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Authors
El-Ibiary, Shareen Y
Hamilton, Steven P
Abel, Rebecca
et al.

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[ORIGINAL RESEARCH]

A Pilot Study Evaluating Genetic and Environmental Factors for Postpartum Depression

by SHAREEN Y. EL-IBIARY, STEVEN P. HAMILTON, REBECCA ABEL, CAROLYN A. ERDMAN, PATRICIA A. ROBERTSON, and PATRICK R. FINLEY

Dr. El-Ibiary is from Midwestern University, College of Pharmacy-Glendale, Department of Pharmacy Practice, Glendale, Arizona, and the Department of Clinical Pharmacy, School of Pharmacy, University of California, San Francisco, California; Drs. Hamilton and Erdman are from the Department of Psychiatry and Institute for Human Genetics, University of California, San Francisco, San Francisco, California; Drs. Abel and Robertson are from the Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, California; and Dr. Finley is from the Department of Clinical Pharmacy, School of Pharmacy, University of California, San Francisco, California.

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ADDRESS CORRESPONDENCE TO:
Shareen Y. El-Ibiary, PharmD, FCCP, BCPS, Midwestern University, College of Pharmacy-Glendale, Department of Pharmacy Practice, 19555 N. 59th Ave., Glendale, AZ 85308
Phone: 623-572-3512; Fax: 623-572-3550;
Email: selibi@midwestern.edu

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ABSTRACT

Objective: To assess the influence of genetic and environmental risk factors upon postpartum depression.

Design: Case-control, prospective study.

Setting: The University of California at San Francisco Obstetric and Gynecology Clinic.

Participants: Mothers screened for postpartum depression six weeks after delivery with the Edinburgh Postnatal Depression Scale and recruited as cases and controls.

Measurements: Eligible subjects completed a series of assessments and a structured clinical interview to confirm diagnosis of depression. Deoxyribonucleic acid was obtained for genotyping of 81 single nucleotide polymorphisms in 12 genes hypothesized to be postpartum depression-related.

Results: Twenty-four cases and 24 controls were eligible for analysis. Three single necleotide polymorphisms in the serotonin 2A receptor (HTR2A) gene were associated with postpartum depression. The strongest association at a functional promoter polymorphism (rs6311), a functional promoter single nucleotide polymorphisms (p=0.002, odds ratio 0.25, 95% confidence interval:0.10-0.63), was a finding robust to population stratification. Gene-wide association was significant for HTR2A (permuted p=0.008), but not when corrected for all 12 genes. Analysis of demographic and psychosocial risk factors identified distressed relationship, unplanned pregnancy, and a previous history of depression as significant predictive variables ($p \leq 0.05$).

Conclusions: This pilot data suggests deoxyribonucleic acid variations in HTR2A may be associated with postpartum depression. Psychosocial variables were also identified as risk factors. The relative influence of these variables on the manifestation of postpartum depression is yet to be determined.

INTRODUCTION

The postpartum period is a stressful time for new mothers as they learn to optimize infant bonding, balance the needs of their child, and tend to their own physical and emotional well-being. Not surprisingly, there is considerable evidence to suggest that the risk for postpartum depression (PPD) is elevated during this timeframe, with a peak incidence reported between four and eight weeks after delivery.[1] A meta-analysis examining the reported incidence of perinatal depression estimated that 14.5 percent of women will suffer a new episode of depression during the first three postpartum months, and that 6.5 percent of mothers will satisfy the diagnostic criteria for an acute episode of major depressive disorder (MDD), figures that are substantially higher than rates reported in the general nulliparous population.[1]

If left untreated, the consequences of PPD can be serious for the mother, her newborn, and the entire family. Depressed mothers may experience unnecessary suffering, deteriorating health status, marital discord, and suicidal ideation.[2–4] Offspring of these depressed mothers have been shown to have significant emotional, cognitive, and developmental delays, as well as an increased risk for mental disorders, which can persist throughout childhood.[5–7] In consideration of these and other findings, PPD has been called "the most significant obstetrical complication after delivery" and the illness was recently elevated to a "global health challenge" by the World Health Organization and the March of Dimes.[8]

