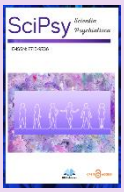

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Biological Predictors of Postpartum Depression: A Literature Review

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A B S T R A C T

Introduction: Maternal mental health problems pose major public health challenges for societies across the globe. PPD affects between 13–19% of women worldwide and has negative consequences on the woman herself and on her entire family. PPD has negative consequences on the woman herself and on her entire family. Biological models of PPD can be conceptualized as withdrawal models that concern the fact that reproductive hormones and stress hormones rise dramatically prior to delivery. A few studies have attempted to identify biological aspect as a predictor of PPD. **Methods:** Searches were conducted in PubMed. The following keywords were applied in the database during the literature search: "Postpartum Depression" OR "Postnatal Depression" OR "Puerperal Depression" AND "Predictor". Study was considered if they were published between January 2010 and August 2021, English language journals. 34 articles were identified. Abstracts were reviewed by researcher and 4 were eliminated. The researcher then reviewed full text of the remaining 26 articles. After full text review, an additional 15 articles did not meet inclusion criteria. The total of 10 articles were identified that met inclusion and exclusion criteria. **Results:** Partial reviews are available that cover biological processes broadly, with emphasis on the endocrine system, the immune system and genetic factors. Endocrine system includes estrogen, progesterone, prolactin, oxytocin, and testosterone. For stress hormone take a part like corticotropic releasing hormone, adrenocorticotropic hormone, β-Endorphin, cortisol, dan catecholamine. The cytokine and C-reactive protein are a group of immune system. The latter is serotonin, MAO-A, estrogen receptor, oxytocin, glucocorticoid, and brain derived neurotropic factor. **Conclusion:** Postpartum depression is a common but treatable condition. Appropriate and timely treatment is crucial in order to help women cope with their situation and reduce the devastating consequences. It is likely that the dramatic hormonal changes occurring in the postnatal period also play a significant role in the etiology of PPD, but the exact nature of these influences remains unknown, and needs further research.

1. Introduction

Maternal mental health problems pose major public health challenges for societies across the globe. For example, psychiatric illness (often associated with suicidality) is one of the leading causes of maternal death, as well as a leading killer of women of childbearing age. The most common psychiatric malady following childbirth is postpartum depression (PPD), a devastating mental illness that can impair maternal behaviors and adversely affect the cognitive, emotional, and behavioral development of children.[1]

Postpartum depression (PPD) is a mental disorder associated with the bearing of a child, during a postpartum period, commencing within six weeks of delivery. Postpartum depression is characterized by depressed mood, loss of interest and enjoyment, reduced energy leading to increased fatigability and diminished activity, feeling of worthlessness and feeling of guilt accompanied by the inability of doing important daily activities and sustaining for at least two weeks and more for diagnose. PPD affects between 13–19% of women worldwide and has negative consequences on the woman herself and on her entire family.[2]

Postpartum depression is a well-known postpartum psychological disorder characterized by a non-psychotic depressive episode of mild to moderate

severity beginning in or extending into the first year after delivery. PPD is distinguished from the postpartum blues and postpartum psychosis. Postpartum blues is a prevalent (40-80%) mood disorder that presents 3 to 5 days after giving birth. It requires no treatment, and its symptoms recess within two weeks at most. Postpartum psychosis, on the other hand, differs from PPD in being infrequent (0.1-0.5%), acute, and accompanied by psychotic episodes, requiring treatment.[3]

PPD has negative consequences on the woman herself and on her entire family. Despite various treatment modalities which have proven successful many women do not seek help for their PPD. Moreover, screening programs for PPD have been implemented around the world in order to assist in identifying women with PPD symptoms, however, also among those who are diagnosed and referred for help, many do not follow up with recommendations. Due to the adverse effects of PPD and low treatment use, it is important to identify many factors that can cause PPD.[4]

Biological models of PPD can be conceptualized as withdrawal models that concern the fact that reproductive hormones and stress hormones rise dramatically prior to delivery and then drop suddenly at delivery, which is hypothesized to trigger system dysregulation and depressive symptoms in a subset of vulnerable women. Support for these theories comes from observations of a reproductive subtype of depression related to hormonal fluctuations during the menstrual cycle, pregnancy, the postpartum period, menopause and from treatment studies documenting a rapid improvement in symptoms after estradiol administration.[5]

Therefore, biological vulnerability is conceptualized as a genetically derived hypersensitivity to hormonal changes and to dysregulation or impaired adaptation mechanisms in the central nervous system. This vulnerability is thought to interact reciprocally with the environment, both shaping the organism's responses to environmental challenges and being shaped by stressors and positive experiences over the life span. Very few studies have attempted to identify the biological aspect as a predictor of PPD.

