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The Heritability of Postpartum Depression

Elizabeth J. Corwin, PhD, RN, CNP[1], **Ruth Kohen, MD**[2], **Monica Jarrett, PhD, RN**[3], and **Brian Stafford, MD, MPH**[4]

[1]Division of Women, Children, and Family Health, The College of Nursing, The University of Colorado–Denver, Aurora, CO, USA

[2]Psychiatry and Behavioral Sciences, The University of Washington, Seattle, Washington, USA

[3]Department of Biobehavioral Nursing and Health Systems, 3The University of Washington, Seattle, Washington

[4]Psychiatry & Behavioral Sciences, The Children's Hospital, Denver, Aurora, Colorado

Abstract

Postpartum depression (PPD) is a serious mood disorder that may carry life-long consequences for a woman and her family. Multiple risk factors for PPD have been identified, including psychosocial, situational, and biological stimuli, several of which are experienced by most, if not all, postpartum women. Given the commonality of these risk factors, it is unclear why fewer than 20% of postpartum women actually develop PPD. In this review, we suggest that different susceptibility to PPD among postpartum women may be explained by the presence or absence of genetic variants that confer increased risk. We review three categories of genes known to code for proteins associated with depression in the general population or proteins known to be affected by childbirth for their possible association with PPD, including genes related to central nervous system monoamine availability, proinflammatory cytokines, and brain neuropeptides. Only two studies are available in the literature to date specifically looking at polymorphisms in postpartum women as related to PPD; both are concerned with monoamine availability. These are discussed in further depth. Conclusions regarding the contribution of genetic polymorphisms to the development of PPD are mixed. Ultimately, the complexity of the disorder and the interrelationships among different genes thought to contribute to depression suggest that much more research is required to understand the heritability of PPD. The complexity of the disorder also suggests that epigenetic influences must be considered as well when discussing susceptibility.

Keywords

postpartum depression; genetic polymorphisms; heritability; depression; serotonin transporter gene; brain-derived neurotrophic factor

Postpartum depression (PPD) is a moderate-to-severe mood disorder that develops in 10–15% of the more than 4 million women who give birth each year in the United States—which comes to more than 600,000 women annually (Centers for Disease Control, 2008; Gavin et al., 2005; Munk-Olsen, Laursen, Pedersen, Mors, & Mortensen, 2006; Wisner, Chambers, & Sit, 2006). PPD carries significant and dangerous implications for a new mother's health and well-being and for the health and development of her infant. The

Corresponding Author: Elizabeth J. Corwin, The University of Colorado College of Nursing 13120 East 19th Avenue, Box C288-18, Aurora, CO 80045, USA. elizabeth.corwin@ucdenver.edu.

disorder may interfere with maternal role development and mother–infant bonding and may increase physical risk in mother and child alike (Beck, 1995; Cooper & Murray, 1998; Logsdon, Wisner, & Pinto-Foltz, 2006). The effects on children may include behavioral, developmental, socioemotional, and cognitive delay and may last years beyond infancy (Beck, 1998; Dawson et al., 2003; Field, 1995; Hay, Pawlby, Angold, Harold, & Sharp, 2003; Logsdon et al., 2006). In addition, spousal/partner relationships and relationships with other children in the home may be compromised.

Over the years, researchers have identified risk factors for PPD, including psychosocial factors such as prenatal depression or other history of depression (Beck & Gable, 2001; Bloch, Rotenberg, Koren, & Klein, 2006; O'Hara, Schlechte, Lewis, & Varner, 1991; Rich-Edwards et al., 2006; Robertson, Grace, Wallington, & Stewart, 2004), situational factors such as a fussy baby, inadequate social support, childcare stress, life stress (Beck, 1996; Beck & Gable, 2001) and poverty (Mayberry, Horowitz, & Declercq, 2007; Rich-Edwards et al., 2006), and biological factors such as hypothyroidism, anemia, and the precipitous fall in reproductive hormone levels that accompanies parturition (Beard et al., 2005; Bloch et al., 2000, 2006; Corwin, Murray-Kolb, & Beard, 2003; Lucas et al., 2000; McCoy, Beal, & Watson, 2003, for review). Recently, researchers have also suggested that abnormal function of the proinflammatory immune response—a condition known to contribute to depression in the general population—increases the risk of depression in postpartum women (Corwin, Johnston, & Pugh, 2008; Groer & Morgan, 2007; Maes et al., 2000; Maes, Ombelet, De Jongh, Kenis, & Bosmans, 2001). Clearly, however, hormonal declines, post-partum inflammation, a fussy baby, life stress, and financial concerns are experienced by many, if not most, postpartum women. Thus, to fully explain the etiology of PPD, a key challenge must be to account for the individual susceptibility inherent in its diagnosis.