Phenomenologically, PPD features the same core symptoms as MDD, though higher levels of anxiety have been reported with perinatal mood disorders.[9,10] As with MDD, PPD is believed to be a product of genetic and environmental factors but the precise underpinnings remain unknown. Historically, PPD was often attributed to the precipitous decline in reproductive hormones that immediately follows delivery in spite of the fact that concentrations of estrogen and progestin typically normalize within the first postpartum week.[11] Other biological factors have also been proposed, including deficiencies in monoamines and related enzymes.[12]

Genetic factors have been implicated in the etiology of perinatal mood disorders, as suggested by familial, twin, and adoption studies.[12–14] A variety of genetic variants have been identified including those associated with monoaminergic functioning (e.g., serotonin transport), stress response (e.g., glucocorticoid receptor sensitivity), and neurogenesis (e.g., brain derived neurotrophic factor).[14] Preliminary evidence suggests these genetic variants may be conferring vulnerability to depression during or after pregnancy as well.[15–18]

There has also been considerable research devoted to potential demographic and psychosocial risk factors including a lack of social support, history of domestic strife, and lower socioeconomic status.[19–21] A previous history of mood disorders is believed to be among the strongest risk factors for PPD, particularly if the episode occurred during the index pregnancy.[2,22–24] Difficult pregnancies, obstetrical complications, season of delivery, and unsuccessful breastfeeding are other risk factors commonly cited as well.[25–28]

Although considerable progress has been made in uncovering the etiology of PPD in recent years, the development of a cogent biopsychosocial model has been elusive. Previous studies have often been compromised by methodological limitations, such as the absence of structured diagnostic assessments or the narrow scope of risk factors considered, and very few have attempted to analyze both environmental and genetic variables.[1,16–18] The objective of our pilot project was to expand the breadth and depth of potential PPD risk factors to include genetic, biological, and psychosocial determinants and potentially illuminate and inspire future areas of research.

METHODS

Participants. Subjects were recruited from the University of California at San Francisco Obstetric and Gynecology Clinic during their six-week well-baby visit and informed about the study. Subjects were screened for eligibility and asked to complete the Edinburgh Postnatal Depression Scale (EPDS). Those with scores greater than 14 or less than 7 were recruited for case and control groups, respectively. Subjects were excluded if they were non-English speaking, exhibited imminent suicidality or psychotic symptoms, had evidence of current substance abuse, or were receiving ongoing antidepressant treatment. If subjects exhibited imminent suicidality or psychotic symptoms, had evidence of current substance abuse, or scored greater than 12 on the EPDS they were referred to the appropriate healthcare provider for follow-up. For eligible subjects, informed consent was obtained and a follow-up appointment was scheduled within one week of their well-baby visit to confirm the presence or absence of depression through a Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) Axis I disorders (SCID)[29] as well as to obtain a venous blood sample for genetic analysis. Prior to the follow-up visit, participants completed a set of questionnaires that included a demographic and reproductive health survey and the following psychometric surveys: Dyadic Adjustment Scale, Medical Outcomes Study (MOS) Social Support Survey, Life Threatening Events Survey, and Quick Inventory of Depressive Symptomatology (Self-Report)-16 (QIDS-SR16) scale. Participants scoring 14 or higher on the EPDS and confirmed by the

SCID to have depression were included in the case cohort. The control group consisted of study subjects who scored less than seven on the EPDS and did not have evidence of depression, based on the results of the SCID interview.

Ethics statement. The investigation protocol and written informed consent documents were approved by the UCSF Committee on Human Research prior to the commencement of study activities and the investigation was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all study subjects. A copy of the consent document was provided to the study subject and a duplicate copy was kept on file with principal investigator in a locked office.