2. Methods

Searches were conducted in PubMed. The following keywords were applied in the database during the literature search: "Postpartum Depression" OR "Postnatal Depression" OR "Puerperal Depression" AND "Predictor". These terms were combined with broader search words: biological, hormonal, endocrine, stress hormon, and genetic. Study was considered if they were published between January 2010 and August 2021 and appeared in literature or systematic review, English language journals. Single case studies, treatment and intervention studies, studies on depression during pregnancy, and abortion studies were not considered. Studies on other psychiatric conditions including postpartum psychosis, anxiety disorders, and posttraumatic stress disorders were excluded. Studies on animals were also considered to be beyond the scope of this review. 34 articles were identified. Abstracts were reviewed by researcher and 4 were eliminated. The researcher then reviewed full text of the remaining 26 articles, and reference sections of these articles were cross-checked for additional material. After full-text review, an additional 15 articles did not meet inclusion criteria. The total of 10 articles were identified that met inclusion and exclusion criteria.

3. Results

Biological predictors of postpartum depression

Normal human pregnancy is characterized by substantial biological changes designed to maintain the pregnancy, support fetal development, and promote labor, delivery, and lactation. To meet the often-conflicting need of the mother and quickly developing fetus, the female body is equipped with considerable adaptive capacity. After delivery of the baby and the placenta, the intricate balance that sustained the maternal-placental-fetal unit throughout gestation is suddenly obsolete, and the maternal systems undergo dramatic biological

changes within the first postnatal days. Depending in part on how long a woman breastfeeds, the new nonpregnant biological balance may take many months to establish. Ultimately, these biological adjustments may also impact maternal mental health.[5]

Partial reviews are available that cover biological processes broadly, with emphasis on the endocrine system, the immune system and genetic factors. This literature review of all qualified studies on endocrine, immune/inflammatory, and genetic predictors of PPD provides an up to date and comprehensive review of the state of the biological evidence.

Review of endocrine system

Reproductive hormone

Reproductive hormones play an important role in orchestrating pregnancy, labor, and birth. They have also been implicated in nonpuerperal depression. A review of 30 years of literature finds that mood disturbance is associated with the sudden withdrawal of estrogen, estrogen fluctuations, and sustained estrogen deficiencies. Likewise, progesterone is thought to be protective against depression because of its anxiolytic and anesthetic properties and because it modulates serotonergic receptors. Thus, shifts in estrogen and progesterone during pregnancy and postpartum may contribute to PPD.[6]

Estrogens

The strongest evidence that estrogen withdrawal plays a causal role in double-blind pregnancy-simulation study in which synthetic estradiol and progesterone were administered and then withdrawn, triggering symptoms of depression in the eight women with a history of PPD but not in the eight women without a history of PPD. Of note, at no time were group differences in estradiol or progesterone levels observed, nor was either hormone correlated with EPDS scores. This small but influential landmark study suggests that women with a history of PPD may be differentially sensitive to the mood-destabilizing effects of changes in gonadal steroids and that the assessment of estradiol and progesterone levels may not be an appropriate measure to adequately reflect the processes through which these hormones impact PPD development.[6]

Progesterone

Similarly, few studies implicate progesterone withdrawal in PPD risk. Progesterone levels after 36 weeks' GA were not associated with PPD symptoms in three small studies. Moreover, two of these studies found no evidence that the magnitude of the perinatal progesterone drops predicted PPD symptoms. If progesterone is psycho-protective, women with higher naturally occurring levels of progesterone postpartum may experience lower rates of PPD symptoms. Consistent with this hypothesis, a longitudinal study of 54 mothers found that progesterone levels within 12 to 48 hours after birth, but not at 1 or 4 weeks postpartum, were inversely related to PPD symptoms 6 months after delivery. Three small studies report on the absence of a link between progesterone and concurrent symptoms of depression between 1 and 17 weeks postpartum. In sum, little evidence suggests that progesterone in late pregnancy or postpartum predicts PPD symptoms, but studies have been small, and moderators associated with vulnerability to hormone changes remain untested.[7,8]

