



Published in final edited form as:

CNS Spectr. 2015 February ; 20(1): 48–59. doi:10.1017/S1092852914000480.

The Role of Reproductive Hormones in Postpartum Depression

Dr. Crystal Edler Schiller, Ph.D.*, **Dr. Samantha Meltzer-Brody, M.D., M.P.H.**, and **Dr. David R. Rubinow, M.D.**

Crystal Edler Schiller* has a Ph.D. from the University of Iowa. Dr. Schiller is an Assistant Professor in the Psychiatry Department at the University of North Carolina at Chapel Hill in Chapel Hill, NC. Samantha Meltzer-Brody has an M.D. from Northwestern University Medical School and an M.P.H. from the University of North Carolina at Chapel Hill. Dr. Meltzer-Brody is an Associate Professor in the Psychiatry Department at the University of North Carolina at Chapel Hill in Chapel Hill, NC. David R. Rubinow has an M.D. from the University of Connecticut School of Medicine. Dr. Rubinow is the Assad Meymandi Distinguished Professor and Chair of the Psychiatry Department at the University of North Carolina at Chapel Hill in Chapel Hill, NC

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.

*Corresponding author at: 234 Medical School Wing D, Campus Box 7160, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC 27599-7160, United States. Tel.: +1 919 966 4810; Fax: +1 919 966 0708. crystal_schiller@med.unc.edu.

Disclosure of Commercial and Non-Commercial Interests

The authors do not have an affiliation with or financial interest in any organization that might pose a conflict of interest.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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 delivery¹. 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 delivery². Although a number of human and non-human animal studies suggest that changes in reproductive hormone levels contribute to PPD³⁻⁸, several studies have failed to detect an association between hormone concentrations and PPD symptoms⁹⁻¹¹. 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 PPD⁹⁻¹¹. 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 PPD¹³⁻¹⁵. The number of previous episodes of depression, a history of PPD, and depression during pregnancy are also significant risk factors for PPD¹⁵⁻¹⁷. 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 disorder⁹⁻¹¹, 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 PPD³, 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 postpartum¹⁹. 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 MDD²⁰. 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 attacks²¹. Indeed, most women with PPD have comorbid anxiety disorders²¹. 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 included¹. The majority of existing studies suggest that PPD is no more common than non-postpartum depression²²; however, the largest epidemiological study to date demonstrated an increased risk of depression during the postpartum period²³.

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 babies²⁴.

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 colleagues²⁸ 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 symptoms¹¹. 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) levels³⁰, which are decreased by depression and stress and increased by antidepressants³¹. Estradiol also increases cAMP response element-binding (CREB) protein activity³² and the neurotrophin receptor protein *trkA*³³, and it decreases GSK-3 beta activity³⁴ in the rat brain similar to antidepressant medications. Progesterone also regulates neurotransmitter synthesis, release, and transport³⁵. For example, progesterone up-regulates BDNF expression in the hippocampus and cerebral cortex³⁶. 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 activity³⁷, 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 addback³⁸. Studies of neural activity during the menstrual cycle have compared activation across menstrual phases within subjects. Goldstein and colleagues³⁹ 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 menstruation⁴⁰. 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 function⁴², lactogenic function⁴³, the hypothalamic-pituitary-adrenal (HPA) axis^{44,45}, and the immune system⁴⁶. 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 depression⁴⁷: 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 (T₄) levels^{54,55}. Thyroid dysfunction is associated with pregnancy⁵⁶ 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 PPD⁶². 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 PPD⁶³. 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 pregnancy⁶³ and the immediate

postpartum period⁶⁶. In a recent study by Stuebe and colleagues⁶³, 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 mothers⁶⁷. 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 depression⁷⁰. Hypercortisolism is associated with depressive symptoms and corrected with antidepressant treatment⁷⁰. Additionally, the HPA axis is dysregulated by stress and trauma⁷¹, 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 delivery⁷⁴. HPA axis function normalizes at approximately 12 weeks postpartum⁷⁴. The effects of pregnancy on HPA axis function may be at least partially attributable to the effects of estrogen on corticosteroid binding globulin⁷⁵, CRH gene expression⁷⁶, and circulating corticotropin concentrations⁴⁴. 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 blunted⁵⁹. 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 ACTH⁷⁷. Some evidence suggests that higher cortisol levels at the end of pregnancy are associated with increased blues symptoms⁷⁸. 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 PPD⁷⁹. 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)-6⁸⁰, and administration of cytokines is associated with the onset of depression⁸¹. 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 function⁸². Differential patterns of gene expression that are functionally related to differences in immunity have been found to distinguish women with PPD from those without⁸³. Although one recent study identified several prenatal immune markers of PPD⁸⁴, other studies have failed to detect an association between immune dysfunction and postpartum depressive symptoms⁸⁵⁻⁸⁷. 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 heritable⁸⁹, and may be genetically distinct from nonpuerperal depression⁸⁹. 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 1⁹⁴, the short version of the serotonin-transporter linked polymorphic region (5-HTTLPR) genotype^{95,96}, three polymorphisms in the serotonin 2A receptor (HTR2A) gene⁹⁷, 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 replicate¹⁰⁰, 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 PPD¹⁰¹. 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 comparisons¹⁰¹, the association between the rs2891230 polymorphism of the HMCN1 gene and PPD was confirmed by a subsequent candidate gene study¹⁰². 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 women¹⁰³. Of these transcripts, ESR1 was the only enriched transcription factor binding site, again potentially implicating estrogen in the pathogenesis of PPD¹⁰³. 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 reprogramming¹⁰⁴. 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 17 β -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 preference¹⁰⁵, 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-stimulation¹⁸. 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 treatment¹⁰⁸. The antidepressant effects of estradiol during the forced swim test appear to involve selective actions at intracellular estrogen receptor- β (ER β) in the ventral tegmental area¹⁰⁹ and, in fact, may require ER β 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 symptoms¹¹¹. 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 symptoms¹¹⁵.