We suggest that individual susceptibility to the development of PPD is related to the presence or absence of specific genetic polymorphisms that confer increased risk. Simply put, depending on her genotype, a woman may be more or less likely to experience depression when confronted with a common post-partum stressor. To support this hypothesis, we present below a brief review of the epidemiological evidence supporting the heritability of depression, first in the general population and then in postpartum women. We follow this with a review of select genetic polymorphisms suggested to carry an increased risk of depression in the general population and a discussion as to whether these polymorphisms may be likewise implicated in the development of PPD. We present this discussion through the lens of the unique risk factors and characteristics of PPD. We also critique the two studies available to date that have investigated whether a targeted polymorphism is in fact over-expressed in women with PPD. Lastly, we introduce a related, though separate, hypothesis to consider as well: that the difference in susceptibility to PPD may be better explained by an epigenetic mechanism than by genetic variation.

As a final note, it should be pointed out that PPD is only one of several mood disorders that may occur during the perinatal period (Gavin et al., 2005). The others, including the short-lived and mild postpartum blues, the rare but devastating puerperal psychosis, and the depressive episodes occurring in bipolar women, may also have genetic or epigenetic underpinnings. We have chosen, however, to limit this review to an in-depth inquiry of the nonbipolar depressive disorder PPD, the most common severe mood disorder afflicting women during the first year after childbirth.

Epidemiological Studies

Anecdotal reports that affective disorders, including depression, run in families are abundant and span centuries of human history and literature. Research investigations to confirm these

anecdotal reports began in earnest in the 1960s and involved well-controlled family, twin, and adoption studies. A meta-analysis conducted in 2000 estimated the heritability of major depression to be 37%, with a relative risk of 2.84 for first-degree relatives of affected siblings (Sullivan, Neale, & Kendler, 2000). Other studies of twins suggest an even higher heritability, with a concordance rate for major depression in identical twins of 70–90% compared to 16–35% in nonidentical twins (Sadock & Sadock, 2008).

The epidemiological evidence as to whether PPD demonstrates similar heritability is less clear. Although several investigators researching risk factors for PPD have collected data on family history, only a few family or twin studies of women with PPD exist in the literature. In the only published study of twins and PPD, 838 parous female twin pairs enrolled in the Australian National Health and Medical Research Council volunteer adult twin register were surveyed regarding their postpartum experiences. As reported by the authors, genetic factors explained 25% of the variance in the occurrence of interview-assessed PPD (Treloar, Martin, Bucholz, Madden, & Heath, 1999). However, because of methodological concerns about subjects' inconsistent responses to the prepared question-naire, the researchers were unable to differentiate true PPD from postnatal dysphoria and determined their findings to be only moderately suggestive of a genetic influence. In another study of 44 pairs of female siblings with unipolar depression (Forty et al., 2006), among women who had a sibling who met the narrowly defined criteria of having had PPD within 4 weeks following a previous pregnancy (the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition* [DSM-IV]), 42% went on to develop PPD following their first delivery compared to only 15% of women with no family history ($p = .01$). In this study, the evidence for familiality was even greater when the postpartum onset was more tightly restricted to that occurring between 6 and 8 weeks postpartum. And finally, Murphy-Eberenz and colleagues (2006) reported on the evidence for familiality of PPD among a subset of 328 women of childbearing age enrolled in the Genetics of Recurrent Early-Onset Depression data set, who were members of a sibship with two or more other women in the data set. The authors found the odds ratio for prediction of sibling PPD by the proband's history was 3.96 and was even higher when the focus was exclusively on younger women diagnosed with PPD (odds ratio 4.39). This same group of investigators more recently expanded their studies to include families with bipolar disorder pedigrees and report much the same findings: that among women diagnosed with bipolar disorder, there is a significant increase in the likelihood that a female sibling will have experienced a major postpartum depressive episode within 4 weeks of delivery (Payne et al., 2008).

