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The Role of Reproductive Hormones in Postpartum Depression

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Abstract

Despite decades of research aimed at identifying the causes of postpartum depression (PPD), PPD remains common, and the causes are poorly understood. Many have attributed the onset of PPD to the rapid perinatal change in reproductive hormones. Although a number of human and non-human animal studies support the role of reproductive hormones in PPD, several studies have failed to detect an association between hormone concentrations and PPD. The purpose of this review is to examine the hypothesis that fluctuations in reproductive hormone levels during pregnancy and the postpartum period trigger PPD in susceptible women. We discuss and integrate the literature on animal models of PPD and human studies of reproductive hormones and PPD. We also discuss alternative biological models of PPD to demonstrate the potential for multiple PPD phenotypes and to describe the complex interplay of changing reproductive hormones and alterations in thyroid function, immune function, HPA axis function, lactogenic hormones, and genetic expression that may contribute to affective dysfunction. There are three primary lines of inquiry that have addressed the role of reproductive hormones in PPD: non-human animal studies, correlational studies of postpartum hormone levels and mood symptoms, and hormone manipulation studies. Reproductive hormones influence virtually every biological system implicated in PPD, and a subgroup of women seem to be particularly sensitive to the effects of perinatal changes in hormone levels. We propose that these women constitute a “hormone-sensitive” PPD phenotype, which should be studied independent of other PPD phenotypes to identify underlying pathophysiology and develop novel treatment targets.

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Despite decades of research aimed at identifying the causes of postpartum depression (PPD) and developing effective methods of screening, prevention, and treatment, PPD remains common, affecting between 7 and 20% of women following delivery[1]. PPD is one of the most important public health problems that we can address: it not only affects women at a highly vulnerable time, but it also has deleterious effects on children and families. Many have speculated that PPD is caused, at least in part, by the rapid change in the reproductive hormones estradiol and progesterone before and immediately after delivery[2]. Although a number of human and non-human animal studies suggest that changes in reproductive hormone levels contribute to PPD[3–8], several studies have failed to detect an association between hormone concentrations and PPD symptoms[9–11]. For example, cross-sectional human studies examining between-group differences in ovarian hormones levels and depressive symptoms during the postpartum period have failed to demonstrate and association between absolute estrogen and progesterone concentrations and PPD[9–11]. In contrast, studies that have treated PPD with estradiol have successfully reduced depressive symptoms[5,12], and animal studies have demonstrated that estradiol and progesterone withdrawal provoke depression-like behavior[4,7,8].

The mixed results regarding the role of estradiol and progesterone in PPD is likely due to three factors. First, the PPD diagnosis contains enormous variability. A postpartum depressive episode can meet the diagnostic criteria in a number of different ways, which results in women with very different symptom presentations receiving the same diagnosis. Two women could share only one symptom of major depression, experience timing of onset of the episode during very different hormonal conditions (e.g., first trimester of pregnancy versus first week postpartum), and both receive a PPD diagnosis. Thus, PPD likely represents a number of depressive phenotypes, which may in large part account for the difficulty in identifying any biological or hormonal factor central to the disorder.

Second, based on epidemiologic studies of risk, social and psychological factors play a large role in the pathogenesis of PPD. For example, decreased social support, poor quality social support, and poor marital satisfaction increase the risk of PPD[13–15]. The number of previous episodes of depression, a history of PPD, and depression during pregnancy are also significant risk factors for PPD[15–17]. PPD, like any mood disorder, is therefore best seen as a clinical integration of risk and protective factors that culminate in the triggering of a mood episode in the context of a biological (or reproductive) state.

Third, the existing studies have used widely diverging methods to examine how reproductive hormones influence depressive symptoms: some have examined absolute hormone concentrations in those with and without the disorder[9–11], some have examined the change in hormone levels during pregnancy and the immediate postpartum period and the attendant changes in depressive symptoms[10,18], some have administered hormones to well individuals at high risk for PPD[3], and some have used hormones as a treatment for PPD[5,12]. Any biological model of PPD has to account for all three of these problems.

