The HPA axis during the Perinatal Period implications for Perinatal Depression

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The HPA axis during the Perinatal Period: implications for Perinatal Depression

(minireview)

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Abstract

The transition to motherhood is characterized by some of the most pronounced endocrine changes a women will experience in her lifetime. Unfortunately matrescence is also a time in a woman's life when she is most susceptible to mental illness such as perinatal depression. A growing body of research has aimed to determine how key endocrine systems, such as the hypothalamic-pituitary-adrenal (HPA) axis, are involved in the dysregulation of perinatal mental health. However, very little research has consistently linked perinatal changes in the HPA axis with maternal mental illness. Therefore the aims of this mini review are to 1) clearly summarize the normative changes in the HPA axis that occur during pregnancy and the postpartum period; 2) summarize what we know about the HPA axis in perinatal depression, and 3) propose key areas for future research. Understanding physiological biomarkers that can predict which women are at risk for perinatal mood disorders will lead to better tools for treating and ultimately preventing these debilitating disorders; improving the health of mother, child and family.

Keywords. Pregnancy; depression; anxiety; postpartum depression; stress; cortisol; motherhood

Introduction

The perinatal period is marked by arguably the most pronounced endocrine changes a women will experience in her lifetime. These physiological changes in the mother are essential for pregnancy, birth, lactation, as well as child development and survival. Unfortunately the perinatal period is also a time when a woman is most susceptible to mental illness (1,2). A growing body of research has aimed to discover how key endocrine systems are involved in the dysregulation of perinatal mental health (3,4). Because of its role in stress and the effects of stress in the development of mental illness (5) the hypothalamic-pituitary-adrenal (HPA) axis has been acknowledged as a key player in perinatal mental illnesses (6). However, very little research has consistently contributed changes in the HPA axis during pregnancy and/or the postpartum period with perinatal mental illnesses such as postpartum depression (arguably the most well studied maternal mental illness) (6-8). Therefore, the aims of this mini review are to 1) clearly summarize the normative changes in the HPA axis that occur during pregnancy, parturition and the postpartum period; 2) summarize what we know about the HPA axis in perinatal depression and, where possible, anxiety, from clinical research and animal models; and 3) propose key areas for future research. We have very little knowledge of the physiological basis of maternal mental illnesses yet the tragic consequences are clear - suicide is the leading cause of death in pregnant and postpartum women (9). Given the role that the HPA axis plays in mental illness outside of the perinatal period we hope this review will provide information for areas of future research on perinatal mental illnesses.

In writing this mini review we relied on recent studies and reviews in the area, as well as essential foundational studies related to HPA regulation and mental health, and HPA regulation during pregnancy and the postpartum period.

HPA and the Perinatal Period

The HPA axis is characterized by a cascade of hormones that regulates glucocorticoids (predominantly cortisol in humans, corticosterone in rodents, and for purposes of this review, we will be referring to *cortisol*). Often the HPA axis is associated with cortisol release in response to stress but its regulation also has important basic homeostatic functionalities beyond responding to acute stressors (e.g. metabolism, immune system regulation)(10). The hormone cascade is initiated in the corticotrophs of the paraventricular nucleus (PVN) of the hypothalamus, which release corticotrophin releasing hormone (CRH) and arginine vasopressin (AVP), hormones that then stimulate the anterior pituitary gland to release adrenocorticotropin releasing hormone (ACTH) which stimulates the adrenal cortex to release cortisol (10). Increased cortisol concentrations exert negative feedback on all levels of the HPA axis via glucocorticoid receptors (GR) to ensure a relatively rapid return of cortisol to baseline concentrations (10,11).

Stimulation and maintenance of the HPA axis and cortisol signaling at the level of the adrenals relies on a number of factors and input from the brain to the circulation. Brain regions, such as the hippocampus, amygdala, and prefrontal cortex, for example, regulate the response to, and recovery from, an acute stress and play a role in daily functions such as cognition (12,13). In the bloodstream, corticosteroid binding globulin (CBG) regulates the bioavailability of cortisol to bind receptors (14). Throughout the body, the presence (or absence) of these mineralocorticoid and glucocorticoid receptors (MR and GR, respectively) impact the response and relative responsiveness to cortisol. In addition, MRs and GRs have different affinities for cortisol with MRs having 10x the affinity for cortisol when compared to GRs (15). For cells that express both of these receptor types (not all do), GRs only bind cortisol when cortisol levels reach stress-induced concentrations. At the cellular level, the enzyme 11β-hydroxysteroid dehydrogenase

(11β-HSD) converts glucocorticoids to an inactive form and, with CBG, determines the bioavailability of cortisol to bind the different receptor types (16-18).

