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THE NEUROENDOCRINOLOGICAL ASPECTS OF PREGNANCY AND POSTPARTUM DEPRESSION

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Abstract

Introduction. Ties between the endocrine system and mental health are undeniably a consistent point of interest in modern day medicine. Furthermore, mental disturbances due to hormonal changes following childbirth have been mentioned in medical literature since Hippocrates. Considering the dramatic endocrine, paracrine and autocrine changes that occur during gestation, labour and postnatal phase, hormonal theories are not to be ignored in the treatment of postpartum disorders.

Results. Reproductive hormones are known to modulate behavioural, emotional and cognitive response, therefore rapid changes in estradiol and progesterone plasma concentrations during pregnancy and labour create a vulnerable terrain leading towards postpartum disorders. New research shows that women suffering from postpartum disorders have abnormal neural responses, suggesting a neuroendocrine explanation for postpartum syndromes.

Conclusion. To facilitate further research in this area, we present new information on several hormonal interactions and the psychiatric response involved in pregnancy and labour, offering an interdisciplinary outlook on pregnancy and postpartum disorders. There is enough evidence to suggest that estradiol, progesterone, oxytocin, cortisol and thyroid hormones are some of many hormones involved in postpartum syndromes and tackling their perinatal imbalance with pharmacological substituents or antagonists could be useful as an adjuvant form of treatment in future patients.

Key words: pregnancy, labour, postpartum, estradiol, progesterone, depression.

INTRODUCTION

Past methodological failures have impeded the progress of studying the biologic basis of postpartum disorders. Previous researchers encountered troubles in measuring the hormone concentration especially for the free plasma levels. There was a lack in consistency when applying a psychological test and scales across multiple studies ending up with various results. As well as some inappropriate assessments, the timing of blood sampling did not take place at regular intervals disregarding the hormonal changes which occur during breastfeeding. Seasonal hormonal variation and circadian rhythms were an often-overlooked factor. Due to the complex nature of endocrine relationships some studies which measured one hormone exclusively as opposed to the cascade of events are to be considered inadequate. We will focus on two neuroendocrine aspects: Perinatal hormonal changes – an etiological factor in developing postpartum psychiatric disorders; Hormonal therapy – an adjuvant treatment in postpartum syndromes.

Hormonal changes during pregnancy

The endocrine aspects of pregnancy are a unique interplay between three major components: the mother, the placenta and the fetus. There are many challenges the female body overcomes during pregnancy; a disturbance in any direction could possibly offer an explanation for mental health issues associated to pregnancy.

The hormonal changes associated to pregnancy can reach levels that mimic hyperthyroidism, pituitary adenoma, Cushing disease, diabetes mellitus, and more, these themselves being associated with psychiatric disturbances.

Not only sex steroid hormones imbalance but also cortisol reactivity has linked to perinatal depressive symptoms. Exposure to high levels of maternal stress during pregnancy has the potential to adversely impact maternal mental and physical health as well as fetal development (1). Women with hypothyroxinemia during early gestation are at risk for poor cognitive function throughout gestation, adjusted for depression and sleeping problems (2).

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The hormonal changes associated to pregnancy can negatively impact the circadian rhythm, which leads to insomnia, especially in mid-to-late pregnancy. Insomnia is known to be associated with depression and suicidal ideation.

Hormonal changes during labour and postpartum

The fetus plasma corticosteroids increase during labor as a consequence of fetal stress which signals the placenta to decrease estradiol and progesterone production as well as it stimulates the secretion of prostaglandins that act as contraction adjuvant.

Progesterone is the most abundant hormone in pregnancy. The dramatic drop in progesterone after birth may have a role in postpartum depression. A possible explanation is that progesterone and its cerebral metabolite known as allopregnanolone seem to decrease irritability. Ovaries will not start secreting progesterone again until the first menstrual cycle, which may create a temporary imbalance.

The organism adapts to lower levels of estradiol postpartum to favour lactation. A long-known fact is that estradiol can facilitate serotonergic transmission by enhancing serotonin synthesis and/or decreasing serotonin reuptake thereby alleviating depressive symptoms (3). The decreased estradiol levels have the opposite effect, depriving the organism of its natural defense against depression.

Beta-endorphins rise during labor, reach a peak immediately before delivery, and decline after parturition. High endorphin levels during labor and birth can produce an altered state of consciousness that can help cope with the process of giving birth. High endorphin levels can make future mothers feel alert, attentive and even euphoric after birth. In this early postpartum period, endorphins together with oxytocin are believed to play a role in strengthening the mother-infant relationship (4).