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 PPD¹¹⁶. 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 neurotransmission¹¹⁷. Abrupt decreases in progesterone are associated with anxiety¹¹⁸, and treatment with progesterone reduces anxiety¹¹⁹. 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 period¹²⁰.

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 shocks⁸. 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 women¹¹.

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 symptoms⁶. Ten of the 11 women remained well during the postpartum and for the first year following delivery⁶. 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 medication⁵. 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 effect¹². 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 pregnancy¹⁵. 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 PPD¹²³. 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 ALLO²⁹. 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 anxiolysis¹³³. 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 function¹⁵⁰. 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 phase¹⁵³. 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 ALLO²⁹. 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

history¹⁵⁴. 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 phenotypes¹⁵⁵. 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 PPD¹⁵⁵. 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 women¹²⁵. In this model, Maguire and Mody¹²⁵ 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 levels¹⁵⁷. 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 behavior¹²⁵. 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 phenotype³. 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.

Acknowledgments

We thank Sarah Johnson and Erin Richardson for assisting with the literature review. This work was supported by the UNC Building Interdisciplinary Careers in Women's Health (BIRCWH) Career Development Program (K12 HD001441) and the National Institute of Mental Health of the National Institutes of Health under Award Number R21MH101409.

References

1. Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. *Obstet Gynecol.* 2005; 106(5 Pt 1):1071–83. [PubMed: 16260528]
2. Hendrick V, Altshuler LL, Suri R. Hormonal changes in the postpartum and implications for postpartum depression. *Psychosomatics.* 1998; 39(2):93–101. [PubMed: 9584534]
3. Bloch M, Schmidt PJ, Danaceau M, Murphy J, Nieman L, Rubinow DR. Effects of gonadal steroids in women with a history of postpartum depression. *Am J Psychiatry.* 2000; 157(10831472):924–930. [PubMed: 10831472]
4. Galea LA, Wide JK, Barr AM. Estradiol alleviates depressive-like symptoms in a novel animal model of post-partum depression. *Behav Brain Res.* 2001; 122(1):1–9. [PubMed: 11287071]
5. Gregoire AJ, Kumar R, Everitt B, Henderson AF, Studd JW. Transdermal oestrogen for treatment of severe postnatal depression. *Lancet.* 1996; 347(9006):930–933. [PubMed: 8598756]
6. Sichel DA, Cohen LS, Robertson LM, Rutenberg A, Rosenbaum JF. Prophylactic estrogen in recurrent postpartum affective disorder. *Biol Psychiatry.* 1995; 38(8750040):814–818. [PubMed: 8750040]
7. Stoffel EC, Craft RM. Ovarian hormone withdrawal-induced “depression” in female rats. *Physiol Behav.* 2004; 83(15581673):505–513. [PubMed: 15581673]
8. Suda S, Segi-Nishida E, Newton SS, Duman RS. A postpartum model in rat: behavioral and gene expression changes induced by ovarian steroid deprivation. *Biol Psychiatry.* 2008; 64(18471802):311–319. [PubMed: 18471802]
9. Buckwalter JG, Stanczyk FZ, McCleary CA, et al. Pregnancy, the postpartum, and steroid hormones: effects on cognition and mood. *Psychoneuroendocrinology.* 1999; 24(10098220):69–84. [PubMed: 10098220]
10. Heidrich A, Schleyer M, Spingler H, et al. Postpartum blues: relationship between not-protein bound steroid hormones in plasma and postpartum mood changes. *J Affect Disord.* 1994; 30(8201129):93–98. [PubMed: 8201129]