Prolactin

Few studies addressed the role of prolactin for PPD risk, and most assessed prolactin postpartum. Prolactin has anxiolytic properties and is thought to contribute to the stress-buffering effects of lactation consistently observed in studies of humans and rats. Therefore, higher basal levels postpartum may be protective against PPD onset. In line with this view, two studies with partially overlapping samples found that women in the highest decile on the Profile of Mood States-Depression subscale between four and six weeks postpartum had lower levels of prolactin compared to the other women in the sample. However, a study of 48 women found no association between PPD symptoms and prolactin at baseline and in

response to breastfeeding at two- and eight-weeks postpartum.[7]

Oxytocin

One prospective study of 73 Swiss women who were symptom free at the time of recruitment found that lower oxytocin levels between 21- and 32-weeks' GA predicted more PPD symptoms within the first two weeks postpartum. Lower baseline oxytocin at two and eight weeks was also associated with concurrent symptoms of PPD in a study of 48 US. In that study, lower oxytocin released in association with breastfeeding or pumping was also linked with more symptoms at eight weeks but not at two weeks postpartum. In sum, this small literature suggests that lower levels of oxytocin in pregnancy or postpartum may be a risk factor for PPD.[5,7,9]

Testosterone

A prospective study of 57 women provided no evidence that testosterone levels late in pregnancy or the magnitude of the perinatal drop were associated with PPD symptoms in the first four postpartum days or at six weeks postpartum. That study also reports on the absence of a link between concurrently assessed testosterone and PPD symptoms within the first four days and at six weeks postpartum. In contrast, a correlational study of 193 women suggests a positive association between testosterone and PPD symptoms within the first three postpartum days.[7]

Summary

The empirical evidence does not support a role for estrogen or progesterone withdrawal in the development of PPD symptoms, but studies have not testedmoderators of biological vulnerability such as a history of depression or life stress. Furthermore, associations of estrogen or progesterone postpartum with PPD symptoms were either significant in the unexpected direction or nonsignificant, with one notable exception for estriol. Conclusions about prolactin and testosterone are limited by the paucity of available studies, but a small but fairly consistent literature links lower perinatal oxytocin to more PPD symptoms. For prolactin, significant inverse correlations only emerged when assessments were made approximately four to six weeks postpartum.

Stress hormone

The negative mood, cognitive difficulties, and heightened anxiety that are characteristic of depressive disorders are hypothesized to involve dysregulation of the body's stress response systems such that affective and biological stress responses occur in disproportion to events or persist for extended periods of time. Stress hormones, in particular those of the hypothalamic-pituitary-adrenal (HPA) axis, have been implicated in nonpuerperal. In principle, stress hormones follow a pattern similar to reproductive hormones, such that they increase over the course of pregnancy and then drop after delivery. Nevertheless, the neuropeptide corticotropin-releasing hormone (CRH) increases exponentially over the course of pregnancy, reaching levels observed only under conditions of stress in the median eminence, a local portal system connecting the hypothalamus with the pituitary gland. This exponential increase occurs because CRH, which is typically released by the hypothalamus, is also produced by the placenta. Because cortisol stimulates placental CRH production, a positive feed-forward loop is established. Thus, (stress-related) cortisol increases early in pregnancy may result in accelerated CRH increases throughout pregnancy.[7]

