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Authors
Glynn, Laura M
Davis, Elysia Poggi
Sandman, Curt A

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New insights into the role of perinatal HPA-axis dysregulation in postpartum depression
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Laura M. Glynn a,b,⇑, Elysia Poggi Davis b,c, Curt A. Sandman b

a Crean School of Health and Life Sciences, Chapman University, United States
b Department of Psychiatry and Human Behavior, University of California, Irvine, United States
c Department of Psychology, University of Denver, United States

A B S T R A C T

Postpartum depression affects 10–20% of women following birth and exerts persisting adverse consequences on both mother and child. An incomplete understanding of its etiology constitutes a barrier to early identification and treatment. It is likely that prenatal hormone trajectories represent both markers of risk and also causal factors in the development of postpartum depression. During pregnancy the maternal hypothalamic–pituitary–adrenal axis undergoes dramatic alterations, due in large part, to the introduction of the placenta, a transient endocrine organ of fetal origin. We suggest that prenatal placental and hypothalamic–pituitary–adrenal axis dysregulation is predictive of risk for postpartum depression. In this model the positive feedback loop involving the systems regulating the products of the HPA axis results in higher prenatal levels of cortisol and placental corticotropin-releasing hormone. Greater elevations in placental corticotropin-releasing hormone are related to a disturbance in the sensitivity of the anterior pituitary to cortisol and also perhaps to decreased central corticotropin-releasing hormone secretion. Secondary or tertiary adrenal insufficiencies of a more extreme nature, which emerge during the prenatal period, may be predictive of an extended or more pronounced postpartum hypothalamic–pituitary–adrenal axis dysregulation which in turn represents a risk factor for development of postpartum depression. In addition to reviewing the relevant existing literature, new data are presented in support of this model which link elevated placental corticotropin-releasing hormone with low levels of ACTH at 3-months postpartum. Future research will further elucidate the role of hypothalamic–pituitary–adrenal axis dysregulation in postpartum depression and also whether prenatal placental and hypothalamic–pituitary–adrenal profiles might prove useful in the early identification of mothers at risk for postpartum mood dysregulation.

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1. Introduction

According to the World Health Organization, depression is the fourth leading contributor to the global burden of disease and the leading cause of disability (Organization, 2009). The lifetime risk of Major Depressive Disorder (MDD) is two to three times
Fig. 1. Schematic illustration of a model of HPA-axis dysregulation predictive of risk for postpartum depression. In this model an augmented positive feedback loop of cortisol and pCRH results in higher prenatal levels of cortisol and pCRH. Elevated pCRH is related to a disturbance in the sensitivity of the anterior pituitary to cortisol and also perhaps to decreased central CRH secretion. Women who exhibit secondary or tertiary adrenal insufficiencies of a more extreme nature (which emerge during the prenatal period) also may exhibit an extended or more pronounced postpartum HPA refractory period, which in turn places these women at risk for development of postpartum depression.

Fig. 2. The regulation of the HPA axis changes dramatically over the course of gestation with profound implications for the mother and the fetus. One of the most significant changes is the development of the placenta, an endocrine organ of fetal origin. During pregnancy, CRH is released from the placenta into both the maternal and fetal compartments. In contrast to the negative feedback regulation of hypothalamic CRH, cortisol increases the production of CRH from the placenta. Placental CRH concentrations rise exponentially over the course of gestation.

