergic system, serotonin receptor binding at the 5HT1A receptor is reduced in major depressive disorder (57) and PPD to a similar extent (58) (although direct comparisons within the same study have not been conducted). For the GABAergic system, research suggests that GABAergic system dysfunction (e.g., reduced brain levels of GABA, reduced expression and function of $GABA_A$ receptors) may underlie both major depressive disorder and PPD (44, 59–61). However, greater evidence exists for PPD than major depressive disorder that lower levels of the progesterone metabolite and potent GABAergic neurosteroid, allopregnanolone, may be involved (61, 62). On the

basis of animal studies, one hypothesis is that women with PPD may not have abnormal levels of allopregnanolone but rather impaired restoration of GABAergic tonic inhibition that typically occurs following childbirth and abrupt withdrawal of allopregnanolone (63).

Differences. Relative to patients with major depressive disorder, patients with PPD exhibit decreased activation of many neural regions (64). Whereas patients with major depressive disorder have been shown to have a heightened amygdala response to negative stimuli (65), mothers with PPD demonstrate a blunted amygdala response to (non–infant related) negative stimuli (66, 67), with more severe anxiety and depressive symptoms corresponding to further blunting of amygdala activation (68). This blunted amygdala response has relevance for maternal behavior: in one study, decreased amygdala response predicted greater self-reported hostility toward the infant among mothers with depression (68). Compared with healthy mothers, mothers with depression have an attenuated response to their own infant's cry in brain regions involved in emotion response and regulation (54). In response to negative emotional stimuli and infant distress cues, women with PPD show dampened activation of critical corticolimbic neurocircuitry involved in emotional salience and threat processing (69). This reaction may underlie decreased maternal sensitivity and greater hostility toward the infant among mothers with PPD compared with healthy mothers (70).

Psychosocial Factors

Similarities. Psychosocial factors contribute to both PPD and major depressive disorder risk. In a systematic review, perceived stress (e.g., feeling overwhelmed) and chronic strain (e.g., financial stress, lack of job security or flexibility) were shown to be associated with PPD (71). These types of chronic psychosocial stressors are also associated with major depressive disorder (40). Social support is a stress buffer (72), and low social support has been consistently and strongly associated with PPD (73) as well as major depressive disorder (74).

Differences. Childbirth and infant care are psychosocial stressors that are unique to the postpartum period. According to a meta-analysis of PPD predictors, child care stress and infant temperament have moderate to large effect sizes, and unplanned or unwanted pregnancy has a small effect size (75). The mode of childbirth also affects PPD risk. Having a caesarean section (regardless of whether it was elected or an emergency) increased the odds of PPD compared with delivering vaginally (76). Unlike genetic and hormonal factors that tend to predict PPD in the early postpartum period, psychosocial stress associated with parenting predicts PPD in the late postpartum period (77). Specifically, parenting stress at 6 weeks postpartum was associated with PPD at 3–6 months postpartum (77).

Gene × Environment Interactions and Epigenetic Factors

Similarities. Although few studies have integrated biological and psychosocial predictors of PPD (71), those that have considered biological and psychosocial factors alongside one another have demonstrated that early life stressors, such as childhood abuse and neglect, are some of the strongest environmental risk factors for the development of PPD and major depressive disorder (78, 79), conferring risk, in part, through epigenetic changes (79). Genetic effects on risk of PPD and major depressive disorder often only emerge when either epigenetic effects or gene × environment interactions are considered (27, 80).

Many of the most commonly studied genes in depression (e.g., COMT, MAO-A, brain-derived neurotrophic factor [BDNF], and 5HTTLPR) show associations with PPD that depend on environmental factors such as stressful life events (81), socioeconomic status (82), and season of delivery (83). Some of the same gene × environment interactions and epigenetic effects have been discovered as risk factors for major depressive disorder as well. For example, a pathway that is likely common to major depressive disorder and PPD is that early life stress can induce epigenetic modifications that alter expression and function of the glucocorticoid receptor (84). In another example, carrying one or two copies of the short allele of the serotonin transporter gene increases risk for depression when exposed to stressful life events (85); likewise, carrying the short allele amplifies the negative effect of dissatisfaction with one's current partner as well as negative life events on depressive symptoms in the late postpartum period (86).

Differences. Although circulating levels of gonadal hormones have not been shown to be predictive of PPD, estrogen can induce DNA methylation at estrogen-responsive genes: TTC9B and HP1BP3 (87, 88). DNA methylation at these genes measured in blood samples collected during early pregnancy predicted PPD with more than 80% accuracy (88). Thus, hormonal changes and estrogen signaling during pregnancy and childbirth could lead to epigenetic changes that increase the risk of PPD (81). In another recent study, those who carried both short alleles for the serotonin transporter gene and experienced a large decrease in estradiol from the third trimester to the first week postpartum had an increased risk of depression at 6 weeks postpartum (89). Given the extreme and rapid fluctuations in estrogens from pregnancy to postpartum, these estrogen-driven epigenetic changes and estrogen-dependent mechanisms are likely a more relevant trigger for depression during the postpartum period than non-PND.

Key Points

The causes of PPD and major depressive disorder are multifactorial. The underlying mechanisms are not mutually exclusive and likely interact to create risk for PPD and major depressive disorder. For example, the effects of estradiol and

progesterone on brain neurochemistry, structure, and function are numerous (90), and both hormones affect other biological systems implicated in PPD, such as neural function (91), thyroid function (92), HPA axis function (93), and immune function (94). More research is needed to determine whether there are multiple PPD phenotypes with distinct etiologies and relevant biomarkers (46). Currently, no biomarkers are being used in a clinical setting to diagnosis depression or differentiate between potential underlying causes of depression. Early evidence suggests that measures of methylation of estrogen-responsive genes could be a promising biomarker to prospectively predict PPD (87, 88), but confirmation in larger samples is needed to justify costs.

Timing of depression onset within the postpartum (or even antenatal) period may be indicative of a particular etiology. Major depressive episodes that begin early postpartum seem to be driven by biological factors that are triggered by hormonal changes, whereas psychosocial stressors may be more relevant triggers for major depressive episodes that begin late in the postpartum period. Although PPD and major depressive disorder both arise from many of the same factors (shared genetics involving monoamines as well as stress and reproductive hormones, chronic psychosocial stressors related to a lack of social support, HPA axis dysregulation, blunted reward responsivity, and interactions between the serotonergic system and the environment), some of the underlying mechanisms also seem to be unique to PPD (sensitivity to changes in reproductive hormones, estrogen-dependent epigenetic changes, hypoactivation of the amygdala and neural regions generally, psychosocial stressors related to childbirth and infant care). Currently, it remains an open question whether PPD is a biologically distinct disorder from major depressive disorder, but researchers are forming consortiums to tackle these difficult questions (95). A summary of key similarities and differences in the etiology of PPD and major depressive disorder can be found in Table 2.

