Original contribution

The HPA axis and perinatal depression: a hypothesis

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Summary

Episodes of depression and anxiety are as common during pregnancy as postpartum. Some start in pregnancy and resolve postpartum, others are triggered by parturition and some are maintained throughout. In order to determine any biological basis it is important to delineate these different subtypes. During pregnancy, as well as the rise in plasma oestrogen and progesterone there is a very large increase in plasma corticotropin releasing hormone (CRH), and an increase in cortisol. The latter reaches levels found in Cushing’s syndrome and major melancholic depression. Levels of all these hormones drop rapidly on parturition.

We here suggest that the symptoms of antenatal and postnatal depression may be different, and linked in part with differences in the function of the hypothalamic-pituitary-adrenal (HPA) axis. There are two subtypes of major depression, melancholic and atypical, with some differences in symptom profile, and these subtypes are associated with opposite changes in the HPA axis. Antenatal depression may be more melancholic and associated with the raised cortisol of pregnancy, whereas postnatal depression may be more atypical, triggered by cortisol withdrawal and associated with reduced cortisol levels. There is evidence that after delivery some women experience mild bipolar II depression, and others experience post traumatic stress disorder. Both of these are associated with atypical depression. It may also be that some women are genetically predisposed to depression of the melancholic type and some to depression of the atypical type. These women may be more or less vulnerable to depression at the different stages of the perinatal period.

Keywords: Depression; antenatal; postnatal; cortisol; HPA axis.

Introduction

There is good evidence for several psychosocial risk factors for both antenatal and postnatal depression, especially the lack support of a partner or confidante (Warner et al., 1996; Gurel & Gurel, 2000). However, the psychosocial factors do not account for all the variance. It is quite probable that biological causes also have a major impact. There are large changes in the levels of several psychologically active hormones over the perinatal period (Fig. 1). Their evolutionary role is probably to help coordinate both parturition and the new maternal role of the mother (Carter et al., 2001). But in vulnerable women it is likely that these large hormonal changes also contribute to changes in mood.

The primary aim of this paper is to suggest that the physiologic changes of the hypothalamic-pituitary-adrenal (HPA) axis in pregnancy, hypercortisolaemia, and in the postpartum period, cortisol withdrawal, may contribute to the depression that can occur during these periods. The symptom profile of depressive episodes may differ antenatally and postnatally. Melancholic depression is associated with raised cortisol levels, and atypical depression with low cortisol. In addition, women with different genetic predispositions (e.g. with genetic differences in the glucocorticoid receptor (GR) polymorphisms) may be at risk of becoming ill with a depressive episode at different times in the perinatal period.

Depression and anxiety during pregnancy and postpartum

The time course of depression in relation to childbirth is complex. While some episodes are triggered specifically
by parturition (Cooper & Murray, 1995) others appear for the first time during pregnancy and can be resolved by childbirth. These two groups may well have a different biological basis or vulnerability. In addition, some women are depressed both during pregnancy and postpartum. Thus in order to understand the biological basis and pathophysiology of perinatal affective disorder it is essential to distinguish the time courses of onset and remission.

Research and discussion of perinatal affective disorder still focuses mostly on postnatal depression. Nevertheless, there is now much evidence that depression is at least as common during pregnancy as postnatally (Kitamura et al, 1996; Evans et al, 2001; Josefsson et al, 2001). In a recent study we have found that 9.1% of women scored above the threshold of depression (13 points or more, i.e. the established cut-off for major depression) on the Edinburgh Postnatal Depression Scale (EPDS) at 8 weeks postpartum. This is similar to the findings of many other studies. However, only about one third of these, or 3.4% of the total cohort, scored in this range postpartum and not also while pregnant (Fig. 2) and (Heron et al, 2004). The majority of women who were depressed postnatally have been depressed in pregnancy also. At 32 weeks gestation the percentage scoring 13 or over on the EPDS was 13.6%.

It does seem that there is a minority of women, depressed in the postnatal period, who are specifically prone to depression triggered by parturition (Cooper & Murray, 1995). However, a recent review of the literature concluded that the strongest predictors of postnatal depression were depression during pregnancy, anxiety during pregnancy, experiencing stressful life events during pregnancy or the early puerperium, low levels of social support, and a previous history of depression (Robertson et al, 2004).