Although suggestive, there are limitations with these studies, including the use of retrospective oral report or chart review, the failure to control for comorbid psychiatric illnesses including a previous history of major depressive disorder (MDD), and the question of environmental versus genetic causation. For example, in each of these studies, it is unclear whether the women sibling pairs grew up in the same household, were exposed to a parent with mental illness, or experienced other environmental stressors that may have influenced their adult experiences. Moreover, in spite of these and other studies suggesting that a family history of mood disorder in general is predictive of PPD (Johnstone, Boyce, Hickey, Morris-Yatees, & Harris, 2001; Steiner, 2002), many other reports identify no relationship between a woman's family history of depression and her own likelihood of developing PPD (Bloch et al., 2006; Dennis, Janssen, & Singer, 2004; Dennis & Ross, 2006; O'Hara & Swain, 1996). Thus, to better clarify the true heritability of PPD, a more objective diagnosis of the disorder with well-defined markers of heritability, including genetic markers, is required.

Genetic Studies

In recent years, several polymorphisms have been identified that may be linked to depression in the general population. In the following paragraphs, we highlight a few of these polymorphisms, focusing on those that are (a) associated with pathophysiological pathways linked mechanistically to depression and (b) theoretically linked to the biological and/or psychological milieu present during the postpartum period. Of these, only polymorphisms of the serotonin transporter (*SERT*), monoamine oxidase A (*MAOA*), and catechol-*O*-methyltransferase (*COMT*) genes have been evaluated for their contributions to PPD. Other polymorphisms reviewed below include those carried on genes coding for inflammatory proteins and a variant of the brain-derived neurotrophic factor (*BDNF*) gene. Although these polymorphisms have not been studied specifically in association with PPD, the proteins for which they code have been linked to depression in the general population, and changes in their levels of expression occur following childbirth.

Genes Influencing Monoamine Availability

Many of the genes identified as candidates for conferring increased risk of depression in the general population are those that affect the synthesis or metabolism of the brain monoamines: norepinephrine, dopamine, and serotonin. Monoamines function in the central nervous system (CNS) as key regulators of mood, and deficits in monoamine availability have been repeatedly linked to depression in the general population (Belmaker & Agam, 2008). Research on the role of serotonin in mood disorders is especially abundant.

After its synthesis from the amino acid tryptophan, serotonin is stored in the terminals of a presynaptic neuron until released into the synaptic cleft. Following its release, serotonin binds to and stimulates receptors on the pre- or postsynaptic neuron (Nichols & Nichols, 2008). It then disengages from the receptors and is taken back up into the presynaptic neuron by SERT. Reuptake of serotonin by its transporter reduces serotonin's availability to bind again to its receptors. Drugs that prolong the exposure of receptors to serotonin by blocking its reuptake (selective serotonin reuptake inhibitors [SSRIs]) function as established antidepressants.

Because of its role in regulating serotonin reuptake, SERT has garnered a great deal of research interest. In 1993, the *SERT* transporter gene was mapped to chromosome 17q11.1-q12 (Ramamoorthy et al., 1993). Two common genetic variants, or length polymorphisms, of SERT—5-HTTLPR and STin2 VNTR—have been extensively investigated in connection with mental illness. The 5-HTTLPR polymorphism is a 43-base-pair insertion/deletion polymorphism present in the promoter region of the *SERT* gene. When the 43-base-pair segment is present, an individual is said to carry the long (*l*) allele; when it is not, he or she is said to carry the short (*s*) allele. Any one person may be homozygous for the long allele (*l*/*l*), heterozygous (*l*/*s*), or homozygous for the short allele (*s*/*s*). In the late 1990s, the *s* allele was shown to be associated with lower transcriptional efficiency, resulting in lower levels of SERT expression, than the *l* allele (Heils et al., 1996; Lesch et al., 1996). The second relatively common polymorphism of the *SERT* gene likewise affects transcriptional efficiency. This polymorphism, STin2 VNTR, is a variable number tandem repeat (VNTR) polymorphism, consisting of 7, 9, 10, or 12 short similar sequence repeats, with the 7-repeat allele quite rare and hence not well characterized. STin2 VNTR is located in the second intron of the *SERT* gene. The 9- and 12-segment repeats (STin2.9 and STin2.12) lead to higher expression of SERT than does the 10-segment repeat (STin2.10; Fiskerstrand, Lovejoy, & Quinn, 1999; Ogilvie et al., 1996). With the discovery of these variants, research quickly focused on whether different SERT polymorphisms were more or less common in persons suffering from depression.