Testosterone is associated with greater reported mood disturbances after delivery.

Plasma corticosteroids reach a peak during labor and decrease significantly within 4 hours postpartum, making this an emotionally vulnerable period.

Mother provides the only source of thyroxine for the fetus in early gestation, maternal hypothyroidism may pose risks not only to the mother, but also to the fetus. Maternal thyroid function normally returns to pre-pregnancy levels approximately 4 weeks after delivery. However, we could find two types of thyroid dysfunction: postpartum thyroiditis characterized by transient hyperthyroidism or transient hyperthyroidism followed by transient or rarely permanent hypothyroidism due to estradiol dominance, links found between thyroid dysfunction and depression have been a point of interest for many studies throughout history. Plasma renin falls after childbirth. Sodium excretion rises and calcium excretion falls. Several days after birth, a rapid weight loss occurs.

Between high prolactin production, low estradiol, no progesterone, potentially lower dopamine and variations in thyroid hormones it is not uncommon that these imbalances produce an important psychological impact.

Prenatal depression

Although transient reactions of anxiety and sadness are common, most women navigate this transition without major psychopathology. However, for women who experience an episode of depression while pregnant, the effects on them and their offspring can be devastating.

Depression is the most common psychiatric morbidity in pregnancy, affecting more than 13% of pregnant women (5). Antenatal depressive symptoms are especially prevalent among adolescents, inner-city women, and women with past histories of major depression, less common in comparison to postpartum depression, yet none the less important (6). Since suicide is a leading cause of maternal mortality, recognizing and treating pregnancy depression is of a vital importance (7). To establish treatment for antepartum depression is particularly complicated and ethically challenging. Moreover, evidence indicates that if left untreated, depression can impair the neurocognitive development of the child. High cortisol levels associated with the emotional distress encountered in the prenatal depression have been linked to congenital fetal anomalies (8). When dealing with antepartum depression it is crucial to weigh the risks of pharmacological treatment *versus* the risk imposed by leaving the patient untreated. Little information exists on the use of tricyclic and other antidepressants in pregnancy and the usage of this form of treatment is reserved for a moderate to severe case, especially in the first trimester, since the drugs pass through the placental barrier and the blood-brain barrier thus increases the level of monoamines in the developing fetus and can affect the functional maturation of the brain. There have still not been a sufficient number

of well-controlled studies to assess the safety of antidepressants; the scientific community is mostly inclined not to treat depression during pregnancy by drugs (9). This opens room for more studies both of antidepressant as well as adjuvant hormonal therapies.

Postpartum depression

Postpartum depression (PPD), the onset of depressive episodes after childbirth, is the most common postnatal neuropsychiatric complication. Risk of depression is quite high for women during the perinatal period, one in approximately four women experience a major depressive episode during postpartum period. Researchers have identified several factors that contribute to this disorder, including hormonal imbalance, psychosocial changes and cultural factors. There is no common consensus among theorists regarding the nature of PPD, which could affect and compromise, from the early beginning, mother-infant bond, thus leading to deficiencies of the overall infant's psycho-social development.

In identifying PPD it is important to exclude postpartum "baby blues" defined as a mild transient dysphoria occurring in the first week after delivery that is recorded in 50 to 80% of new mothers (10).

Typically, symptoms related to hormone imbalance should only be prevalent for about 6 to 8 weeks after delivery usually. Postpartum depression is similar to many other forms of depression, although some symptoms are more associated with negative thoughts about the newborn, diagnosed by using the usual criteria, but with a pregnancy or postpartum onset.

The dangers of neglecting postpartum depression are of suicide and infanticide. If postpartum depression reaches psychotic intensity the infanticide rate is high (4.5%) compared to lower rates in episodes without overt depression (less than 1 %), and some of these appear to be accidental, without intent to kill (11). The treatment of breastfeeding mothers with depression raises several dilemmas, both SSRI and SNRI pass into the milk, which may concern the newborn`s well-being. The highest infant plasma levels, due to breastfeeding, have been reported for Fluoxetine, Citalopram and Venlafaxine, the first two mentioned have been correlated with the most infant adverse reactions. Regarding tricyclic antidepressants, their use has considerably decreased during the last decade hence no new information has been collected on this matter (12).

Hormonal imbalance during pregnancy is a possible cause of postpartum disorders.