Pregnancy, birth, and lactation significantly change the way the HPA axis and circulating cortisol functions. Many important basic and new functionalities of the HPA hormones overlap such that increased cortisol concentrations (and to some degree, placental CRH (pCRH) that we will describe below) are responsible for critical stages of a healthy pregnancy. These stages include (but are not limited to) preparing the fetus for the outside world (maturation of systems thermoregulation, glucose metabolism, lung development, etc) (19-21), parturition (22), labor (23), and activation of mammary glands and milk synthesis (24). Perhaps due to these increased functionalities, basal cortisol concentrations rise throughout pregnancy. The steepest increase in cortisol levels occurs in the final weeks of pregnancy, reaching 2-5 times non-pregnant concentrations, but with great variability between individuals (as reviewed in (25)). The diurnal rhythm of the HPA axis appears to be blunted during this time (26) as is the HPA response to acute stress in pregnancy (27) and lactation (28,29).

The predominant factor responsible for the elevated basal cortisol concentrations in human pregnancy is not the HPA axis, but it is the placenta. During pregnancy, the placenta increasingly exerts its role as an endocrine gland. In addition to secreting estrogens and progesterone, the placenta releases its own version of CRH (placental CRH, pCRH) which is identical in structure and bioactivity to hypothalamic CRH (30) but due to its size likely does not cross the blood brain barrier (31). Placental CRH is responsible for the elevation in circulating cortisol concentrations (32). Importantly, pCRH, and subsequent increases in cortisol concentrations, do not follow the classic negative feedback system seen with hypothalamic CRH. Instead, cortisol *stimulates* the human placenta to produce pCRH (33,34) and, pCRH, in turn,

continues to stimulate cortisol production which results in a positive feedback loop (Figure 1B). CBG levels also increase during pregnancy and decrease in the weeks and days prior to delivery (35). The rise in CBG levels during gestation is not enough to decrease (or 'normalize') free cortisol concentrations; possibly due to the high affinity of CBG for rising progesterone levels (36).

Another marked difference between hypothalamic CRH and pCRH is that circulating pCRH is bound to a binding protein, CRH-BP. CRH-BP can modify the bioactivity of pCRH throughout pregnancy. This is especially true in the last few weeks of pregnancy when CRH-BP levels fall by nearly 50% and free circulating pCRH levels rise (37). With changes in CRH-BP, pCRH concentrations increase exponentially across pregnancy (likely due to the positive feedback loop with cortisol), and a decreased response to cortisol negative feedback occurs along the HPA axis (38). Thus, circulating cortisol concentrations continue to increase throughout pregnancy. Cortisol concentrations at the end of a healthy pregnancy reach concentrations only seen in non-pregnant individuals with severe HPA dysregulation, such as Cushing's Disease (30).

Even though pCRH is the factor responsible for circulating levels of maternal cortisol, the HPA axis during pregnancy still maintains a role in the maintenance of maternal HPA pulsatility (both circadian and ultradian rhythms)(39). Since CRH in the brain is at nearly undetectable levels, AVP from the PVN is likely responsible for this prenatal HPA pulsatility (30).