In spite of a great deal of research addressing this question, neither the 5-HTTLPR nor the STin2 VNTR polymorphisms were initially shown to have a convincing association with depression. That is, none of the allele combinations for these polymorphisms were reliably found to be more or less prevalent in individuals diagnosed with depression (Anguelova, Benkelfat, & Turecki, 2003). In 2003, however, the research field was rejuvenated with the publication of data that showed that persons with the *s*/*s* 5-HTTLPR genotype did indeed experience a significantly greater incidence of depression compared to *l*/*l* individuals but only when exposed to significant life stressors (Caspi et al., 2003). In their study, Caspi and colleagues (2003) gathered data from a birth cohort of 847 young adults who had been participating in a larger multidisciplinary study since the age of 3. Subjects were (a) screened for their 5-HTTLPR genotype, (b) interviewed for the number of stressful life events occurring between the 21st and 26th birthday, and (c) assessed for past-year depression at age 26 using the Diagnostic Interview Schedule (DIS). Genetic findings were that 31% of participants carried the *l*/*l* genotype, 51% the *l*/*s* genotype, and 17% the *s*/*s* genotype, with no differences in genotype based on gender. Results from this study indicated that, in response to an increasing number of stressful life events, individuals with the *s*/*s*, and, to a lesser extent, the *l*/*s* genotypes exhibited more depressive symptoms, had a higher rate of suicidal ideation, and were more likely to be diagnosed with depression than those with the *l*/*l* genotype.

Although conclusions of Caspi and colleagues (2003) recently have been brought into serious question (see below), the implication, if true, that SERT polymorphisms moderate the influence of stressful life events on depression is potentially paradigm shifting. It also is potentially relevant to PPD, given that the postpartum period is rich in life stressors, for example, a fussy baby, economic concerns, and role demands to name just a few. That less than 20% of the sample carried the *s*/*s* genotype may also help explain why, in spite of the commonality of postpartum stressors, only a minority of women develop PPD.

In one of the two studies to date focusing on serotonin-related polymorphisms and PPD, Sanjuan and colleagues (2008) sought to identify similar associations between SERT genotype and depression in postpartum women. Researchers collected data from postpartum women to determine whether the presence of high- or low-expressing genotype combinations at the 5-HTTLPR and STin2 VNTR loci were associated with a higher incidence of PPD. This was of particular pertinence since both pregnancy and delivery are accompanied by lower plasma tryptophan levels but only susceptible postpartum women develop PPD, leading the authors to hypothesize that the difference between women might be a genetic tendency in depressed women toward accelerated serotonin reuptake, i.e., higher-expressing SERT genotypes. The investigators genotyped 1,804 women and administered the Edinburgh Postnatal Depression Scale (EPDS) to assess their depressive symptoms at 2–3 days postpartum. At the 8-week follow-up, 1,407 women remained in the study and again completed the EPDS. At 32 weeks postpartum, 1,337 women were evaluated. Women scoring 9 of 10 on the EPDS were considered experiencing significant symptoms of depression and were further interviewed using the Diagnostic Interview for Genetic Studies (DIGS) Spanish version. Three genotype combinations of 5-HTTLPR and STin2 VNTR were put together to reflect three levels of SERT expression: high, medium, and low. Depression scores were reported as a continuous variable and compared between genotype groups. Results indicated that at 8 weeks postpartum, the EPDS score was related to the SERT high-expression polymorphisms in a dose–response fashion (; = 0.45 (95%CI, 0.09–0.82), $p = .015$); however, this was not true at 32 weeks. A relationship between symptoms meeting the criteria for major depression ($n = 112$) and SERT genotype was weaker ($p = .09$) at 8 weeks and 32 weeks ($p = .12$) postpartum. The frequency of the 5-HTTLPR polymorphisms were 28% *l*/*l*, 48% *l*/*s*, and 24% *s*/*s*, values similar to those found by Caspi et al. (2003). For the STin2 VNTR polymorphism, 46% of the women were

homozygous for STin2.12, 42% were heterozygous, and 10% were homozygous for the STin2.10 variant.

In the second publication to date involving serotonin-related polymorphisms that may confer an increased risk of PPD (Doornbos et al., in press), researchers investigated the association of PPD with, not only the 5-HTTLPR polymorphism, but also with polymorphisms of two additional genes, *MAOA* and *COMT*, both enzymes associated with the degradation of serotonin, dopamine, and norepinephrine (Sabol, Hu, & Hamer, 1998; Yavich, Forsberg, Karayiorgou, Gogos, & Mannisto, 2007). The *MAOA* gene, carried on the X chromosome, contains a variable number of tandem repeats of a 30-base-pair segment in the gene's promotor region, the uMAOA polymorphism. The repeat sequence may occur 2, 3, 3.5, 4, or 5 times; the 3.5 repeat variant is between the 3 and 4 repeat segments in length and also contains a sequence variation. Transcription efficiency of the 3.5 and 4 repeat variants is 2–10 times greater compared to the other variants. Greater transcription efficiency theoretically is associated with increased enzyme production and as a result could lead to enhanced monoamine degradation. If true, then, these variants should confer a greater risk of depressed mood (Belmaker & Agam, 2008), which has been confirmed in a large population sample (Rivera et al., 2009). The scenario is similar for the *COMT* gene, located on chromosome 22. In this case, a functional polymorphism involving a guanine-to-adenine substitution in codon 158 (val158met) leads to a three- to fourfold reduction in enzyme activity (Lotta et al., 1995). Although it could be argued that, analogous to MAOA, higher COMT enzymatic activity should be associated with depression, COMT association studies have proven inconclusive (Wray et al., 2008).