TABLE 2. Similarities and differences in putative causes of PPD and major depressive disorder[a]

Factor type	Similarities	Differences
Genetic	Genetic risk factors overlap (27). Genes involved in reproductive and stress hormone pathway are predictors for both types of depression (28–31). Two thirds of the genetic variance are shared (32).	A third of the genetic variance of PPD is distinct from non-PPD (32). PPD has higher heritability than major depressive disorder (32). Genetic contribution to PPD is greater in the early postpartum period (20, 36, 40).
Hormonal	Stress can trigger both types of depression (41). Both have HPA axis dysregulation (43, 44).	Depression is triggered by hormonal fluctuations in a subset of women (48, 60).
Neural	Activation in reward-related regions is decreased (52–54). Reduced serotonin receptor binding and reduced GABA activity have been implicated in both (58–62).	Amygdala response to negative stimuli is heightened for major depressive disorder but blunted for PPD (65–69).
Psychosocial	Both are associated with chronic psychosocial stress (72, 73) and low social support (75, 76).	Stressors, such as childbirth and infant care, are unique to PPD (77).
Epigenetic	Early life stressors are strong risk factors (80, 81, 83, 86, 87).	Estrogen-dependent epigenetic changes are associated with PPD (90–92). Homozygous short alleles for serotonin transporter gene plus large decrease in estradiol predict higher risk of PPD (93).

[a] PPD, postpartum depression; HPA, hypothalamic-pituitary-adrenal; GABA, gamma-aminobutyric acid.

TREATMENT

Treatment Goals and Considerations

Similarities. The main goal of treatment for both PPD and major depressive disorder is the reduction of symptoms, with an ultimate goal of symptom remission. In addition, treatment of both major depressive disorder and PPD aims to improve quality of life (96, 97) and functioning at work and home (98, 99). Treatments for both PPD and major depressive disorder should be feasible, be acceptable, and aim to minimize side effects and adverse outcomes.

Differences. Given that PPD is occurring in the context of childbirth and infant care, treatments for PPD are also aimed at improving maternal care. Compared with mothers without depression, mothers with PPD tend to have lower quality interactions with their infants, consisting of more disengagement and less positive affect (100, 101). Targeting maternal behavior is important for role gratification and self-efficacy in the mother as well as ensuring optimal infant developmental outcomes. PPD is associated with deficits in cognitive and socioemotional development among infants (102, 103), and evidence suggests that the quality of the mother-infant interaction mediates developmental outcomes (104, 105). Thus, ideal treatment of PPD would involve not only inducing symptom remission but also improving maternal care and minimizing the developmental

impact on the child. Although treating major depressive disorder among mothers of older children is also seen as important for improving child outcomes (106), infancy represents a particularly critical developmental period (107), increasing the urgency of achieving treatment goals for PPD.

A second major treatment consideration for PPD that does not apply to major depressive disorder is whether the treatment is compatible with breastfeeding. Although the decision of whether to breastfeed is a decision that should ultimately be made by the mother, breastfeeding continues to be recommended by the American Academy of Pediatrics on the basis of benefits for the mother and the infant (108). Evaluating the pharmacokinetics of medications as it relates to both passage into breast milk and exposure to the infant becomes an important consideration that is uniquely applicable to the treatment of postpartum women. Infant exposure to most antidepressants via breastmilk is within acceptable ranges and does not lead to adverse effects in most cases (109) (although potential long-term effects have not been studied).

Sertraline is often considered a first-line antidepressant for PPD because of the relatively large number of studies demonstrating no detectable drug in breastfeeding infants. However, switching from one antidepressant to an untried medication for a woman who is stable on her current regimen is discouraged because this change increases the risk of relapse (109, 110). Nonpharmacological interventions, such as psychotherapy, bright light therapy, and transcranial magnetic stimulation (TMS), do not expose the infant to medications. Among breastfeeding women with mild depression symptoms who have a desire to avoid medication exposure and who exhibit no risk of harm to self or others, psychotherapy alone may be appropriate. Bright light therapy and TMS have shown some benefit for perinatal mood disorders and are promising areas of investigation (111–113).

Traditional Antidepressants

Similarities. According to expert guidelines and results of randomized controlled trials (RCTs), monoaminergic-based antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), are considered first-line options for the treatment of major depressive disorder and PPD (114–116). Although fewer pharmacologic trials for the treatment of PPD exist, drugs with known efficacy for major depressive disorder also seem to be efficacious for PPD, including sertraline (117), fluoxetine (118), escitalopram (98), fluvoxamine (119), bupropion (120), venlafaxine (121), and nortriptyline (122). Furthermore, the response and remission rates for SSRIs seem to be similar for PPD and major depressive disorder (123).

Differences. Whereas a recent meta-analysis on antidepressant efficacy and tolerability for major depressive disorder analyzed 522 randomized placebo-controlled trials (124), to our knowledge, only nine RCTs of antidepressants have been conducted for PPD (117, 118, 122, 125–130), all of which evaluated SSRIs (120). The trials of non-SSRIs, such as bupropion (120) and venlafaxine (121), have been open label. Thus, the evidence supporting the efficacy of antidepressants is less extensive for PPD than for major depressive disorder, particularly for drugs other than sertraline, which has been investigated more thoroughly because of its relative safety during breastfeeding.

Although the evidence from RCTs has been sufficient to support the use of SSRIs for PPD (116, 123, 131), a small study that compared the charts of 26 women with PPD and 25 women with major depressive disorder found that postpartum women had greater depression severity, took longer to respond to treatment, and were more likely to require multiple antidepressant agents (23). However, the small sample size and study methods (e.g., retrospective chart review of treatment-seeking women) limit the generalizability of these findings. Finally, regarding maternal role functioning, although evidence suggests that antidepressants can improve maternal role gratification, they do not seem to influence actual maternal-infant interactions (132). This observation is in line with research suggesting that the influence of PPD on mother-infant interactions may remain despite symptomatic remission (133, 134).

Hormonal status may influence antidepressant response. In two trials of sertraline (117, 135), women who developed PPD within 4 weeks of delivery had the most robust responses to the drug. These findings, however, should be interpreted cautiously given the relatively small sample size for this subgroup with early-onset PPD. Because the early postpartum period is a time of acute withdrawal of ovarian steroids, including allopregnanolone (a $GABA_A$ receptor modulating neurosteroid with both antidepressant and anxiolytic effects), and because SSRIs have been shown to increase peripheral levels of allopregnanolone, these drugs may be particularly efficacious in women whose symptoms are triggered by hormonal withdrawals. Therefore, women with depression related to hormonal perturbations might be more likely to benefit from the purported SSRI-induced increases in allopregnanolone and serotonin activity, which may be deficient because of postpartum decreases in estradiol (117).