### 2. The endocrine stress system

Systemic stress activates the expression of the master stress hypothalamic hormone, corticotrophin releasing hormone (CRH), which stimulates the cascade of events preparing the organism for “fight or flight”. CRH, a 41-amino acid neuropeptide, is synthesized primarily in the paraventricular nucleus of the hypothalamus and has a major role in regulating pituitary–adrenal function and the physiologic response to stress (Chrousos, 1992; Vale et al., 1981). CRH stimulates the synthesis of a bioactive 31 K Dalton prohormone, proopiomelanocortin (POMC) in the pituitary which is converted by enzymes into adrenocorticotropic hormone higher in women than men (Gutierrez-Lobos et al., 2002), and the childbearing years represent a particular period of vulnerability (Kessler, 2003). Postpartum depression (PPD) occurs in up to 15 percent of women and has adverse consequences for both mother and child that may last a lifetime. Untreated PPD poses a serious threat to the emotional well-being of the mother and is associated with substance abuse, loss of employment, divorce, and at its most extreme, suicide and infanticide (Goodman, 2007). In addition to the severe psychological distress experienced by the mother, PPD persistently undermines the mother’s confidence and her capacity to care for her infant (Lovejoy et al., 2000). As early as 3 months of age, the infant is able to detect the depressed mother’s restricted affective displays and modify his or her own responses to them (Cohn and Tronick, 1988; Jones, 2012). Children of depressed mothers are at risk for developing poorer cognitive, neuropsychological, social, and emotional skills, higher rates of psychopathology and altered physiological stress regulation across childhood and into adolescence (Beck, 1998; Dawson et al., 2003; Feldman et al., 2009; Goodman, 2007; Halligan et al., 2004; Murray et al., 2011; Verbeek et al., 2012).

Although successful and cost effective therapies exist, it is estimated that less than 50 percent of women suffering from PPD are identified and treated (Hendrick, 2003). Given the profound disruptive influences of PPD for both mother and child, the detection of vulnerable women at risk for PPD is essential. Despite its prevalence and devastating consequences, little is known about the etiology of this condition, the causes of which are complex and heterogeneous. The most consistently identified risk factors include a history of depression, previous PPD, anxiety, stress, and depression during pregnancy, stressful life events, lack of social support, and low self-esteem (O’Hara, 2009; Robertson et al., 2004). However, these risk factors explain only a portion of the variance in the incidence of PPD. Accumulating evidence suggests that hormone exposures during pregnancy and the postpartum period may play an important part. Our work has focused on elucidating the role of endocrine risk markers in PPD, specifically placental and hypothalamic-pituitary-adrenal (HPA) axis hormones (Sandman and Glynn, 2009; Yim et al., 2009, 2010). A focus on the HPA axis as a contributor to risk for PPD is supported by three factors. First, stress is cited as a precipitating factor in 85% of cases of depression (Parker et al., 2003). Second, one of the most widely documented findings in biological psychiatry is the presence of dysregulated HPA axis function in MDD. Third, the function of the maternal HPA axis is profoundly altered during the prenatal period. Here we review the data supporting a model of perinatal HPA-axis dysregulation and risk for postpartum depression (see Fig. 1).
(ACTH) and other active peptides. ACTH enters the blood stream and elicits secretion of glucocorticoids (cortisol in humans) from the adrenal gland. There is negative feedback between the adrenal gland and both the hypothalamus and pituitary gland that shuts down the stress response under normal conditions (Fig. 2). In addition, cortisol crosses the blood–brain barrier and activates specific receptors in limbic brain structures. These limbic structures, especially the hippocampus, prefrontal cortex and amygdala have both excitatory and inhibitory connections with HPA axis (Avishai-Eliner et al., 2002).

The integrity and function of the HPA axis is routinely determined with standardized challenges, both pharmacologic and naturalistic. In the Dexamethasone Suppression Test, dexamethasone, an exogenous glucocorticoid, is administered which should exert negative feedback, suppressing the secretion of ACTH and CRH. A normal result is an observed decrease in cortisol levels following administration of the dexamethasone. However, in certain pathological conditions, such as Cushing’s Disease, characterized by a chronic state of hypercortisolism, no cortisol suppression is observed. Another commonly used challenge is the assessment of diurnal cortisol rhythm or, more specifically, the Cortisol Awakening Response (CAR). Among humans, there is a substantial increase in cortisol secretion between awakening and 30 min later, a pattern referred to as the CAR (Pruessner et al., 1997) and different patterns of output have been associated with different clinical conditions. For example, those suffering from Posttraumatic Stress Disorder or Chronic Fatigue Syndrome exhibit attenuated awakening responses (Heim et al., 2009; Neylan et al., 2005) indicative of a hyporesponsive system.

