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Clinical phenotypes of perinatal depression are associated with time of symptom onset: Findings from an International Consortium

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Abstract (250 words)

Background: The perinatal period is a high risk time for onset of depressive disorders and is associated with significant morbidity and mortality, including maternal suicide. Perinatal depression (PND) constitutes a heterogeneous group of clinical subtypes, and further refinement is needed to improve treatment outcomes. **Objective:** We sought to empirically identify and describe clinically relevant phenotypic subtypes of PND based on NIMH Research Domain Criteria (RDoC) symptom dimensions (i.e., depression, anhedonia, anxiety), and further characterize subtypes with respect to time of symptom onset within pregnancy or postpartum periods. **Methods:** Using a subset of the PACT (Postpartum Depression: Action Towards Causes and Treatment) Consortium dataset**,** principal components and common factor analysis were applied to define symptom dimensions using the 10-item Edinburgh Postnatal Depression Scale (EPDS). K-means clustering was used to identify subtypes of women sharing symptom patterns. Univariate and bivariate statistics were used to describe the subtypes. **Findings:** We found evidence for three underlying dimensions measured by the EPDS; depressed mood, anxiety and anhedonia. Using those dimensions, five distinct subtypes of PND were identified with clear differences related to symptom quality and time of onset. Anxiety and anhedonia emerged as prominent symptom dimensions with postpartum onset and were notably severe. **Interpretation:** Our findings show that there may be different types and severity of perinatal depression with varying time of onset throughout pregnancy and postpartum. These findings support the need for tailored treatments that improve outcomes for women with different phenotypes and severity of PND.
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Background

In recent decades, a robust literature documented the perinatal period as a high risk time for onset of depressive disorders with significant morbidity for mother, infant, and family that includes increased risk for low birth weight and prematurity, impaired mother-infant attachment, and,infant malnutrition during the first year of life [1,2] . Maternal suicide is a leading cause of maternal mortality[3]. Perinatal depression (PND), broadly defined by the World Health Organization as onset of a major depressive episode during pregnancy or across the first 12 months postpartum, has a lifetime prevalence of 10-15%[2] in industrialized countries and higher risk in lower income countries[4]. The greatest point prevalence for onset of symptoms is the acute postpartum period[5], but there is growing evidence that many women have onset of symptoms during pregnancy[6]. The public health importance of identifying women who suffer with PND was highlighted by new recommendations of the United States Preventative Services Task Force for depression screening during both pregnancy and postpartum[7]. This is consistent with guidelines from the National Institute for Health and Care Excellence (NICE) in the United Kingdom[8], the Australian Perinatal Depression Initiative[9] and the World Health Organization recommendations[10].

Recent work using the large international PACT (Postpartum Depression: Action Towards Treatment) consortium dataset demonstrated significant heterogeneity associated with PND. The PACT Consortium dataset represents 19 institutions in seven countries. This work utilized latent class analysis and described three specific latent classes (subtypes) of women with postpartum depression (PPD) who differed by symptom severity, timing of onset (pregnancy versus postpartum), history of previous mood or anxiety disorder, pregnancy/obstetrical complications, and presence of suicidal ideation[11]. These previous PACT findings support the need for further investigation to increase our understanding of the different phenotypes and type/quality of presentation associated with PND in those women with pregnancy versus postpartum onset. These findings extended previous work documenting that comorbid anxiety is an important symptom in women with the most severe illness (e.g., worry, ruminating thoughts)[12] Additionally, these findings are consistent with a clinical trial that demonstrated differential treatment response by time of symptom onset in women with PPD[13].