Corticotropin-releasing hormone

A prospective study of 100 women found accelerated CRH trajectories between 23 and 26 weeks' GA and higher CRH levels between 18 weeks' GA and the end of pregnancy among women with PPD symptoms at 9 weeks postpartum. Similarly, a prospective study of 210 pregnant women found more pronounced increases in CRH from 29 to 37 weeks' GA and higher absolute levels at 37 weeks' GA with PPD symptoms at 8 weeks postpartum. However, suggests a lack of association between CRH levels between 25

and 37 weeks' GA and PPD symptoms at 6 months postpartum. A study reconciles these seemingly contradictory findings by showing a significant association of CRH levels and trajectories with PPD symptoms at 3 months but not at 6 months postpartum. Only one study assessed the magnitude of the perinatal CRH drop and found larger CRH decreases from 36 weeks' GA to the first week postpartum with less pronounced PPD symptoms, contradicting the withdrawal hypothesis. None of the studies assessing CRH postpartum report a significant link with PPD symptoms.[5,7]

Adrenocorticotropic hormone

The emerging link between CRH in pregnancy and PPD symptoms does not replicate for adrenocorticotropic hormone (ACTH). One study tested the link between PPD symptoms and the magnitude of the perinatal ACTH drop and reports null. Two studies assessed baseline levels of ACTH after birth, with one confirming null findings at 4 to 6 weeks postpartum, and the other reporting higher ACTH with more symptoms in the first postnatal week. Finally, a study using treadmill exercise as a stressor to elicit ACTH responses did not find differences in ACTH reactivity between women with and without PPD symptoms at 6 and 12 weeks postpartum. However, the ACTH-to-cortisol regression line differed, such that cases showed higher ACTH with lower cortisol levels at each assessment.[7]

β-Endorphin

One study tested the link between β-endorphin in pregnancy and PPD symptoms and suggests the absence of an overall effect. However, among women who report being euthymic at 25 weeks' GA, those with higher β-endorphin levels across pregnancy were more likely to experience symptoms at 9 weeks postpartum. This finding highlights the importance of studying subgroups of women and lends support to the CRH literature that found the time around 25 weeks' GA to be a crucial one in predicting PPD risk.[5]

Cortisol

Studies of cortisol fairly consistently report null findings. Only two studies, both conceptualizing PPD as a categorical variable and both assessing cortisol postpartum, found significant associations with PPD symptoms. Two studies tested the link between cortisol responses to external stimuli and PPD symptoms. Women with more pronounced cortisol responses to an acute psychosocial laboratory stressor between 13 and 31 weeks' GA had greater PPD symptoms 2 to 27 days following delivery. The same study yielded null findings for baseline cortisol levels, suggesting that stress reactivity may be more important in the pathophysiology leading to PPD than baseline hormone levels. However, a small study of 22 new mothers using treadmill exercise as a stressor did not find differences in cortisol reactivity between women with and without PPD symptoms at 6 and 12 weeks postpartum.[5,7,9]

Catecholamines

One study suggests a link between higher peripheral norepinephrine (but not epinephrine) levels and PPD symptoms assessed concurrently between 1 and 11 months postpartum in 35 new mothers, 10 of whom used cocaine during pregnancy. The small sample size, the unique population, and the large postpartum time frame in this study make it impossible to draw inferences at this time.[7,10]

Summary

Emerging evidence indicates that accelerated CRH trajectories and higher levels of CRH in mid-to-late pregnancy may be predictive of PPD symptoms during the first few postpartum months. This association does not seem to extend to other HPA axis hormones. The finding from the β-endorphin literature that associations may emerge for subgroups of individuals holds promise. The majority of studies on postpartum stress hormones yielded null findings. The few studies assessing stimulated HPA axis activity suggest that stress reactivity may be an important area for future research.

Review of immune system

The immune system function protects the body from pathogenic organisms and foreign substances by attacking what it identifies as foreign while recognizing and protecting what it identifies as self. During pregnancy, this task is complicated by the genetically distinct fetus, which carries paternal antigens that are foreign to the maternal immune system but that nevertheless should not be attacked by it. The exact mechanism by which the developing fetus is tolerated by the maternal immune system is not completely understood, but evidence suggests that this process involves a shift in the inflammatory balance of the innate immune system.[7]