11. O'Hara MW, Schlechte JA, Lewis DA, Varner MW. Controlled prospective study of postpartum mood disorders: psychological, environmental, and hormonal variables. *J Abnorm Psychol.* 1991; 100(1):63–73. [PubMed: 2005273]
12. Ahokas A, Kaukoranta J, Wahlbeck K, Aito M. Estrogen deficiency in severe postpartum depression: successful treatment with sublingual physiologic 17beta-estradiol: a preliminary study. *J Clin Psychiatry.* 2001; 62(5):332–6. [PubMed: 11411813]
13. Beck CT. Predictors of postpartum depression: an update. *Nurs Res.* 2001; 50(5):275–85. [PubMed: 11570712]
14. Collins NL, Dunkel-Schetter C, Lobel M, Scrimshaw SC. Social support in pregnancy: psychosocial correlates of birth outcomes and postpartum depression. *J Pers Soc Psychol.* 1993; 65(6):1243–58. [PubMed: 8295121]
15. O'Hara MW, Swain AM. Rates and risk of postpartum depression-A meta-analysis. *Int Rev Psychiatry.* 1996; 8(1):37–54.
16. Bloch M, Rotenberg N, Koren D, Klein E. Risk factors for early postpartum depressive symptoms. *Gen Hosp Psychiatry.* 2006; 28(16377359):3–8. [PubMed: 16377359]
17. O'Hara MW, Neunaber DJ, Zekoski EM. Prospective study of postpartum depression: prevalence, course, and predictive factors. *J Abnorm Psychol.* 1984; 93(2):158–71. [PubMed: 6725749]
18. Schiller CE, O'Hara MW, Rubinow DR, Johnson AK. Estradiol modulates anhedonia and behavioral despair in rats and negative affect in a subgroup of women at high risk for postpartum depression. *Physiol Behav.* 2013; 119:137–144. [PubMed: 23770328]
19. American Psychiatric Association, et al. *Diagnostic and Statistical Manual of Mental Disorders.* 5. Arlington, Va: American Psychiatric Publishing; 2013.
20. Bernstein IH, Rush AJ, Yonkers K, et al. Symptom features of postpartum depression: are they distinct? *Depress Anxiety.* 2008; 25(1):20–26. [PubMed: 17187349]
21. Wisner KL, Sit DY, McShea MC, et al. Onset timing, thoughts of self-harm, and diagnoses in postpartum women with screen-positive depression findings. *JAMA Psychiatry.* 2013; 70(5):490–498. [PubMed: 23487258]
22. O'Hara, MW. *Postpartum Depression: Causes and Consequences.* New York: Springer-Verlag; 1995.
23. Vesga-Lopez O, Blanco C, Keyes K, Olfson M, Grant BF, Hasin DS. Psychiatric disorders in pregnant and postpartum women in the United States. *Arch Gen Psychiatry.* 2008; 65(7):805–15. [PubMed: 18606953]
24. Sit D, Rothschild AJ, Wisner KL. A review of postpartum psychosis. *J Womens Health.* 2006; 15(4):352–68.
25. Wisner KL, Peindl K, Hanusa BH. Symptomatology of affective and psychotic illnesses related to childbearing. *J Affect Disord.* 1994; 30(2):77–87. [PubMed: 8201128]
26. Brockington IF, Cernik KF, Schofield EM, Downing AR, Francis AF, Keelan C. Puerperal psychosis: Phenomena and diagnosis. *Arch Gen Psychiatry.* 1981; 38(7):829–833. [PubMed: 7247645]
27. Kendell RE, Chalmers JC, Platz C. Epidemiology of puerperal psychoses. *Br J Psychiatry.* 1987; 150(3651704):662–673. [PubMed: 3651704]
28. 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(9):1549–53. [PubMed: 16946179]
29. Deligiannidis KM, Sikoglu EM, Shaffer SA, et al. GABAergic neuroactive steroids and resting-state functional connectivity in postpartum depression: A preliminary study. *J Psychiatr Res.* 2013; 47(6):816–828. [PubMed: 23499388]
30. Sohrabji F, Miranda RC, Toran-Allerand CD. Estrogen differentially regulates estrogen and nerve growth factor receptor mRNAs in adult sensory neurons. *J Neurosci Off J Soc Neurosci.* 1994; 14(2):459–471.
31. Shimizu E, Hashimoto K, Okamura N, et al. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biol Psychiatry.* 2003; 54(1):70–75. [PubMed: 12842310]

32. Zhou Y, Watters JJ, Dorsa DM. Estrogen rapidly induces the phosphorylation of the cAMP response element binding protein in rat brain. *Endocrinology*. 1996; 137(5):2163–2166. [PubMed: 8612562]
33. Sohrabji F, Greene LA, Miranda RC, Toran-Allerand CD. Reciprocal regulation of estrogen and NGF receptors by their ligands in PC12 cells. *J Neurobiol*. 1994; 25(8):974–988. [PubMed: 7525871]
34. Cardona-Gomez P, Perez M, Avila J, Garcia-Segura L, Wandosell F. Estradiol inhibits GSK3 and regulates interaction of estrogen receptors, GSK3, and beta-catenin in the hippocampus. *Mol Cell Neurosci*. 2004; 25(3):363–373. [PubMed: 15033165]
35. Finocchi C, Ferrari M. Female reproductive steroids and neuronal excitability. *Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol*. 2011; 32 (Suppl 1):S31–35.
36. Pluchino N, Russo M, Santoro AN, Litta P, Cela V, Genazzani AR. Steroid hormones and BDNF. *Neuroscience*. 2013; 239:271–279. [PubMed: 23380505]
37. Rubinow DR, Girdler SS. Hormones, heart disease, and health: individualized medicine versus throwing the baby out with the bathwater. *Depress Anxiety*. 2011; 28(4):282–296. [PubMed: 21456038]
38. Berman KF, Schmidt PJ, Rubinow DR, et al. Modulation of cognition-specific cortical activity by gonadal steroids: a positron-emission tomography study in women. *Proc Natl Acad Sci U S A*. 1997; 94(16):8836–41. [PubMed: 9238064]
39. Goldstein JM, Jerram M, Poldrack R, et al. Hormonal cycle modulates arousal circuitry in women using functional magnetic resonance imaging. *J Neurosci Off J Soc Neurosci*. 2005; 25(40):9309–9316.
40. Protopopescu X, Pan H, Altemus M, et al. Orbitofrontal cortex activity related to emotional processing changes across the menstrual cycle. *Proc Natl Acad Sci U S A*. 2005; 102(44):16060–16065. [PubMed: 16247013]
41. Dreher JC, Schmidt PJ, Kohn P, Furman D, Rubinow D, Berman KF. Menstrual cycle phase modulates reward-related neural function in women. *Proc Natl Acad Sci U S A*. 2007; 104(7):2465–70. [PubMed: 17267613]
42. Santin AP, Furlanetto TW. Role of Estrogen in Thyroid Function and Growth Regulation. *J Thyroid Res*. 2011; 2011:e875125.
43. Schumacher M, Coirini H, Pfaff DW, McEwen BS. Behavioral effects of progesterone associated with rapid modulation of oxytocin receptors. *Science*. 1990; 250(4981):691–694. [PubMed: 2173139]
44. Walf AA, Frye CA. Antianxiety and Antidepressive Behavior Produced by Physiological Estradiol Regimen may be Modulated by Hypothalamic–Pituitary–Adrenal Axis Activity. *Neuropsychopharmacology*. 2005; 30(7):1288–1301. [PubMed: 15756306]
45. Roca CA, Schmidt PJ, Altemus M, et al. Differential menstrual cycle regulation of hypothalamic-pituitary-adrenal axis in women with premenstrual syndrome and controls. *J Clin Endocrinol Metab*. 2003; 88(7):3057–63. [PubMed: 12843143]
46. Butts CL, Sternberg EM. Neuroendocrine factors alter host defense by modulating immune function. *Cell Immunol*. 2008; 252(1–2):7–15. [PubMed: 18329009]
47. Bunevicius R, Kusminskas L, Mickuviene N, Bunevicius A, Pedersen CA, Pop VJM. Depressive disorder and thyroid axis functioning during pregnancy. *World J Biol Psychiatry*. 2009; 10(4):324–329. [PubMed: 19921974]
48. Placidi GPA, Boldrini M, Patronelli A, et al. Prevalence of Psychiatric Disorders in Thyroid Diseased Patients. *Neuropsychobiology*. 1998; 38(4):222–225. [PubMed: 9813461]
49. Gulseren S, Gulseren L, Hekimsoy Z, Cetinay P, Ozen C, Tokatlioglu B. Depression, Anxiety, Health-Related Quality of Life, and Disability in Patients with Overt and Subclinical Thyroid Dysfunction. *Arch Med Res*. 2006; 37(1):133–139. [PubMed: 16314199]
50. Berent D, Zboralski K, Orzechowska A, Galecki P. Thyroid hormones association with depression severity and clinical outcome in patients with major depressive disorder. *Mol Biol Rep*. 2014; 41(4):2419–2425. [PubMed: 24443228]
51. Nemeroff CB, Simon JS, Haggerty JJ Jr, Evans DL. Antithyroid antibodies in depressed patients. *Am J Psychiatry*. 1985; 142(7):840–843. [PubMed: 4014506]