Psychotherapy

Similarities. Similar to major depressive disorder, psychotherapy is considered the treatment of choice for mild to moderate cases of PPD (115); furthermore, many of the same treatments are efficacious for PPD and major depressive disorder, including cognitive-behavioral therapy (CBT) (136), psychodynamic psychotherapy (137–139), and interpersonal psychotherapy (IPT) (140, 141). Psychotherapy interventions may even be efficacious at preventing both major depressive disorder and PPD (142, 143).

Differences. Some evidence suggests that certain types of psychotherapy may be more efficacious depending on whether the treatment is for PPD versus major depressive disorder. For example, whereas evidence suggests that PPD

therapies with more of an interpersonal component, such as IPT, may be more efficacious than CBT (144), CBT and IPT interventions both have efficacy in preventing and treating major depressive disorder (142). This difference may reflect the fact that PPD is occurring within a social context (taking on a new role as a mother while maintaining and adapting other interpersonal relationships).

One intervention that is more unique to PPD is mother-infant psychotherapy, in which the focus is on improving mother-infant interactions (145). These interventions appear effective in alleviating depressive symptoms (146) and potentially improving infant attachment security (147). Although a systematic review noted that both individual and mother-infant psychotherapy interventions reduced PPD symptoms, effect sizes were smaller for improvements in the quality of the mother-infant relationship as well as child development outcomes (146), suggesting that the treatment of PPD may be necessary but not sufficient to have a significant impact on these outcomes (148).

Neuromodulatory Therapies

Similarities. Two major neuromodulatory therapies for major depressive disorder are electroconvulsive therapy (ECT) and TMS. ECT remains one of the most effective psychiatric treatments and is considered more effective than medications for major depressive disorder (149). Systematic reviews and meta-analyses of TMS have also shown impressive effect sizes for major depressive disorder (150, 151). Although the evidence is not as extensive for PPD, it seems to be similarly responsive to TMS (150–152) and ECT (153).

Treatments Specific to PPD

Estradiol. Given that one of the (potential) etiologic differences between major depressive disorder and PPD is hormonal withdrawal across the shift from pregnancy to postpartum, hormonal therapies have been used to treat PPD. Although exogenous sex steroids have also been used to treat major depressive disorder, these therapies seem to be most efficacious when a hypogonadal state exists (e.g., during perimenopause) (154). Two small RCTs (155, 156) and one open-label trial (157) have demonstrated promising results for using transdermal estradiol to relieve symptoms of PPD. Interestingly, two trials of estradiol for PPD showed that the treatment arm actually did not have significantly different estradiol levels from the placebo arm (156, 158). This finding suggests that estradiol treatment may involve stabilizing estradiol fluctuations that can occur postpartum rather than replenishing a deficient state (156). Given that research on estradiol therapy is still limited and estradiol therapy carries the risk of thromboembolic events, it is not currently recommended as a first-line treatment for PPD (116).

Allopregnanolone. In addition to the sudden decrease in estradiol, progesterone and its neurosteroid metabolite, allopregnanolone, are also rapidly withdrawn following childbirth and have been identified as potential targets for the treatment of PPD. The dramatic rise and fall of allopregnanolone during pregnancy and postpartum, respectively, are thought to alter GABAergic tone, although this process may be dysregulated among women with PPD (60–63, 159). Recently, a synthetic version of allopregnanolone, brexanolone (Zulresso; Sage Therapeutics, Cambridge, MA), has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate to severe PPD with onset no later than 4 weeks after delivery (160). Currently, it is available through the Zulresso Risk Evaluation and Mitigation Strategies program (161). Safety data in breastfeeding are currently limited; however, available evidence suggests low levels of potential infant exposure (1%–2% of maternal weight-adjusted dose) (162).

Although the mechanism underlying brexanolone's efficacy for PPD is not known, modulation of GABAergic tone through neurosteroid-mediated GABAergic inhibition has demonstrated efficacy in decreasing depressive symptoms (63, 163). Although substantial evidence implicates GABAergic dysregulation in the pathophysiology of major depressive disorder (for recent reviews, see Maguire [44], Lüscher and Möhler [59], and Frieder et al. [60]), it is not currently known whether neurosteroid preparations such as brexanolone are an effective treatment for major depressive episodes occurring outside of the postpartum period. However, an oral version of allopregnanolone that can be taken once daily is being developed (Zuranolone; Sage Therapeutics, Cambridge, MA) and is currently in phase III clinical trials for PPD and major depressive disorder. A recent phase II clinical trial among patients with major depressive disorder indicated that Zuranolone was more effective than placebo at reducing depressive symptoms at their primary endpoint (day 15 of treatment) (164).

Key Points

The available evidence suggests that the majority of efficacious treatment strategies used for PPD are similar to those commonly used for major depressive disorder. SSRIs and psychotherapy remain cornerstone treatments in both populations. Currently, brexanolone is the only FDA-approved treatment specifically for PPD. Despite the similarities of PPD and major depressive disorder in responsiveness to many of the same treatments, this outcome should not be taken as evidence of similar etiology or pathology given that these treatments are effective for multiple distinct disorders. Antidepressant and psychotherapy efficacy may be due to their ability to influence transdiagnostic aspects of neurobiology related to emotion regulation (165–167). Understanding how the etiologies of PPD and major depressive disorder differ, however, is important in allowing for a more targeted treatment strategy.

For example, despite evidence of GABAergic dysfunction in major depressive disorder, PPD occurs in the context of hormone withdrawal. Targeting GABAergic dysfunction

TABLE 3. Similarities and differences in treatments for PPD and major depressive disorder[a]

Treatment type	Similarities	Differences
Antidepressant treatments	SSRIs are an effective treatment for major depressive disorder and show efficacy for PPD (102, 116, 119–121, 164), with similar response and remission rates for PPD and major depressive disorder (165).	PPD may take longer to respond to treatment (24).
Hormonal therapies	Treatment with exogenous sex steroids is efficacious during hypogonadal states (153). Synthetic allopregnanolone theoretically could be efficacious for all depression types (60, 61, 166).	Evidence exists for estradiol as treatment for PPD (154–156). Synthetic allopregnanolone has been shown to be efficacious in treating PPD (61).
Psychotherapies	Interpersonal psychotherapy (141, 142) and other psychotherapies (136–140) improve depressive symptoms.	For PPD, psychotherapies with an interpersonal component may have greater efficacy than other psychotherapies (143).
Neuromodulatory therapies	Both are similarly responsive to TMS (149–151) and ECT (152).	

[a] PPD, postpartum depression; SSRIs, selective serotonin reuptake inhibitors; TMS, transcranial magnetic stimulation; ECT, electroconvulsive therapy.

may be more effective for PPD, particularly in the early postpartum period. Furthermore, given the significant changes in interpersonal roles that come with motherhood, IPT may be particularly beneficial for PPD (144). Finally, the unique challenges of parenting a newborn may be best addressed through mother-infant interventions. Ongoing study of these and newer interventions will be essential to ensure that treatment options are effective in relieving PPD symptoms, improving maternal role functioning, and optimizing child outcomes. A summary of key similarities and differences in the treatment of PPD and major depressive disorder can be found in Table 3.