The innate immune system is regulated by an intricate balance of proinflammatory cytokines [e.g., interleukin (IL)-6, IL-1β, tumor necrosis factor-alpha (TNF-α)] that initiate the inflammatory response and anti-inflammatory cytokines (e.g., IL-10) counteracting these effects. Pregnancy is characterized by moderate increases in IL-6 and unchanged levels of IL-10 until 35 weeks' GA, followed by a sevenfold increase in IL-6 and an approximately 50% increase in IL-10 by the time of delivery. A few days after delivery, this proinflammatory state is further enhanced and is not unlike that characteristic of depression. Heightened inflammation associated with psychological or biological stressors or sickness is consistently associated with depressive symptoms in nonpuerperal cases of depression. Because of these parallels, the proinflammatory state that is characteristic of late pregnancy and the early postpartum period has been argued to be of relevance for PPD.[5,7]

Cytokines

Most studies assessed proinflammatory cytokines around the time of delivery and PPD symptoms within the first six weeks postpartum. For example, a study of 91 women showed that those whose depressive symptoms increased over the first few days after delivery had higher levels of IL-6 and the IL-6 receptor. Another small study linked depressive symptoms with increased levels of IL-1β and with the absence of the expected declines in IL-6 concentrations over the first four weeks after birth. One study tested report in 56 mothers that IL-6 and TNF-α at the time of labor are positively correlated with EPDS scores within the first four days and six weeks postpartum, although some associations were significant in cerebrospinal fluid but not in maternal peripheral blood. Although these three studies suggest an exaggerated inflammatory response with PPD symptoms, others, including some with larger sample sizes, suggest no link between PPD symptoms and proinflammatory cytokines during labor or within the first months postpartum.[5,7]

Two publications with overlapping samples, both reporting on approximately 200 women, tested the association between IL-10 (an anti-inflammatory cytokine) and IFN-γ (interferon gamma, a facilitator of the inflammatory response) and symptoms of PPD at four to six weeks postpartum. Women scoring in the highest decile of the Profile of Mood States-Depression subscale, an unspecific measure of PPD symptoms, had lower IFN-γ levels and a lower IFN-γ:IL-10 ratio, the latter indicating suppressed cellular immunity among symptomatic mother. Findings further highlight the importance of breastfeeding, as IFN-γ levels were correlated with depressive symptoms among exclusively formula-feeding mothers but not among exclusively breastfeeding mothers. IL-10 was not associated with PPD symptoms in either study.[5,7]

C-reactive protein

Two studies assessed C-reactive protein (CRP), an overall marker of systemic inflammation. The larger study of 1,053 women found no link between CRP on the second postnatal day and PPD risk assessed concurrently and at 8 and 32 weeks postpartum. In contrast, a study of 27 women at high risk for PPD showed a positive association between CRP and the likelihood of developing PPD in the first five postnatal days but not between five and six weeks postpartum.[7]

Summary

Studies examining inflammatory processes in the context of PPD have yielded inconsistent results.

Among the studies yielding significant findings, most provide evidence for an exaggerated proinflammatory response in women with depressive symptoms. But, many studies had very small sample sizes and used unspecific screeners for depression. We surmise that future work on inflammatory processes in the context of PPD symptoms may be one of the most exciting areas of empirical investigation.

Review genetic factor

Many studies and meta-analytic reviews have investigated the role of genetics in major depression in the general population, and studies on the contribution of epigenetic factors have gained much momentum. In comparison, studies addressing genetic and epigenetic contributions to PPD remain rare. The largest of these studies is an association study of 508 polymorphisms in 44 genes conducted on 1,804 new mothers from Spain. Genes were selected for their proposed role in PPD symptoms, including those involved in the regulation of the HPA axis, in sex hormones, and in the effects of stress on the prefrontal cortex. A haplotype analysis found an association between three single nucleotide polymorphisms (SNPs) at protein kinase C with PPD during the first 32 weeks after delivery. When depressive symptoms were screened with the EPDS, only a SNP at the transcriptional start site of kininogen 1 remained significant. These sites may be interesting candidates for future research in this area. The remaining studies tested a smaller number of SNPs as possible predictors of PPD symptoms.[5]

