Postpartum Mood Disorders: Genetic Progress and Treatment Paradigms

Mood symptoms frequently occur during pregnancy and the postpartum period and may cause morbidity for both mother and baby. The majority—up to 80%—of women experience the self-limited postpartum "baby blues" (1). Depending on the population surveyed, postpartum depression occurs in approximately one in seven women (10%–20%) (1, 2). The more emergent and rarer postpartum psychosis occurs at a rate of 0.1%–0.2% of women in the general population. Women with bipolar disorder have dramatically elevated rates of postpartum psychosis as well as an increased risk of postpartum depression.

Family and twin studies suggest a genetic contribution to postpartum depression and postpartum psychosis. A recent study of postpartum psychosis in bipolar mothers found an association between polymorphisms in genes encoding components of serotonergic pathways (SERT and 5-HT2A, 5-HT2C), further suggesting that genetic factors modulate susceptibility (3). However, postpartum depression and postpartum psychosis are multifactorial, and contributors include biological/hormonal, psychological, and social factors (such as relationship and financial problems) as well as family history and sleep deprivation (1, 2). Moreover, bipolar disorder increases the risk of postpartum psychosis specifically, while history of mood or anxiety disorder increases the risk of postpartum depression.

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Because of the genetic components, it is logical to use psychiatric genetics to help us further understand these phenomena. However, this is not the simple Mendelian genetics of sickle cell anemia, and any genetic studies need to be interpreted bearing in mind the complexities of genetic and nongenetic contributory factors.

Genome-wide linkage analysis (GWLA) allows us to assess the chromosomal location of variants involved in the genesis of a disorder, including complex traits, without initially knowing the loci responsible. A more recently developed method, the genome-wide association study (GWAS), allows testing of almost all genes in the genome for their association with a trait. The challenges are that GWLA requires families in which the disorder clearly segregates, while GWAS requires quite large population samples. Usually, illnesses must be carefully defined and phenotypically distinct (a challenge for psychiatric disorders). The ultimate goal of such work is identification of susceptibility genes and the development of appropriate prevention and treatment strategies based on this knowledge. For example, a recent study (4) used a GWAS design to study the response to lithium prophylaxis in bipolar disorder.

In a sample of patients with bipolar or schizoaffective disorder, Jones et al. (5) conducted a genome-wide linkage study for postpartum psychosis ("bipolar affective puerperal psychosis"), which they defined specifically as a manic or psychotic episode within 6 weeks of delivery and identified using a semistructured interview and case notes. A significant linkage signal was observed on chromosome 16p13, and suggestive linkage on chromosome 8q24, meaning that 16p and 8q are likely to hold genes predisposing these women to postpartum psychosis.

As reported in this issue of the *Journal,* Mahon and colleagues (6) performed two genetic studies. The first was a GWLA seeking to identify regions that carry genes predisposing women to more general postpartum mood symptoms. The second was an association study that focused on the regions identified in the linkage study, using fine mapping with single-nucleotide polymorphisms (SNPs) to study specific genes in those regions. The authors used secondary data from the National Institute of Mental Health Bipolar Disorder Genetics Initiative and the Genetics of Recurrent Early-Onset Depression studies. The study included over 1,100 women who had been pregnant, who had a mood disorder, and for whom information about postpartum symptoms was available. Bipolar disorder or major depression was diagnosed with medical records and family informant data as well as use of the Diagnostic Interview for Genetic Studies, a psychiatric diagnostic interview. The sample was diagnostically heterogeneous, including women primarily with major depressive disorder (62.6%) and bipolar I disorder (26.9%) but also with other mood spectrum disorders. Postpartum mood symptoms were ascertained by two questions in the interview—whether the individual had "severe emotional problems" within a month of childbirth and whether "the most severe depression" occurred after a pregnancy; 22.9% recalled experiencing one of these.

A significant linkage signal for postpartum symptoms was identified on chromosome 1q with a suggestive linkage peak on 9p, suggesting that genetic variations in these locations may increase a woman's risk of postpartum mood symptoms. Subsequent association studies using SNPs in these regions provided the strongest evidence for association with SNPs at the HMCN1 gene and additional suggestive evidence for association at the METTL13 gene, although this association did not reach criteria for statistical significance when adjusted for the many statistical tests involved. Nevertheless, the findings focus attention on these two genes as potentially important in these disorders.

