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# Biomarker or pathophysiology? The role of DNA methylation in postpartum depression

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Postpartum depression (PPD) affects between 10 and 20% of women in the general population [1–4] but the risk is much higher in women with a history of major depression disorder (MDD) or bipolar disorder (BP), with at least 30% developing PPD [5,6]. Known risk factors in addition to a history of mood disorder include depression or anxiety during pregnancy, a family history of PPD, a history of significant premenstrual mood symptoms, recent stressful life events and poor social support. Other factors that may play a role include the hormonal changes that occur during and after delivery, the stress associated with having a newborn and sleep disturbance. Similar to most psychiatric illnesses, PPD is probably the result of environmental stressors in the setting of a biological vulnerability.

In the literature, the term ‘PPD’ has been applied to a number of different clinical scenarios, including a depressive episode that starts during pregnancy and continues postpartum, a depressive episode that clearly starts in the immediate postpartum period (generally within the first 4 weeks) and a depressive episode that starts after the birth of a child but not necessarily in the immediate postpartum period, including time periods up to a year

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postpartum. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, the 'postpartum' specifier for a major depressive episode (MDE) can only be used in the setting of a MDE that clearly began after delivery and began within the first 4 weeks postpartum. In support of this definition, a number of genetic studies (including our own) indicate that episodes that begin within the first 4 weeks postpartum have a genetic basis in both families with MDD and BP [7–10]. Furthermore, there is evidence that women with a history of PPD are effectively susceptible to hormonal change. Bloch *et al.* demonstrated that 62% of women with a history of PPD developed mood symptoms in response to a blinded withdrawal of supraphysiological levels of estrogen and progesterone when compared with none of the controls [11]. It is likely that women who develop a MDE after delivery in the setting of hormonal change represent a more genetically homogeneous group and the time period of 4 weeks postpartum is the critical time period during which, if a woman's mood is susceptible to times of hormonal change, she will be at an elevated risk for PPD [7–11].

There is, however, controversy in the literature as to whether PPD as defined by DSM-IV is a unique entity from depression that begins during pregnancy and continues postpartum. As a result of this, the newly published DSM-5 has chosen to eliminate the 'postpartum' specifier and incorporate a 'peripartum' specifier. Significant hormonal changes occur during pregnancy, with rising levels of estrogen and progesterone, and as noted one of the strongest predictors of being depressed postpartum is being depressed during pregnancy. Studies examining differences (and similarities) between these two populations will help to determine whether there are significant and meaningful differences in the pathophysiology underlying depression during and after pregnancy.

We used a cross-species translational design to identify estrogen-mediated epigenetic changes associated with PPD [12]. DNA methylation pro-files were generated using methylation micro-arrays in a sample of women who were followed prospectively through pregnancy and after delivery, who were at high risk of PPD due to a history of a mood disorder. In this sample, PPD was defined as a MDE that clearly began within 4 weeks of delivery and not during pregnancy. These profiles were cross-referenced with syntenic locations that demonstrated hippo-campal DNA methylation changes in response to long-term treatment with 17-β-estradiol (E2) in the mouse. We identified two biomarker loci at *HP1BP3* and *TTC9B* that predicted PPD with an area under the receiver operator characteristic curve of 0.87. These results suggest that there is an enhanced sensitivity to estrogen-based DNA methylation reprogramming in the hippocampus of those at risk for PPD. This finding is consistent with current thinking that PPD is a result of sensitivity to changing hormone levels for certain women [11].

We also studied a sample of women who were depressed during pregnancy, a subsample of whom remained depressed postpartum. Given previous work suggesting a genetic vulnerability only in women whose PPD clearly began post-partum, we were interested to see if our biomark-ers were or were not predictive of postpartum mood status in women who were depressed during pregnancy. In this sample, we found that we could segregate the PPD status with 88% accuracy during pregnancy, meaning that women without PPD were predicted as having PPD and vice versa. This suggests that DNA methylation at these two

loci interact with mood status during pregnancy to affect mood status after delivery. We found that there was a decrease in the ratio of monocytes to lymphocytes and granulocytes in the antenatally depressed women, and incorporation of these data enabled us to predict the PPD status in the entire cohort with an area under the curve of 0.82.

Therefore, we have identified a biomarker for postpartum mood status that correctly identifies whether or not a woman will be depressed during the postpartum time period, regardless of whether or not she is depressed during pregnancy. Do our findings merely represent a biomarker for PPD or do they point to the underlying etiology of PPD? *HP1BP3* has been shown to associate with the β-estrogen receptor [13] and *TTC9B* has been shown to be responsive to gonadal hormones [14]. It is, therefore, conceivable that DNA methylation changes in genes related to hippo-campal plasticity are induced by high levels of estrogen circulating during pregnancy in women susceptible to PPD and that these biomarkers are therefore one ‘step’ in the pathophysiology underlying PPD. While research is ongoing, *TTC9B* may be linked to regulation of AMPA receptor levels, which in turn have been shown to be associated with resilience or vulnerability to stress [15]. One hypothesis is that the molecular changes exhibited by the biomarkers are indicative of a biological vulnerability, which may interact with the various stressors in the postnatal period inherent with caring for a newborn that ultimately lead to depression.

Since our results also apply to women who were depressed during pregnancy, what does that imply about the previous findings that there is a genetic basis for episodes of PPD that begin shortly after delivery? PPD is likely to have heterogeneous underlying causes, as evidenced by the range of risk factors, which include both biological and environmental factors. The epi-genetic changes we have observed may represent a ‘final common pathway’ that indicates whether a woman will either remain or become depressed postpartum. The epigenetic findings were influ-enced by mood status during pregnancy, with increased methylation at *HP1BP3* in the ante-partum depressed sample and decreased methylation at *HP1BP3* in the euthymic sample, indicting that it is the degree of change at this loci that is associated with PPD, not the direction. It will be important to explore this further and identify whether other differences exist between the two populations.

Given these findings, it is important that future research ensures that the populations studied are well defined. It remains unclear whether our findings are unique only to women with a history of MDD or BP, and replication in a more general community sample is warranted. The utility of these biomarkers as a ‘test’ for PPD is also unclear. For example, would the knowledge of an impending PPD lead to greater stress and a self-fulfilling prophecy with a possible worse outcome? Does PPD occur in identified women despite medication and other psychiatric treatments, or does early identification allow early intervention that can prevent the onset of PPD? While more research is necessary, the current state of knowledge suggests the latter, as a comprehensive review of PPD intervention trials demonstrated that numerous factors, including even simply identifying ‘at risk’ women, can reduce the risk of developing depressive symptomology [16].

It is clear that the DNA methylation changes identified are an important piece in better understanding PPD and may be a clue to the underlying pathophysiology of PPD. Future

research will need to incorporate an understanding of how other environmental and biological risk factors affect methylation patterns at these loci and whether genetic predispositions play a role. Studying whether or not identification of risk allows modification of the outcome of PPD is perhaps most important and would be a milestone for psychiatry in general given the need for a test for psychiatric illness that allows intervention. Finally, it is important, to continue to identify clinical differences in psychiatric populations that may result in 'cleaner' biological findings. Had the two populations studied here (the antenatally depressed and antenatally euthymic groups) been studied together, it is likely that the biomarkers would not have been identified given that the methylation changes occurred in the opposite direction. Continued cooperation between clinicians and basic scientists will increase the chances that the complicated biology underlying psychiatric conditions can be unraveled.

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