Serotonin

The role of the serotonin transporter (5-HTT) is to remove serotonin from the synaptic cleft, thereby determining the magnitude and duration of the postsynaptic serotonin signal and implicating it in psychiatric disease, including depression. Polymorphisms of the serotonin transporter gene studied in the context of PPD include 5-HTTLPR (5HTT-linked polymorphic region), a functional polymorphism affecting transcriptional activity of the serotonin promoter, and STin2 VNTR, a variable number tandem repeat in the second intron region. The short allele of the 5-HTTLPR has been associated with reduced transcriptional efficiency and lower serotonin expression, implying that carriers of the short allele may be at higher risk of developing depression. For STin2 VNTR, a rare allele with nine repeats has been associated with major depression in the general population.[10]

Accordingly, in a study of 188 women with a psychiatric history, carriers of the short allele were at increased PPD risk at less than 8 weeks but not at 9 to 24 weeks postpartum. Similarly, in a study of 419 women, reported more symptoms among carriers of the short allele at 6 to 8 months postpartum when negative life events were present, but at 2 to 3 days no effects were detected. However, other studies suggest that the long allele may confer risk. One study tested report increased PPD risk among carriers of the high-expression genotypes (long allele of 5-HTTLPR, high-activity variant of STin2 VNTR) at 8 weeks but not at 32 weeks among 1,407 women. In another study, the long allele variant of the 5-HTTLPR was also associated with PPD symptoms at 6 weeks, and only among women who reported previous contact with a psychiatrist.[7]

The discrepancy between studies linking the short versus the long allele with symptoms might be reconciled by a study of 1,206 women reporting a crossover interaction between the 5-HTTLPR gene variant and socioeconomic status (SES). In that study, homozygous carriers of the short allele had higher levels of PPD if they were also low in SES, whereas short allele carriers high in SES showed a low incidence of PPD, similar to that of carriers of the long allele of both high and low SES. The authors suggest that whether or not interactive effects were found in previous studies may have depended on the socioeconomic distribution in that sample. Three studies measured tryptophan hydroxylase; an enzyme involved in the synthesis of serotonin. One of study documented in 361 women that a haplotype block in the promoter region of the tryptophan hydroxylase

type 2 isoform, but not a haplotype block in intron 8, associated with PPD symptoms at 6 to 8 months postpartum but not immediately after birth. In contrast, the absence of a link for the tryptophan hydroxylase type 1 and type 2 isoforms was reported in studies with similar sample sizes.[7]

COMT and MAO-A

Allelic variations in two other genes of the monoaminergic system that have been associated with major depression in nonpuerperal populations are catechol-Omethyltransferase (COMT), which is involved in dopamine and noradrenalin metabolism, and monoamine oxidase-A (MAO-A), which is involved in serotonin and noradrenaline degradation in the brain. One study tested reported that the low-activity variants of the MAO-A (uVNTR) andCOMT (Val158Met; Met carriers) polymorphisms were associated with increased depressive symptoms at 6 but not 12 weeks postpartum, an effect that was particularly pronounced among carriers of both low-activity variants. The key finding was replicated and further extended such that a multivariate model indicated that 30% of the variance in PPD could be explained by COMT Val158Met (Met/Met genotype), previous contact with a psychiatrist, and maternity stressors. Another study provides further confirmation that the low-activity (Met/Met) genotype is associated with higher PPD risk. Finally, an association of MAO-A and COMT with PPD symptoms was observed in an additive model.[7]

Estrogen receptor

As discussed in the section on endocrine factors, estrogens are implicated in depression, in part by influencing serotonin transmission. Two studies tested the role of the estrogen receptor gene (ESR1) in PPD, one of which is the above-mentioned study of 1,804 women that examined the role of 508 SNPs from 44 genes in PPD. Of the seven polymorphisms that initially emerged as significant, four were located on introns four and five of the ESR1 receptor; however, findings did not hold after statistical correction for multiple comparisons. Another study found a link between the ESR1 (TA repeat) and a PPD diagnosis within the first 12 weeks after birth, as well as an interaction between the ESR1 (TA repeat) and the 5-HTT (5-HTTLPR) with PPD symptoms.[7]

Oxytocin

One study investigated the association between PPD and three polymorphisms on the oxytocin peptide gene and the oxytocin receptor gene. Women who as children perceived their own care to be of high quality scored lower on depression at six months postpartum, in particular if they were also carriers of the C/C variant (rs2740210) and G/G variant (rs4813627) of the two oxytocin peptide gene polymorphisms.[5]