52. Cooper-Kazaz R, Lerer B. Efficacy and safety of triiodothyronine supplementation in patients with major depressive disorder treated with specific serotonin reuptake inhibitors. *Int J Neuropsychopharmacol*. 2008; 11(05):685–699. [PubMed: 18047754]
53. Cooper-Kazaz R, Apter JT, Cohen R, et al. Combined treatment with sertraline and liothyronine in major depression: A randomized, double-blind, placebo-controlled trial. *Arch Gen Psychiatry*. 2007; 64(6):679–688. [PubMed: 17548749]
54. ZB-R, SJBA-D, MLGIF. Changes in thyroid function tests and sex hormone binding globulin associated with treatment by gonadotropin. *Fertil Steril*. 1987; 48(2):318–320. [PubMed: 3111894]
55. Arafah BM. Increased Need for Thyroxine in Women with Hypothyroidism during Estrogen Therapy. *N Engl J Med*. 2001; 344(23):1743–1749. [PubMed: 11396440]
56. Vaidya B, Anthony S, Bilous M, et al. Detection of thyroid dysfunction in early pregnancy: Universal screening or targeted high-risk case finding? *J Clin Endocrinol Metab*. 2007; 92(1):203–207. [PubMed: 17032713]
57. Pedersen CA, Johnson JL, Silva S, et al. Antenatal thyroid correlates of postpartum depression. *Psychoneuroendocrinology*. 2007; 32(3):235–45. [PubMed: 17346901]
58. Pedersen CA, Stern RA, Pate J, Senger MA, Bowes WA, Mason GA. Thyroid and adrenal measures during late pregnancy and the puerperium in women who have been major depressed or who become dysphoric postpartum. *J Affect Disord*. 1993; 29(2–3):201–211. [PubMed: 8300979]
59. Bloch M, Daly RC, Rubinow DR. Endocrine factors in the etiology of postpartum depression. *Compr Psychiatry*. 2003; 44(3):234–46. [PubMed: 12764712]
60. Albarcar G, Sans T, Martín-Santos R, et al. Thyroid function 48h after delivery as a marker for subsequent postpartum depression. *Psychoneuroendocrinology*. 2010; 35(5):738–742. [PubMed: 19939574]
61. Kent GN, Stuckey BG, Allen JR, Lambert T, Gee V. Postpartum thyroid dysfunction: clinical assessment and relationship to psychiatric affective morbidity. *Clin Endocrinol (Oxf)*. 1999; 51(4):429–438. [PubMed: 10583309]
62. Stuebe AM, Grewen K, Pedersen CA, Propper C, Meltzer-Brody S. Failed Lactation and Perinatal Depression: Common Problems with Shared Neuroendocrine Mechanisms? *J Womens Health*. 2011
63. Stuebe AM, Grewen K, Meltzer-Brody S. Association between maternal mood and oxytocin response to breastfeeding. *J Womens Health* 2002. 2013; 22(4):352–361.
64. Amico JA, Crowley RS, Insel TR, Thomas A, O’Keefe JA. Effect of gonadal steroids upon hypothalamic oxytocin expression. *Adv Exp Med Biol*. 1995; 395:23–35. [PubMed: 8713949]
65. Broad KD, Kendrick KM, Sirinathsinghji DJS, Keverne EB. Changes in Oxytocin Immunoreactivity and mRNA Expression in the Sheep Brain during Pregnancy, Parturition and Lactation and in Response to Oestrogen and Progesterone. *J Neuroendocrinol*. 1993; 5(4):435–444. [PubMed: 8401567]
66. Skrudnz M, Bolten M, Nast I, Hellhammer DH, Meinschmidt G. Plasma oxytocin concentration during pregnancy is associated with development of postpartum depression. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol*. 2011; 36(9):1886–93.
67. Apter-Levy Y, Feldman M, Vakart A, Ebstein RP, Feldman R. Impact of maternal depression across the first 6 years of life on the child’s mental health, social engagement, and empathy: The moderating role of oxytocin. *Am J Psychiatry*. 2013; 170(10):1161–1168. [PubMed: 23846912]
68. Kim S, Soeken TA, Cromer SJ, Martinez SR, Hardy LR, Strathearn L. Oxytocin and postpartum depression: Delivering on what’s known and what’s not. *Brain Res*.
69. Mah BL, Van IJzendoorn MH, Smith R, Bakermans-Kranenburg MJ. Oxytocin in postnatally depressed mothers: Its influence on mood and expressed emotion. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013; 40:267–272. [PubMed: 23085508]
70. Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of Depression. *Neuron*. 2002; 34(1):13–25. [PubMed: 11931738]
71. Heim C, Newport DJ, Wagner D, Wilcox MM, Miller AH, Nemeroff CB. The role of early adverse experience and adulthood stress in the prediction of neuroendocrine stress reactivity in women: A multiple regression analysis. *Depress Anxiety*. 2002; 15(3):117–125. [PubMed: 12001180]