The phenomena of anxiety and mood symptoms in PND have not been adequately described to date. We hypothesized that women who become depressed during pregnancy will differ in type and quality of presentation compared to those with postpartum onset. We wanted to examine this important issue in the PACT Consortium dataset, which had not been previously addressed in the first PACT paper[11]. We hypothesized that the underlying etiology for onset and quality of symptoms across the perinatal period could be quite different based on underlying pathophysiological mechanisms such the hormonal fluctuations that characterize the perinatal period[14]. Therefore, rather than focus on traditional diagnostic criteria for PND that do not account for co-occurring anxiety symptoms, we sought to examine the symptom constructs described in the NIMH Research Domain Criteria (RDoC) mandate[15]. The NIMH RDoC was developed to create a framework for research on pathophysiology that helps inform future neuroscience based diagnostic classification systems and ultimately leads to novel treatment and detection of subtypes for treatment selection[16]. Application of the RDoC framework to examine the performance of mapping screening or diagnostic measures of depression to RDoC constructs has been an informative approach in other work[17]. We examined the RDoC functional constructs (i.e., negative valence and arousal/regulatory systems)[16], based on patient report of symptoms using the Edinburgh Postnatal Depression Scale (EPDS) in the PACT Consortium.[18]. Examination of the EPDS factor structure has been described in the literature with consistent reports of subscales measuring mood and anxiety[19]. There is also a smaller literature on a potential third EPDS subscale for anhedonia[20] or suicidal thoughts[21]. We focused on the RDoC functional constructs of negative valence (anxiety) and arousal since the symptom of anxiety is often a hallmark phenotypic feature of the perinatal period.

The primary objective of the present study was to empirically identify and describe clinically relevant subtypes of PND based on RDoC symptom dimensions in the PACT Consortium dataset, and further characterize them

with respect to time of symptom onset in each trimester of pregnancy and three postpartum periods (0-4, 4-8, and 8+ weeks).

Methods

Sample

Data were assembled from a subset of 7 of 19 international sites in the PACT consortium who contributed de-identified clinical data. PACT's mission, data collection and aggregation are described in detail elsewhere[11,22]. Subjects included women with reported depression in the postnatal period and were recruited from multiple settings including psychiatric clinics, obstetric clinics, primary care and community advertisements. In this subset of the PACT sample, the cohort was restricted to women aged 19-40 years with information on the onset of depressive symptoms in the perinatal period and complete prospective data for the 10-item EPDS. The most severe EPDS rating was selected for women with longitudinal PACT records. Timing of depression onset was submitted to the PACT consortium either as a clinician assessed or self-reported onset depending on the site. Figure 1 illustrates the selection of 663 women from 7 of the 19 PACT sites who met inclusion criteria for this study.

Edinburgh Postnatal Depression Scale (EPDS)

The EPDS is one of the most widely studied and validated instruments for assessing perinatal depressive symptoms[23]. Based on distributions observed in this sample, the EPDS scores were categorized into 4 severity levels reported in the literature[11,24]. At time of EPDS assessment, 25.3% of women reported having no depression/none (EPDS 0-9), 21.4% reported mild/moderate symptoms (EPDS 10-16), 45.1% reported moderate/severe symptoms (EPDS 17-21), and 8.1% had very severe symptoms (EPDS 22-30). The median EPDS measurement used in these analyses was conducted 4.5 months postpartum (median=135 days; IQR =164 days).

Statistical Approach

Our analytic approach extends the first PACT study in several ways. We began with an examination of the dimensionality of the EPDS. Using the factor score symptom dimensions as quantitative traits, subtypes of women having similar symptom dimensions were identified. The subtypes were next profiled with respect to demography, pregnancy characteristics, perinatal complications, and previous history of a mood or anxiety disorder. This approach allowed identification of subtypes using EPDS symptom dimensions and not by differences in perinatal or demographic features. This study builds on the prior PACT work by a cross sectional examination of the EPDS symptom dimensions with symptom reported onset across each trimester of pregnancy and three postpartum periods. We selected the three postpartum time points (0-4, 4-8, and 8+ weeks) based on the DSM-5 and World Health Organization ICD-10 criteria for PND[25,26]. Univariate and bivariate descriptive statistics described the characteristics of the overall sample and subtypes. All analyses were conducted with SAS 9.4 software[27].