In their study, Doornbos and colleagues (in press) asked women to complete the EPDS a total of four times: once each on Weeks 16 and 36 of pregnancy and again on Weeks 6 and 12 postpartum. They also genotyped subjects for the three polymorphisms of interest: 5-HTTLPR of SERT, uMAOA, and COMT val158met. The authors evaluated the associations between the gene polymorphisms and the EPDS scores in the 89 women who completed the study. Results indicated that, similar to the study of Sanjuan et al. (2008), women carrying one or two *l* alleles of the 5-HTTLPR polymorphism trended toward increased depression scores at 6 weeks postpartum ($p = .07$), while those carrying the low-activity variants of the MAOA and COMT (i.e., the variants that lead to reduced enzyme production) had significantly higher depression scores at both 6 weeks postpartum and 36 weeks of pregnancy ($p = .018$ and .022, respectively). Especially notable was the effect of the interaction between the low-activity COMT and MAOA variants: when the low-activity MAOA polymorphism was accompanied by the low-activity COMT polymorphism, average EPDS scores rose dramatically ($p < .001$). Important limitations to this study were its very small sample size and the authors' use of a screening instrument rather than a structured clinical interview, as 3 of the 10 questions on the EPDS inquire about anxiety. Moreover, variables known to affect depression such as previous history of depression, smoking, use of antidepressants, and concurrent illness of mother or infant were not considered. The authors also point out that their findings related to MAOA and COMT conflict with several other studies, showing that the high-activity variants (rather than low) are associated with depression, particularly in women (Schulze et al., 2000) but suggest that the specific nature of pregnancy and the postpartum period may explain the discrepancy.

It should be noted that, although the findings of Sanjuan et al. (2008) and to a lesser extent those of Doornbos et al. (in press) suggest that the SERT genotype is associated with depression, they differ from those of Caspi et al. (2003) in an important way. The results of the first two studies support the theoretically based hypothesis that the high-expressing SERT genotype (*l*/*l*) is associated with depression, while the Caspi findings suggest the opposite: that the low-expressing genotype (*s*/*s*) is associated with depression in response to

life stressors. This is particularly interesting in view of the observations of Doornbos and colleagues (in press) about the association of low- rather than high-activity variants of COMT and MAOA with PPD. Taken together, these findings support the idea that PPD may have different genetic and biological underpinnings than depression occurring outside of the postpartum period. Not only does this idea call for a more intensive investigation of PPD as a separate biological entity, but it may also highlight examples of the genetic heterogeneity underlying depression, which would explain why genetic association studies of depression have led to conflicting results. For example, although Caspi's findings have been fully or partially replicated by other researchers in a variety of nonpregnant, nonpostpartum populations (Cervilla et al., 2007; Jarrett et al., 2007; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005; Kim et al., 2007; Kohen et al., 2008; Taylor et al., 2006), several other authors report either no effect or, like Sanjuan et al., an opposite one, as described below. Because of these discrepancies, Risch and colleagues (2009) recently performed a meta-analysis that has raised serious questions regarding the evidence linking the 5-HTTLPR polymorphism with depression. The authors, under the sponsorship of the National Institute of Mental Health, reviewed the status of research on gene–environment interactions and depression including only studies that reported data on stressful life events, 5-HTTLPR genotype, and depression. The primary meta-analysis included 14 studies with over 14,000 participants, of whom approximately 12% were classified as depressed. Although results again demonstrated a clear relationship between the number of stressful life events and depression, there was no significant association between genotype and the risk of depression when considered alone, nor did 5-HTTLPR genotypes (*s*/*s*, *l*/*s*, or *l*/*l*) interact with stressful life events on the risk of depression. Of the 14 studies, 7 partially or fully replicated Caspi's findings (Cervilla et al., 2007; Eley et al., 2004; Grabe et al., 2005; Kim et al., 2007; Taylor et al., 2006; Wilhelm et al., 2006), while 7 failed to replicate the study (Chipman et al., 2007; Chorbov et al., 2007; Gillespie, Whitfield, Williams, Heath, & Martin, 2005; Laucht et al., 2009; Middeldorp, Cath, Beem, Willemsen, & Boomsma, 2008; Power et al., in press; Surtees et al., 2006). Of those failing to replicate, two (Chorbov et al., 2007; Laucht et al., 2009) reported effects in the opposite direction of Caspi's (*l*/*l* polymorphism associated with increased risk of depression). The authors of the meta-analysis concluded by warning against seeking gene–environment interactions when the effect of the environmental exposure is small or the gene effect is modest. Because the study of Sanjuan et al. (2008) did not include the number of stressful life events experienced by women in the postpartum period, it was not included in the meta-analysis. Clearly further evaluation of the evidence regarding associations among the 5-HTTLPR polymorphisms, stressful life events including labor and delivery, and depression is needed.