3. HPA in MDD

Major depressive disorder (MDD) has been repeatedly characterized by dysregulated HPA axis function at multiple levels. For example, those suffering from MDD exhibit elevated concentrations of CRH in cerebrospinal fluid and these levels are reduced following ECT therapy (Kasckow et al., 2001; Nemeroff et al., 1984). In addition, decreased CRH1 receptor affinity, and increased numbers of CRH neurons, CRH mRNA expression and CRH immunoreactivity have been observed in the brains of depressed individuals and suicide victims (Austin et al., 2003; Bissette et al., 2003; Nemeroff et al., 1988; Raadsheer et al., 1994, 1995). There also is evidence for an enhanced CAR and a failure to suppress in response to dexamethasone challenge among depressed patients (Gold and Chrousos, 2002; Jarcho et al., 2013; Vrshek-Schallhorn et al., 2013).

Refinements of models linking HPA regulation to MDD suggest that different clinical subtypes may be characterized by unique HPA profiles (Antonijevic, 2006; Gold and Chrousos, 2002; O’Keane et al., 2012). The Diagnostic and Statistical Manual of Mental Disorders (DSM-V), the principle reference for diagnosis of psychiatric disorders in the United States, identifies two distinct clinical depressive syndromes melancholic and atypical depression. These are based on patterns of psychological and neurovegetative symptoms and are independent of the unipolar/bipolar distinction. Melancholic Depression, with symptoms including loss of pleasure, depressed mood at its worst in the morning, insomnia, reduced appetite and/or substantial weight loss and psychomotor alterations, is consistently associated with the HPA hyperactivation described above. In contrast, Atypical Depression which is characterized by retention of mood reactivity, weight gain, hypersomnia, interpersonal rejection sensitivity and depressive symptoms that worsen as the day progresses, is associated with hyporesponsiveness in the system1. Atypical patients exhibit enhanced glucocorticoid suppression (Levant et al., 2002), lower cortisol levels at awakening and also flattened diurnal cortisol patterns (Lamers et al., 2012). Due to the fact that the postpartum period is one of mild adrenal suppression, it has been proposed that PPD is more closely aligned with the hyporesponsive atypical subtype (Kammerer et al., 2006; Mastorakos and Iliaz, 2000).

Currently the DSM-V applies the “postpartum onset” specifier when a depressive episode begins within the first 4 weeks after delivery and the International Classification of Diseases and Health Related Conditions (ICD-10), developed by the World Health Organization, extends this window to 6 weeks postpartum. Although a debate exists concerning whether or not MDD and PPD represent distinct syndromes, there is evidence that PPD is a significant risk factor for the later development of non-puerperal depression and vice versa (Robertson et al., 2004; Stowe et al., 2005), suggesting they may share common etiological roots. Consistent with this view, accumulating data implicate dysregulated HPA axis function in puerperal affective disorders as well as nonpuerperal.