Anxiety follows a similar pattern to depression; most women who are anxious postnatally are also anxious antenatally. In addition, antenatal anxiety is an extra risk factor for postnatal depression. Women who were anxious antenatally had a threefold increased risk for symptoms of depression in the postnatal period (Heron et al, 2004).

Other mental disorder triggered by parturition

There are several different forms of mental disorder that are triggered by childbirth (Steiner, 1998), and it is of interest to consider these also when considering the hormonal contribution to perinatal mental disturbance. First and most serious is postnatal psychosis. This is clearly triggered by parturition, starts in the first two weeks postpartum, and is often of the manic depressive type. It is rare, occurring after 1/500 to 1/1000 births; however the risk of recurrence is very high. A family or
personal history of manic depression are known risk factors (Robertson et al, 2004; Kendell et al, 1987). The incidence of schizophrenia is not affected by pregnancy or parturition (Kendell et al, 1987; Davies et al, 1995).

At the other end of the spectrum is the blues, experienced by up to 80% of mothers, depending on which scale is used for measurement (Stein, 1980; Kennerley & Gath, 1989). This is a period of lability of mood, crying, and headaches, that starts on about the third day postpartum and peaks on days 3–5. Elevated scores on a blues questionnaire, or a depression scale in the first postpartum week, are a risk factor for later depression, (Hannah et al, 1992).

Some women become over-elated postpartum (Glover et al, 1994; Lane et al, 1997). This has been called the highs and is a mild form of hypomania or bipolar II. It has a distinct range of symptoms and a different time course from the blues, starting on the first, rather than the third or fourth, postpartum day. It also is a risk factor for later depression, (Hannah et al, 1992).

The physiological changes of several hormones, including those of the hypothalamic pituitary gonadal and hypothalamic pituitary adrenal (HPA) axes may play an important role in the cause of perinatal depression and other mental illness that occur at this time (for a review see Parry et al, 2003). Here we are focussing on the HPA axis, but will first discuss the possible contributions of oestrogen and progesterone.

The role of oestrogen and progesterone

It is clear from animal models that sex hormones such as oestrogen and progesterone, which rise greatly during pregnancy, and then show a sharp drop immediately after parturition, have a great effect on the functioning of parts of the brain. They act on monoamine rich regions such as the locus coereleus and the raphe, which are known in turn to be involved in the control of mood. For example, oestradiol has been shown to regulate the serotonin (5-HT) system, which has been strongly implicated in affective disorders (Ostlund et al, 2003). Oestrogen and progesterone are thus good candidates for a role in the etiology of perinatal mental disturbance.

Although Harris et al (1994) have shown that women with the blues suffered a greater drop in progesterone from the antenatal to postnatal period than controls, studies which have examined peripheral levels of oestrogen and progesterone in women with or without postnatal depression have generally proved negative (Wieck, 1989; Bloch et al, 2003). It may well be that women prone to an affective disturbance in response to the large changes in sex hormone levels during pregnancy and parturition, differ from others in their central reaction to these changes.
changes, rather in the actual level of their sex hormones (Harris et al, 1994). Some evidence for a sex hormonal component for postnatal depression is given by its association with other reproductive endocrine related mood disorders, especially the premenstrual syndrome (Sugawara et al, 1997).

Bloch et al (2000, 2003) have provided the best evidence so far for a role for sex hormones in the generation of postnatal depression. They investigated the possible role of changes in gonadal steroid levels by simulating two hormonal conditions related to pregnancy and parturition in non-pregnant women. The very high oestrogen and progesterone levels of pregnancy, and the withdrawal from these high levels postpartum, were induced in women both with and without a history of postnatal depression. The steroids were given for 8 weeks and then withdrawn under double-blind conditions. Five of the eight women with a history of postnatal depression (62.5%) and none of the eight women in the comparison group developed significant increases in depressive symptoms during the withdrawal period. Even though this was a small study, the authors plausibly conclude that these results do provide some direct evidence in support of the involvement of these hormones in the development of postnatal depression in a subgroup of women. This study supports the hypothesis that susceptible women have a different sensitivity to the increase and/or withdrawal of these hormones rather than different levels of the hormones themselves (Rubinow et al, 1998).