CONCLUSIONS

We have reviewed the most recent literature on epidemiology, etiology, and treatments to characterize the state of the evidence on whether PPD should be considered a distinct disorder from major depressive disorder (Box 1). Although the evidence for late-onset PPD is mixed, a growing literature indicates that PPD with onset proximal to childbirth may be distinct from major depressive disorder with respect to symptom severity, hormone contributions, heritability, epigenetic mechanisms, and response to standard and novel treatment interventions. Depending on whether a woman breastfeeds, hormones tend to return to early follicular levels within a week, and ovulation may begin again within 4–12 weeks (47). Given this timeline during which hormones return to prepregnancy levels and cyclicity, there is a rationale for considering the early postpartum window as a distinct period of risk for PPD (71).

Major depressive disorder shares as much genetic variance with PPD (32) as it does with borderline personality disorder, posttraumatic stress disorder, and generalized anxiety disorder (168), which are considered to be distinct disorders from major depressive disorder with respect to current classifications and nomenclature (although, notably, no guidelines exist regarding the degree of distinction in genetic variance necessary for a disorder to be considered distinct). Moreover, many psychiatric disorders, which are currently considered to be distinct, have overlapping symptomatology, putative mechanisms of disease, and treatments. In recent years, the National Institute of Mental Health has promoted transdiagnostic research, suggesting this approach may prove more effective in advancing the science of the pathophysiology and treatment of mental illness more broadly.

Regardless of whether sufficient evidence exists to consider PPD to be a distinct disorder in the *DSM-5*, there are likely benefits to treating early-onset PPD as if it were distinct from major depressive disorder. For example, a separate diagnosis for PPD might lead to more effective screening and greater support for investments in research and development of treatments specifically targeting major depressive episodes with onset during the early postpartum period. Currently, the standard of care for postpartum medical follow-up is at 6 weeks postpartum, which would be inadequate for helping women with onset of illness during the first month following delivery. Screening all women during pregnancy is now recommended by the U.S. Preventive Services Task Force, the American College of Obstetrics and Gynecology, and the American Psychiatric Association. Identifying at-risk women during pregnancy and cases of PPD early could prevent needless suffering.

This review makes clear that many important research questions remain unanswered. Namely, the extent to which the etiologies of PPD and major depressive disorder differ is still largely unknown. Further investigation regarding the pathophysiologic triggers and potential biomarkers for early-onset PPD could inform screening, referral for treatment, and research regarding prevention and targeted drug development. Finally, given that the early postpartum period seems to have unique biological and psychological risk factors, future research comparing PPD and major

BOX 1. Take home messages for clinicians

- Screening and treatment are critical given the negative impact of postpartum depression (PPD) on the mother and child.
- Data are mixed but suggest that PPD with onset within 8 weeks postpartum might be distinct from major depressive disorder.
- Little evidence exists on whether the effectiveness of current treatment strategies for depression differ depending on timing of PPD onset.
- The U.S. Food and Drug Administration recently approved brexanolone as the first medication specifically for the treatment of PPD.

depressive disorder in terms of their epidemiology, etiology, and treatments should focus on PPD with onset in the early postpartum period.

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REFERENCES

1. Jolley SN, Betrus P: Comparing postpartum depression and major depressive disorder: issues in assessment. Issues Ment Health Nurs 2007; 28:765–780
2. Pitt B: "Atypical" depression following childbirth. Br J Psychiatry 1968; 114:1325–1335
3. Wisner KL, Moses-Kolko EL, Sit DKY: Postpartum depression: a disorder in search of a definition. Arch Women Ment Health 2010; 13:37–40
4. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Arlington, VA, American Psychiatric Publishing, 2013
5. Gavin NI, Gaynes BN, Lohr KN, et al: Perinatal depression: a systematic review of prevalence and incidence. Obstet Gynecol 2005; 106:1071–1083
6. O'Hara MW, Engeldinger J: Treatment of postpartum depression: recommendations for the clinician. Clin Obstet Gynecol 2018; 61: 604–614
7. The *ICD-10* Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva, World Health Organization, 1992
8. Holden J: The role of health visitors in postnatal depression. Int Rev Psychiatry 1996; 8:79–86
9. Kettunen P, Koistinen E, Hintikka J: Is postpartum depression a homogenous disorder: time of onset, severity, symptoms and hopelessness in relation to the course of depression. BMC Pregnancy Childbirth 2014; 14:402
10. Cox JL, Holden JM, Sagovsky R: Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry 1987; 150:782–786
11. Walker LO, Gao J, Xie B: Postpartum psychosocial and behavioral health: a systematic review of self-administered scales validated for postpartum women in the United States. Womens Health Issues 2015; 25:586–600
12. Guintivano J, Manuck T, Meltzer-Brody S: Predictors of postpartum depression: a comprehensive review of the last decade of evidence. Clin Obstet Gynecol 2018; 61:591–603
13. Silverman ME, Reichenberg A, Savitz DA, et al: The risk factors for postpartum depression: a population-based study. Depress Anxiety 2017; 34:178–187
14. Fisher SD, Wisner KL, Clark CT, et al: Factors associated with onset timing, symptoms, and severity of depression identified in the postpartum period. J Affect Disord 2016; 203:111–120
15. Di Florio A, Meltzer-Brody S: Is postpartum depression a distinct disorder? Curr Psychiatry Rep 2015; 17:76
16. Hoertel N, López S, Peyre H, et al: Are symptom features of depression during pregnancy, the postpartum period and outside the peripartum period distinct? Results from a nationally representative sample using item response theory (IRT). Depress Anxiety 2015; 32:129–140
17. Cox JL, Murray D, Chapman G: A controlled study of the onset, duration and prevalence of postnatal depression. Br J Psychiatry 1993; 163:27–31
18. Augusto A, Kumar R, Calheiros JM, et al: Post-natal depression in an urban area of Portugal: comparison of childbearing women and matched controls. Psychol Med 1996; 26:135–141
19. Eberhard-Gran M, Eskild A, Tambs K, et al: Depression in postpartum and non-postpartum women: prevalence and risk factors. Acta Psychiatr Scand 2002; 106:426–433
20. Payne JL: Genetic basis for postpartum depression; in Biomarkers of Postpartum Psychiatric Disorders. Edited by Payne JL, Osborne LM. Amsterdam, Elsevier, 2020
21. Lux V, Kendler KS: Deconstructing major depression: a validation study of the *DSM-IV* symptomatic criteria. Psychol Med 2010; 40: 1679–1690
22. Postpartum Depression: Action Towards Causes and Treatment (PACT) Consortium: Heterogeneity of postpartum depression: a latent class analysis. Lancet Psychiatry 2015; 2:59–67
23. Hendrick V, Altshuler L, Strouse T, et al: Postpartum and nonpostpartum depression: differences in presentation and response to pharmacologic treatment. Depress Anxiety 2000; 11: 66–72
24. Wisner KL, Peindl KS, Gigliotti T, et al: Obsessions and compulsions in women with postpartum depression. J Clin Psychiatry 1999; 60:176–180
25. Bernstein IH, Rush AJ, Yonkers K, et al: Symptom features of postpartum depression: are they distinct? Depress Anxiety 2008; 25:20–26
26. Putnam KT, Wilcox M, Robertson-Blackmore E, et al: Clinical phenotypes of perinatal depression and time of symptom onset: analysis of data from an international consortium. Lancet Psychiatry 2017; 4:477–485
27. Couto TC, Brancaglion MYM, Alvim-Soares A, et al: Postpartum depression: a systematic review of the genetics involved. World J Psychiatry 2015; 5:103–111
28. Engineer N, Darwin L, Nishigandh D, et al: Association of glucocorticoid and type 1 corticotropin-releasing hormone receptors gene variants and risk for depression during pregnancy and postpartum. J Psychiatr Res 2013; 47:1166–1173
29. Pinsonneault JK, Sullivan D, Sadee W, et al: Association study of the estrogen receptor gene ESR1 with postpartum depression—a pilot study. Arch Women Ment Health 2013; 16: 499–509