The purpose of this review is to examine the evidence for a reproductive hormone model of PPD in which fluctuating reproductive hormone levels trigger affective dysregulation. We will define PPD and discuss the diagnostic issues that contribute to difficulties in identifying

a single biomarker for the disorder. We will discuss alternative biological models of PPD to demonstrate the potential for multiple PPD phenotypes and to describe the complex interplay of changing reproductive hormones and alterations in thyroid function, immune function, HPA axis function, lactogenic hormones, and genetic expression that may contribute to affective dysfunction. We will present animal models and human studies of reproductive hormones and PPD and discuss methodological issues that have contributed to conflicting findings in the literature. We will provide evidence of a "hormone-sensitive" PPD phenotype, and discuss the potential neurobiological pathophysiology of PPD for this group of women. Finally, we will review human brain imaging and genetic studies as they pertain to the hormonal contribution to affective dysregulation during the perinatal period.

Defining PPD

The DSM-5 expanded the definition of PPD to include major depressive episodes with a perinatal onset as those beginning in either pregnancy or within the first four weeks postpartum[19]. Although PPD and non-perinatal major depressive disorder have the same DSM diagnostic criteria (i.e., depressed mood, anhedonia, sleep and appetite disturbance, impaired concentration, psychomotor disturbance, lethargy, feelings of worthlessness or guilt, and suicidal ideation)[19], the symptoms of psychomotor agitation and lethargy are more prominent in PPD than MDD[20]. Additional symptoms of PPD include mood lability and preoccupation with infant well-being. PPD also is frequently associated with symptoms of anxiety, ruminative thoughts, and panic attacks[21]. Indeed, most women with PPD have comorbid anxiety disorders[21]. Recent estimates suggest that 7% of women experience an episode of major depression in the first three months following delivery, and the prevalence increases to 20% when episodes of minor depression are also included[1]. The majority of existing studies suggest that PPD is no more common than non-postpartum depression[22]; however, the largest epidemiological study to date demonstrated an increased risk of depression during the postpartum period[23].

PPD is distinguished from the postpartum blues, which are defined as normative "mild dysphoria occurring in the first week after delivery"[22]. Also distinct from PPD is postpartum psychosis, which has a rapid onset associated with hallucinations or bizarre delusions, mood swings, disorganized behavior, and cognitive impairment[24,25]. Many cases of postpartum psychosis are manifestations of bipolar disorder[26,27], which may present as mania for the first time during the postpartum period. The perturbation in mood, limited reality testing, and gross functional impairment make postpartum psychosis particularly dangerous for mothers and babies[24].

An important limitation of the DSM criteria for PPD is that it is not mechanistically based, which is why the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) project may be an ideal framework for studying PPD. The RDoC project advocates study of basic dimensions of functioning (e.g., emotion processing) across multiple units of analysis (e.g., genetic risk and epigenetic modification, limbic system, self-reported affective state) in a specific context (e.g., reproductive hormonal state). The RDoC initiative, therefore, allows researchers to go beyond the DSM criteria to identify women who demonstrate patterns affective dysregulation related to reproductive states and examine the

underlying neurobiological pathophysiology. For example, while some previous studies have strictly defined PPD according to the DSM criteria, most have used more inclusive criteria, including episodes of depression that began before or during pregnancy and carried over into the postpartum and episodes with an onset several months following delivery. A study by Forty and colleagues[28] demonstrated that defining PPD onset within 8 weeks of delivery is optimal for studying the biological triggering of affective dysregulation. Using this definition, Deligiannidis et al.[29] identified functional neural correlates of postpartum depressive symptoms that occur in the context of changing reproductive hormone and neurosteroid levels.