Ahokas and colleagues have shown in small studies that oestradiol was successful in the treatment of both postnatal depression (Ahokas, 2001) and postnatal psychosis (Ahokas et al, 2000). At baseline the women had low serum oestradiol concentrations. Their results add to the evidence that with a sub-group of subjects with postpartum depression, levels of oestradiol may have a role in the pathophysiology of this condition, and may be an option in treatment (Gregoire et al, 1996). Kumar et al (2003) tested oestradiol in a clinical trial, in women with a history of postnatal psychosis, beginning within 48 hours after delivery. They found that oestradiol at all dose regimens did not reduce the rate of relapse, although there was a suggestion that those on the highest dose needed less neuroleptic medication such as chlorpromazine and haloperidol. More research with larger cohorts is clearly needed in this area.

The stress system and the gonadal system are generally closely interrelated (Rivier et al, 1986). For example, in the non pregnant population, ACTH inhibits the secretion of gonadotropin releasing hormone (GnRH) from the arcuate nuclei of the hypothalamus and glucocorticoids inhibit both GnRH secretion and reduce tissue sensitivity to sex hormones (Mastorakos & Ilias, 2003; Kalantaridou et al, 2004). However during pregnancy the activity of the HPA axis is not inversely related to oestrogen and progesterone, which together with CRH are produced from the placenta, and all increase markedly, although with a different time course (Fig. 1).

The studies described in this section provide some evidence that withdrawal of sex hormones may precipitate postnatal depression in vulnerable subjects. There may be a parallel response to cortisol withdrawal in some women also.

The role of the HPA axis during pregnancy and postpartum

The HPA axis is increasingly regarded as central to affective disorder (Tsigos & Chrousos, 2002). Sufferers from melancholic depression have significantly raised cortisol levels, and also fail to suppress cortisol output in the dexamethasone suppression test (Meyer et al, 2001). In contrast, those with atypical depression have been reported to have a hypofunctional HPA axis (Bouwer et al, 2000; Gold et al, 2002a; Gold & Chrousos, 2002).

The function of the HPA axis changes considerably during pregnancy and postpartum (Magiakou et al, 1997; Wadhwa et al, 1996). CRH, the driving hormone of the HPA axis which is normally only released from the hypothalamus into the portal circulation, and is not detectable in the plasma, is generated and released into the blood stream, from the placenta as pregnancy progresses (see Fig. 3). Plasma CRH levels start to become detectable at mid gestation and rise exponentially towards term. Placental CRH is produced in syncytiotrophoblast cells, in placental decidua and fetal membranes (Riley & Challis, 1991; Jones et al, 1989), and CRH expression increases as much as 100 times during the last 6–8 weeks of pregnancy (Frim et al, 1988; Kalantaridou et al, 2003). The biological activity of CRH is attenuated by the presence of circulating CRH binding protein produced by the liver and the placenta (Challis et al, 1995; Linton et al, 1993). However, concentrations of this binding protein decrease during the last 6 weeks of pregnancy leading to elevations of free CRH. CRH may be the placental clock triggering the onset of parturition (McLean et al, 1995) and in animal research with sheep it has been shown that antalarmin, a CRH antagonist, can delay parturition (Challis et al, 2000; Majzoub & Karalis, 1999; Chan, 1998).
Cortisol levels also rise considerably during gestation, probably driven by this raised placental CRH, and at the end of pregnancy, reach values comparable to those found in Cushing’s disease or in severe depression (Magiakou et al, 1997). This increase appears to be more pronounced in the evening, with a flattening in the diurnal pattern of output (Kammerer, Taylor and Glover, unpublished observations). The early morning peak, which occurs 30 min after awakening, is unchanged in late pregnancy and in the postpartum period ((de Weerth & Buitelaar, 2005a) and unpublished observations). At the end of pregnancy the ratio free/total cortisol in the plasma also increases, meaning that more of the total will be physiologically available (Linton et al, 1993).

Pregnancy buffers the physiological responses to stress, especially towards term (de Weerth & Buitelaar, 2005b). There is evidence that towards the end of pregnancy well, non depressed, women lose the cortisol response to an acute stressor. Kammerer et al (2002) showed that whereas non perinatal control women showed a strong cortisol response to an acute stressor, women with fear of labour were characterized by changes in noradrenaline but not in ACTH, cortisol or beta-endorphin before and during a cold pressor test (Saisto et al, 2004).