Analyses of Symptom Dimensionality and Subtypes

Principal components and common factor analysis based on the tetrachoric correlation matrix were used to identify the symptom dimensionality in the EPDS. The RDoC functional constructs of negative valence and arousal were applied to the EPDS dimensions reflecting states of depressed mood, anhedonia, and anxiety. Quantitative scores were assigned to each study participant on each of the three dimensions. These scores were subsequently used to identify subtypes of women with similar patterns on the three dimensions using k-means clustering. A five subtype solution met the statistical criterion of the Cubic Clustering Criterion[28] and made the most clinical sense. The subtypes were described using descriptive statistics and analysis of variance (ANOVA) with post-hoc Scheffe comparison of means to identify which pairs of subtypes were significantly different. The Scheffe is a statistical method applied after an ANOVA to identify which groups are significantly different when

there are more than two groups being tested. Additional details of these methods are described in the Supplement.

Classification algorithms
Scoring algorithms for the three symptom dimensions and subtype membership (logistic regression probability of membership in each subtype) were developed to allow for replication in other samples. Additional details of the analyses and algorithms are presented in the Supplement enabling researchers and clinicians using the EPDS to examine the utility of this approach in their unique settings.

Results

Data from 663 women contributed from 7 of 19 sites who met the study inclusion criteria were included in these analyses. We found five subtypes of PND that differed both with respect to severity and type of symptoms. These subtypes are described by the onset of symptoms spanning across the pregnancy trimesters and early versus later postpartum periods. Demographic and perinatal characteristics are shown in Table 1. Among the 7 sites included in the analyses, 11 of the 13 characteristics reported in Table 1 had 70% or more data available. However, data was missing for demographic and perinatal characteristics and ranged from 2% missing for marital status up to 49% missing for the birth complication of preeclampsia described in Table 1. In the overall sample the mean age was approximately 32 years; 63% had given birth to ≥2 children; 82% were of European ancestry; 53% had a college education; and 86% were married. Ethnicity, education level, marital status, as well as medical and pregnancy complications contributed to distinguishing the subtypes.

Timing of Depression Onset
The timing of onset of depressive symptoms during the perinatal period was associated with EPDS score. Figure 2 illustrates that among women with first trimester onset, 62% had ongoing moderate/severe to very severe symptoms at the time of EPDS rating. However, half of women with second and third trimester onset had remitted completely by that time. Later onset of depressive symptoms during pregnancy was associated with a better outcome at the postpartum EPDS assessment. Women with depression onset in the second or third trimesters were more likely to be in the "Mild/Moderate" or "None" categories at assessment (50%, and 70% respectively) compared to women with onset in the first trimester (32%).

PPD onset of symptoms was associated with more severe depression. More than 20% of women with PPD reported onset within the first 8 weeks postpartum (postpartum intervals 0-4 and 4-8 weeks) were still categorized as "Very Severe" at assessment; an almost 4-fold increase compared with women who experienced depression onset during pregnancy. [Figure 2]

Symptom Dimensionality in the EPDS
The three symptom dimensions of depressed mood, anxiety and anhedonia using EPDS items are presented in Table 2. The bolded EPDS items in Table 2, define which items contribute to each of the three symptom dimensions. The three symptom dimensions identified five subtypes of women using k-means clustering on the quantitative scores.

The subtypes differed on symptom dimensions by type of depression and severity of illness. The five subtypes are labeled 1 to 5. Subtype 1 is characterized as "Severe Anxious Depression" and subtype 2 as "Moderate Anxious Depression." These 2 subtypes shared anxious depression symptoms of comorbid anxiety yet differed with respect to depression and anxiety severity. Subtypes 3 and 4 are broadly characterized as anhedonia. Subtype 3 had "Anxious Anhedonia" and subtype 4 was defined as "Pure Anhedonia". Subtype 5, "Resolved Depression" reported onset of symptoms during the perinatal period, which had resolved at the time of EPDS assessment. Half of this sample was in either the Severe or Moderate Anxious Depression subtype (31.8% and

18.6% respectively). One in four (26.4%) had the subtype of "Resolved Depression." Subtypes characterized by anhedonia had 11.9% with Anxious Anhedonia and 11.3% with Pure Anhedonia.