Glucocorticoids and CRH

One study of 140 women investigated the role of two polymorphisms of the glucocorticoid receptor gene and three polymorphisms of the CRH receptor 1 gene at two to eight weeks postpartum. Findings suggest higher PPD risk exists among carriers of the glucocorticoid receptor BclI (C/G) and CRH receptor CRHR1 (A/G) minor allele carriers, with more pronounced effects for carriers of both high-risk alleles. Findings also indicate an overrepresentation of the C-G-T haplotype of the CRHR1 among women with EPDS scores suggestive of PPD.[5]

Brain-derived neurotropic factor

The brain-derived neurotrophic factor (BDNF) system plays an important role in many neuronal functions including the regulation of synaptic plasticity. It interacts with the serotonin system, and the BDNF polymorphism Val66Met has been associated with nonpuerperal depression. Two studies tested the link between the Val66Met polymorphism and PPD. A study in a sample of 227 women nor a study in a sample of 219 women detected differences in the genotype distribution between women with and without depressive symptoms. However, the latter study suggests a seasonal effect, such that Met allele carriers were more likely to develop symptoms at six

weeks postpartum if they delivered in fall or winter, which may hint toward an involvement of BDNF in seasonal affective disorders.[7]

Summary

Findings point to possible effects of polymorphic variations in candidate genes within the monoaminergic system, but also for the estrogen receptor, the oxytocin peptide, the glucocorticoid receptor, and the CRH receptor 1 genes. No definitive answer to whether the short or long allele of the 5-HTTLPR is associated with PPD risk and under which conditions. The study of epigenetic factors in the pathophysiology of PPD holds exceptional promise in further elucidating these complex associations.

4. Discussion

The literature that published between 2000 and 2013 on biological (hormones, immune/inflammatory, genetic) risk factors for PPD. These literatures have evolved separately and remain remarkably distinct, with rare examples of rigorous, integrative empirical research. Below, the conclusions for literatures and enumerate challenges in advancing the field henceforth.

The theoretical rationale for the role of various biological factors in the etiology of PPD is fairly convincing, but empirical support is lacking. At best, results are equivocal, and at worst, the predominance of findings does not support the premises. The key question in evaluating the biological literature is therefore a rather provocative one: Are biological factors largely inconsequential in the etiology of PPD? And, in moving forward, where should researchers focus their attention? We argue that the real challenge facing this field is not the absence of biological effects but rather the need to take a more sophisticated approach in testing theoretical premises. It is not surprising that most studies have failed to yield significant results, and the emerging overall picture is one of inconsistency if one takes into account issues related to PPD theory and research design.[8]

One reason for equivocal results is that most empirical work on the role of biological factors in PPD risk does not carefully test theoretical propositions. For example, withdrawal theories imply that the intricate system of hormonal adaptations established over the course of pregnancy is suddenly disrupted, which challenges the maternal organism to restore a new endocrine balance. Hormone trajectories during and after pregnancy may well be an important piece of the puzzle, but other factors, in particular receptor sensitivity to the hormonal signal in the target tissue, are at least as relevant but remain largely unstudied. This is of concern because insensitivity to glucocorticoid signals has been suggested as a central mechanism in the development of depression. Moving forward, studies testing withdrawal theories should address levels of circulating hormones in combination with measures of tissue sensitivity. Promising approaches may include testing tissue sensitivity using in vitro models, using positron emission tomography scanning to access the hormonal signal received by receptors in key brain areas, or assessing gene transcriptional activity in peripheral blood.[7]

Furthermore, empirical tests of stress vulnerability models are rare in this literature. These models propose that associations between biological variables and PPD should be more pronounced among high-risk populations, whereas links may be absent in low-risk or mixed-risk samples. The few studies that have tested this model confirm that these moderated associations do exist. However, most studies in this field rely on mixed-risk samples. Future work might focus on high-risk populations or consider risk status as a moderator. It should also address genetic variations in other relevant biological systems (e.g., CRH, glucocorticoid, and gonadal systems as well as immune factors, including receptor variations) and psychological risk factors (e.g., life stress, lack of social support, psychiatric history). The inclusion of epigenetic changes related to pregnancy and to various types of stressors also holds great promise in furthering this line of research.[8]