Blood pressure responsitivity to cognitive challenges has also been reported to be blunted at the end of pregnancy with well participants (Matthews & Rodin, 1992). DiPietro and her group found a heart rate and electrophysiological response to repeat administration of a cognitive challenge to diminish from 24 to 36 weeks of pregnancy (DiPietro et al, 2003). Blunted renin response has been observed after thermal stress (Vaha-Eskeli et al, 1992). Compared with non pregnant women, pregnant women report less pain. Women with fear of labour were characterized by changes in noradrenaline but not in ACTH, cortisol or beta-endorphin before and during a cold pressor test (Saisto et al, 2004).

Maternal cortisol levels reach their maximum very high levels during delivery, both vaginal and caesarean, and are often several times the normal non pregnant level (Gitau et al, 2001). Cortisol levels drop postpartum, although it can be some weeks until they reach normal...
values. The dexamethasone suppression test also takes some weeks to normalise (Owens et al, 1987).

### Melancholic and atypical depression in the perinatal period

Depression is a heterogeneous illness and two of its subtypes are melancholic depression and atypical depression (Table 1). Melancholic depression is characterised by loss of appetite and sleep; sufferers are anxious and lose responsiveness to the environment. In contrast those with atypical depression have symptoms which are the reverse. They overeat and oversleep, are lethargic and reactive to the environment. They share many symptoms with sufferers from chronic fatigue syndrome and seasonal affective disorder. Those with melancholic depression tend to be worse in the morning and those with atypical depression worse in the evening. However it should be noted that many sufferers from depression do not fully conform to either of these classifications. About 15–30% of patients with major depression present with an atypical episode and 25–30% with a melancholic type (Gold et al, 2002b; Matza et al, 2003).

Melancholic and atypical depression have also been found to have opposite disturbances in the HPA axis, with the former showing an activated HPA axis, raised plasma cortisol levels and some evidence for a strong CRH drive. In contrast, the latter appear to have a down regulated HPA axis, less CRH and possibly lower than normal cortisol output (Gold & Chrousos, 2002). Whereas those with melancholic depression fail to suppress cortisol output after dexamethasone, those with atypical depression have an exaggerated suppression (Levitan et al, 2002). It seems that high levels of cortisol can stimulate a specific subgroup of CRH neurones within the paraventricular nucleus of the hypothalamus which in turn stimulates the release of noradrenaline in the brainstem. Cortisol also activates the CRH system in the amygdala. These are two of several possible mechanisms by which peripheral cortisol can affect brain function in a way that controls mood.

One might expect that a vulnerability to melancholic depression would worsen during pregnancy, with a natural increase of cortisol, whereas those with a vulnerability to atypical depression might improve as the cortisol level normalised. Conversely those with a vulnerability to atypical depression might be more prone to postnatal depression when there is a marked withdrawal of cortisol. As with the depressive response to oestrogen and progesterone withdrawal, it is possible that vulnerable women are especially sensitive to the altered levels of cortisol in the perinatal period.

Currently, there is no good published data that shows whether depression during pregnancy differs in symptom profile from depression postpartum and whether either differ from depression at other times. While the prevalence rates of depressive episodes in the perinatal period are well researched, the extent to which symptoms of depression are confounded by pregnancy has not been well explored (Gavin, 2005).

It is in support of our hypothesis that atypical depression, rather than melancholic depression, is associated with bipolar II or hypomania, as “the highs” are often triggered postpartum, and are associated with later depression (Glover et al, 1994; Lane et al, 1997; Heron et al, 2004). PTSD is also quite common after childbirth (Cohen et al, 2004) and is associated with atypical rather than melancholic depression. PTSD may be precipitated in vulnerable women by the high cortisol of parturition, PTBD.