Table 3 shows the statistically significant differences on the three symptom dimensions across the five subtypes. The Severe Anxious Depression (subtype 1) has significantly higher depressed mood and anxiety ratings compared to all of the other subtypes (2, 3, 4, 5) but do not have higher scores than any subtype on the anhedonia symptom dimension. Similarly, women with Resolved Depression (subtype 5) have significantly lower ratings than all other subtypes on all of the dimensions, with the exception of higher scores on the anhedonia factor than the Severe Anxious Depression subtype.

Table 4 contains the distribution of EPDS scores in each subtype with overall EPDS means, the proportion of each subtype across the severity categories, and the mean anxiety subscale scores. Notably 98% of the Severe Anxious Depression subtype are in the moderate/severe or very severe EPDS categories. The Anxious Anhedonia subtype has the highest proportion of women in the very severe EPDS category. The final item in the EPDS assesses thoughts of self-injury. Such thoughts are prominent in the subtypes with comorbid anxiety, and to a lesser extent in the Pure Anhedonia subtype. Both of the subtypes characterized with anxiety symptoms (Severe Anxious Depression and Anxious Anhedonia) have significantly higher scores on the EPDS anxiety subscale[29].

Subtypes and Time of Symptom Onset

Figure 3 shows the distribution of subtypes in each onset period, including the three trimesters of pregnancy and three post-partum periods examined. A bar representing the sample total is included on the right side graph for comparison purposes. If there was no difference by onset period, each of the other bars would reflect the distribution of the total sample. The Severe Anxious Depression subtype is more likely to have depression onset in the first trimester or in the period following birth at 2 months or more. A similar pattern is seen in women characterized by the subtype Moderate Anxious Depression. The Anxious Anhedonia subtype is represented almost 6-fold more than expected in the immediate postpartum period and nearly 4-fold in the following 4 weeks. Women with the subtype of Anxious Anhedonia were much more likely to have the onset of illness during the first (60.5%) and second (37.9%) postpartum periods. They are notably absent in the onset periods during pregnancy. The subtype with Pure Anhedonia is notable in their absence in the immediate postpartum onset period. Otherwise, they are fairly evenly represented across the onset periods we examined. Women with Resolved Depression subtype reported depression onset predominantly in the third trimester of pregnancy and not in the postpartum onset periods.

Discussion

We sought to empirically identify and describe clinically relevant subtypes of PND in a subset of the PACT Consortium dataset, and further characterize them with respect to time of symptom onset within each of the 3 trimesters of pregnancy and 3 postpartum periods (0-4, 4-8, and 8+ weeks). This extends prior work[24] by including an examination of onset and quality of depression symptoms during both pregnancy and three postpartum periods. Using a framework derived from the RDoC principles, we described 3 underlying symptom constructs or dimensions in the EPDS, depressed mood, anxiety, and anhedonia.

The subtypes that emerged from clustering women on patterns of factor scores identified women with subtype Anxious Depression, both severe and moderate, and women with anhedonic symptoms, alone and in combination with anxiety. We also found a subtype of women whose depression started in the second or third trimesters of pregnancy and had resolved at the time of the EPDS measurement. Women with subtype Anxious Anhedonia were much more likely to have the onset of illness during the first and second postpartum periods. Onset in the first trimester included many of the women with the subtype of Anxious Depression. It may be that some of these women were suffering from depression prior to the pregnancy. Additionally, our results indicate

that comorbid anxiety and anhedonia are prominent symptoms associated with both pregnancy and obstetric complications and, in a subgroup of women, depression onset.