4. The HPA axis in pregnancy and postpartum

During human pregnancy, the neuroendocrine stress system is profoundly altered. The pituitary gland doubles in size and the output of pituitary peptides increases several fold as gestation progresses. But it is the growth and development of a new organ, the placenta that is primarily responsible for the profound changes in the stress circuit (Fig. 2). By the seventh week of gestation, CRH is additionally synthesized by syncytiotrophoblast cells in the human placenta (Jones et al., 1989; Riley et al., 1991) and is released into the maternal and fetal compartments (Economides et al., 1987; Goland et al., 1988). Placental CRH production increases dramatically over gestation with levels in maternal circulation reaching those only observed within the hypothalamic-pituitary portal system during stress (Lowry, 1993). This is in stark contrast to the non-pregnant state in which CRH immunoreactivity in the plasma is very low or undetectable. Although the CRH gene and mRNA of pCRH and hypothalamic CRH appear identical (Arbiser et al., 1988; Frim et al., 1988), their regulation is tissue specific. In contrast to the inhibitory influence of glucocorticoids on expression of the CRH gene in the hypothalamus, glucocorticoids activate the promoter region in the placenta and stimulate the synthesis of CRH (Cheng et al., 2000; Robinson et al., 1988). The difference in behavior of the CRH gene in the placenta and hypothalamus is due to the expression of different transcription factors, co-activators and corepressors in these two tissues (King et al., 2002). In vivo and in vitro studies have demonstrated that glucocorticoids stimulate the production of CRH mRNA and protein from placental cells in a dose–response manner (Cheng et al., 2000; Glynn et al., 2007; King et al., 2001; Sandman et al., 2006). This positive feedback loop results in dramatic elevations of maternal ACTH, cortisol and pCRH across gestation (see Fig. 3; Glynn and Sandman, 2012).

The rising circulating levels of HPA axis hormones and pCRH have consistent implications for the endocrine response to challenge. Across a range of stressors during pregnancy, the HPA axis response diminishes (see de Weerth and Buitelhaar, 2005, for a detailed review) and this is true for many non-human species as well (Mastroianni and D’Amedio, 1991; Vierin and Bouissou, 2001; Wartella et al., 2003). For example, administration of CRH, which stimulates the release of cortisol in nonpregnant women, does not produce detectable responses in women during the third trimester of pregnancy (Schulte et al., 1990). Cortisol responses to cold pressor challenge in pregnant women are similarly absent (Kammerer et al., 2002) and there is evidence that the CAR is attenuated (Entinger et al., 2009). Consistent with these changes, it also is the case that during gestation, reduced suppression in response to

1 Although the evidence is more equivocal than the findings regarding melancholic depression.
Increased risk for preterm delivery (Buss et al., 2010; Glynn et al., 2001) is more likely to result in preterm birth than are later exposures. It has been shown that early exposures to stress are serving an adaptive purpose, providing some protection for mother and fetus from the adverse effects of stress. There is reason to believe that the down-regulation of stress responding during pregnancy serves an adaptive purpose, providing some protection for mother and fetus from the adverse effects of stress.

During the postpartum period, due to the delivery of the placenta, the HPA axis is exposed to extreme perturbations in the form of the acute withdrawal of pCRH. The hypertrophied adrenal glands of gestation persist into the postpartum period and cortisol levels gradually decline after birth. Other conditions with chronic high glucocorticoid exposures, similar to those seen in pregnancy, result in adrenal suppression (Agerinos et al., 1987; Fitzgerald et al., 1982; Gomez et al., 1993; Graber et al., 1965; Streck and Lockwood, 1979). In these cases, the return to normal of the HPA axis can take weeks, months and in some rare cases, even years. The duration of the suppression is moderated by the length and dose of the treatment and the extent of the hypercortisolism. Given these findings, it is not surprising that postpartum, women exhibit persisting alterations HPA axis function. Best estimates suggest that it takes a minimum of two to three months for HPA function to return to its prepregnancy dynamic equilibrium (Magiakou et al., 1996; Owens et al., 1987). During the first postpartum months women exhibit a blunted ACTH response to an exogenous CRH challenge (Magiakou et al., 1996) and a reduction or failure to suppress in response to dexamethasone administration for at least five weeks following delivery (Owens et al., 1987). It has been previously proposed that this reorganization or HPA refractory period may play a role in the pathophysiology of PPD (Kammerer et al., 2006; Mastorakos and Ilias, 2000).