Biological Models of PPD in Humans

Reproductive Hormone Model of PPD

Many have hypothesized a role for reproductive hormones in PPD because of the temporal association between the substantial and rapid changes in hormone concentrations that occur at delivery and the onset of depressive symptoms[11]. However, there are several important reasons for hypothesizing that reproductive hormones play a role in PPD. First, reproductive hormones play a major role in basic emotion processing, arousal, cognition, and motivation, and thus, may contribute to PPD indirectly by influencing the psychological and social risk factors. However, reproductive hormones also regulate each of the biological systems implicated in major depression, which suggests that hormones may impact a woman's risk for PPD directly. In the forebrain and hippocampus, ovariectomy decreases and estradiol increases brain-derived neurotrophic factor (BDNF) levels[30], which are decreased by depression and stress and increased by antidepressants[31]. Estradiol also increases cAMP response element-binding (CREB) protein activity[32] and the neurotrophin receptor protein trkA[33], and it decreases GSK-3 beta activity[34] in the rat brain similar to antidepressant medications. Progesterone also regulates neurotransmitter synthesis, release, and transport[35]. For example, progesterone up-regulates BDNF expression in the hippocampus and cerebral cortex[36]. The relevance of gonadal steroids to affective regulation is further suggested by modulatory effects on stress and the HPA axis, neuroplasticity, cellular energetics, immune activation, and cortical activity[37], all processes that have been implicated as dysfunctional in depression.

Of particular note are the manifold effects of gonadal steroids on brain function as revealed by brain imaging studies. These studies, employing positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) in asymptomatic women, have demonstrated that physiologic levels of gonadal steroids modulate the neurocircuitry involved in normal and pathological affective states. In a study of healthy women, regional cerebral blood flow (rCBF) was attenuated in the dorsolateral prefrontal cortex, inferior parietal lobule, and posterior inferior temporal cortex during GnRH agonist-induced hypogonadism, whereas the characteristic pattern of cortical activation reemerged during both estradiol and progesterone addback[38]. Studies of neural activity during the menstrual cycle have compared activation across menstrual phases within subjects. Goldstein and colleagues[39] found increased amygdala activity during the late follicular phase (higher estradiol levels) compared to the early follicular phase (lower estradiol levels), and Protopopescu et al.[40] demonstrated

increased activity in the medial orbitofrontal cortex (a region that exerts inhibitory control over amygdalar function) during the luteal phase (higher estradiol levels) compared with the follicular phase (relatively lower estradiol levels). The opposite was true for the lateral orbitofrontal cortex, suggesting that sensory and evaluative neural functions are suppressed in the days prior to menstruation[40]. Ovarian hormones also modulate neural reward function in humans, with increased activation of the superior orbitofrontal cortex and amygdala during reward anticipation and of the midbrain, striatum, and left ventrolateral prefrontal cortex during reward delivery in the follicular phase (compared with the luteal phase)[41]. Thus, there is evidence that reproductive hormones influence the biological systems and neural circuits implicated in depression directly, suggesting that the hormone instability inherent in the perinatal period could contribute to mood dysregulation in PPD.

Alternative Biological Models

The hormonal changes of pregnancy and the postpartum period do not occur in isolation: several other biological systems are altered during pregnancy and have been implicated in PPD. Alterations in any of these systems may provoke PPD independent of the changing hormonal milieu, which would suggest that there are a number of PPD phenotypes, each with their own relevant biomarkers. Thus far, the search for one biomarker for the general category of PPD has been elusive, and further research is needed to determine whether there are multiple PPD phenotypes with distinct etiologies. It also stands to reason that perturbations of other biological systems act in concert with rapidly changing hormone levels to contribute to affective dysregulation. Indeed, reproductive hormones have been shown modulate all of the other biological systems implicated in PPD: thyroid function[42], lactogenic function[43], the hypothalamic-pituitary-adrenal (HPA) axis[44,45], and the immune system[46]. As such, we will discuss the potential contribution of each of these systems to affective dysregulation during pregnancy and the postpartum period, and we will discuss the evidence of a genetic susceptibility to PPD.

Thyroid hormones have been proposed as a biomarker of PPD in large part because of the presumed relationship between thyroid dysfunction and major depression[47]: depression accompanies thyroid pathologies[48,49], thyroid dysregulation accompanies depression[50,51], and the administration of thyroid hormones is thought to augment and accelerate antidepressant treatment[52,53]. Estrogen increases thyroxine-binding globulin (TBG) and consequently increases circulating thyroxine (T_4) levels[54,55]. Thyroid dysfunction is associated with pregnancy[56] and may contribute to PPD in some women[57,58]. However, previous studies have failed to detect a clear association between thyroid hormone dysregulation and PPD in the majority of patients[59–61].