We also found that onset of symptoms in the first eight weeks of the postpartum period were associated with more severe depression, characterized as subtype Anxious Anhedonia. Moreover, 20% of women were still categorized as "Very Severe" at the postpartum EPDS assessment; an almost 4-fold increase compared with women who experienced depression onset during pregnancy. Given the enormous hormonal fluctuations that occur in the transition from pregnancy to postpartum[14], it is reasonable to speculate there may be important conceptual and biological differences underlying both the severity and phenomenology of depression between women with onset of symptoms during pregnancy versus postpartum onset. Further, there is a growing literature on the important role of reproductive hormones in modulating neural circuits and biological systems implicated in depression, suggesting that the characteristic hormone instability of the perinatal period could contribute to mood dysregulation in PPD[14,30]

The present study has several limitations that should be mentioned: First, this is secondary analysis of existing data; the sample includes 7 of 19 sites in PACT and is a subset of the full PACT Consortium. The current study was restricted to sites able to answer the time of onset question spanning the prenatal and postpartum period. PACT was originally created by aggregating extant data across international independent sites with various protocols to examine the phenotypic heterogeneity of PPD. There were inherent differences among protocols including the selection criteria and the recruitment setting of study participants at each site. Missingness of data occurred in two ways: 1) extraction from the PACT parent larger dataset created a subset where the data was not missing at random since it was not collected at the site level, ie., when 'time of reported onset' or 'complete 10 item EPDS prospective data' was not available for a particular site; and *2)* data was also missing at random within the seven sites for demographic and perinatal characteristics due to not being collected or available to PACT at time of the analyses. This additional layer of missingness may further bias results and the characteristics are only presented within as numbers and percentages. Therefore, the missing data can contribute to ascertainment bias, which is an inherent concern when pooling data and could potentially influence the robustness of the findings. Second, the EPDS ratings occurred 4.5 months postpartum and thus are a cross-sectional examination rather than a longitudinal assessment. Third, study protocols had differences including ascertainment criteria, recruitment settings and the variables collected. Such differences and missing sociodemographic data could contribute to bias and the strength of the results. Fourth, this dataset is mostly a Caucasian sample of women and we cannot exclude the role of socioeconomic status and country of origin on our findings, thereby potentially limiting generalizability.[22]. Fifth, the analyses were limited to variables collected across studies, and onset of depression included both clinical and self-report assessments. Sixth, there may be other attributes relevant to identifying and characterizing subtypes of PND. There was little data about history of stressful life events, such as abuse or trauma, which may also play a role in PND. Lastly, we do not have detailed information about the pre-pregnancy depression status of the women in the dataset. For women that reported first trimester onset of symptoms and continued to be symptomatic over time, it is possible that this group is more chronically depressed and may have experienced depressive symptoms prior to pregnancy.

However, we believe that the strengths of the results outweigh the limitations as an important hypothesis-generating foundation for future work. The strengths of this study include the novel approach to further examine subtypes of PPD from a subset of the PACT Consortium with diverse characteristics for sites and countries, inclusion of women from a wide range of socioeconomic statuses, and detailed symptom assessment using standardized measures. It will be important to validate this work, including the factor structure, subtype types and associations with onset period.

In conclusion, we applied 3 underlying symptom dimensions measured by the EPDS that correlate with the RDoC framework to further examine PND. Using these dimensions, we identified 5 distinct subtypes of PND and found clear differences related to time of depression onset in the perinatal period. This was particularly true for the

subtypes of comorbid anxiety and anhedonia. The subtypes differ with respect to time of onset at stages of pregnancy and in the postpartum periods. In particular, women with postpartum onset of symptoms had severe and persistent symptoms. Women with onset in their first trimester also remained highly symptomatic at the postpartum period. Therefore, in order to deliver the most effective treatment, it is vital that future clinical and research efforts focus on the potential phenomenological and biological differences characterizing onset of depression during pregnancy versus the postpartum period utilizing prospective and longitudinal approaches. The recent development of guidelines by many countries on screening and treatment for PND provides a strong mandate to improve mental health care for all perinatal women. Consequently, it is imperative to develop effective screening strategies across a range of global settings that allow for the delivery of targeted therapies to women with different clinical phenotypes and severity of PND. These strategies must address the complexities associated with differences in time of symptom onset during the perinatal period and the diverse symptom constructs including anxiety, low mood and anhedonia.