30. Ryan J, Scali J, Carrière I, et al: Estrogen receptor alpha gene variants and major depressive episodes. J Affect Disord 2012; 136: 1222–1226
31. Skalkidou A, Poromaa IS, Iliadis SI, et al: Stress-related genetic polymorphisms in association with peripartum depression symptoms and stress hormones: a longitudinal population-based study. Psychoneuroendocrinology 2019; 103:296–305
32. Viktorin A, Meltzer-Brody S, Kuja-Halkola R, et al: Heritability of perinatal depression and genetic overlap with nonperinatal depression. Am J Psychiatry 2016; 173:158–165
33. Treloar SA, Martin NG, Bucholz KK, et al: Genetic influences on post-natal depressive symptoms: findings from an Australian twin sample. Psychol Med 1999; 29:645–654
34. Figueiredo FP, Parada AP, de Araujo LF, et al: The influence of genetic factors on peripartum depression: a systematic review. J Affect Disord 2015; 172:265–273
35. Binder EB, Newport DJ, Zach EB, et al: A serotonin transporter gene polymorphism predicts peripartum depressive symptoms in an at-risk psychiatric cohort. J Psychiatr Res 2010; 44: 640–646
36. Schneider M, Engel A, Fasching PA, et al: Genetic variants in the genes of the stress hormone signalling pathway and depressive symptoms during and after pregnancy. BioMed Res Int 2014; 2014:469278
37. Doornbos B, Dijck-Brouwer DAJ, Kema IP, et al: The development of peripartum depressive symptoms is associated with gene polymorphisms of MAOA, 5-HTT and COMT. Prog Neuropsychopharmacol Biol Psychiatry 2009; 33:1250–1254
38. Forty L, Jones L, Macgregor S, et al: Familiality of postpartum depression in unipolar disorder: results of a family study. Am J Psychiatry 2006; 163:1549–1553
39. Monroe SM, Simons AD: Diathesis-stress theories in the context of life stress research: implications for the depressive disorders. Psychol Bull 1991; 110:406–425
40. Hammen C, Kim EY, Eberhart NK, et al: Chronic and acute stress and the prediction of major depression in women. Depress Anxiety 2009; 26:718–723
41. Bale TL, Epperson CN: Sex differences and stress across the lifespan. Nat Neurosci 2015; 18:1413–1420
42. Magiakou M-A, Mastorakos G, Rabin D, et al: Hypothalamic corticotropin-releasing hormone suppression during the postpartum period: implications for the increase in psychiatric manifestations at this time. J Clin Endocrinol Metab 1996; 81: 1912–1917
43. Otte C, Gold SM, Penninx BW, et al: Major depressive disorder. Nat Rev Dis Primers 2016; 2:16065
44. Maguire J: Neuroactive steroids and GABAergic involvement in the neuroendocrine dysfunction associated with major depressive disorder and postpartum depression. Front Cell Neurosci 2019; 13:83
45. Glynn LM, Davis EP, Sandman CA: New insights into the role of perinatal HPA-axis dysregulation in postpartum depression. Neuropeptides 2013; 47:363–370
46. Schiller CE, Meltzer-Brody S, Rubinow DR: The role of reproductive hormones in postpartum depression. CNS Spectr 2015; 20:48–59
47. Bloch M, Daly RC, Rubinow DR: Endocrine factors in the etiology of postpartum depression. Compr Psychiatry 2003; 44:234–246
48. Bloch M, Rotenberg N, Koren D, et al: Risk factors associated with the development of postpartum mood disorders. J Affect Disord 2005; 88:9–18
49. Bloch M, Schmidt PJ, Danaceau M, et al: Effects of gonadal steroids in women with a history of postpartum depression. Am J Psychiatry 2000; 157:924–930
50. Stewart DE, Boydell KM: Psychologic distress during menopause: associations across the reproductive life cycle. Int J Psychiatry Med 1993; 23:157–162
51. Post C, Leuner B: The maternal reward system in postpartum depression. Arch Women Ment Health 2019; 22:417–429
52. Stoy M, Schlagenhauf F, Sterzer P, et al: Hyporeactivity of ventral striatum towards incentive stimuli in unmedicated depressed patients normalizes after treatment with escitalopram. J Psychopharmacol 2012; 26:677–688
53. Admon R, Pizzagalli DA: Dysfunctional reward processing in depression. Curr Opin Psychol 2015; 4:114–118
54. Laurent HK, Ablow JC: A cry in the dark: depressed mothers show reduced neural activation to their own infant's cry. Soc Cogn Affect Neurosci 2012; 7:125–134
55. Laurent HK, Ablow JC: A face a mother could love: depression-related maternal neural responses to infant emotion faces. Soc Neurosci 2013; 8:228–239
56. Nguyen AJ, Hoyer E, Rajhans P, et al: A tumultuous transition to motherhood: Altered brain and hormonal responses in mothers with postpartum depression. J Neuroendocrinol 2019; 31:e12794
57. Wang L, Zhou C, Zhu D, et al: Serotonin-1A receptor alterations in depression: a meta-analysis of molecular imaging studies. BMC Psychiatry 2016; 16:319
58. Moses-Kolko EL, Wisner KL, Price JC, et al: Serotonin 1A receptor reductions in postpartum depression: a positron emission tomography study. Fertil Steril 2008; 89:685–692
59. Lüscher B, Möhler H: Brexanolone, a neurosteroid antidepressant, vindicates the GABAergic deficit hypothesis of depression and may foster resilience. F1000 Res 2019; 8:751
60. Frieder A, Fersh M, Hainline R, et al: Pharmacotherapy of postpartum depression: current approaches and novel drug development. CNS Drugs 2019; 33:265–282
61. Epperson CN, Gueorguieva R, Czarkowski KA, et al: Preliminary evidence of reduced occipital GABA concentrations in puerperal women: a 1H-MRS study. Psychopharmacology 2006; 186: 425–433
62. Deligiannidis KM, Kroll-Desrosiers AR, Mo S, et al: Peripartum neuroactive steroid and γ-aminobutyric acid profiles in women at-risk for postpartum depression. Psychoneuroendocrinology 2016; 70:98–107
63. Maguire J, Mody I: GABA(A)R plasticity during pregnancy: relevance to postpartum depression. Neuron 2008; 59: 207–213
64. Stickel S, Wagels L, Wudarczyk O, et al: Neural correlates of depression in women across the reproductive lifespan—an fMRI review. J Affect Disord 2019; 246:556–570
65. Hamilton JP, Chen MC, Gotlib IH: Neural systems approaches to understanding major depressive disorder: an intrinsic functional organization perspective. Neurobiol Dis 2013; 52:4–11
66. Silverman ME, Loudon H, Safier M, et al: Neural dysfunction in postpartum depression: an fMRI pilot study. CNS Spectr 2007; 12: 853–862
67. Silverman ME, Loudon H, Liu X, et al: The neural processing of negative emotion postpartum: a preliminary study of amygdala function in postpartum depression. Arch Women Ment Health 2011; 14:355–359
68. Moses-Kolko EL, Perlman SB, Wisner KL, et al: Abnormally reduced dorsomedial prefrontal cortical activity and effective connectivity with amygdala in response to negative emotional faces in postpartum depression. Am J Psychiatry 2010; 167: 1373–1380
69. Moses-Kolko EL, Horner MS, Phillips ML, et al: In search of neural endophenotypes of postpartum psychopathology and disrupted maternal caregiving. J Neuroendocrinol 2014; 26: 665–684
70. Pechtel P, Murray LMM, Brumariu LE, et al: Reactivity, regulation, and reward responses to infant cues among mothers with and without psychopathology: an fMRI review. Transl Dev Psychiatry 2013; 1:19673