The lactogenic hormones oxytocin and prolactin have been implicated in PPD[62]. Failed lactation and PPD commonly co-occur, and lactogenic hormones regulate not only the synthesis and secretion of breast milk, but also maternal behavior and mood. Oxytocin, in particular, may account for the shared pathogenesis of unplanned early weaning and PPD[63]. Estrogen and progesterone modulate oxytocin mRNA expression in brain regions associated with maternal behavior and lactation[64,65]. Lower oxytocin levels during the third trimester are associated with increased depressive symptoms during pregnancy[63] and the immediate

postpartum period[66]. In a recent study by Stuebe and colleagues[63], oxytocin secretion during breastfeeding was inversely associated with depression and anxiety symptoms at 8 weeks postpartum. Although depression and anxiety symptoms were not associated with breastfeeding success in this study, reduced oxytocin may predispose women to PPD and subsequently lead to unsuccessful breastfeeding. Moreover, low oxytocin levels in mothers with PPD are associated with low oxytocin levels in fathers and their children, suggesting a potential neuroendocrine mechanism for the increased risk of depression in children of depressed mothers[67]. Lastly, oxytocin has also been examined as a potential treatment for a wide range of psychiatric disorders, including PPD, but with inconsistent findings to date[68,69].

Hypothalamic-pituitary-adrenal (HPA) axis dysfunction has also been implicated in the pathogenesis of PPD. HPA axis hyperactivity is one of the most consistent findings in the neuroendocrinology of depression[70]. Hypercortisolism is associated with depressive symptoms and corrected with antidepressant treatment[70]. Additionally, the HPA axis is dysregulated by stress and trauma[71], both of which are known precipitants of PPD[13,72,73]. Levels of corticotropin-releasing hormone (CRH), ACTH, and cortisol increase substantially during pregnancy and drop four days following delivery[74]. HPA axis function normalizes at approximately 12 weeks postpartum[74]. The effects of pregnancy on HPA axis function may be at least partially attributable to the effects of estrogen on corticosteroid binding globulin[75], CRH gene expression[76], and circulating corticotropin concentrations[44]. Similar to the HPA axis dysregulation seen in nonpuerperal depression, basal concentrations of plasma cortisol are increased in women with PPD, and suppression of cortisol by dexamethasone is blunted[59]. In one study, for women with PPD there was no association between ACTH and cortisol levels in response to a stress test, whereas among non-depressed control women, there was a more regulated association with cortisol levels rising following the increase in ACTH[77]. Some evidence suggests that higher cortisol levels at the end of pregnancy are associated with increased blues symptoms[78]. However, it remains unclear whether HPA dysregulation contributes to the onset of PPD or occurs as an epiphenomenon.

Immune dysregulation has been hypothesized to contribute to the development of PPD[79]. During pregnancy, anti-inflammatory cytokines responsible for immunosuppression are elevated and promote pregnancy maintenance, whereas proinflammatory cytokines are downregulated. Delivery abruptly shifts the immune system into a proinflammatory state, which lasts for several weeks. Patients with depression tend to have higher levels of the proinflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-6[80], and administration of cytokines is associated with the onset of depression[81]. The immune axis is regulated by estradiol. Estradiol modulates cytokine production, cytokine receptor expression, activation of effector cells, both the number and function of dendritic cells and antigen presenting cells, and monocyte and macrophage immune function[82]. Differential patterns of gene expression that are functionally related to differences in immunity have been found to distinguish women with PPD from those without[83]. Although one recent study identified several prenatal immune markers of PPD[84], other studies have failed to detect an association between immune dysfunction and postpartum depressive symptoms[85–87]. Thus, the role of immune function in PPD remains unclear.

