Perinatal Mental Health: Advances and Opportunities

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The past 60 years have seen increasing awareness and advancement in the area of perinatal mental health. The initial formation of the International Society for Psychosomatic Obstetrics and Gynecology over six decades ago, followed by the founding of the International Marcé Society for Perinatal Mental Health (https://marcesociety.com/) in 1980, has fostered environments for bringing together different avenues of research in puerperal maternal mental disorders. In 1987, a support and advocacy group, Postpartum Support International (https://www.postpartum.net/), was founded to increase awareness among public and professional communities about the emotional changes that women experience during the perinatal period. The Centers for Disease Control and Prevention (CDC) has expanded the information and links available on perinatal mental health (https://www.cdc.gov/reproductivehealth/features/maternal-depression/index.html). Several specialized programs focusing on women's mental health have been established at academic centers, and these have been complemented by a wave of private practice groups focusing on perinatal psychiatry. Additional groups, subgroups, and task forces have been established, including the National Task Force on Women's Reproductive Mental Health, formed in 2013. The effort to meet clinical needs has created a challenge in education (1) and brought increased attention to the need to provide an inclusive educational program. The National Curriculum in Reproductive Psychiatry (https://ncrptraining.org/) includes a comprehensive educational program. Most recently, the American Psychiatric Association established the Perinatal Mental Health Toolkit (https://www.psychiatry.org/psychiatrists/practice/professional-interests/women-s-mental-health/maternal-mental-health-toolkit). These resources provide considerable information and references.

CHALLENGES IN IDENTIFICATION AND DIAGNOSIS: IMPACT ON DATA INTERPRETATION

A challenge in assimilating the available literature on perinatal maternal depression is related to how depression group assignments are defined, including the screening and group inclusion tools used, changes in diagnostic criteria, the presence of comorbidities, and heterogeneity of the symptoms. The diagnosis of postpartum depression continues to undergo considerable scrutiny, with various symptom patterns being discussed (2, 3). A recent review by Batt et al. (4) incorporates a synopsis of the evolution of postpartum and perinatal nosology as well as an overview comparing postpartum depression to nonpuerperal major depression. Much of the literature on the incidence and purported consequences of maternal depression is reliant on self-rating scale scores. The Edinburgh Postnatal Depression Scale (EPDS) (5), a 10-item self-rated scale that has been translated into a variety of languages, is a widely used screening instrument that was developed to trigger further evaluation. In research studies, the EPDS has become a common tool for making group assignments, and it is recommended as a screening tool by the U.S. Preventive Services Task Force (6). Notably, there continues to be variation in the EPDS cutoff score utilized across investigations.

Historical descriptions of postpartum mental illness likely include a continuum of postnatal illnesses—for example, "baby blues," depression, anxiety, and psychosis—and the timing of symptom onset is often obscure. The DSM specifier for postpartum onset applied to depression changed from DSM-IV (onset of episode within 4 weeks postpartum) to DSM-5 (onset of symptoms during pregnancy or up to 4 weeks postpartum) (7). The DSM diagnostic system generally provides an interpretable system to support a variety of health care components. The ICD-10 and ICD-11 criteria include "syndromes associated with pregnancy or the puerperium (commencing within about 6 weeks after delivery)," and other assessments, such as the Pregnancy Risk Assessment Monitoring System, developed by the CDC to assess the prevalence of perinatal health issues (www.cdc.gov/prams/Questionnaire.htm), queries a more extended time frame of up to 12 months postpartum. While the DSM-5 and ICD-11 perinatal specifiers are more inclusive with respect to onset during pregnancy, the time frame of including pregnancy through 4 or 6 weeks postpartum is a broad range, especially if the goal is to incorporate a relatively specific window of hormonal/neuroendocrine change. One study examining postpartum depression utilizing a strict definition

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of symptom onset postpartum demonstrated that maximum familiality was observed using the criterion of symptom onset within 6–8 weeks postpartum (8). The changes in diagnostic criteria and the lack of consistency in their use have a significant impact on our ability to combine data across investigations. For example, the two placebo-controlled antidepressant trials in postpartum depression (9, 10) report enrollment of women with symptom onset within 4 weeks postpartum, per DSM-IV, and in the second of the two studies (10), some women with symptom onset within 3 months postpartum were included. The more recent novel treatment studies in postpartum depression with brexanolone (11) and zuranolone (12) enrolled women with symptom onset in late pregnancy or within 4 weeks postpartum. It may be important to be aware of how the timing of symptom onset may influence treatment response, as differences in timing may hinder the ability to compare studies based on inclusion criteria. This is not limited to treatment studies but may also pertain to other biological and psychosocial studies relevant to maternal depression across the perinatal period.