72. Records K, Rice MJ. A Comparative Study of Postpartum Depression in Abused and Nonabused Women. *Arch Psychiatr Nurs*. 2005; 19(6):281–290. [PubMed: 16308128]
73. Ross LE, Dennis CL. The prevalence of postpartum depression among women with substance use, an abuse history, or chronic illness: a systematic review. *J Womens Health*. 2009; 18(4):475–86.
74. Mastorakos G, Ilias I. Maternal and fetal hypothalamic-pituitary-adrenal axes during pregnancy and postpartum. *Ann N Y Acad Sci*. 2003; 997:136–49. [PubMed: 14644820]
75. Young EA. Glucocorticoid cascade hypothesis revisited: Role of gonadal steroids. *Depression*. 1995; 3(1–2):20–27.
76. Vamvakopoulos NC, Chrousos GP. Evidence of direct estrogenic regulation of human corticotropin-releasing hormone gene expression. Potential implications for the sexual dimorphism of the stress response and immune/inflammatory reaction. *J Clin Invest*. 1993; 92(4):1896–1902. [PubMed: 8408641]
77. Jolley SN, Elmore S, Barnard KE, Carr DB. Dysregulation of the hypothalamic-pituitary-adrenal axis in postpartum depression. *Biol Res Nurs*. 2007; 8(3):210–22. [PubMed: 17172320]
78. Handley SL, Dunn TL, Waldron G, Baker JM. Tryptophan, cortisol and puerperal mood. *Br J Psychiatry*. 1980; 136:498–508. [PubMed: 7388254]
79. Corwin EJ, Pajer K. The psychoneuroimmunology of postpartum depression. *J Womens Health*. 2008; 17(9):1529–34.
80. Dowlati Y, Herrmann N, Swardfager W, et al. A Meta-Analysis of Cytokines in Major Depression. *Biol Psychiatry*. 2010; 67(5):446–457. [PubMed: 20015486]
81. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol*. 2006; 27(1):24–31. [PubMed: 16316783]
82. Cunningham M, Gilkeson G. Estrogen Receptors in Immunity and Autoimmunity. *Clin Rev Allergy Immunol*. 2011; 40(1):66–73. [PubMed: 20352526]
83. Segman RH, Goltser-Dubner T, Weiner I, et al. Blood mononuclear cell gene expression signature of postpartum depression. *Mol Psychiatry*. 2010; 15(1):93–100. 2. [PubMed: 19581911]
84. Krause D, Jobst A, Kirchberg F, et al. Prenatal immunologic predictors of postpartum depressive symptoms: a prospective study for potential diagnostic markers. *Eur Arch Psychiatry Clin Neurosci*. 2014:1–10. [PubMed: 24370997]
85. Blackmore ER, Moynihan JA, Rubinow DR, Pressman EK, Gilchrist M, O'Connor TG. Psychiatric Symptoms and Proinflammatory Cytokines in Pregnancy. *Psychosom Med*. 2011; 73(8):656–663. [PubMed: 21949424]
86. Blackmore ER, Groth SW, (Din) Chen D-G, Gilchrist MA, O'Connor TG, Moynihan JA. Depressive symptoms and proinflammatory cytokines across the perinatal period in African American women. *J Psychosom Obstet Gynecol*. 2013; 35(1):8–15.
87. Okun ML, Luther J, Prather AA, Perel JM, Wisniewski S, Wisner KL. Changes in sleep quality, but not hormones predict time to postpartum depression recurrence. *J Affect Disord*. 2011; 130(3):378–84. [PubMed: 20708275]
88. Murphy-Eberenz K, Zandi PP, March D, et al. Is perinatal depression familial? *J Affect Disord*. 2006; 90(1):49–55. [PubMed: 16337009]
89. Treloar SA, Martin NG, Bucholz KK, Madden PA, Heath AC. Genetic influences on post-natal depressive symptoms: findings from an Australian twin sample. *Psychol Med*. 1999; 29(3):645–54. [PubMed: 10405086]
90. Figueira P, Malloy-Diniz L, Campos SB, et al. An association study between the Val66Met polymorphism of the BDNF gene and postpartum depression. *Arch Womens Ment Health*. 2010; 13(3):285–289. [PubMed: 20169377]
91. Comasco E, Sylvén SM, Papadopoulos FC, Oreland L, Sundström-Poromaa I, Skalkidou A. Postpartum depressive symptoms and the BDNF Val66Met functional polymorphism: effect of season of delivery. *Arch Womens Ment Health*. 2011; 14(6):453–463. [PubMed: 21997575]
92. Comasco E, Sylvén SM, Papadopoulos FC, Sundström-Poromaa I, Oreland L, Skalkidou A. Postpartum depression symptoms: a case-control study on monoaminergic functional polymorphisms and environmental stressors. *Psychiatr Genet*. 2011; 21(1):19–28. [PubMed: 21099450]