Genes Influencing Cytokine Expression

Although yet to be tested in postpartum women, the hypothesis that polymorphisms of candidate genes controlling pro- and anti-inflammatory cytokines or their receptors or receptor antagonists may be associated with PPD is based on research publications over the last 20 years, linking elevated levels of proinflammatory cytokines with depression in the general population. These data are multidimensional, reproducible, and cross-species. As recently described in a comprehensive review (Anisman, 2009), administration of proinflammatory cytokines, including interleukin 1β (IL-1β), tumor-necrosis factor a (TNF-α), interferon γ [IFN-γ], and IL-6, induces depressive symptoms in animal studies, human research subjects, and in clinical trials when given to patients with cancer, hepatitis, or other illnesses. The effects are reproducible and dose dependent and, in animal studies, preventable by pretreatment with cytokine antagonists and in genetic knockouts. Several studies report that in persons with major depression, IL-1β, IL-6, TNF-α,TNF–R1, and baseline IL-10 are elevated (Anisman, 2009; Owen, Eccleston, Ferrier, & Young, 2001; Schiepers, Wichers, & Maes, 2005).

In mechanistic terms, it is suggested that proinflammatory cytokines contribute to depression via stimulation of the hypothalamic-adrenal-pituitary (HPA) axis leading to increased cortisol synthesis and/or via activation of the tryptophan- and serotonin-degrading enzyme indoleamine 2,3-dioxygenase (IDO), leading to decreased availability of brain serotonin (Belmaker & Agam, 2008; Miller,Maletic,&Raison, 2009). This latter hypothesis is supported by animal studies showing that, in mice, acute and chronic infusion of IL-1β leads to increased expression of proinflammatory cytokines and their receptors in the brain, increased utilization of serotonin and norepinephrine in the prefrontal cortical and hippocampal regions of the brain, increased expression of presynaptic serotonin receptors, and behavioral indicators of depressed affect including anhedonia, loss of appetite, fatigue, and social withdrawal (Anisman, Gibb, & Hayley, 2008).

In addition to being rich in life stressors, the postpartum period is characterized by immune system activation and inflammation (Østensen et al., 2005). Many of the hallmarks of labor and delivery, including perineal tissue injury (Connolly & Thorp, 1999; Salamonsen, 2003), pain, physical exertion, and psychological stress, are known stimulators of proinflammatory cytokine production (Maier & Maloni, 1997; Watkins, Nguyen, Lee, & Maier, 1999; Witek-Janusek, Stoddard, & Mathews, 1998). Postpartum uterine involution is likewise a cytokine-driven process (Kayisli, Mahutte, & Arici, 2002; Melendez, Vinci, Jeffrey, & Wilcox, 2001). Still, less than 20% of women develop PPD. It may be that women carrying a genetic variant that contributes to excessive, prolonged, or dysregulated postpartum inflammation are at increased risk of PPD while other women are not.

Although women suffering from PPD have been reported to have elevated IL-1β (Corwin et al., 2008), IL-6 (Maes et al., 2000), and IL-1 receptor antagonist levels (Schmeelk, Granger, Susman, & Chrousos, 1999) as well as a decreased IFN-γ-to-IL-10 ratio (Groer & Morgan, 2007) compared to postpartum women without PPD, there are no studies to date that have reported on cytokine gene polymorphisms in women with PPD. The only studies linking cytokine gene polymorphisms to increased risk of depression are in the general (nonpregnant, nonpostpartum) population, as described below.