71. Yim IS, Tanner Stapleton LR, Guardino CM, et al: Biological and psychosocial predictors of postpartum depression: systematic review and call for integration. Annu Rev Clin Psychol 2015; 11: 99–137
72. Stein ER, Smith BW: Social support attenuates the harmful effects of stress in healthy adult women. Soc Sci Med 2015; 146:129–136
73. Kimmel MC, Bauer A, Meltzer-Brody S: Toward a framework for best practices and research guidelines for perinatal depression research. J Neurosci Res (Epub March 28, 2019).
74. Bulloch AG, Williams JV, Lavorato DH, et al: The relationship between major depression and marital disruption is bidirectional. Depress Anxiety 2009; 26:1172–1177
75. Beck CT: Predictors of postpartum depression: an update. Nurs Res 2001; 50:275–285
76. Yang S-N, Shen L-J, Ping T, et al: The delivery mode and seasonal variation are associated with the development of postpartum depression. J Affect Disord 2011; 132:158–164
77. Venkatesh KK, Phipps MG, Triche EW, et al: The relationship between parental stress and postpartum depression among adolescent mothers enrolled in a randomized controlled prevention trial. Matern Child Health J 2014; 18:1532–1539
78. Guintivano J, Sullivan PF, Stuebe AM, et al: Adverse life events, psychiatric history, and biological predictors of postpartum depression in an ethnically diverse sample of postpartum women. Psychol Med 2018; 48:1190–1200
79. Heim C, Binder EB: Current research trends in early life stress and depression: review of human studies on sensitive periods, gene-environment interactions, and epigenetics. Exp Neurol 2012; 233:102–111
80. Saveanu RV, Nemeroff CB: Etiology of depression: genetic and environmental factors. Psychiatr Clin North Am 2012; 35:51–71
81. Elwood J, Murray E, Bell A, et al: A systematic review investigating if genetic or epigenetic markers are associated with postnatal depression. J Affect Disord 2019; 253:51–62
82. Mitchell C, Notterman D, Brooks-Gunn J, et al: Role of mother's genes and environment in postpartum depression. Proc Natl Acad Sci USA 2011; 108:8189–8193
83. Comasco E, Sylvén SM, Papadopoulos FC, et al: Postpartum depressive symptoms and the BDNF Val66Met functional polymorphism: effect of season of delivery. Arch Women Ment Health 2011; 14:453–463
84. Farrell C, O'Keane V: Epigenetics and the glucocorticoid receptor: a review of the implications in depression. Psychiatry Res 2016; 242:349–356
85. Caspi A, Sugden K, Moffitt TE, et al: Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 2003; 301:386–389
86. Mehta D, Quast C, Fasching PA, et al: The 5-HTTLPR polymorphism modulates the influence on environmental stressors on peripartum depression symptoms. J Affect Disord 2012; 136: 1192–1197
87. Guintivano J, Arad M, Gould TD, et al: Antenatal prediction of postpartum depression with blood DNA methylation biomarkers. Mol Psychiatry 2014; 19:560–567
88. Osborne L, Clive M, Kimmel M, et al: Replication of epigenetic postpartum depression biomarkers and variation with hormone levels. Neuropsychopharmacology 2016; 41:1648–1658
89. Hu J, Zhou B, Li Y, et al: The interaction between estradiol change and the serotonin transporter gene (5-HTTLPR) polymorphism is associated with postpartum depressive symptoms. Psychiatr Genet 2019; 29:97–102
90. Shanmugan S, Epperson CN: Estrogen and the prefrontal cortex: towards a new understanding of estrogen's effects on executive functions in the menopause transition. Hum Brain Mapp 2014; 35: 847–865
91. Engman J, Sundström Poromaa I, Moby L, et al: Hormonal cycle and contraceptive effects on amygdala and salience resting-state networks in women with previous affective side effects on the pill. Neuropsychopharmacology 2018; 43:555–563
92. Santin AP, Furlanetto TW: Role of estrogen in thyroid function and growth regulation. J Thyroid Res 2011; 2011:875125
93. Barel E, Abu-Shkara R, Colodner R, et al: Gonadal hormones modulate the HPA-axis and the SNS in response to psychosocial stress. J Neurosci Res 2018; 96:1388–1397
94. Butts CL, Sternberg EM: Neuroendocrine factors alter host defense by modulating immune function. Cell Immunol 2008; 252: 7–15
95. Guintivano J, Putnam KT, Sullivan PF, et al: Clinical phenotypes of peripartum depression and time of onset: the PACT Consortium; in Biomarkers of Postpartum Psychiatric Disorders. Edited by Payne JL, Osborne L. Cambridge, MA, Academic Press, 2020
96. Badr HE: Postpartum depression and health related quality of life: a necessary assessment. Int J Fam Community Med 2017; 1: 1–8
97. Zimmerman M, McGlinchey JB, Posternak MA, et al: How should remission from depression be defined? The depressed patient's perspective. Am J Psychiatry 2006; 163:148–150
98. Misri S, Abizadeh J, Albert G, et al: Restoration of functionality in postpartum depressed mothers: an open-label study with escitalopram. J Clin Psychopharmacol 2012; 32:729–732
99. Sheehan DV, Nakagome K, Asami Y, et al: Restoring function in major depressive disorder: a systematic review. J Affect Disord 2017; 215:299–313
100. Brummelte S, Galea LA: Postpartum depression: etiology, treatment and consequences for maternal care. Horm Behav 2016; 77: 153–166
101. Lovejoy MC, Graczyk PA, O'Hare E, et al: Maternal depression and parenting behavior: a meta-analytic review. Clin Psychol Rev 2000; 20:561–592
102. Beck CT: The effects of postpartum depression on child development: a meta-analysis. Arch Psychiatr Nurs 1998; 12:12–20
103. Kingston D, Tough S, Whitfield H: Prenatal and postpartum maternal psychological distress and infant development: a systematic review. Child Psychiatry Hum Dev 2012; 43:683–714
104. Caldji C, Tannenbaum B, Sharma S, et al: Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat. Proc Natl Acad Sci USA 1998; 95:5335–5340
105. Milgrom J, Westley DT, Gemmill AW: The mediating role of maternal responsiveness in some longer term effects of postnatal depression on infant development. Infant Behav Dev 2004; 27: 443–454
106. Weissman MM, Pilowsky DJ, Wickramaratne PJ, et al: Remissions in maternal depression and child psychopathology: a STAR*D-child report. JAMA 2006; 295:1389–1398
107. Cirulli F, Berry A, Alleva E: Early disruption of the mother-infant relationship: effects on brain plasticity and implications for psychopathology. Neurosci Biobehav Rev 2003; 27:73–82
108. Section on Breastfeeding: Breastfeeding and the use of human milk. Pediatrics 2012; 129:e827–e841
109. Lanza di Scalea T, Wisner KL: Antidepressant medication use during breastfeeding. Clin Obstet Gynecol 2009; 52:483–497
110. Pinheiro E, Bogen DL, Hoxha D, et al: Sertraline and breastfeeding: review and meta-analysis. Arch Women Ment Health 2015; 18:139–146
111. Deligiannidis KM, Freeman MP: Complementary and alternative medicine therapies for perinatal depression. Best Pract Res Clin Obstet Gynaecol 2014; 28:85–95
112. Swanson LM, Burgess HJ, Zollars J, et al: An open-label pilot study of a home wearable light therapy device for postpartum depression. Arch Women Ment Health 2018; 21:583–586
113. Kim DR, Wang E, McGeehan B, et al: Randomized controlled trial of transcranial magnetic stimulation in pregnant women with major depressive disorder. Brain Stimul 2019; 12:96–102