93. Alvim-Soares A, Miranda D, Campos SB, Figueira P, Romano-Silva MA, Correa H. Postpartum depression symptoms associated with Val158Met COMT polymorphism. *Arch Womens Ment Health*. 2013; 16(4):339–340. [PubMed: 23636476]
94. Engineer N, Darwin L, Nishigandh D, Ngianga-Bakwin K, Smith SC, Grammatopoulos DK. Association of glucocorticoid and type 1 corticotropin-releasing hormone receptors gene variants and risk for depression during pregnancy and post-partum. *J Psychiatr Res*. 2013; 47(9):1166–1173. [PubMed: 23726670]
95. Binder EB, Jeffrey Newport D, Zach EB, et al. A serotonin transporter gene polymorphism predicts peripartum depressive symptoms in an at-risk psychiatric cohort. *J Psychiatr Res*. 2010; 44(10):640–6. [PubMed: 20045118]
96. Mitchell C, Notterman D, Brooks-Gunn J, et al. Role of mother’s genes and environment in postpartum depression. *Proc Natl Acad Sci U S A*. 2011; 108(20):8189–93. [PubMed: 21576482]
97. El-Ibiary SY, Hamilton SP, Abel R, Erdman CA, Robertson PA, Finley PR. A pilot study evaluating genetic and environmental factors for postpartum depression. *Innov Clin Neurosci*. 2013; 10(9–10):15–22. [PubMed: 24307977]
98. Costas J, Gratacòs M, Escaramís G, et al. Association study of 44 candidate genes with depressive and anxiety symptoms in post-partum women. *J Psychiatr Res*. 2010; 44(11):717–724. [PubMed: 20092830]
99. Pinsonneault JK, Sullivan D, Sadee W, Soares CN, Hampson E, Steiner M. Association study of the estrogen receptor gene ESR1 with postpartum depression--a pilot study. *Arch Womens Ment Health*. 2013; 16(6):499–509. [PubMed: 23917948]
100. Pinheiro RT, da Coelho FMC, da Silva RA, et al. Association of a serotonin transporter gene polymorphism (5-HTTLPR) and stressful life events with postpartum depressive symptoms: a population-based study. *J Psychosom Obstet Gynaecol*. 2013; 34(1):29–33. [PubMed: 23394411]
101. Mahon PB, Payne JL, MacKinnon DF, et al. Genome-wide linkage and follow-up association study of postpartum mood symptoms. *Am J Psychiatry*. 2009; 166(11):1229–1237. [PubMed: 19755578]
102. Alvim-Soares AM, Miranda DM, Campos SB, Figueira P, Correa H, Romano-Silva MA. HMNC1 gene polymorphism associated with postpartum depression. *Rev Bras Psiquiatr São Paulo Braz* 1999. 2014; 36(1):96–97.
103. Mehta D, Newport DJ, Frishman G, et al. Early predictive biomarkers for postpartum depression point to a role for estrogen receptor signaling. *Psychol Med*. :1–14. FirstView.
104. Guintivano J, Arad M, Gould TD, Payne JL, Kaminsky ZA. Antenatal prediction of postpartum depression with blood DNA methylation biomarkers. *Mol Psychiatry*. 2013
105. Green AD, Barr AM, Galea LAM. Role of estradiol withdrawal in “anhedonic” sucrose consumption: A model of postpartum depression. *Physiol Behav*. 2009; 97(2):259–265. [PubMed: 19258020]
106. Bekku N, Yoshimura H. Animal model of menopausal depressive-like state in female mice: prolongation of immobility time in the forced swimming test following ovariectomy. *Psychopharmacol Berl*. 2005; 183(16228195):300–307.
107. Bernardi M, Vergoni AV, Sandrini M, Tagliavini S, Bertolini A. Influence of ovariectomy, estradiol and progesterone on the behavior of mice in an experimental model of depression. *Physiol Behav*. 1989; 45:1067–1068. [PubMed: 2780868]
108. Estrada-Camarena E, Fernandez-Guasti A, Lopez-Rubalcava C. Antidepressant-like effect of different estrogenic compounds in the forced swimming test. *Neuropsychopharmacology*. 2003; 28(5):830–8. [PubMed: 12637949]
109. Walf AA, Rhodes ME, Frye CA. Antidepressant effects of ERbeta-selective estrogen receptor modulators in the forced swim test. *Pharmacol Biochem Behav*. 2004; 78(3):523–9. [PubMed: 15251261]
110. Walf AA, Frye CA. A review and update of mechanisms of estrogen in the hippocampus and amygdala for anxiety and depression behavior. *Neuropsychopharmacology*. 2006; 31(16554740): 1097–1111. [PubMed: 16554740]