Some have argued that the National Institute of Mental Health's Research Domain Criteria (RDoC) project may be an ideal framework for studying perinatal mental illnesses (13). The RDoC project seeks to define transdiagnostic dimensions of functioning and facilitate the development of new and/or optimally targeted treatments for mental disorders (14, 15). The RDoC initiative may serve to identify women who demonstrate patterns of emotional dysregulation across periods of hormonal variation and to examine potential underlying neurobiological pathophysiology.

An additional rationale for looking beyond the DSM criteria or screening tools focused on depression for perinatal mental illness is the high rate of comorbidity in perinatal mood disorders. For example, some investigators have identified a high rate of obsessions and/or compulsions among postpartum women (16, 17). Reports of obsession and/or compulsions in the absence of obsessive-compulsive disorder (OCD) in women with postpartum depression have also been described (18). There is also evidence that the perinatal period may be a time of increased vulnerability for obsessions (19), and in one study, over 30% of women with OCD reported onset during pregnancy (20). A meta-analysis of comorbid anxiety and depression provided substantial evidence for comorbid anxiety across pregnancy and the postpartum period (21). Perinatal complaints of anxiety are common, and the extent to which anxiety symptoms contribute to the heterogeneity of perinatal depression warrants further attention (22).

Heterogeneity of nonpuerperal mood and anxiety disorders is common, and it is unclear whether previous investigations of this patient population have included women with perinatal episodes of depression or anxiety (23). For example, a review of depression symptom patterns among participants in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study demonstrated substantial variation in symptom profiles (24). Recently, in an investigation of almost 6,000 women at sites affiliated with the National Network of Depression Centers, Weiss et al. (25) identified several subclasses of depression and noted that the somatic symptom class had menstrual cycle irregularity and more neurovegetative symptoms. There is limited inclusion of perinatal modifiers when examining heterogeneity in nonpuerperal major depression, as it is feasible that a history of perinatal depression episodes may contribute to the heterogeneity observed in major depression. In relation to heterogeneity in perinatal depression, in a systematic review of perinatal depression that included 23 studies examining 20 distinct cohorts (26), only one study was noted to focus on symptom profile; the majority of studies examined symptom trajectory. The International Postpartum Depression: Action Towards Causes and Treatment (PACT) Consortium utilized data from 19 institutions from seven countries to conduct latent class analyses on women with postpartum depression, using the EPDS (27). The study extended the original identification of several distinct phenotypes by employing principal components and common factor analysis to identify symptom dimensions in the EPDS. Application of the RDoC functional constructs of negative valence and arousal were applied to the EPDS. Three dimensions were identified, leading to the characterization of five distinct subtypes of perinatal depression: severe anxious depression, moderate anxious depression, anxious anhedonia, pure anhedonia, and resolved depression (28).

Our group recently utilized the items from seven symptom scales collected prospectively across pregnancy and the postpartum period from women with a history of neuropsychiatric illness (29). A priori categorization into six transdiagnostic factors was performed—four based on RDoC (loss, potential threat, frustrative non-reward, and sleep-wakefulness) and two based on the depression literature (somatic and coping symptoms). There was limited measurement congruency of these transdiagnostic factors across the perinatal period. The findings suggest that symptom phenotypes vary across the perinatal period. These data were recently confirmed and expanded by including a measure of positive affect (30). Such data underscore the importance of understanding the impact of the perinatal timing of symptom assessment as well as the perinatal timing of symptom onset. The data also support the need for investigators to use similar assessment times across the perinatal period as well as broadening assessments to better account for comorbid disorders. Additionally, the incorporation of measures assessing maternal hormones, hypothalamic-pituitary-adrenal axis activity (31), immune system activity (32), and thyroid function (33)—all of which demonstrate considerable changes across pregnancy and a variable timeline for return to pre-pregnancy levels—may serve to improve our understanding of phenotypes and outcomes.