A few studies have investigated the association with depression of a common polymorphism of the gene coding for the potent proinflammatory cytokine interleukin-1 beta (IL-1β). This polymorphism was first identified in 1992 as a cytosine/thymine (C/T) polymorphism (−511C/T) located in the promoter region of the IL-1β gene, itself carried on chromosome 2 (Pociot, Mølvig, Wogensen, Worsaae, & Nerup, 1992). Individuals homozygous for the −511T polymorphism secrete significantly more IL-1β in response to endotoxin (lipopolysaccharide [LPS]) than either heterozygous individuals or, especially, those homozygous for the C allele. Yu and colleagues (Yu, Chen, Hong, Chen, & Tsai, 2003) and McCulley and colleagues (McCulley, Day, & Holmes, 2004) tested the hypothesis that persons homozygous for the T allele would be at increased risk of suffering from depressive symptoms. McCulley et al. (2004) found a strong association between the T allele and depression in elderly Caucasian patients with Alzheimer's disease in their cross-sectional study, while Yu et al. (2003) reported that in an ethnic Han Chinese population there was no significant difference in genotype between 157 patients diagnosed with MDD and 112 psychiatrically healthy controls recruited from the medical staff. A key limitation to the generalizability of these studies includes the very specific populations investigated. In addition, including as the "normal control" subjects members of the medical staff in the Yu study may have resulted in subjects being incorrectly identified as nondepressed. Additional studies are available in the literature, reporting associations between MDD and other cytokine gene polymorphisms including IL-10 (Traks et al., 2008) and TNF-α (Jun et al., 2003); however, others report no association (Misener et al., 2008). Further research related to cytokine gene polymorphisms and MDD, as well as PPD, are required.

BDNF

The last candidate gene for PPD we will review is the gene coding for BDNF, located on chromosome 11. BDNF is a peptide critical for brain neurogenesis including neuron survival, axon growth, and synaptic plasticity. In this capacity, BDNF promotes the development and function of neurons, including serotonergic neurons, and has been reported to influence mood (see Belmaker & Agam, 2008, for review). Levels of BDNF are reduced by proinflammatory cytokines, psychological stress, and cortisol. A reduction of hippocampal BDNF has been associated with depression in victims of suicide. Antidepressant therapy, including serotonin reuptake inhibitors and electro-convulsive therapy, upregulate BDNF expression. In knockout animals, a loss of the *BDNF* gene is associated with brain monoamine deficiencies and, in female, but not male, mice, an increased appearance of depressive behavior in response to environmental stressors. And finally, in the one study to date looking at pregnant and postpartum women, maternal serum BDNF levels were decreased in pregnant and postpartum women compared to control women, and levels correlated with serum serotonin (Lommatzsch et al., 2006). In that study, there was a (nonsignificant) trend toward a decrease in both BDNF and serotonin in cases of maternal depression.

A common polymorphism of the *BDNF* gene, val66met, has been associated with depression, especially depression developing in response to environmental adversity and stress—a phenomenon also associated with the SERT polymorphism 5-HTTLPR. In a study of 374 European subjects assessed for depression and anxiety symptoms, those carrying the met allele, who were also exposed to early life stress showed greater symptoms of depression and anxiety and, using brain-imaging techniques, significantly reduced gray matter in the hippocampus and lateral prefrontal cortex compared to those with the val/val genotype ($p < .001$; Gatt et al., 2009). Interestingly, anxiety is frequently present with PPD, as previously described (Beck, 1995). Moreover, evidence exists of epistatic interaction between SERT and BDNF polymorphisms in the pathogenesis of depression in response to environmental stressors (Pezawas et al., 2008).

Epistasis is the interaction among genes that takes place when the effects of one gene are modified by one or several other genes, as seen in the complex relationships among the genes discussed in this review. For example, BDNF production has been reported to be reduced in response to both proinflammatory cytokines and stressful life events, and both decreased BDNF and increased proinflammatory cytokines are associated with decreased levels of brain serotonin. This complexity is perhaps a good reminder that the etiology of a multifactorial disorder such as depression will not be explained by considering either its genetic or its environmental risk factors alone, nor by evaluating just one gene plus one environmental factor. A thorough review of the monoamine-deficiency hypothesis of depression, including a presentation of serotonin and its transporter, and the contribution of decreased BDNF and increased inflammation to the development of depression has been published recently (Belmaker & Agam, 2008).

