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Postpartum depression: Etiology, treatment and consequences for maternal care

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ABSTRACT

This article is part of a Special Issue "Parental Care".

Pregnancy and postpartum are associated with dramatic alterations in steroid and peptide hormones which alter the mothers' hypothalamic pituitary adrenal (HPA) and hypothalamic pituitary gonadal (HPG) axes. Dysregulations in these endocrine axes are related to mood disorders and as such it should not come as a major surprise that pregnancy and the postpartum period can have profound effects on maternal mood. Indeed, pregnancy and postpartum are associated with an increased risk for developing depressive symptoms in women. Postpartum depression affects approximately 10–15% of women and impairs mother–infant interactions that in turn are important for child development. Maternal attachment, sensitivity and parenting style are essential for a healthy maturation of an infant's social, cognitive and behavioral skills and depressed mothers often display less attachment, sensitivity and more harsh or disrupted parenting behaviors, which may contribute to reports of adverse child outcomes in children of depressed mothers. Here we review, in honor of the "father of motherhood", Jay Rosenblatt, the literature on postnatal depression in the mother and its effect on mother–infant interactions. We will cover clinical and pre-clinical findings highlighting putative neurobiological mechanisms underlying postpartum depression and how they relate to maternal behaviors and infant outcome. We also review animal models that investigate the neurobiology of maternal mood and disrupted maternal care. In particular, we discuss the implications of endogenous and exogenous manipulations of glucocorticoids on maternal care and mood. Lastly we discuss interventions during gestation and postpartum that may improve maternal symptoms and behavior and thus may alter developmental outcome of the offspring.

Major depressive disorder (MDD) affects 12–20% of the population and according to the World Health Organization is the first leading cause of disability in the world (Greenberg et al., 2003; Ustun et al., 2004). Women are twice as likely to develop depression (Gutierrez-Lobos et al., 2002), have more severe symptoms and present with comorbid anxiety compared to men (Kornstein et al., 2002; Sloan and Kornstein, 2003). The sex difference in incidence of depression is greatest during the reproductive years, suggesting that sex hormones and reproductive events play some role in the etiology of depression (Brummelte and Galea, 2010b; Gutierrez-Lobos et al., 2002; Hammarstrom et al., 2009; Sloan and Kornstein, 2003). Indeed, steroid and peptide hormones (such as cortisol, estrogens, progesterone and oxytocin) fluctuate dramatically during these reproductive years particularly during pregnancy and the postpartum (Brett and Baxendale, 2001). Because these periods of hormone fluctuations coincide with the greatest risk to develop depression during a woman's lifetime (Noble, 2005) this suggests an intimate association that is important to investigate in order to develop biomarkers to determine susceptibility to depression and new treatments.

Depression occurring after birth is referred to as postpartum depression (PPD), while depression occurring during pregnancy is referred to as antenatal depression. The prevalence of antenatal depression is estimated at approximately 12%, with the highest prevalence in the last two trimesters (Bennett et al., 2004). The prevalence of PPD ranges from approximately 10–15%, but can be as high as 30% depending on the criteria used for diagnosis (Darcy et al., 2011; Gavin et al., 2005; Vesga-Lopez et al., 2008). One of the greatest risk factors for developing PPD is antenatal depression and/or depression prior to pregnancy (O'Hara, 2009; Robertson et al., 2004). The trajectory of depressive symptoms can continue or even worsen throughout the course of the pregnancy and postpartum period. Unfortunately the new Diagnostic and Statistical Manual of Mental Disorders (DSM-5) does not consider that depressive symptoms can develop beyond 4 weeks postpartum. Further, it does not distinguish between a prenatal or postnatal onset of depression and collectively refers to the episodes as 'peripartum episodes' (American Psychiatric Association, DSM-5, 2013). Thus this classification of peripartum depression cannot distinguish between the consequences of

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antenatal and postpartum depression for both the mother and child, which becomes problematic as there are differences in manifestation, treatment and incidence as discussed below. Furthermore it is widely recognized that 4 weeks postpartum for perinatal depression is too limited a time frame and that the term 'maternal depression' may be a better descriptor of depression during pregnancy and the postpartum during the first year after giving birth (Stuart-Parrigon and Stuart, 2014).

Maternal depression is a serious mental illness that not only concerns the affected mother, but also impacts the fetus and child. A recent study by Dubber et al. (2014) suggests that both maternal–fetal bonding measured with the Maternal–Fetal Attachment scale (Cranley, 1981) and PPD are significant predictors of postpartum bonding between the mother and her infant (Dubber et al., 2014). This implies that a disturbed mother–fetal attachment during pregnancy can impact the relationship between the mother and her child in the postpartum. This underlines the importance of taking timing of depression, during pregnancy and/or the postpartum, into account when investigating the effects of maternal depression. Antenatal depression can result in reprogramming of the fetus (Buss et al., 2012; Sandman et al., 2011; Welberg and Seckl, 2001), while PPD can interfere with the child's maturation in a way that includes direct interactions with caregivers. Women with PPD can have different characteristics than women with antenatal plus postnatal depression (Cooper and Murray, 1995), arguing for distinguishing between these two periods of depression. It should also be noted that, while prior depression is the greatest risk factor for PPD, approximately 40% of women will have their first episode of depression during the postpartum (Wisner et al., 2013). In addition, as mentioned earlier, while the DSM-5 criteria also encompass only the first 4 weeks postpartum, the greatest incidence of new depression postpartum occurs 2–3 months after parturition (Gavin et al., 2005; O'Hara, 2009; O'Hara and McCabe, 2013). Interestingly, untreated PPD increases the risk for depression beyond the postpartum period with women experiencing approximately six times the risk for depression later in life in comparison to non-PPD women (Josefsson and Sydsjo, 2007).