Giving birth triggers permanent changes regarding the brain of the mother, namely the neurogenesis in the hippocampus, linked to depression. To this extent, Galea (13) showed that the steroid hormone-hippocampus interaction is mediated by sex and experience, in reproductive and cognitive ways. This could play a major role in treating and understanding postpartum depression, by understanding the hormonal modulation of neurogenesis involved in cognitive and stress regulation. Sex steroids pass the blood-brain barrier, and receptors for them are abundant in brain areas important for the regulation of emotions, cognition and behavior. The important effects of sex steroids on human behaviour are illustrated by, for example, the effect of reduced levels of these hormones on sexual drive and conditions such as premenstrual dysphoric disorder, premenopausal dysphoria, postpartum depression, postpartum psychosis, dysphoria induced by oral contraceptives or hormonal replacement therapy and anabolic steroid–induced aggression. A systematic review and meta-analysis showed that from the total of nineteen studies, eleven reported premenstrual syndrome (PMS) as a risk factor for postpartum depression (14). One explanation could be found in an older study given by Schiller (15) that targets the changing levels of estradiol and progesterone, which determine affective dysregulations, based on the hormonal fluctuations, during the premenstrual and postpartum periods. Moreover, animal models that utilize hormone manipulations to simulate pregnancy are useful for investigating mood effects that may be associated with hormone withdrawal. Lab testing of ovarian hormones decrease induced "depression" in female rats suggesting that postpartum decrease of estradiol and progesterone may contribute to depressive symptoms experienced after giving birth (16).

Significantly high testosterone levels were observed in women diagnosed with depression following childbirth in some studies (17). High testosterone could play a major role in mood changes in women, therefore the occurrence of postpartum depression (PPD). Moreover, cut off value of serum testosterone (42.71 ng/mL) could serve as a biomarker to PPD at 24-28 h after delivery, in a woman with 79% sensitivity, 63% specificity, positive predictive value of 68% and 74% negative predictive value (17). Bränn (18) conducted a study that revealed five biomarkers which may enhance postpartum depression, namely: TRANCE, HGF, IL-18, FGF-23 and CXCL1. First three biomarkers's values (TRANCE, HGF and IL-18) were

already higher in women suffering from depression during pregnancy. For instance, HGF is linked to pro-inflammatory processes and subclinical symptoms of depression, thus supporting other previous researcher's findings. Moreover, low values of CXCL1 and IL-18 correlate with stress responses.

Changes in neuroendocrine function during human pregnancy include a progressive increase in placental CRH and maternal adenocorticotropic hormone (ACTH) and cortisol levels over the course of gestation. ACTH, respectively cortisol can potentially increase the chances of puerperal depression (1). Succeeding, a longitudinal study, conducted on forty-nine women with uncomplicated pregnancies, revealed that higher cortisol metabolite production rates measured at 12 months enhance postpartum depression symptoms. BMI and urinary steroid metabolites were measured at 1 week and 1, 3, 6 and 12 months postpartum and postpartum depression was measured at 1, 6 and 12 months (19). Duan's review (20) shows that increasing the stress hormones and immune-inflammatory processes determined tryptophan to the production of neuroregulatory kynurenine pathway products and lowers the serotonin and melatonin pathways, resulting in decreased serotonin and melatonin levels, thus, enhancing postpartum depression. As a consequence, the newborns of mothers exposed to perinatal depressive symptoms displayed the reduced newborn social interactive behavior accompanied by decreased maternal serum PRL as well as increased maternal and neonatal serum cortisol (21).

Regarding hormonal changes in mothers with postpartum depression, a number of studies showed that low oxytocin levels in mothers with high psychosocial stress are linked to PPD. Moreover, early-life adversity, namely trauma, could have a major effect on the oxytocin level in mothers, thus preceding postpartum depression. On this regard, King *et al.* reveal that oxytocin receptor hypermethylation and vasopressin (AVP) intergenic regions hypomethylation found in mothers with persistent perinatal depression could both affect the oxytocin system, and also compromise maternal behavior, thus resulting in negative outcomes for the growing infant and also weakening the mother-child bond (22). Women with peripartum exposure to synthetic oxytocin were more susceptible to develop depressive symptoms in the first year after giving birth, than women who were not exposed (23).