Although concentrations of cortisol during pregnancy reach levels well beyond what is normally seen in a healthy, non-pregnant, individual, it has been suggested that maternal cortisol can't be *too high*. Exposure to *optimal* and *adaptive* circulating cortisol concentrations facilitate growth and development of the fetus and supports the maintenance of pregnancy. To protect the

fetus from cortisol levels outside of an optimal range placental 11β-HSD metabolizes maternal cortisol (40). In addition, during pregnancy and into the postpartum period the responsiveness of the HPA axis to stress is blunted, and this reduced HPA axis response may act to further protect the mother and neonate (41)(as reviewed in (42)). From the data available, it remains unclear what neuroendocrine mechanisms in the human maternal brain underlie the changes in HPA reactivity across the perinatal period. Specifically, how the perinatal changes in concentrations of cortisol and placental CRH (pCRH) affect the regulatory regions of the HPA axis and the ability of the maternal HPA axis to respond to stress remains to be determined. For example, the down regulation of hypothalamic CRH from the PVN during gestation, as described above, may be due to strong negative feedback of the elevated circulating cortisol concentrations. As it is unlikely that pCRH crosses the blood brain barrier from the circulation (31), therefore the blunted HPA response to stress may be due to elevated concentrations of cortisol reaching the brain and changes in GR density in the hippocampus. However, any alterations at the level of the PVN, prefrontal cortical areas, or additional brain regions via pregnancy-related cortisol concentrations or lack of CRH release have not been well defined in humans.

During parturition there is a marked increase in cortisol, particularly during a vaginal delivery as compared to C-section (23,43,44). This increase in cortisol at delivery is a response to the intensity of labor and is likely essential for preparing the neonate for the outside world. Then, with the delivery of the placenta, the source of pCRH is removed. Plasma CRH levels return to normal, pre-pregnancy, concentrations within 15 hours of delivery (45). Cortisol also dramatically decreases in the days and weeks postpartum (46) contributing to a dramatic shift in HPA axis regulation (6).

It is interesting to note that glucocorticoid levels differ with maternal experience in both humans and rodent models. For example, multiparous women show a smaller magnitude of change in circulating cortisol levels postpartum compared to primiparous women (47) and biparous female rats have less pronounced changes in corticosterone and CBG levels compared to age-matched primiparous females (48). Others report that parity and feeding type (lactation vs bottle feeding) play a role in cortisol levels and HPA function postpartum such that breastfeeding multiparous mothers show reduced cortisol levels and reduced cortisol responsiveness to psychology stress compared to non-breastfeeding multiparous mothers (49,50). In this study, feeding type did not affect cortisol levels of primiparous mothers (49,50). This suggests that maternal experience may act to further alter the maternal HPA axis. This is perhaps not surprising given that glucocorticoids play an important role in the initiation and maintenance of maternal care-giving behaviors, particularly in primiparous mothers. For example, Fleming et al (1997) report that first-time mothers with elevated cortisol concentrations are more attracted to their own infant's body odor (51). In rodents, corticosterone is important for the pup retrieval, maternal memory, and maintenance of maternal care (52-54). Thus maternal experience alone may be an important regulator of the HPA axis during the postpartum period and, perhaps, during pregnancy.

HPA and Perinatal Mood Disorders

As Pariante and Lightman (2008) point out in their review focused on the HPA axis and major depression: “Considering its role at the interface between stress and brain functioning, it is perhaps not surprising that the HPA axis has been found abnormal in psychiatric disorders, and in particular in major depression.” (55). But to truly understand how the HPA axis appropriately

responds to stress and initiates, adapts, and maintains homeostasis, several factors must be considered. In the brain the response to stress is modulated by the distribution and localization of the two types of receptors, MR and GR, and their affinity for glucocorticoids, the release pattern of glucocorticoids (circadian and ultradian), circulating CBG, 11β-HSD concentrations and activity, and alterations in transcriptional regulators (56). These factors determine how quickly neurons will respond to cortisol. There are a wide range of potential mechanisms - genetic, epigenetic, inflammatory, microbial, biochemical - regulating the HPA axis that may result in individual vulnerability to depression or anxiety (57-61).

The important thing to point out is that a majority of studies to date that link the HPA axis with major depression (and those included in the review above) have been conducted in young male humans and rodents. The female brain is grossly understudied. This sex/gender bias in the literature is especially problematic given the differences between males and females, particularly with regards to gonadal steroid effects on the HPA axis (62), HPA responsiveness and female vulnerability to stress-related mental health concerns (63).