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**Table 1. Differences between melancholic and atypical depression**

<table>
<thead>
<tr>
<th></th>
<th>Melancholic</th>
<th>Atypical</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>hyperaroused, anxious, relatively unreactive to environment</td>
<td>hypoaroused, apathetic, generally reactive to environment</td>
<td>Gold et al, 2002b</td>
</tr>
<tr>
<td></td>
<td>weight loss, undersleeping</td>
<td>weight gain, oversleeping, leaden paralysis, interpersonal rejection sensitivity</td>
<td>Akiskal &amp; Benazzi, 2005</td>
</tr>
<tr>
<td>Cortisol output</td>
<td>worse in morning</td>
<td>worse in evening</td>
<td>Stewart et al, 2005; Bouwer et al, 2000</td>
</tr>
<tr>
<td>CRH</td>
<td>high</td>
<td>low</td>
<td>Gold &amp; Chrousos, 2002</td>
</tr>
<tr>
<td>Dexamethasone suppression test</td>
<td>high suppression</td>
<td>low suppression</td>
<td>Levitan et al, 2002</td>
</tr>
<tr>
<td>Response to prednisone treatment</td>
<td>–</td>
<td>yes</td>
<td>Bouwer et al, 2000</td>
</tr>
<tr>
<td>Sympathetic activity</td>
<td>increased</td>
<td>decreased</td>
<td>Gold &amp; Chrousos, 2002</td>
</tr>
<tr>
<td>Strong Link with bipolar II</td>
<td>no</td>
<td>yes</td>
<td>Akiskal &amp; Benazzi, 2005</td>
</tr>
</tbody>
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and the sudden cortisol withdrawal postpartum. Like atypical depression, PTSD is characterised by hypoco-
rtsisolaemia (Griffin et al, 2005).
It also may be relevant that anxiety during pregnancy appears to be a risk factor for postnatal depression (Heron et al, 2004). It may be that in some women the high cortisol during pregnancy stimulates feelings of anxiety, whereas the cortisol withdrawal on parturition causes a depression. However it must be emphasised that changes in the HPA axis can be controlled at many different levels of the system, including the hippocampus, the hypothalamus, the pituitary and the adrenal. Feedback mechanisms and receptors at all these sites can be either up or down regulated under different circumstances. The changes that occur during pregnancy, although sharing some features with melancholic depression such as hypercortisolaemia, also differ in other respects, such as the peripheral increase of CRH.

There is some preliminary support for the idea that the changes in the HPA axis during the postnatal period may be of the type associated with atypical depression. Magiakou et al (1996) have shown that the postpartum period is associated with suppression of response to CRH, which was especially marked in those with the blues. They followed the pattern of increase in plasma ACTH after a challenge with CRH in 17 healthy euthymic women starting at the 20th week of gestation. 7 women developed the blues and 1 developed depression. Overall, the mean plasma ACTH response to an intravenous bolus of CRH was markedly blunted at 3 and 6 weeks postpartum but normal at 12 weeks. The mean plasma cortisol response was at the upper limit of normal at all 3 times. The blunting of ACTH was significantly more severe and long lasting in those with the blues or depression. This pattern of a suppressed ACTH response to CRH is similar to that observed in atypical rather than melancholic depression.

Parry et al (2003) have found decreased levels of cortisol in postnatally depressed women compared with non depressed postnatal controls. However this group also found reduced levels of cortisol in antenatally depressed women \( (n = 3) \) compared with non depressed pregnant women \( (n = 2) \). The small numbers mean that these results must be regarded as very preliminary. Bloch et al (2005) have also recently used their oestrogen and progesterone model of pregnancy and parturition in women, with and without a history of postnatal depression, with a CRH challenge test. They found that an acute bolus of CRH induced a significantly greater increase of cortisol in the antenatal model period in those with a history of postnatal depression. There were no differences between the groups responses in the postnatal model period. This is of interest, and shows the interaction between the gonadal systems and the HPA axis, but is clearly different from the physiological situation as their model did not include sustained addition or withdrawal of CRH or cortisol.

There is no evidence to date for the hypothesis that depression during pregnancy is more of the melancholic type, and little that there is any association between depression and anxiety during pregnancy and raised cortisol. However, in one recent study, Obel et al (2005) have shown that life event stress was associated with raised evening but not morning cortisol at 30 weeks gestation. Of course it may be that women who suffer from depression during later pregnancy differ from others in their central and psychological responses to raised cortisol that occurs during pregnancy, rather than higher than normal levels of cortisol itself. The blunting of response to a stressor at the end of pregnancy also raises questions about any possible link between cortisol and acute depression or anxiety as pregnancy progresses. However the studies to date were acute ones on a healthy population, rather than specifically with depressed or anxious women; the latter may well be different. Genetic variability may be relevant here.