CONSORTIUMS AND COLLABORATIONS

The perinatal period is a unique time to investigate vulnerability and resilience. Pregnancy is considered to be among the top 15 stressors (34), and others among the listed stressors are also common during pregnancy and childbirth—for example, adding a family member, sexuality, and marital conflict. The interaction between biological, social, and dynamic constructs all occurs around a well-defined event—childbirth. The vast majority of pregnancies have predictable changes in neuroendocrine, immune, and metabolic capacity and a variable timeline for these changes to return to pre-pregnancy baseline. Pregnancy brings individuals into the "medical spotlight," and during pregnancy there are considerable clinical contacts. The perinatal period is an opportunity to develop a better understanding of how diverse systems interact in a context-dependent fashion that contributes to vulnerability. Viewing pregnancy as a "stress test" is not a new concept—some investigators have argued that it serves as a window for vulnerability to future health risks such as diabetes (35) and cardiovascular disease (36). Of note, both gestational diabetes (37) and preeclampsia (38) are considered risk factors for perinatal maternal depression. The role of perinatal depression as a risk for long-term depression is unclear and needs further study. A 5-year follow-up study (39) suggested that a subgroup of women with depression in the postpartum period continued to have both depressive and anxiety symptoms.

Multisite collaborations and consortiums are a valuable mechanism for addressing medical challenges during the perinatal period. The Maternal-Fetal Medicine Units Network, funded through the National Institute of Child Health and Human Development, has made substantial contributions to clinical research on the perinatal period. There is also precedence for successful collaborations to address neuropsychiatric illnesses in the perinatal period. For example, the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (ClinicalTrials.gov identifier: NCT01730170), utilizing 20 sites, has made substantial progress in improving the treatment of epilepsy during the perinatal period, including antiepileptic drug pharmacokinetic studies, course of illness (40), optimizing treatment guidelines, and offsprings' development after in utero antiepileptic drug exposure (41). The well-documented adverse effects of perinatal maternal depression on a variety of outcomes underscores the need for longitudinal collaborations.

Attention to women's mental health appears to have momentum, and this includes improved recognition and policy implementation, as well as U.S. Food and Drug Administration (FDA) recognition of treatment for perinatal depression. As presented in a study by Guintivano et al. in this issue of the *Journal* (42), while the majority of the genetic data for perinatal depression parallel data observed in major depression, there are some potentially interesting exceptions. Of particular interest are the cell type enrichment analyses reported by Guintivano et al. implicating potential alterations in GABAergic neurons that are enriched for genetic variants contributing to the heritability of postpartum depression. As discussed in the report, this is an exciting finding when considering the recent FDA approval of novel treatments for perinatal depression such as the neurosteroid allopregnanolone, which is a $GABA_A$ allosteric modulator. Advances have been achieved in the treatment of postpartum depression, and as noted by Gordon in a 2019 commentary in these pages (43), allopregnanolone treatment represents one of the initial examples of moving from basic science discoveries to the development of novel treatments. The future availability of larger sample sizes and the incorporation of transdiagnostic approaches and additional measures of biological, psychological, and social domains will serve to refine our understanding of pathogenesis in perinatal mental illness and allow optimization of intervention and prevention strategies.

Establishing further collaborations, such as PACT, and continued interactions with other established groups, such as the National Network of Depression Centers and the Psychiatric Genomics Consortium, will improve our chances of developing new treatments based on alternative mechanisms. Furthermore, further characterization of perinatal mental illness phenotypes will support the development of personalized treatment planning. Given the potential transgenerational impact of perinatal depression, expediting such collaborations will have considerable longitudinal impact.

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Accepted October 19, 2023.

Am J Psychiatry 2023; 180:874–877; doi: 10.1176/appi.ajp.20230822

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