Even without a detailed knowledge of the HPA axis in pregnancy and the postpartum period we do know that the dysregulation of the HPA axis is often implicated in mental illness in men and women; a recent meta-analysis shows that women with major depression or an anxiety disorder have blunted cortisol stress responses (64), and increased cortisol awakening response (CAR) is often predictive to increased vulnerability of depression (13,65). The maternal brain, which is exposed to extreme changes in steroid hormones and HPA axis functionality, is even less understood but potentially far more complex and prone to dysregulation. Thus, dysregulation of the HPA axis seems a likely candidate for the onset of perinatal depression and anxiety.

When talking about rates of maternal mental illness rates it should be noted that psychiatric admissions for women during the early postpartum period are higher than at any other time in a woman's life and that suicide is the leading cause of death in pregnant and postpartum women (9,58). The perinatal period is also a time when a significant number of women suffer from elevated depression and/or anxiety. Up to 15% of women in industrialized countries will suffer from perinatal depression (PND) (66-68) and rates of PND can be 2 to 3 times higher in developing countries (69). Four to twenty percent of women will experience mood disorders during pregnancy, the postpartum, or throughout the perinatal period (70,71). Anxiety disorders during the perinatal period are nearly as prevalent as PND (66,72), however much less research has focused on the endocrinology of perinatal anxiety in women. For the purposes of this mini review, we focus on the HPA axis in PND.

The symptom profile of PND includes persistent factors such as sad mood, restlessness/agitation, and impaired concentration as well as a major depressive episode during pregnancy or the recent postpartum (73), resembling that of a major depressive disorder experienced at other times in life. PND is diverse, with up to 5 distinct subtypes being evident such as severe anxious depression, moderate anxious depression, and anxious anhedonia based on the type of symptoms, time of onset and severity (74). Thus, the profile of PND can be markedly different from woman to woman and the etiology, detection and treatment can vary widely. PND is often predicted by a prepartum history of either depression or anxiety, a number of psychosocial risk factors including abuse/trauma, family history of psychiatric illness, and discontinuing antidepressant medication during gestation (8,75). If left untreated PND can have detrimental effects on the mother leading to increased risk of substance abuse, poor nutrition, marital conflict, further episodes of depression and, in extreme cases, suicide (76,77). Poor

maternal mental health is also associated with a host of negative outcomes in children such as preterm birth, decreased cognitive ability, increased risk of psychiatric illness and altered social behaviors (77-79).

Despite its prevalence and pervasive costs for the mother, child and family, our understanding of the biological bases of perinatal mood disorders is limited (80). As mentioned previously, the HPA axis may be a key player in PND as it is strongly implicated in depression at other times in life, and its significant plasticity during the perinatal period may increase a mother's vulnerability to mental illness. But what do we really know about the HPA and PND?

In 2006 Krammer et al proposed that depression during pregnancy could be characterized by high levels of cortisol but depression during the postpartum period would be characterized by low levels of cortisol. They further hypothesized that depression during pregnancy would be more melancholic and depression during the postpartum period would be more atypical (81). This was an interesting idea that mapped on to the inherent physiological changes that occur in the HPA axis in pregnancy and the postpartum, as discussed above. Now, 12 years later, recent reviews of the studies that have taken place over the past 20 years investigating how the HPA axis may be linked to PND have shown that 1) often no relationship exists between cortisol and depressive symptoms during the perinatal period in women, 2) of the studies that do show a relationship between the HPA and PND it appears that indeed depression in pregnancy is characterized by very different HPA profiles from those of depression during the postpartum period (6,7). During pregnancy a recent systematic review on antepartum depression and cortisol levels shows that of the studies reporting an association between maternal depressive symptoms and cortisol, *elevated* cortisol concentrations during the 2^{nd} and 3^{rd} trimester are most often associated with antepartum depressive symptoms (6,7). Others report that maternal morning

cortisol levels are reduced in pregnant women with major depression as diagnosed by a clinician (82). In line with this, O'Connor et al (2014) note that pregnant women with major depression have significantly lower cortisol levels at waking but overall elevated average cortisol levels compared to controls (83). Interestingly CBG, which is responsible for free cortisol levels in serum (18), and has also be implicated in depression (84) but less well studied with regards to PND. Recent research has shown that both total serum levels of cortisol and CBG are negatively associate with depression symptoms in late pregnant women such that elevated levels of total cortisol or CBG are related to lower scores of depression during late pregnancy (43).