When it comes to thyroid hormones up to 23% of all new mothers experience thyroid dysfunction postpartum compared with a prevalence of 3–4% in the general population (24). An interaction between thyroid autoantibodies and mood disorders was first evaluated in early 1980s, and ever since the correlation between thyroid autoimmunity and postpartum depression is still controversial, in spite of many studies on this topic. Furthermore, one study shows that fT4 concentrations below the 2.5th, 5th or 10th percentiles and with TSH within reference ranges are independently related to poor perceived cognitive functioning at first trimester of pregnancy and this association was independent of other psychosocial risk factors of cognitive impairment. Moreover, prospective follow-up showed that cognitive dysfunction remained significantly worse throughout the pregnancy in the hypothyroxinemia group compared to the TPO-Ab–negative control group with sufficient fT4 (between 10 and 90th percentiles). Women with hyperthyroxinemia showed less (but not significantly) cognitive dysfunction compared with the TPO-Ab–negative control group. Finally, within the hypothyroxinemic subgroups of women, those with elevated titres of TPO-Ab showed the poorest cognitive function (2).

In mid-pregnancy, women with high sleep reactivity report elevated symptoms of insomnia, depression, and anxiety, and are more likely to endorse suicidal ideation. (25) Age also seems to play a part in the development of insomnia-related pregnancy depression as seen in one of the review studies. Pregnant women between 16 and 24 years are at very high risk of mental disorders; services need to target resources for pregnant women under 25, including those in their early 20s (26).

Also, it is reported that smaller sample sizes placental CRH (pCRH) at 25 weeks postpartum has a major impact in mothers, regarding PPD symptoms after delivery, but larger sample studies could not find a significant relationship between pCRH and PPD, thus remaining a topic of interest in furthers studies (27).

Other studies tried to find correlations between serum levels of BDNF (brain derived neurotrophic factor), hippocampal volume and clinical symptoms in patients with major depressive disorder. BDNF serum levels might be associated with an increase of left hippocampal volume, for depressed patients treated with escitalopram, although the correlation had no statistical significance (28).

Hormonal treatment options in postpartum disorders

Modern medicine has shown interest in the effect of sex steroids on the brain, estradiol, progestin,

and testosterone, and how to benefit from using hormones as new and improved forms of treatment in neuropsychiatric disorders. In this spirit recent literature established that hormone therapy plays a major role in managing postpartum depression.

In relation to progesterone, synthetic allopregnanolone (Brexanolone ®) was the first drug to be approved by the FDA in March 2019 for this specific indication. Brexanolone acts as a highly potent positive allosteric modulator of the GABAA receptor. A total of 3 multicenter, randomized, double-blind, placebo-controlled trials were conducted in women (aged 18–45 years) with moderate and severe PPD. These studies found reductions in the degree of depression (the primary outcome) as measured by using the Hamilton Rating Scale for Depression compared with placebo (29). Treatment with estradiol reverse the negative mood symptoms experienced by women with PPD, and prevent depression-like behavior in rats tested during the "postpartum" period, as well as in ovariectomized rodents (30).

To that extent taken together, reduced TH combined with enhanced estradiol and progestogen confers neuroprotection in PPD, highlighting a potential target in prevention and treatment of PPD (31). Administrating both progesterone and Fluoxetine treatments increase the numbers of dendritic spines pyramidal neurons in the CA3 region of the hippocampus as well as protein expression levels of microtubule-associated protein 2 (MAP-2) and synaptophysin (SYP). CUMS-induced decrement of MAP-2 and SYP protein expressions can be prevented by treatment with progesterone in advanced pregnant stage and Fluoxetine in the postpartum period (32).

Combining reduced thyroid hormone with enhanced estradiol and progesterone determines neuroprotection in PPD. This discovery could lead not only to a treatment method, but also to the prevention of PPD in years to come. Moreover, postpartum depression could be controlled by administrating Dexmedetomidine (DEX) following cesarean section (31). Yu conducted a randomized interventional study, containing 600 Chinese women, who were listed for cesarean section, while being under spinal anesthesia. The intervention group which received DEX infusion 0.5ug.kg-1 after delivery and PCIA with DEX plus sufentani, compared to the control group, had significantly lower postpartum depression symptoms, as well as better pain scores and sleep quality (33).

In conclusion, several advances in the physiopathology and diagnosis of pregnancy and postpartum depression have been reported in recent years and are yet to come, a cumulus of factors, neurohormonal and psychosocial, are strongly linked to the development of these disorders. Further research on hormonal adjuvant therapy is needed.

Conflict of interest

The authors declare that they have no conflict of interest.

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