Another issue that may contribute to the many null results is the piecemeal approach commonly taken in biological studies where each measure is tested individually for associations with depression, limiting our ability to examine how biological risk factors interact to contribute to PPD risk. For instance, cortisol may affect the function of other biological systems implicated in depression, for example by altering gonadal and inflammatory, stimulating increases in placental CRH, and by impairing serotonin function. Systems approaches that take into account interactive processes might help to integrate this fragmented literature and resolve some of the inconsistencies. In a related vein, there is a relative lack of appreciation that pregnancy and the postpartum period are periods of dynamic change. Our review suggests that studies that took a process approach by investigating change were more likely to yield significant findings compared to studies that treated biological measures as a static construct.[9]

Insufficient attention has also been got to the issue of timing. Any some indication that the most promising time to assess biological measures is not at the end of pregnancy when concentrations are uniformly high in preparation for delivery, but rather earlier in pregnancy (first and second trimesters) when the rate of change in biological measures may be more sensitive to individual differences in vulnerability. Regarding the timing of the assessment of PPD, it has been argued that pregnancy-related biological measures can affect PPD symptoms only as long as they still exert physiological effects. Our review supports the notion that associations between biological measures and PPD are more likely to be detected when symptoms are assessed earlier in the postpartum period. For example, significant familial aggregation was detected when depression onset was defined within four weeks but not when defined within six months of delivery. The emerging literature on the link between placental CRH trajectories and PPD suggests associations only until three months postpartum. Thus, research design decisions related to the timing of predictor and outcome assessment may obscure true associations.[7]

Few studies have used structural clinical interviews to establish the diagnosis of PPD or at least categorized their sample based on cut off scores in validated screening instruments. This is because the relatively low sample size in biological studies that typically involve higher financial cost and invasive data collection. To ameliorate the resulting power issue, studies have often treated depressive symptoms as a continuous variable and conducted analyses that presume linear effects even though a threshold model may be superior for understanding PPD etiology. In a related vein, most studies conceptualized PPD as a unidimensional construct instead of distinguishing between subtypes. There is accumulating evidence that HPA axis and inflammatory dysregulations differ between subtypes of depression, such as typical and atypical depression, which may suggest differences in pathophysiological processes.[7]

With reference to studies testing the withdrawal model, we propose that the deluge of null findings may be due to the result of a ceiling effect. Late in pregnancy, hormone levels are extraordinarily high in all women, and all experience a massive perinatal hormonal drop. As such, subtle differences in the magnitude of the decline may not be the primary force driving these effects. Instead, women who are vulnerable to the mood effects of hormonal fluctuations will tend to experience associated mood effects, whereas women without this vulnerability will not, irrespective of where they rank among all women undergoing this transition.[9]

Amid the paucity of significant findings, it is important to note emerging patterns such as the relatively small literatures reporting relationships between PPD and peripheral levels of oxytocin, studies testing interactions between serotonin transporter gene polymorphisms and psychological stressors, and studies assessing CRH trajectories in mid-pregnancy. Looking toward the next decade of PPD research, studies ideally would be designed to explicitly test various iterations of the proposed biopsychosocial

models, using prospective study designs and testing genetic, epigenetic, and life history moderators of the relationships between changes in endocrine and inflammatory measures, psychosocial risk and resilience factors, and PPD.[7]

5. Conclusion

Postpartum depression is a common but treatable condition. PPD is a common disorder with serious personal and familial consequences. Appropriate and timely treatment is crucial in order to help women cope with their situation and reduce the devastating consequences. The small numbers of women who utilize treatment for PPD is of concern, and the issue should be further examined with an understanding that a complexity of biological, intrapersonal, interpersonal, communal and societal factors impact the seeking help process. It is likely that the dramatic hormonal changes occurring in the postnatal period also play a significant role in the etiology of PPD, but the exact nature of these influences remains unknown, and is an area of active research. Efforts at treating PPD have involved hormonal, pharmacologic, psychotherapeutic, and cultural interventions. Measures to prevent PPD have not yet been well established.

6. References

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