During the postpartum period there is a fall in cortisol and CRH in the days and weeks after birth. This decrease in cortisol and CRH may be linked to the onset of postpartum depression. Of the studies that do show a relationship between changes in the HPA axis and postpartum depression it is *lower* cortisol levels that are evident in women with postpartum depression (up to one year postpartum)(6,82,85,86). Recently Glynn et al (2013) proposed that prenatal HPA axis dysregulation may be predictive of postpartum depression with elevated or accelerated pCRH trajectories during gestation being associated with an exaggerated postpartum drop in cortisol leading to postpartum depression (87,88). Antepartum and postpartum depression are often in continuum and a recent study has shown that pregnant women with consistently elevated salivary cortisol levels have increased ante- and post-natal self-reported mood symptoms (89). This points to the value of longitudinal research in determining the link between the HPA axis and maternal mood. Although these findings show that HPA axis dysregulation is linked to PND, more research is needed to determine how depression during pregnancy and/or the postpartum period is related to different factors of the HPA axis.

Furthermore, this future research needs to take into account the severity of depression, depression subtype and time point during pregnancy or postpartum.

One way to understand how the HPA axis is dysregulated is to assess how effective treatments alter its output via cortisol concentrations or HPA responsiveness. Although limited, some research shows that mothers with a high risk of developing depression who attend cognitive behavior therapy (CBT) classes have lower salivary cortisol levels and display lessened stress reactivity after a few sessions of CBT compared to non-treated high risk mothers (90,91). Others have shown that yoga or a support group can reduce depression, anxiety and anger in pregnant women as well as significantly reduce salivary cortisol levels (92). SSRIs are often the first-line of treatment for PND (2,93,94) and even though SSRIs can alter the HPA axis in some individuals with depression (95,96) and animal models are pointing to a role of SSRIs in attenuating the stress response during the postpartum period (97), clinical research has not clearly shown an effect of SSRIs on the HPA axis in women during the perinatal period (43).

Although there are significant differences between pregnancy and the postpartum period in humans and rodent models, rodents, and other animal models, can be valuable tools to manipulate and understand the contribution of the HPA axis to perinatal depression. A growing body of rodent research is showing that stress, or activation of the HPA axis prior to, or during, gestation can be a valuable model of postpartum depression. This activation of the maternal HPA axis prior to parturition can alter the HPA axis postpartum by decreasing basal corticosterone (similarly to what is seen in women with postpartum depression) and lead to increased depressive- and anxiety-like behavior in the rat dam postpartum (97-103). More recent research has shown that dysregulation of the HPA axis at the level of CRH neurons in the PVN (specifically the loss of K+/Cl-co-transporter) is sufficient to induce postpartum behavioral

profiles modelling postpartum depression suggesting a potential target for future treatments (104).

As with research on the link between HPA activation and depression during pregnancy in women, rodent models are not clear on how activation of the HPA axis during gestation affects depressive-like behavior in the pregnant female. We do know that repeated stress during gestation can lead to decreased basal and stress-induced corticosterone levels in late pregnancy and decreased GR density in the CA3 region of the hippocampus (105,106). How these changes link to depressive- or anxiety-like behaviors in rodents during pregnancy remain to be determined.

Future directions

There is much more research that is needed in order to understand the link between the HPA axis and maternal mental illness. First, the mechanisms underlying HPA axis regulation and dysregulation in the *human* brain during pregnancy and postpartum are relatively unknown. Much of what we know about the perinatal period at the neural level comes from rodent models (e.g. (42)). However, there are marked differences between gestation in humans and rodents (namely the rodent placenta does not produce pCRH and therefore does not exert effects on the perinatal HPA axis). In addition, we still have much to learn about the basic sex differences in the regulatory pathways feeding into the HPA axis (see review in (63,107), but evidence is mounting that the hormone fluctuations of the estrous/menstrual cycle may underlie female vulnerability to mental illness. Given that the perinatal period exposes females to even more extremes in hormone fluctuations, the connection between the HPA axis during the perinatal period and maternal mental illness should be an important target for future research.