114. Practice Guideline for the Treatment of Patients With Major Depressive Disorder, 3rd ed. Arlington, VA, American Psychiatric Association, 2010. www.psychiatryonline.com/pracGuide/PracticePDFs/PG_Depression3rdEd.pdfS. Accessed Feb 13, 2020
115. Guille C, Newman R, Fryml LD, et al: Management of postpartum depression. J Midwifery Womens Health 2013; 58:643–653
116. Kim DR, Epperson CN, Weiss AR, et al: Pharmacotherapy of postpartum depression: an update. Expert Opin Pharmacother 2014; 15:1223–1234
117. Hantsoo L, Ward-O'Brien D, Czarkowski KA, et al: A randomized, placebo-controlled, double-blind trial of sertraline for postpartum depression. Psychopharmacology 2014; 231:939–948
118. Appleby L, Warner R, Whitton A, et al: A controlled study of fluoxetine and cognitive-behavioural counselling in the treatment of postnatal depression. BMJ 1997; 314:932–936
119. Suri R, Stowe ZN, Cohen LS, et al: Prospective longitudinal study of predictors of postpartum-onset depression in women with a history of major depressive disorder. J Clin Psychiatry 2017; 78: 1110–1116
120. Nonacs RM, Soares CN, Viguera AC, et al: Bupropion SR for the treatment of postpartum depression: a pilot study. Int J Neuropsychopharmacol 2005; 8:445–449
121. Cohen LS, Viguera AC, Bouffard SM, et al: Venlafaxine in the treatment of postpartum depression. J Clin Psychiatry 2001; 62:592–596
122. Wisner KL, Hanusa BH, Perel JM, et al: Postpartum depression: a randomized trial of sertraline versus nortriptyline. J Clin Psychopharmacol 2006; 26:353–360
123. De Crescenzo F, Perelli F, Armando M, et al: Selective serotonin reuptake inhibitors (SSRIs) for post-partum depression (PPD): a systematic review of randomized clinical trials. J Affect Disord 2014; 152–154:39–44
124. Cipriani A, Furukawa TA, Salanti G, et al: Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 2018; 391:1357–1366
125. Bloch M, Meiboom H, Lorberblatt M, et al: The effect of sertraline add-on to brief dynamic psychotherapy for the treatment of postpartum depression: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2012; 73:235–241
126. Milgrom J, Gemmill AW, Ericksen J, et al: Treatment of postnatal depression with cognitive behavioural therapy, sertraline and combination therapy: a randomised controlled trial. Aust N Z J Psychiatry 2015; 49:236–245
127. Misri S, Reebye P, Corral M, et al: The use of paroxetine and cognitive-behavioral therapy in postpartum depression and anxiety: a randomized controlled trial. J Clin Psychiatry 2004; 65: 1236–1241
128. O'Hara MW, Pearlstein T, Stuart S, et al: A placebo controlled treatment trial of sertraline and interpersonal psychotherapy for postpartum depression. J Affect Disord 2019; 245:524–532
129. Sharp DJ, Chew-Graham CA, Tylee A, et al: A pragmatic randomised controlled trial to compare antidepressants with a community-based psychosocial intervention for the treatment of women with postnatal depression: the RESPOND trial. Health Technol Assess 2010; 14:1–153
130. Yonkers KA, Lin H, Howell HB, et al: Pharmacologic treatment of postpartum women with new-onset major depressive disorder: a randomized controlled trial with paroxetine. J Clin Psychiatry 2008; 69:659–665
131. Thomson M, Sharma V: Therapeutics of postpartum depression. Expert Rev Neurother 2017; 17:495–507
132. Logsdon MC, Wisner K, Hanusa BH: Does maternal role functioning improve with antidepressant treatment in women with postpartum depression? J Womens Health 2009; 18:85–90
133. Stein A, Gath DH, Bucher J, et al: The relationship between postnatal depression and mother-child interaction. Br J Psychiatry 1991; 158:46–52
134. Murray L, Cooper P: Effects of postnatal depression on infant development. Arch Dis Child 1997; 77:99–101
135. Stowe ZN, Casarella J, Landry J, et al: Sertraline in the treatment of women with postpartum major depression. Depression 1995; 3: 49–55
136. Huang L, Zhao Y, Qiang C, et al: Is cognitive behavioral therapy a better choice for women with postnatal depression? A systematic review and meta-analysis. PLoS One 2018; 13:e0205243
137. Cooper PJ, Murray L, Wilson A, et al: Controlled trial of the short- and long-term effect of psychological treatment of postpartum depression. I. Impact on maternal mood. Br J Psychiatry 2003; 182:412–419
138. Murray L, Cooper PJ, Wilson A, et al: Controlled trial of the short- and long-term effect of psychological treatment of postpartum depression: 2. Impact on the mother-child relationship and child outcome. Br J Psychiatry 2003; 182:420–427
139. Soares MC, Mondin T, Silva GDG, et al: Comparison of clinical significance of cognitive-behavioral therapy and psychodynamic therapy for major depressive disorder: a randomized clinical trial. J Nerv Ment Dis 2018; 206:686–693
140. Miniati M, Callari A, Calugi S, et al: Interpersonal psychotherapy for postpartum depression: a systematic review. Arch Women Ment Health 2014; 17:257–268
141. Ravitz P, Watson P, Lawson A, et al: Interpersonal psychotherapy: a scoping review and historical perspective (1974–2017). Harv Rev Psychiatry 2019; 27:165–180
142. van Zoonen K, Buntrock C, Ebert DD, et al: Preventing the onset of major depressive disorder: a meta-analytic review of psychological interventions. Int J Epidemiol 2014; 43:318–329
143. Werner E, Miller M, Osborne LM, et al: Preventing postpartum depression: review and recommendations. Arch Women Ment Health 2015; 18:41–60
144. Sockol LE, Epperson CN, Barber JP: A meta-analysis of treatments for perinatal depression. Clin Psychol Rev 2011; 31:839–849
145. Clark R, Tluczek A, Brown R: A mother-infant therapy group model for postpartum depression. Infant Ment Health J 2008; 29: 514–536
146. Tsivos ZL, Calam R, Sanders MR, et al: Interventions for postnatal depression assessing the mother-infant relationship and child developmental outcomes: a systematic review. Int J Womens Health 2015; 7:429–447
147. Barlow J, Bennett C, Midgley N, et al: Parent-infant psychotherapy for improving parental and infant mental health. Cochrane Database Syst Rev 2015; 1:CD010534
148. Forman DR, O'Hara MW, Stuart S, et al: Effective treatment for postpartum depression is not sufficient to improve the developing mother-child relationship. Dev Psychopathol 2007; 19:585–602
149. UK ECT Review Group: Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. Lancet 2003; 361:799–808
150. Andriotti T, Stavale R, Nafee T, et al: ASSERT trial—how to assess the safety and efficacy of a high frequency rTMS in postpartum depression? A multicenter, double blinded, randomized, placebo-controlled clinical trial. Contemp Clin Trials Commun 2017; 5: 86–91
151. Ganho-Ávila A, Poleszczyk A, Mohamed MMA, et al: Efficacy of rTMS in decreasing postnatal depression symptoms: a systematic review. Psychiatry Res 2019; 279:315–322
152. Brock DG, Demitrack MA, Groom P, et al: Effectiveness of NeuroStar transcranial magnetic stimulation (TMS) in patients with major depressive disorder with postpartum onset. Brain Stimul 2016; 9:e7
153. Gressier F, Rotenberg S, Cazas O, et al: Postpartum electroconvulsive therapy: a systematic review and case report. Gen Hosp Psychiatry 2015; 37:310–314
154. Rubinow DR, Johnson SL, Schmidt PJ, et al: Efficacy of estradiol in perimenopausal depression: so much promise and so few answers. Depress Anxiety 2015; 32:539–549