Evidence of a genetic vulnerability to PPD has emerged from family, candidate gene, genome-wide, and gene manipulation studies. Family and twin studies suggest that PPD aggregates in families[28,88], is heritable[89], and may be genetically distinct from nonpuerperal depression[89]. Although multiple genes likely contribute to PPD, the role of specific genetic variations remains unclear. Candidate gene studies of PPD have identified several of the same polymorphisms implicated in non-puerperal depression, including the Val66Met polymorphism of the BDNF gene[90,91], the Val158Met polymorphism of the COMT gene[92,93](p-), the BcII polymorphism of the glucocorticoid receptor and the rs242939 polymorphism of the CRH receptor 1[94], the short version of the serotonin-transporter linked polymorphic region (5-HTTLPR) genotype[95,96], three polymorphisms in the serotonin 2A receptor (HTR2A) gene[97], and three polymorphisms at protein kinase C, beta (PRKCB)[98]. There is also evidence of PPD biomarkers that are theoretically distinct from those of MDD and that implicate reproductive hormones. For example, polymorphisms in the estrogen receptor alpha gene (ESR1) have been found to be associated with PPD[98,99]. However, to date, the results of candidate gene studies of MDD and PPD have failed to replicate[100], have not been statistically significant after correcting for multiple comparisons[97,98], and there is little consistency in the specific polymorphisms tested and identified across studies, which means that any one genetic variant or set of genetic variants is of limited utility as a diagnostic indicator. Genomic studies aim to address some of these shortcomings, and there have been a few small genomic studies of PPD to date. In a genome-wide linkage study of 1,210 women, researchers identified genetic variations on chromosomes 1q21.3-q32.1 and 9p24.3-p22.3 that may increase susceptibility to PPD[101]. Of particular relevance here, the strongest implicated gene was Hemicentin 1 (HMCN1), which contains multiple estrogen binding sites. Although the results were no longer significant after accounting for multiple comparisons[101], the association between the rs2891230 polymorphism of the HMCN1 gene and PPD was confirmed by a subsequent candidate gene study[102]. Similarly, a genome-wide association study yielded a third-trimester biomarker panel of 116 transcripts that predicted PPD onset with 88% accuracy in both the discovery sample of 62 women and the independent replication sample of 24 women[103]. Of these transcripts, ESR1 was the only enriched transcription factor binding site, again potentially implicating estrogen in the pathogenesis of PPD[103]. Estrogen-induced DNA methylation change has also been implicated in PPD, which suggests that women with PPD have an enhanced sensitivity to estrogen-based DNA methylation reprogramming[104]. In order to serve as reliable biomarkers of PPD, these genetic variants will require replication in larger, independent samples, which is currently an active area of investigation in the field.

Reproductive Hormone Models of PPD in Rodents

Non-human animal studies largely support the role of reproductive hormones in PPD. Ovariectomized rats treated with 17β-estradiol and progesterone followed by vehicle only, to induce a hormone withdrawal state similar to the rodent postpartum period, show increased immobility during the forced swim test[4,7], a behavioral indicator of despair, and decreased sucrose consumption and preference[105], a behavioral indicator of anhedonia. One recent study demonstrated that estradiol supplementation and withdrawal alone was sufficient to provoke immobility during the forced swim test and anhedonic behavior during lateral

hypothalamic self-stimulation[18]. Increased depression-like behavior during the "postpartum" demonstrated in previous studies could therefore be attributed to estradiol withdrawal alone.

The effects of estradiol withdrawal on depressive behavior in non-human animals are well documented. Following bilateral ovariectomy, rats demonstrate increased immobility during the forced swim test, and these effects are reversed by treatment with estradiol alone[106,107]. In addition, reduced immobility following a single administration of estradiol lasts 2–3 days, and the behavioral effects are the same as those following fluoxetine treatment[108]. The antidepressant effects of estradiol during the forced swim test appear to involve selective actions at intracellular estrogen receptor-β (ERβ) in the ventral tegmental area[109] and, in fact, may require ERβ[110]. In addition, abrupt estradiol withdrawal following sustained high estradiol levels results in elevated brain cortical dehydroepiandrosterone sulfate (DHEA-S), a neuroactive steroid synthesized endogenously in the brain that attenuates GABA-ergic activity and may be relevant to postpartum depressive symptoms[111]. Chronic administration of estradiol leads to dopamine receptor up-regulation and increased presynaptic dopamine activity in the striatum[112–114], which, when followed by abrupt estradiol withdrawal, leads to dysregulation in brain dopaminergic pathways and depressive symptoms[115].