Since our ability to study the human brain is limited one theoretical approach that may be valuable in understanding the relationship between the HPA axis, stress, hormone fluctuations and maternal mental illness is The Reactive Scope Model. This model expands the Allostasis Model for stress, and considers the delicate balance of maintaining homeostasis in the face of adaptive change (108). Pregnancy itself is not a disease state, yet it makes the body more *vulnerable* to a range of pathologies, from mood disorders to hypertension (109), diabetes (110), or cardiovascular disease (109). In the Reactive Scope Model, the range between Predictive/Reactive Homeostasis (adaptive - normal, non-pathological state) and Homeostatic Overload (maladaptive - pathological) becomes smaller when the physiological mechanisms maintaining homeostatic balance increasingly compensate for pressure on the system - elephants maintaining the balance on a seesaw rather than mice maintaining the balance. As the range between adaptive and maladaptive gets closer together, the likelihood of the body to 'tip' into pathology increases, the *vulnerability* increases. The third and "fourth" trimester (the first days and months into postpartum) represent a unique homeostatic state in a woman's body - in balance yet pushed to an extreme. Considering the HPA axis specifically, when additional predispositions are added that make the threshold even smaller, any activation beyond the normal functioning system such as an acute stress from any number of sources - a difficult birth, challenges with breastfeeding, adjusting to new motherhood - may push the maternal HPA axis into a state of overload and dysregulation. Applying this model allows researchers, clinicians, women, and their care team to consider the benefits of more "holistic" approaches to decrease the likelihood of her activating the stress pathways. Perhaps this is the underlying reason for the growing evidence that mindfulness, labor support and postpartum support have a positive effect on maternal mental health (111-114).

Clinical studies often rely on peripheral biomarkers of the HPA axis, of which cortisol is the most popular due to its detectability in saliva, hair or urine. However, AVP and CRH (during pregnancy) can also be detected from serum samples and it may be that the relationship of these factors to each other, or their change across time, is more important than the change in any one factor at any given time point. Previous research suggests that the progesterone to estradiol ratio across parturition is important for maternal attachment (115) and thus it may be that the AVP-Cortisol ratio or Cortisol-CRH ratio may be a better indicator of PND. That being said, it could also be the change over time of one, or a few, of these HPA biomarkers is a better indicator of PND. For these type of studies to be performed serum or plasma samples would have to be collected regularly and the relationship of these factors with their binding globulins would need to be accounted for.

Functional studies of the HPA axis prior to pregnancy may also be valuable in detecting how the HPA axis during pregnancy or the postpartum period may increase the susceptibility to the development perinatal depression or anxiety. Although there is limited research in this area, promising work by Bloch et al (2005) shows that women with a history of postpartum depression (PPD) have enhanced sensitivity at the level of the pituitary-adrenal axis to CRH stimulation tests (116). Thus, HPA stimulation tests may be valuable tools to investigate the risk of dysregulation of the HPA axis and how it relates to perinatal mental illness.

It should also be noted that the variability amongst individuals, the interplay between systems, and how homeostasis is maintained during pregnancy from the endocrine pathways to the level of cellular signaling is far too complex (and grossly understudied) for simple solutions to a growing health concern: 1 in 5 women will have a mental illness during the perinatal period!

We need more resources dedicated for research on maternal mental illness to effectively treat and prevent the effects of these illnesses on mother, child and family.

Conclusions

The first recorded accounts of postpartum depression occurred in the 11th or 13th century where it was stated that “if the womb is too moist, the brain is filled with water, and the moisture running over the eyes, compels them to involuntarily shed tears” (117). Although we have moved forward in our understanding of perinatal depression, we still are in our infancy as to how a mother’s physiology may be involved in her mental health during the perinatal period.