155. Gregoire AJ, Kumar R, Everitt B, et al: Transdermal oestrogen for treatment of severe postnatal depression. Lancet 1996; 347: 930–933
156. Li HJ, Martinez PE, Li X, et al: Transdermal estradiol for postpartum depression: results from a pilot randomized, double-blind, placebo-controlled study. Arch Women Ment Health (Epub August 1, 2019).
157. Ahokas A, Kaukoranta J, Wahlbeck K, et al: Estrogen deficiency in severe postpartum depression: successful treatment with sublingual physiologic 17beta-estradiol: a preliminary study. J Clin Psychiatry 2001; 62:332–336
158. Wisner KL, Sit DK, Moses-Kolko EL, et al: Transdermal estradiol treatment for postpartum depression: a pilot, randomized trial. J Clin Psychopharmacol 2015; 35:389–395
159. Deligiannidis KM, Fales CL, Kroll-Desrosiers AR, et al: Resting-state functional connectivity, cortical GABA, and neuroactive steroids in peripartum and peripartum depressed women: a functional magnetic resonance imaging and spectroscopy study. Neuropsychopharmacology 2019; 44:546–554
160. Meltzer-Brody S, Deligiannidis KM, Colquhoun H, et al: Brexanolone injection for postpartum depression. Curr Psychiatr 2019; 18:43–48
161. What Is the ZULRESSO REMS (Risk Evaluation and Mitigation Strategies)? Cambridge, MA, Sage Therapeutics, 2019
162. ZULRESSO: Full Prescribing Information. Cambridge, MA, Sage Therapeutics, 2019
163. Meltzer-Brody S, Colquhoun H, Riesenberg R, et al: Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet 2018; 392:1058–1070
164. Gunduz-Bruce H, Silber C, Kaul I, et al: Trial of SAGE-217 in patients with major depressive disorder. N Engl J Med 2019; 381:903–911
165. Novick AM: Antidepressant psychopharmacology and the social brain. Psychiatry 2011; 74:72–86
166. Shou H, Yang Z, Satterthwaite TD, et al: Cognitive behavioral therapy increases amygdala connectivity with the cognitive control network in both MDD and PTSD. Neuroimage Clin 2017; 14: 464–470
167. Umemori J, Winkel F, Didio G, et al: iPlasticity: induced juvenile-like plasticity in the adult brain as a mechanism of antidepressants. Psychiatry Clin Neurosci 2018; 72:633–653
168. Smoller JW: Disorders and borders: psychiatric genetics and nosology. Am J Med Genet B Neuropsychiatr Genet 2013; 162B: 559–578