Estradiol-withdrawal models of PPD have two weaknesses: 1) they have low face validity as models of PPD given that the human postpartum period is characterized by a drop in both estradiol and progesterone (whereas progesterone drops before delivery in rodents), and 2) they result in depression without the attendant anxiety often seen in women with PPD[116]. The addition of progesterone to hormone withdrawal models of PPD is relevant given that progesterone withdrawal provokes anxiety. As noted above, progesterone metabolites act on GABA receptors in the brain, producing sedative-like effects by enhancing GABA neurotransmission[117]. Abrupt decreases in progesterone are associated with anxiety[118], and treatment with progesterone reduces anxiety[119]. The anxiolytic effects of progesterone appear to be mediated by the progesterone metabolite allopregnanolone (ALLO)[120]. Indeed, postpartum rats show increased depressive behavior (increased immobility, decreased struggling and swimming) compared with pregnant rats, and this affect appears to be mediated by low hippocampal ALLO levels during the postpartum period[120].

To examine the effects of concurrent estradiol and progesterone withdrawal, Suda et al.[8] created a novel rodent model of PPD by administering hormone levels more consistent with human pregnancy than rat pregnancy. The concurrent withdrawal of estradiol and progesterone resulted in *decreased* immobility during the forced swim test (i.e., less depression-like behavior); however, it also resulted in learned helplessness, which was indicated by a failure to avoid repeated foot shocks[8]. Animals in this study also showed increased anxiety. Taken together, the existing animal models suggest that the abrupt withdrawal of estradiol alone produces behavioral despair and anhedonia, whereas the concurrent withdrawal of progesterone and estradiol produces learned helplessness and anxiety. However, these studies do not explain how the same putative stimulus (i.e., hormone change) is capable of causing depression in some women and not others.

Fluctuating Reproductive Hormone Levels Trigger PPD

There is no consistent or convincing evidence that women who develop PPD experience more rapid postpartum hormone withdrawal, have lower reproductive hormone concentrations during the postpartum period, or experience greater reductions in hormone levels from pregnancy to the postpartum than women without PPD[9–11,29,121]. The onset of depressive symptoms, however, is temporally coincident with the rapid changes in estradiol and progesterone levels that occur at delivery, leading some researchers to view the change in reproductive hormones as a potent stressor in susceptible women[11].

Evidence that a subgroup of women are vulnerable to perinatal changes in reproductive hormones comes from treatment studies examining the effects of administering exogenous estradiol to women at high risk for PPD or those with active PPD symptoms. In a pilot study of 11 women with a history of PPD and no other history of affective disorder, participants were prophylactically administered oral Premarin, a conjugated estrogen, immediately following delivery to prevent estrogen withdrawal and the onset of depressive symptoms[6]. Ten of the 11 women remained well during the postpartum and for the first year following delivery[6]. A later double-blind, placebo-controlled study of 61 women with PPD that began within three months following delivery, showed that women treated with estradiol (*n*=34) (delivered via a transdermal patch) improved significantly more than women who received placebo (*n*=27), although nearly half of the women in both groups were also taking antidepressant medication[5]. A subsequent study examined the effects of estradiol treatment on a group of 23 women with severe postpartum depression, many of whom had attempted treatment with antidepressant medication or psychotherapy without effect[12]. At baseline, 16 of the 23 patients had serum estradiol concentrations consistent with gonadal failure. All women in the study received sublingual estradiol treatment for 8 weeks. After the first week, depressive symptoms significantly decreased, and by the end of the eight weeks all patients had achieved depressive symptom scores consistent with clinical recovery. Although Ahokas et al.[12] suggest that postpartum “gonadal failure” is a risk factor for PPD, they did not compare estradiol levels in women with and without PPD. Instead, their data support the notion that, in susceptible women, low or declining estradiol levels may trigger PPD, while stable or increasing estradiol levels may ameliorate depressive symptoms. Although these treatment studies suggest a role for estradiol in the pathogenesis of PPD, they are small, lacking control groups, and confounded by the effects of stress, lack of sleep, and homeostatic shifts attendant to childbirth.