The precise mechanisms underlying the mild hyporesponsivity in the HPA axis observed in the postpartum period are not fully understood, but it is believed to be most likely due to one of two underlying causes, which are not mutually exclusive. In pregnancy corticotrophs are exposed to sustained elevations of CRH which may desensitize the anterior pituitary to CRH. In vitro models confirm that CRH receptors are down-regulated with exposure to their ligands (Reisine and Hoffman, 1983) and that anterior pituitary cells continuously exposed to CRH exhibit a loss of ability for maximal response (Thomson et al., 1990). Second, similar to what is observed in individuals exposed to chronic elevations in glucocorticoids (e.g., due to glucocorticoid treatment or endogenous hypercortisolism), the mild adrenal suppression may be due to sensitivity at the level of the hypothalamus and/or its higher regulatory inputs both of which would be associated with decreased CRH secretion (Gomez et al., 1993).

Although it may be the case that dysregulation of the endocrine adaptations of the perinatal period are predictive of risk for mood disorders and also adverse birth and infant outcomes (Davis et al., 2005, 2007, 2011; Glynn and Sandman, 2012; Grey et al., 2013; McLean et al., 1995), it is important to emphasize that the introduction of the placenta and the subsequent alterations of the maternal HPA axis during the prenatal period together play a fundamental role in successful fetal development, gestation and parturition. Placental CRH has been characterized as controlling a “placental clock” that determines or alters the timing of onset of parturition (McLean et al., 1995; Smith et al., 2002). Elevated levels and steeper trajectories of placental CRH initiate a cascade of events resulting in myometrial activation (Hobel et al., 1999; McGrath et al., 2002; Smith et al., 2009; Wadhwa et al., 2004, 1998). Animal models demonstrate that CRH exposures, particularly early in development, have pervasive consequences on both brain and behavior (Williams et al., 1995). CRH affects the developing nervous system directly, due to extensive expression of CRH receptors throughout the brain (Avishai-Eliner et al., 1996), as well as through effects on the fetal HPA axis (Sirianini et al., 2005). Further, the increase of CRH, particularly over the latter part of human gestation plays a crucial role in the organization of the fetal nervous system (Sandman et al., 1999). Placental CRH is associated with human fetal maturation (Class et al., 2008) and physical and neuromuscular maturation during the neonatal period (Elliott et al., 2008). Analogously, cortisol plays an instrumental part in normal fetal development, specifically in the regulation of intrauterine homeostasis and differentiation and maturation of vital organ systems including the lungs, liver, and central nervous system (Mesiano and Jaffe, 1997; Rose et al., 1998). It also has been pro-

Fig. 3. Prenatal ACTH, plasma cortisol and placental CRH trajectories.
posed that the hyporesponsive HPA axis which characterizes the postpartum period, may serve similarly adaptive functions for the mother including: facilitating energy conservation required for lactation, enhancing maternal defense and protection of offspring, buffering from stress-associated inhibition of lactation, and improved immune function (Altemus et al., 1995; Hahn-Holbrook et al., 2011; Lightman et al., 2001).

5. Evidence supporting a model of perinatal HPA axis dysfunction and PPD

Our model (see Fig. 1) predicts first, that some evidence of an exaggerated cortisol-pCRH feed forward loop would be apparent among women who develop PPD. This would be supported by documented associations between elevations in pCRH and risk of PPD. The evidence linking pCRH trajectories to PPD risk is growing. Previously, two studies have shown that women who exhibit elevated levels of pCRH at midgestation and/or accelerated pCRH trajectories are at increased risk for development of PPD at 2–3 months postpartum (Hahn-Holbrook et al., 2013; Yim et al., 2009). There is one study which failed to detect this relation, but it seems likely that this may be due to the methodology used to assess pCRH (a notoriously sensitive assay; Glynn and Sandman, in press; Latendresse and Ruiz, 2011). Most recently we again confirmed the link between pCRH and midgestational pCRH, showing that women who exhibit elevated levels and accelerated trajectories are at increased risk for development of PPD at 2 months after delivery (Glynn and Sandman, in press).