Epigenetics

The previous paragraphs review the heritability of PPD and highlight several candidate genes that may play a role in its etiology. In addition to genetic factors, epigenetic changes are also likely to play a role in the etiology of PPD. The term epigenetics refers to heritable changes in gene expression that are not due to changes in the DNA sequence but rather to changes that affect DNA transcription into messenger RNA (mRNA) and subsequent translation into protein (Corwin, 2004; Mill & Petronis, 2007; Verma, Maruvada, & Srivastava, 2004). Epigenetic processes typically involve one of two mechanisms that affect chromatin structure: DNA methylation, or histone modification.

DNA methylation is the process whereby a methyl group (CH_3) is added to a cytosine base which is directly 5′ to a guanine base, called a CpG dinucleotide. (The other two DNA bases are adenine and thymine). Clusters of CpG dinucleotides occur in the promoter (regulatory) regions of many genes. In general, genes that are methylated on or near their promoters are turned off (silenced) and thus are not transcribed into mRNA (Miranda & Jones, 2007). In contrast, if a gene's regulatory area is unmethylated, it is more likely to be accessible to transcription factors, which leads to increased transcription and ultimately higher expression of its protein product. Because methylation does not change the DNA sequence itself, it is potentially reversible; that is, if the methyl residue is removed from the cytosine base in the promoter, the gene should again be available for transcription.

Similarly, histone modification refers to epigenetic modification resulting from the methylation, acetylation, or phosphorylation of histones, packaging proteins that surround DNA in the nucleus of eukaryotic cells. Via histone modification, chromatin structure is affected in such a way that the transcription of DNA is either blocked or facilitated. DNA methylation and histone modification are essential for normal development, X-chromosome inactivation, genomic imprinting, and tissuespecific gene regulation. An epigenetic explanation of PPD would assume that one woman's risk of developing PPD compared to another's is not dependent exclusively on the genetic variation and environmental differences between them but also on whether the transcription of certain genes is blocked or facilitated through epigenetic mechanisms.

Although there are no studies available at this time regarding epigenetic influences on PPD specifically, epigenetic alterations have been identified in MDD as well as several other psychiatric conditions. Pertinent to the discussion above are animal studies demonstrating that chronic social defeat leads to repressive histone modification at the promoter region of the gene coding for BDNF and a resultant prolonged down-regulation of BDNF expression (Tsankova, Renthal, Kumar, & Nestler, 2007). The authors found this modification to be reversible via treatment with the antidepressant imipramine. Along the same lines, Berton and colleagues (2006) demonstrated that chronic electroconvulsive therapy leads to chromatin remodeling and enhanced transcription of the gene coding for BDNF and increased BDNF protein expression. Other environmentally mediated changes to the genome associated with MDD have been shown to occur as well (Mehler, 2008, for review), none of which, again, have been studied with regard to PPD. Others have, however, proposed epigenetic mechanisms by which perinatal maternal adversities may affect fetal development mediated by adrenal hormone activity, specifically suggesting that maternal glucocorticoid levels may program gene expression in the direction of impaired HPA function and altered health in offspring (Meaney, Szyf, & Seckel, 2007). These proposals lead to the intriguing possibility that the allostatic load (accumulated stress) that a woman's mother experienced during her lifetime or pregnancy could be a greater contributor to the risk for PPD than her own current social risk factors or her genetic risk.

Summary

PPD is a serious, relatively common disorder that has lifelong implications for a woman and her family. Although anecdotal evidence may point to PPD being inherited, the epidemiological evidence to support such a claim is inconclusive. While several genetic polymorphisms can be linked theoretically to an increased risk of PPD, no clear genetic risk profile has emerged. Ultimately, to better understand a complex disorder such as PPD, it will be necessary to identify genes that are associated with the disease and clarify the interactions among them as well as to study the possibility of epigenetic phenomena. To this end, future studies will surely include genome-wide association studies, wherein the genome of thousands of women can be compared with respect to the presence or absence of PPD, as

well as continued research to evaluate the prevalence of specific candidate gene polymorphisms in women with PPD compared to those without. In fact, one such study very recently has been published (Mahon et al., 2009) wherein genome-wide techniques were used to search for genotypes that associated with any retrospectively reported postpartum mood symptoms. The data suggested a linkage between recalled postpartum mood symptoms and genes on chromosomes 1 and 9. The authors called for more well-controlled studies to replicate their findings. Additionally, animal studies involving genetic knockouts or cross-fostering of pups will allow for the controlled evaluation of specific gene contributions and epigenetic influences, respectively, on the development of symptoms suggestive of maternal depression. In the meantime, the simple recognition that a woman's personal and perhaps family history may put her at increased risk of PPD can be a valuable tool, serving to heighten awareness of the disorder's early symptoms and treatment options.

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