**Possible genetic predispositions**

The recent studies of Caspi et al (2003) have shown that it is only if one looks at a combination of life events and genetic vulnerability that one obtains an understanding of vulnerability of depression in general. It is to be expected that vulnerability in the perinatal period will also be found to depend on genetic predisposition or resilience, with different relative contributions in different types of disorder, and in different individuals. The only gene polymorphism that has been identified so far in relation to perinatal mental illness is in the serotonin transporter (5-HTT) gene. Coyle et al (2000) have reported that variation at this gene exerts a substantial (odds ratio = 4) and important (population attributable fraction = 69%) influence on susceptibility to postnatal psychosis. However this may not be a very specific effect, as variation in this gene has also been recently reported to reflect a vulnerability to non-psychotic depression in the general population, when considered together with life events (Caspi et al, 2003).

Other polymorphisms that may be of especial interest with respect to perinatal depression are those for the glucocorticoid receptor. Cortisol regulates activity within
the HPA axis via multiple feedback inhibition loops at hypothalamic and pituitary levels (Chrousos & Gold, 1992). There are two types of intracellular glucocorticoid receptor: type 1, mineralocorticoid receptor (MR) and type 2, glucocorticoid receptor (GR). The MR has high affinity for cortisol and occupancy rates are high throughout the diurnal cycle, whereas GR has much lower affinity and only becomes occupied during the diurnal peak or stress related cortisol release (Reul et al, 1987). MR predominates in the hippocampus where cortisol binding results in a tonic inhibitory signal to the paraventricular nucleus (Cummings et al, 1983).

Several polymorphisms have recently been described at the GR receptor, with some individuals having a greater than normal response to the acute stress of a mental challenge and others having a blunted response (Wust et al, 2004, 2005). One might predict that those with the polymorphism that predisposes to higher cortisol responses would be more prone to melancholic and antenatal depression, and have elevated cortisol levels. In contrast those with the hyperresponsive polymorphism, may be more prone to atypical and postnatal depression, associated with low cortisol levels.

**Research gaps and hypotheses**

We are only beginning to study the possible biological contributions to antenatal and postnatal affective disorder. In this paper we have started to outline some of the possible complexity of the subject and identified important research gaps. To start to understand any hormonal contributions we need to differentiate women who are depressed or anxious during pregnancy and remit postnatally, from those whose symptoms appear to be triggered by parturition. These could well have different biological bases.

We need more detailed descriptions of depression both antenatally and postnatally. We should examine individual symptoms, such as reactivity to the environment and co-morbid anxiety (both symptoms that may help to distinguish atypical and melancholic depression) in a more detailed way than previously. It may be that depressions in pregnancy and the postpartum period do not exactly fit into the standard diagnostic criteria developed and tested at other times in women’s life. For example it is often reported that postnatally there is a considerably lability of mood (Kendell et al, 1981) and the two weeks of continuous symptoms required by criteria such as those of the “gold standard” DSM1V may not be appropriate. Both antenatally and postnatally there can be sleep, appetite, and concentration disturbances as well as fatigue, that are associated with normal physiological changes, or the presence of a new baby, and this also makes the use of established criteria for distinguishing major and minor depression more problematic for the perinatal period.

We suggest here that as well as the large rise and fall in oestrogen and progesterone that may contribute to perinatal affective disorder, the major changes in the function of the HPA axis could also play an important role. One would expect this role to be different antenatally from postnatally. Both symptoms and hormonal changes antenatally may be more of the melancholic type, associated with raised cortisol. Postnatally the cortisol withdrawal and lower HPA function would be predicted to be associated with atypical symptoms. Cortisol levels, across the day, need to be examined in depressed women both antenatally and postnatally to test these hypotheses. There is likely to also be a contribution from different genetic polymorphisms, and it will be of great interest to study a range of candidate genes in these women.

These ideas are presented with due caution with a hope that they may act as an impetus for further studies of these important and interesting questions.

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Perinatal depression and the HPA axis


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