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

2 (minireview)

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19

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23

24 Abstract

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

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

41

42 **Introduction**

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

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

65 **HPA and the Perinatal Period**

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

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

88 (11 β -HSD) converts glucocorticoids to an inactive form and, with CBG, determines the
89 bioavailability of cortisol to bind the different receptor types (16-18).

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

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

111 continues to stimulate cortisol production which results in a positive feedback loop (Figure 1B).
112 CBG levels also increase during pregnancy and decrease in the weeks and days prior to delivery
113 (35). The rise in CBG levels during gestation is not enough to decrease (or ‘normalize’) free
114 cortisol concentrations; possibly due to the high affinity of CBG for rising progesterone levels
115 (36).

116 Another marked difference between hypothalamic CRH and pCRH is that circulating
117 pCRH is bound to a binding protein, CRH-BP. CRH-BP can modify the bioactivity of pCRH
118 throughout pregnancy. This is especially true in the last few weeks of pregnancy when CRH-BP
119 levels fall by nearly 50% and free circulating pCRH levels rise (37). With changes in CRH-BP,
120 pCRH concentrations increase exponentially across pregnancy (likely due to the positive
121 feedback loop with cortisol), and a decreased response to cortisol negative feedback occurs along
122 the HPA axis (38). Thus, circulating cortisol concentrations continue to increase throughout
123 pregnancy. Cortisol concentrations at the end of a healthy pregnancy reach concentrations only
124 seen in non-pregnant individuals with severe HPA dysregulation, such as Cushing’s Disease
125 (30).

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

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

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

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

156 It is interesting to note that glucocorticoid levels differ with maternal experience in both
157 humans and rodent models. For example, multiparous women show a smaller magnitude of
158 change in circulating cortisol levels postpartum compared to primiparous women (47) and
159 biparous female rats have less pronounced changes in corticosterone and CBG levels compared
160 to age-matched primiparous females (48). Others report that parity and feeding type (lactation vs
161 bottle feeding) play a role in cortisol levels and HPA function postpartum such that breastfeeding
162 multiparous mothers show reduced cortisol levels and reduced cortisol responsiveness to
163 psychology stress compared to non-breastfeeding multiparous mothers (49,50). In this study,
164 feeding type did not affect cortisol levels of primiparous mothers (49,50). This suggests that
165 maternal experience may act to further alter the maternal HPA axis. This is perhaps not
166 surprising given that glucocorticoids play an important role in the initiation and maintenance of
167 maternal care-giving behaviors, particularly in primiparous mothers. For example, Fleming et al
168 (1997) report that first-time mothers with elevated cortisol concentrations are more attracted to
169 their own infant's body odor (51). In rodents, corticosterone is important for the pup retrieval,
170 maternal memory, and maintenance of maternal care (52-54). Thus maternal experience alone
171 may be an important regulator of the HPA axis during the postpartum period and, perhaps,
172 during pregnancy.

173

174 **HPA and Perinatal Mood Disorders**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

292 profiles modelling postpartum depression suggesting a potential target for future treatments
293 (104).

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

301

302 **Future directions**

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

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

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

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

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

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

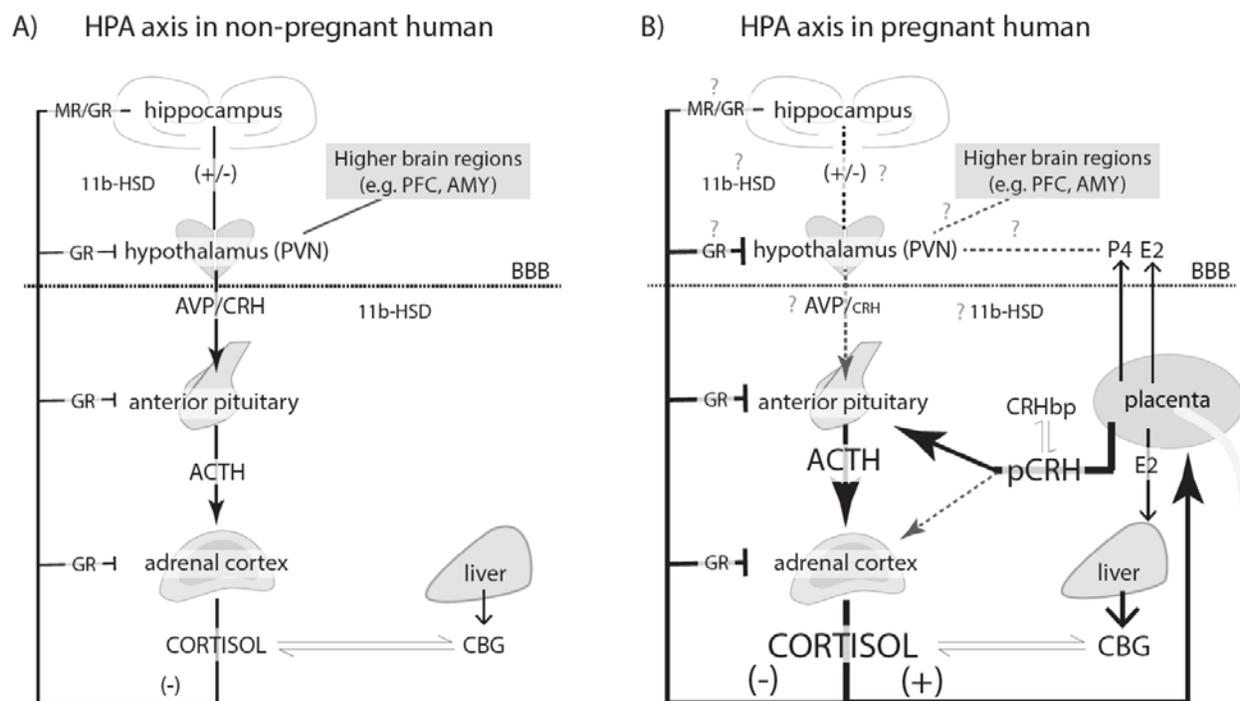
362

363 **Conclusions**

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

369

370

371 **Figure Legend**

372

373

374 **Figure 1.** Schematic representation summarizing the key components of the hypothalamic-
 375 pituitary-adrenal (HPA) axis in (A) non-pregnant and (B) pregnant humans. Cortisol release by
 376 the hormonal cascade along the HPA axis regulates the axis in a classic negative feedback loop,
 377 acting through glucocorticoid receptors (GR) and both GR and mineralocorticoid receptors (MR)
 378 in the hippocampus. Due to the addition of the placenta during gestation, the dynamics of this
 379 system greatly change. As displayed by thicker lines, and larger font, cortisol increases due to
 380 positive feedback loop via placental corticotropin releasing hormone (pCRH) stimulating the
 381 anterior pituitary and possibly the adrenal directly. Most of what is known about the dynamics of
 382 the HPA axis and the potential dysregulation of this axis in relation to mental illness has come
 383 from studies conducted in young male humans and rodent models. Given the very different
 384 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.

392

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