It is important to understand that while PPD has many of the same characteristics of major depressive disorder (MDD) it presents during a unique time physiologically and women with PPD tend to present with greater co-morbid anxiety than women with MDD (Hendrick et al., 2000). Further, if symptom onset is within 1–14 days after delivery, women with PPD convert to bipolar disorder to a greater extent than women with MDD (Munk-Olsen et al., 2012). Thus, we urge the research community to continue to label, classify and analyze maternal depression as antenatal and/or postnatal as it is clear that there are differences in incidence and trajectory of depression, outcome on child development and potentially different requirements for treatment. In this review, we will focus on the effects of PPD on the mother and interactions with her offspring, however we will also highlight findings from antenatal depression to underscore different development outcomes where appropriate. We will discuss the underlying mechanisms for PPD, focusing on hormones, existing animal models of maternal depression and how those can help us to study treatments and interventions for PPD. Lastly we will discuss the effects of PPD and antenatal depression on maternal care, mother–infant interactions as well as child development.

Possible underlying mechanisms of PPD

Steroid hormones: ovarian hormones

Steroid hormones play a significant role in depression including PPD (Bloch et al., 2003; Brummelte and Galea, 2010b). During pregnancy and postpartum, levels of steroid and peptide hormones fluctuate dramatically which could contribute to the etiology of PPD (Bloch et al., 2003; Brummelte and Galea, 2010b). These changes in hormone levels, such as estradiol, corticosterone, corticotropic releasing hormone (CRH) and oxytocin, occur in rodents and humans albeit with different profiles and gestational periods (see Fig. 1). Briefly, in women, progesterone

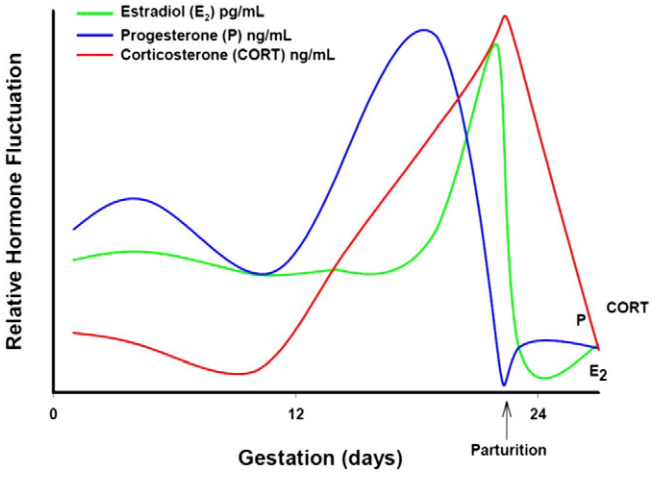

Fig. 1. Hormonal changes during pregnancy and the postpartum. The relative hormone levels of progesterone (ng/mL), corticosterone (ng/mL) and estradiol (pg/mL) over the course of pregnancy and parturition. Figure reprinted with permission from (Pawluski et al., 2009a).

levels are approximately 20× higher during gestation and remain elevated throughout pregnancy, while estradiol levels are very high (200–300× higher) by week 20 of gestation and remain high throughout the rest of pregnancy in women and both these steroid hormones drop with the expulsion of the placenta (for review see: Brett and Baxendale, 2001). In rodents, progesterone is elevated throughout the first two weeks of gestation but declines a few days prior to parturition, while estradiol levels are at modest levels (approximately diestrous levels) during gestation until just a few days prior to parturition when they increase dramatically (Rosenblatt, 1980). In both rodents and women, cortisol and corticosterone levels are higher during gestation (for review see: Brett and Baxendale, 2001).

In women, elevated estradiol levels continue to increase during the third trimester but drop dramatically after parturition, leading to the hypothesis that an "estradiol-withdrawal state" during the first few weeks after parturition contributes to PPD (Bloch et al., 2003; Hendrick et al., 1998). Consistent with this hypothesis, women with a previous history of PPD showed increased negative affect in response to ovarian steroid withdrawal compared to women without a previous history of PPD (Bloch et al., 2000), illustrating that women with a predisposition for depression may be more sensitive to large fluctuations in steroid hormone levels. In an elegant study, Frokjaer et al. found that biphasic estradiol (induction and then reduction via a gonadotropin releasing hormone agonist but not progesterone resulted in increased HAM-D scores that were correlated with decreased estradiol levels and increased levels of the serotonin transporter (SERT) in neocortex of women (Frokjaer et al., 2015). These data illustrate that dramatically fluctuating estradiol levels from high to hypogonadal status, such as seen during the early postpartum, are associated with reduced mood that is correlated with increased SERT levels, likely resulting in reduced serotonin. Insufficient serotonin levels have long been implicated in the etiology of depression, however, a causal link has not been established (Lacasse and Leo, 2005).

Interestingly, despite the prominent hypothesis of steroid involvement in PPD, not many studies have investigated this relationship in women. A recent study by Parizek et al. (2014) found that increased levels of androgens and estrogens measured 4 weeks before birth or from mixed umbilical cord blood at birth were associated with depressive mood in the postpartum period in a small sample of moderately depressed women. Furthermore other studies find that fetal sex may play a modest role with women pregnant with boys more likely to report postpartum blues 5 days after parturition but fetal sex was not linked to depression 6 months later (Sylven et al., 2011). These findings suggest that changes in maternal and fetal steroidogenesis may be involved in the etiology of PPD.