Our model would further predict that PPD would be associated with a hyporesponsive HPA axis or adrenal insufficiency in the postpartum period. Consistent with this possibility, in a small sample, Parry et al. (2003) documented reduced cortisol levels in women with PPD compared to women who were not depressed postnatally. Groer and Morgan (2007) also documented lower morning cortisol levels among depressed mothers at 4–6 weeks postpartum. Further, a lack of a CAR at 7 weeks postpartum was observed among women expressing depressive symptoms (Taylor et al., 2009). Additional compelling evidence for a link between a hyporesponsive HPA profile and PPD was provided from study in which depressed and non-depressed women were exposed to an exogenous CRH challenge at 3, 6 and 12 weeks postpartum. Magiajou et al. (1996) demonstrated that the blunting of the plasma ACTH response to ovine CRH was more extreme and prolonged among those women suffering from postpartum blues or depression.

A last critical piece of the proposed model requires demonstrated links between prenatal placental and HPA axis function and postpartum HPA axis regulation. To date, we are only aware of one published study addressing this question. Meinschmidt et al. (2010) found that the CAR assessed at 36 weeks’ gestation predicted the HPA response to challenge at 8 weeks postpartum. Specifically, a larger prenatal CAR was associated with reduced ACTH, plasma and salivary cortisol postpartum responses to challenge (all ∶⁄ > .6). These are the only known data linking prenatal HPA axis regulation to regulation in the postpartum period, but they are consistent with our model suggesting that an accelerated feed-forward loop resulting in increased levels of cortisol and pCRH is predictive of PPD.

An examination of the links between pCRH and postpartum HPA axis function among a sample of 228 women followed longitudinally in our laboratory, allows the first examination of whether an accelerated placental-HPA feedback loop is predictive of postpartum HPA profile. Placental CRH was assessed at 15, 19, 25, 31 and 36+ weeks’ gestation and ACTH at 3 months postpartum (see Glynn and Sandman (in press), for biological sample collection and assay details; the prenatal gestational ages for assessment were chosen to maximize the probability that we captured the dramatic changes in HPA axis and placental functioning). Table 1 presents partial correlations between pCRH and ACTH (these analyses adjust for maternal age, race/ethnicity, education, parity length of gestation and gestational age at blood draw). Beginning at 25 weeks’ until the end of gestation, higher levels of pCRH predicted lower levels of ACTH at 3 months postpartum. Although this is not an assessment of HPA axis function under challenge conditions, these findings are consistent with our model suggesting that accelerated pCRH trajectories are associated with more exaggerated HPA hyporesponsivity in the postpartum period. These are the first data to document this link and they clearly justify further examination of the link between pCRH and postpartum HPA axis dysregulation.

Acknowledging that the physiology of rodent pregnancy differs substantially from that of the human, animal models do offer the opportunity to experimentally manipulate prenatal HPA axis regulation, and thus the ability to draw causal conclusions. Based on the findings from these paradigms, there is some evidence to suggest that activation of the HPA axis during pregnancy is predictive of depressive behaviors in the rat dam in the postpartum. It has been demonstrated that females subjected to restraint stress during gestation exhibit enlarged adrenals and elevations in corticosterone levels during the prenatal period (Hillerer et al., 2011; Misdrahi et al., 2005) and also exhibit higher rates of depressive like behaviors during the postpartum period (O'Mahony et al., 2006; Smith et al., 2004). Further, Hillerer et al. (2011) has shown that gestational stress exposure produced increased depressive behaviors and also impaired the normal physiological adaptations of the maternal HPA axis during the postpartum period.

6. Conclusion

Human pregnancy is a singular physiological condition in which a feed-forward or positive feedback loop exists with the systems regulating the products of the HPA axis. The development of the placenta, a transient endocrine organ of fetal origin produces exponentially rising levels of CRH, the activities of which are identical to hypothalamic CRH in bioactivity and immunoreactivity. The regulation of the HPA axis is profoundly altered during gestation and has implications for function that persist well into the postpartum period. Future research will need to further explore the unique postpartum HPA axis profile and how dysregulation in these necessary adaptations may be associated with risk for PPD. In addition, a promising avenue of identification of those women at risk may be afforded by markers of HPA and placental function during the prenatal period.

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