Figure Legend

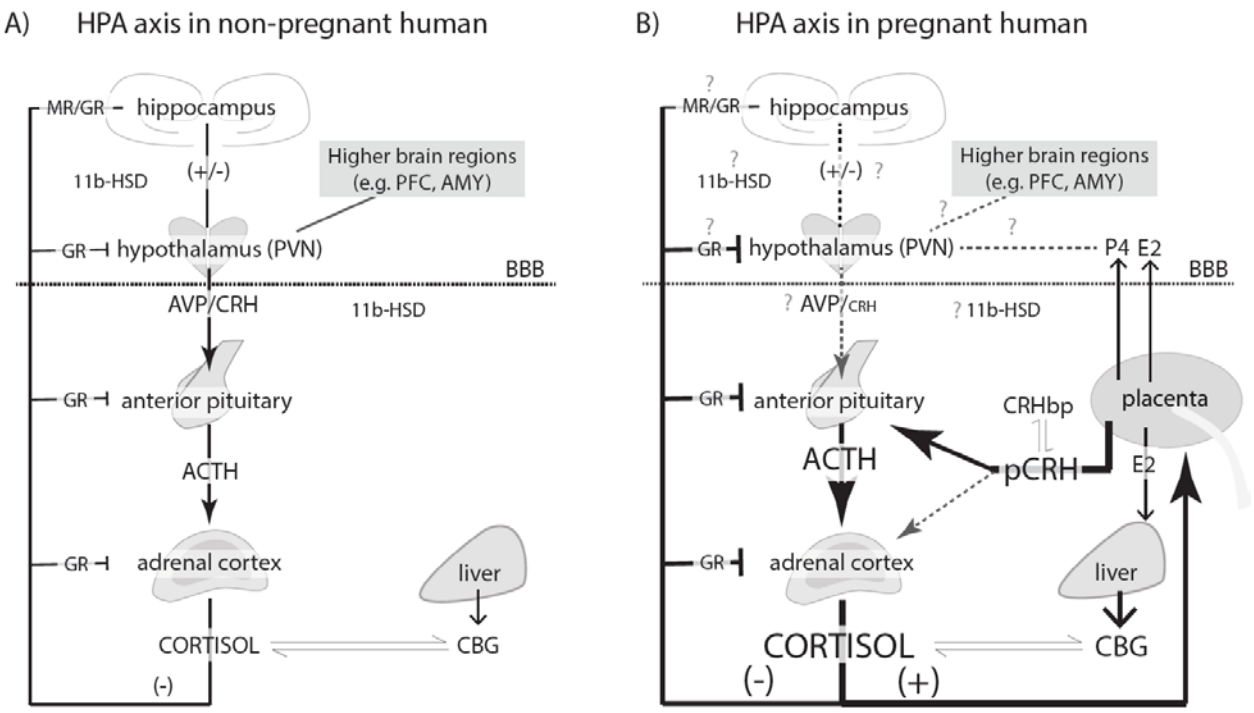

Figure 1. Schematic representation summarizing the key components of the hypothalamic-pituitary-adrenal (HPA) axis in (A) non-pregnant and (B) pregnant humans. Cortisol release by the hormonal cascade along the HPA axis regulates the axis in a classic negative feedback loop, acting through glucocorticoid receptors (GR) and both GR and mineralocorticoid receptors (MR) in the hippocampus. Due to the addition of the placenta during gestation, the dynamics of this system greatly change. As displayed by thicker lines, and larger font, cortisol increases due to positive feedback loop via placental corticotropin releasing hormone (pCRH) stimulating the anterior pituitary and possibly the adrenal directly. Most of what is known about the dynamics of the HPA axis and the potential dysregulation of this axis in relation to mental illness has come from studies conducted in young male humans and rodent models. Given the very different dynamics of the female HPA axis, especially during pregnancy, many of the points of

385 dysregulation of the HPA axis related to perinatal mental illnesses, such as postpartum
386 depression, remain to be investigated and are represented by question marks and/or dotted lines.
387 11β-HSD - 11β-hydroxysteroid dehydrogenase, ACTH - adrenocorticotropin releasing hormone,
388 AMY - amygdala, AVP – arginine vasopressin, BBB-blood brain barrier, CBG – corticosteroid
389 binding globulin, pCRH – placental corticotrophin releasing hormone, E2 - estradiol, GR –
390 glucocorticoid receptor, MR – mineralocorticoid receptor, P4 - progesterone, PFC – prefrontal
391 cortex, PVN-paraventricular nucleus.

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