111. Maayan R, Strous RD, Abou-Kaoud M, Weizman A. The effect of 17beta estradiol withdrawal on the level of brain and peripheral neurosteroids in ovariectomized rats. *Neurosci Lett*. 2005; 384(15927368):156–161. [PubMed: 15927368]
112. Bossé R, Rivest R, Di Paolo T. Ovariectomy and estradiol treatment affect the dopamine transporter and its gene expression in the rat brain. *Mol Brain Res*. 1997; 46(1–2):343–346. [PubMed: 9191114]
113. Di Paolo T, Poyet P, Labrie F. Effect of prolactin and estradiol on rat striatal dopamine receptors. *Life Sci*. 1982; 31(25):2921–2929. [PubMed: 7162358]
114. Di Paolo T, Poyet P, Labrie F. Prolactin and estradiol increase striatal dopamine receptor density in intact, castrated and hypophysectomized rats. *Prog Neuropsychopharmacol Biol Psychiatry*. 1982; 6(4–6):377–382. [PubMed: 6891804]
115. Byrnes EM, Byrnes JJ, Bridges RS. Increased sensitivity of dopamine systems following reproductive experience in rats. *Pharmacol Biochem Behav*. 2001; 68(3):481–9. [PubMed: 11325402]
116. Wenzel A, Haugen EN, Jackson LC, Brendle JR. Anxiety symptoms and disorders at eight weeks postpartum. *J Anxiety Disord*. 2005; 19(15686858):295–311. [PubMed: 15686858]
117. Beckley EH, Finn DA. Inhibition of progesterone metabolism mimics the effect of progesterone withdrawal on forced swim test immobility. *Pharmacol Biochem Behav*. 2007; 87(4):412–9. [PubMed: 17597197]
118. Smith SS, Gong QH, Li X, et al. Withdrawal from 3 α -OH-5 α -Pregnan-20-One Using a Pseudopregnancy Model Alters the Kinetics of Hippocampal GABAA-Gated Current and Increases the GABAAR Receptor α 4 Subunit in Association with Increased Anxiety. *J Neurosci*. 1998; 18(14):5275–5284. [PubMed: 9651210]
119. Dennerstein L, Spencer-Gardner C, Gotts G, Brown JB, Smith MA, Burrows GD. Progesterone and the premenstrual syndrome: a double blind crossover trial. *Br Med J*. 1985; 290(3924191):1617–1621. [PubMed: 3924191]
120. Frye CA, Walf AA. Hippocampal 3 α ,5 α -THP may alter depressive behavior of pregnant and lactating rats. *Pharmacol Biochem Behav*. 2004; 78(3):531–540. [PubMed: 15251262]
121. Chatzicharalampous C, Rizo D, Pliatsika P, et al. Reproductive hormones and postpartum mood disturbances in Greek women. *Gynecol Endocrinol*. 2010; 27(8):543–550. [PubMed: 20653338]
122. Silverman ME, Loudon H, Safier M, et al. Neural dysfunction in postpartum depression: an fMRI pilot study. *CNS Spectr*. 2007; 12(11):853–62. [PubMed: 17984858]
123. Moses-Kolko EL, Perlman SB, Wisner KL, James J, Saul AT, Phillips ML. 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(11):1373–80. [PubMed: 20843875]
124. Moses-Kolko EL, Fraser D, Wisner KL, et al. Rapid habituation of ventral striatal response to reward receipt in postpartum depression. *Biol Psychiatry*. 2011; 70(4):395–9. [PubMed: 21507385]
125. Maguire J, Mody I. GABAAR Plasticity during Pregnancy: Relevance to Postpartum Depression. *Neuron*. 2008; 59(2):207–213. [PubMed: 18667149]
126. Goodyer IM, Herbert J, Altham PM, Pearson J, Secher SM, Shiers HM. Adrenal secretion during major depression in 8- to 16-year-olds, I. Altered diurnal rhythms in salivary cortisol and dehydroepiandrosterone (DHEA) at presentation. *Psychol Med*. 1996; 26(2):245–256. [PubMed: 8685281]
127. Yaffe K, Ettinger B, Pressman A, et al. Neuropsychiatric function and dehydroepiandrosterone sulfate in elderly women: a prospective study. *Biol Psychiatry*. 1998; 43(9):694–700. [PubMed: 9583004]
128. Heuser I, Deuschle M, Luppa P, Schweiger U, Standhardt H, Weber B. Increased diurnal plasma concentrations of dehydroepiandrosterone in depressed patients. *J Clin Endocrinol Metab*. 1998; 83(9):3130–3133. [PubMed: 9745415]
129. Michael A, Jenaway A, Paykel ES, Herbert J. Altered salivary dehydroepiandrosterone levels in major depression in adults. *Biol Psychiatry*. 2000; 48(10):989–995. [PubMed: 11082473]