How could these two genes be involved in postpartum depression? The HMCN1 gene contains estrogen receptor binding sites, and METTL13 is putatively involved with methyltransferase activity, which plays a role in estrogen receptor-induced gene transcription. This is in keeping with mood symptoms fluctuating with hormonal variation.

Many questions remain. First, neither of the sites identified in the Jones et al. (5) postpartum psychosis study reached significance in the Mahon et al. study. The definition of postpartum mood symptoms used in the Mahon et al. study was much broader and less specific. Careful definitions of specific phenotypes are often important in genetics studies. This study did not use the Edinburgh Postnatal Depression Scale or another validated test for postpartum mood symptoms and could pick up any of the various entities, including self-limited baby blues. Recall bias and self-diagnosis are also of concern. Also, the sample included only women who were known to have a major mood disorder and not de novo cases of postpartum depression or postpartum psychosis.

The Mahon et al. study is the first to look at a genetic contribution of the self-reported experience of postpartum mood symptoms in women with depression or bipolar disorder using a systematic genome-wide approach. While the findings are intriguing, a long history of disappointing results in genetic linkage and association studies in psychiatric disorders indicates that these findings will require replication. However, postpartum mood symptoms are a budding area for the application of genetic tools, and this study demonstrates that such studies are indeed feasible.

Also in this issue of the *Journal* is an article by Sharma and colleagues (7) that focuses on bipolar depression in the postpartum period, a topic that has received little attention in the literature. The authors cite a retrospective sample (8) in which one-fifth of women with bipolar disorder recalled experiencing postpartum mood episodes and another (9) in which two-thirds of 30 women with bipolar disorder experienced a mood episode in the month after delivery—the vast majority of which were depressive episodes. Misdiagnosis of bipolar depression in the postpartum is of relatively high stakes because antidepressants carry the risk of worsening bipolar illness by leading to mania, mixed or rapid cycling states, or treatment refractoriness.

Sharma et al. highlight the lack of categorization of postpartum hypomania in DSM-IV and consequently a lack of awareness or screening. Moreover, there has been a lack of nosological agreement regarding a definition of postpartum psychosis and regarding the time of onset of postpartum depression. DSM-IV allows for a "postpartum onset" specification for depressive, manic, and mixed episodes within 4 weeks of delivery but does not have a specific diagnosis of postpartum psychosis or baby blues. The risk of mental illness remains elevated beyond the first 4 weeks after delivery, however, extending through the postpartum year. Compared to other psychiatric entities, the treatment and prevention of bipolar depression in the postpartum period has been examined in fewer studies, in part because of obvious ethical concerns.

Screening for postpartum depression is often done in the obstetrics and pediatrics departments rather than in the psychiatry department, which highlights the importance of collaboration and education across disciplines. If a woman is referred for "postpartum depression," it should be determined whether she has baby blues, postpartum depression (including a bipolar depressive episode), postpartum psychosis, or an organic problem mimicking postpartum depression. In addition to eliciting symptoms, family history and personal history should be investigated for clues. For example, if there is a family or personal history of bipolar disorder, suspicion of a bipolar depressed episode would be elevated, and treatment implications different than for a unipolar depressed episode.

Treatment of postpartum mood disorders must always balance the risk of untreated mental illness and the risks of treatment to both mother and infant, including through breastfeeding. As Sharma et al. note, limited studies indicate that lithium, carbamazepine, and olanzapine have shown reduction in postpartum recurrence or risk of bipolar episodes. Sleep is critical, as is support. Women should also be carefully monitored during future pregnancies.

Both articles serve to remind physicians that we need further studies of the prophylaxis and treatment of postpartum depression and postpartum psychosis, as well as screening tools and a careful approach to diagnosis. These disorders are genetically complex and multifactorial. Genetic studies of postpartum mental illness hold promise not only for screening but also for prevention and treatment. It is not unreasonable to expect in the distant future a genetic screen for risk of postpartum depression and postpartum psychosis at prenatal appointments along with other screening tests.

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