In order to assess the role of reproductive hormones in PPD directly, Bloch et al.[3] created a scaled-down hormonal model of the puerperium wherein euthymic women with or without a history of PPD were blindly administered high-dose estradiol and progesterone during ovarian suppression and then abruptly withdrawn. Women with a history of PPD showed increasing depressive symptoms during hormone addback and further exacerbation during hormone withdrawal, but women lacking a history of PPD experienced no perturbation of mood despite identical hormonal conditions. Increasing depressive symptoms during both hormone addback and withdrawal among those with a history of PPD is consistent with research demonstrating that one of the biggest risk factors for PPD is depression during pregnancy[15]. The advantage of this design is that the effects of reproductive hormones on

mood were examined without the confounding biological and psychosocial stressors associated with childbirth. The results provide support for a hormone-sensitive PPD phenotype in which reproductive hormone change alone is sufficient to provoke mood dysregulation in otherwise euthymic women.

Some have hypothesized that the source of PPD vulnerability is in abnormal neural responses to the normal perinatal fluctuations in reproductive hormones. PPD is characterized by abnormal activation of the same brain regions implicated in non-puerperal major depression: the amygdala, insula, striatum, orbitofrontal cortex, and dorsomedial prefrontal cortex[122–124]. PPD is also associated with reduced connectivity between the amygdala and prefrontal regions, which implicates dysregulation of the limbic system in the neural pathophysiology of PPD[123]. Despite similar levels of circulating progesterone and ALLO to controls, women with PPD also show reduced resting state functional connectivity between the anterior cingulate cortex, amygdala, hippocampus, and dorsolateral prefrontal cortex in the context of the postnatal decline progesterone and ALLO[29]. These neuroimaging studies suggest that the neural abnormalities associated with PPD are unique to the perinatal period and may be unmasked by changes in circulating reproductive hormone concentrations. Taken together, the results of the human studies are suggestive of a hormone-sensitive PPD phenotype characterized by neural abnormalities present during the puerperium when reproductive hormone concentrations change rapidly.

One potential mechanism by which changing reproductive hormone levels trigger PPD involves neurosteroid regulation of affect. Neurosteroids are metabolites of steroid hormones that are synthesized in the brain and nervous system and modulate γ-aminobutyric acid (GABA) and glutamate. Two neurosteroids in particular play a role in affective dysregulation: dehydroepiandrosterone (DHEA) and ALLO. Abnormal DHEA secretion has been implicated in major depression [126–130], and DHEA is an effective antidepressant in both men and women[131,132]. The majority of research on neurosteroids in reproductive mood disorders, however, has focused on the progesterone metabolite ALLO. There are several reasons to speculate that ALLO plays a role in PPD. ALLO modulates the GABA receptor, which mediates anxiolysis[133]. ALLO supplementation has anxiolytic effects[134–136], whereas ALLO withdrawal produces anxiety and insensitivity to benzodiazepines[118,137]. ALLO levels are decreased in depression and increased with successful antidepressant treatment[138–143]. ALLO also modulates the biological processes dysregulated in major depressive disorder, including HPA axis regulation[144–147], neuroprotection[148,149], and immune function[150]. ALLO also regulates the neural circuits implicated in depression, including the limbic system[151,152].

Cortical GABA and ALLO are reduced in postpartum women, regardless of the presence of PPD, compared with healthy women in the follicular phase[153]. Although there is no evidence of abnormalities in basal circulating ALLO levels in PPD, women with PPD show reduced resting state functional connectivity between the anterior cingulate cortex, amygdala, hippocampus, and dorsolateral prefrontal cortex in the context of the postnatal decline in ALLO[29]. In addition, we recently reported an association between changes in ALLO levels and depressive symptoms during GnRH agonist-induced ovarian suppression and ovarian steroid addback in women with a history of PPD but not in those without such a

history[154]. These studies suggest that, even in the presence of normal absolute levels, perinatal fluctuations in reproductive hormones may precipitate symptoms in a vulnerable subpopulation of women as a result of changing ALLO levels.