130. Schmidt PJ, Murphy JH, Haq N, Danaceau MA, St Clair L. Basal plasma hormone levels in depressed perimenopausal women. *Psychoneuroendocrinology*. 2002; 27(8):907–920. [PubMed: 12383452]
131. Wolkowitz OM, Reus VI, Keebler A, et al. Double-blind treatment of major depression with dehydroepiandrosterone. *Am J Psychiatry*. 1999; 156(4):646–649. [PubMed: 10200751]
132. Schmidt P, Daly RC, Bloch M, et al. Dehydroepiandrosterone monotherapy in midlife-onset major and minor depression. *Arch Gen Psychiatry*. 2005; 62(2):154–162. [PubMed: 15699292]
133. Majewska MD, Harrison NL, Schwartz RD, Barker JL, Paul SM. Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor. *Science*. 1986; 232(2422758):1004–1007. [PubMed: 2422758]
134. Bitran D, Hilvers RJ, Kellogg CK. Anxiolytic effects of 3 α -hydroxy-5 α [β]-pregnan-20-one: endogenous metabolites of progesterone that are active at the GABAA receptor. *Brain Res*. 1991; 561(1):157–161. [PubMed: 1686744]
135. Wieland S, Lan NC, Mirasedeghi S, Gee KW. Anxiolytic activity of the progesterone metabolite 5 α -pregnan-3 α -ol-20-one. *Brain Res*. 1991; 565(2):263–268. [PubMed: 1688192]
136. Bitran D, Purdy RH, Kellogg CK. Anxiolytic effect of progesterone is associated with increases in cortical allopregnanolone and GABAA receptor function. *Pharmacol Biochem Behav*. 1993; 45(2):423–428. [PubMed: 8392205]
137. Smith SS, Gong QH, Hsu FC, Markowitz RS, ffrench-Mullen JM, Li X. GABA(A) receptor alpha4 subunit suppression prevents withdrawal properties of an endogenous steroid. *Nature*. 1998; 392(6679):926–30. [PubMed: 9582073]
138. Uzunova V, Sheline Y, Davis JM, et al. Increase in the cerebrospinal fluid content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine. *Proc Natl Acad Sci*. 1998; 95(6):3239–3244. [PubMed: 9501247]
139. Romeo E, Ströhle A, Spalletta G, et al. Effects of antidepressant treatment on neuroactive steroids in major depression. *Am J Psychiatry*. 1998; 155(7):910–913. [PubMed: 9659856]
140. Ströhle A, Romeo E, Hermann B, et al. Concentrations of 3 α -reduced neuroactive steroids and their precursors in plasma of patients with major depression and after clinical recovery. *Biol Psychiatry*. 1999; 45(3):274–277. [PubMed: 10023501]
141. Schüle C, Romeo E, Uzunov DP, et al. Influence of mirtazapine on plasma concentrations of neuroactive steroids in major depression and on 3 α -hydroxysteroid dehydrogenase activity. *Mol Psychiatry*. 2005; 11(3):261–272. [PubMed: 16344854]
142. Eser D, Schüle C, Baghai TC, Romeo E, Rupprecht R. Neuroactive Steroids in Depression and Anxiety Disorders: Clinical Studies. *Neuroendocrinology*. 2006; 84(4):244–254. [PubMed: 17159334]
143. Schüle C, Baghai TC, di Michele F, et al. Effects of combination treatment with mood stabilizers and mirtazapine on plasma concentrations of neuroactive steroids in depressed patients. *Psychoneuroendocrinology*. 2007; 32(6):669–680. [PubMed: 17560730]
144. Patchev VK, Shoaib M, Holsboer F, Almeida OFX. The neurosteroid tetrahydroprogesterone counteracts corticotropin-releasing hormone-induced anxiety and alters the release and gene expression of corticotropin-releasing hormone in the rat hypothalamus. *Neuroscience*. 1994; 62(1):265–271. [PubMed: 7816204]
145. Patchev VK, Hassan AHS, Holsboer F, Almeida OFX. The neurosteroid tetrahydroprogesterone attenuates the endocrine response to stress and exerts glucocorticoid-like effects on vasopressin gene transcription in the rat hypothalamus. *Neuropsychopharmacology*. 1996; 15(6):533–540. [PubMed: 8946427]
146. Barbaccia ML, Roscetti G, Trabucchi M, et al. The effects of inhibitors of GABAergic transmission and stress on brain and plasma allopregnanolone concentrations. *Br J Pharmacol*. 1997; 120(8):1582–1588. [PubMed: 9113382]
147. Kehoe P, Mallinson K, McCormick CM, Frye CA. Central allopregnanolone is increased in rat pups in response to repeated, short episodes of neonatal isolation. *Dev Brain Res*. 2000; 124(1–2):133–136. [PubMed: 11113522]

148. Djebaili M, Guo Q, Pettus EH, Hoffman SW, Stein DG. The neurosteroids progesterone and allopregnanolone reduce cell death, gliosis, and functional deficits after traumatic brain injury in rats. *J Neurotrauma*. 2005; 22(1):106–118. [PubMed: 15665606]
149. Sayeed I, Parvez S, Wali B, Siemen D, Stein DG. Direct inhibition of the mitochondrial permeability transition pore: A possible mechanism for better neuroprotective effects of allopregnanolone over progesterone. *Brain Res*. 2009; 1263:165–173. [PubMed: 19368823]
150. He J, Evans C-O, Hoffman SW, Oyesiku NM, Stein DG. Progesterone and allopregnanolone reduce inflammatory cytokines after traumatic brain injury. *Exp Neurol*. 2004; 189(2):404–412. [PubMed: 15380490]
151. Bixo M, Andersson A, Winblad B, Purdy RH, Bäckström T. Progesterone, 5 α -pregnane-3,20-dione and 3 α -hydroxy-5 α -pregnane-20-one in specific regions of the human female brain in different endocrine states. *Brain Res*. 1997; 764(1–2):173–178. [PubMed: 9295207]
152. Akwa Y, Purdy RH, Koob GF, Britton KT. The amygdala mediates the anxiolytic-like effect of the neurosteroid allopregnanolone in rat. *Behav Brain Res*. 1999; 106(1–2):119–125. [PubMed: 10595427]
153. Epperson CN, Gueorguieva R, Czarkowski KA, et al. Preliminary evidence of reduced occipital GABA concentrations in puerperal women: a 1H-MRS study. *Psychopharmacology (Berl)*. 2006; 186(3):425–433. [PubMed: 16724188]
154. Schiller CE, Schmidt PJ, Rubinow DR. Allopregnanolone as a mediator of affective switching in reproductive mood disorders. *Psychopharmacology (Berl)*. 2014:1–11.
155. Tarantino LM, Sullivan PF, Meltzer-Brody S. Using animal models to disentangle the role of genetic, epigenetic, and environmental influences on behavioral outcomes associated with maternal anxiety and depression. *Front Psychiatry Front Res Found*. 2011; 2:44.
156. Maguire JL, Stell BM, Rafizadeh M, Mody I. Ovarian cycle-linked changes in GABA(A) receptors mediating tonic inhibition alter seizure susceptibility and anxiety. *Nat Neurosci*. 2005; 8(15895085):797–804. [PubMed: 15895085]
157. Maguire J, Ferando I, Simonsen C, Mody I. Excitability Changes Related to GABAA Receptor Plasticity during Pregnancy. *J Neurosci*. 2009; 29(30):9592–9601. [PubMed: 19641122]