Research In Context Panel

Evidence before this study

We performed two comprehensive searches to identify all relevant articles. First, we searched PubMED using the keywords “perinatal depression”, “postpartum depression”, “time of onset”, “pregnancy” and “phenotypes” from inception until 02/06/17. We did not restrict by year of publication and included all published articles. Next, we searched PsycInfo using the same keywords. The search yielded 38 articles from PubMED and 4 articles from PsycInfo that were applicable to our study objective.

Previous work in this area is scant and there are very few studies examining differences between women that develop depression during pregnancy compared to those with onset of symptoms in the postpartum period. Further, prior work is limited by either very small sample sizes or inadequate phenotyping by time of symptom onset. Overall, research that investigates functional symptom constructs that may differentiate meaningful differences between depression during pregnancy versus postpartum are rare, and to date, no previous studies have examined the time of symptom onset in each trimester of pregnancy and three postpartum periods (0-4, 4-8, and 8+ weeks) in relation to specific symptom dimensions that are based on a framework to understand the underlying pathophysiology.

Added value of this study

We addressed the limitations in prior work using data from the PACT consortium, which includes 19 international investigators who contributed de-identified clinical data. The consortium allowed us to have a robust and comprehensive sample for this present study from 7 of the 19 sites to examine the time of onset of symptoms in the perinatal period. The present study extends the prior work of the PACT Consortium by focusing on the onset of depression during both pregnancy and in three postpartum periods. Specifically, we sought to examine the symptom constructs described in the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) mandate, a framework for research on pathophysiology that helps inform future neuroscience based diagnostic classification systems and ultimately leads to novel treatment and detection of subtypes for treatment selection. Therefore, we examined the RDoC functional constructs (i.e., negative valence and arousal/regulatory systems) based on patient report of symptoms using the Edinburgh Postnatal Depression Scale (EPDS) in the PACT Consortium.

We found evidence for three underlying dimensions of depressed mood, anxiety and anhedonia in PND. Using those dimensions, five distinct subtypes of PND were identified with clear differences related to symptom quality and time of onset. Anxiety and anhedonia emerged as prominent symptom dimensions with postpartum onset and were notably severe.

Implications of all available evidence:

Our findings have important public health implications to address the morbidity and mortality associated with PND. First, clinicians should be aware that there there may be different types and severity of PND with varying time of onset throughout pregnancy and postpartum. We can no longer afford to apply a one size fits all approach if we want to adequately meet the mental health needs of mothers with perinatal psychiatric illness. Second, we identified 5 distinct subtypes of PND and found clear differences related to time of depression onset in the perinatal period. This was particularly true for the subtypes of comorbid anxiety and anhedonia. Third, these findings support the need for depression screening throughout both pregnancy and the postpartum period. Lastly, tailoring treatment based on subtype can improve outcomes for women with different phenotypes and severity of PND.

Author Contributions:
The individual studies contributing to the PACT analyses were led by SMB, DRR, PFS, ERB, KMS, JLP, VB, KMD, MA, GA, AB, MWO, SR, CG, CNE, PKM, BWP, PJS, KLW, ZNS, and IJ. Together with the core statistical analysis group led by KTP, MW, SMB, this group comprised the management group led by SMB and KTP who were responsible for the management of the project and the overall content of the manuscript. KW and MW also provided input on the manuscript, data analyses and figures. The PACT phenotype committee comprised ERB, KMS, JLP, VB, KMD, MA, DJN, GA and SMB. The executive/coordinating committee comprised JPS, KLW, ZNS, IJ, DRR, PFS and SMB. The remaining authors contributed to the recruitment or data processing for the contributing components of the PACT secondary analyses. SMB and KTP with input from MW and KW took responsibility for the primary drafting of the manuscript that was shaped by the phenotype and executive committees. All other authors saw, had the opportunity to comment on, and approved the final draft.

Declarations of Interest:

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