The identification of biomarkers in humans is difficult because of a lack of experimental control over the patient's environment and genetic background and inaccessibility of brain tissue required for analysis. Gene manipulation studies in non-human animals can help model how genetic variants and the environment interact to yield a distinct behavioral phenotypes[155]. Animal models that have demonstrated that the behavioral effects of maternal care are associated with gene expression changes that persist into adulthood and can be transmitted across generations provide a potent epigenetic model of PPD[155]. For example, estradiol withdrawal is clearly associated with estradiol-reversible anxiety in a strain-dependent fashion (Schoenrock et al., unpublished manuscript). One genetic knockout model potentially explains both the specificity of affective dysregulation during the perinatal period and also the variation in susceptibility to PPD among women [125]. In this model, Maguire and Mody[125] demonstrated a $GABA_A$ receptor subunit knockout that is behaviorally silent until an animal is exposed to pregnancy and the postpartum state, following which the dam displays depression-like behavior and cannibalizes its young. Thus, reproductive events may unmask the genetic susceptibility to affective dysregulation. Maguire and Mody[125,156,157] observed that alterations in the $GABA_A$ receptor δ-subunit occur as ovarian hormone levels fluctuate during the menstrual cycle, pregnancy, and the postpartum period. During pregnancy, the expression of the $GABA_A$ receptor δ-subunit is downregulated as ALLO levels increase, and at parturition, the expression of the $GABA_A$ receptor δ-subunit recovers in response to rapidly declining neurosteroid levels[157]. The failure to regulate these receptors during pregnancy and the postpartum, consequent to the knockout of the $GABA_A$ receptor δ-subunit, appears to provoke behavioral abnormalities consistent with PPD. Thus, as noted above, $GABA_A$ receptor δ-subunit deficient mice exhibit normal behaviors prior to pregnancy, but they show insensitivity to ALLO during pregnancy, depression-like and anxiety-like behavior, and abnormal maternal behavior[125]. This model suggests that changes in reproductive hormone concentrations during pregnancy and the postpartum are capable of provoking affective dysregulation, particularly in those with a genetically determined susceptibility.

Conclusion

The cross-species role of reproductive hormones in depressive behavior suggests a neuroendocrine pathophysiology for PPD. PPD, as defined in contemporary research, includes depression that began during or before pregnancy; depression that occurred in the context of a childhood trauma history, traumatic labor or delivery, subthreshold thyroid dysfunction, psychosocial stress, or sleep deprivation; and depression that co-occurred with obsessive-compulsive disorder, PTSD, generalized anxiety disorder, or personality pathology. Logic would preclude consideration of all of these as the same disorder; consequently, when attempting to understand the contribution of hormonal signaling to postpartum affective dysregulation, it is therefore necessary to carefully define the study population and attempt to characterize and disentangle individual PPD phenotypes. The extant literature supports the existence of a hormone-sensitive PPD phenotype[3]. In order to

study the clinical and neuroendocrine correlates of this phenotype, some researchers have selected women with a history of PPD and without a history of non-puerperal depressive episodes[3,18]. Although these studies are primarily relevant for understanding the risk of PPD recurrence, they represent the first step toward identifying factors that predict first onset PPD. There is sufficient evidence to suggest that reproductive hormone fluctuations trigger affective dysregulation in sensitive women. Even within the hormone-sensitive phenotype, alterations in multiple biological systems — the immune system, HPA axis, and lactogenic hormones — likely contribute to the pathophysiology of PPD. Studies are underway to disentangle the complex interplay of fluctuating reproductive hormones, neurosteroids, HPA axis reactivity, neural dysfunction, and genetics with a specific focus on identifying genomic, brain, and behavior relationships that contribute to affective dysfunction in the context of specific reproductive states. Consistent with the RDoC mission, this line of research represents not only an opportunity to identify novel treatment targets for PPD but also—critically—the potential to prevent PPD in susceptible women.

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