Genetic analysis. We selected 12 genes for analysis, including those involved with steroid hormone function (NR3C1, FKBP5, ESR1, ESR2, PGR, AR, AKR1C2), neurotransmitter function (SLC6A4, MAOA, COMT, HTR2A), and neurotrophin function (BDNF). Given the preliminary nature of the project, we A) focused on variation near exons in larger genes; B) lightly tagged smaller genes; or C) incorporated variants that had previously been associated with related phenotypes or had potential functional effects. We genotyped 80 SNPs with Sequenom's iPlex assay and the 5-HTTLPR using our published protocol.[30] There were from 3 to 17 variants per gene (Supplemental Table 1). An additional 56 ancestry informative markers (AIMs) were genotyped to reduce the potential for ancestry as a confounding variable. Analyses were carried out using multidimensional scaling. Sequenom genotyping was completed using the manufacturer's protocol for the iPlex assay. The individual SNP call rate was 98.8 percent. A total of 100 percent of 5,076 duplicate genotypes were concordant. SNPs were selected for minor allele frequencies (MAF) that were 0.01 or greater, leaving 77 SNPs for analysis with a mean MAF of 0.230 (median MAF=0.229).

TABLE 1. Demographics

CHARACTERISTICS	CASES (N=24)	CONTROLS (N=24)	*P* VALUE
Age (mean)	27.58	27.79	n/a
EPDS score (mean)	19.08	4.17	<0.0001
Ethnicity Hispanic African American Asian White Other Undisclosed	 3 4 3 2 1 11	 4 4 2 1 0 10	n/a
Education (highest achievement) Some high school or completed Some college or completed	 11 12	 9 15	0.47
Previous pregnancies (mean)	1.33±1.37	1.79±1.74	0.49
Previous history of depression (diagnosed)	10	1	0.002
Relationship status Alone/separated/divorced Married/living together	 7 18	 5 16	0.50
Distressed relationship (DAS score >13)	15	3	<0.0001
LTE (mean)	2.29±2.16	1.42±1.61	0.18
QIDS-SR (mean)	18.6±5.07	6.08±3.88	<0.0001

EPDS: Edinburgh Postnatal Depression Scale; DAS: Dyadic Adjustment Scale; LTE: Life-Threatening Events; QIDS-SR: Quick Inventory of Depressive Symptomatology (Self-Report)-16

Statistical analysis. *Genetic factors.* Allelic association and logistic regression analyses were used to examine associations of the SNPs to the PPD phenotype. Regression analysis was performed adjusting for potential confounding effects of ancestry. We used the 56 AIMs to calculate multidimensional scaling (MDS) vectors, which were not associated with PPD. For example, the first MDS vector was associated with self-reported African-American ancestry (Supplemental Figure 1), although PPD itself was not (p=0.20, logistic regression). We found that adjustment for ancestry did not influence the results, thus the primary genetic analyses reported here are unadjusted. The estimated odds ratios (OR) and 95-percent confidence intervals (CIs) were estimated, and the empirical significance was determined using 100,000 permutations in PLINK, which is a a tool set for whole-genome association and population-based linkage analyses.[31] Set-based analyses were also carried out with PLINK, allowing us to test the gene

TABLE 2. Association between PPD and candidate gene variants

CHR	GENE	SNP	POSITION	A1	fA1 PPD/CTRL	P	OR (95% CI)
13	HTR2A	rs6311	46369478	T	0.19/0.48	0.002	0.25 (0.10,0.63)
13	HTR2A	rs2070040	46365626	A	0.54/0.25	0.003	3.55 (1.49,8.43)
13	HTR2A	rs6314	46307034	T	0.02/0.19	0.008	0.09 (0.01,0.76)
6	FKBP5	rs10498734	35667750	G	0.17/0.02	0.01	9.40 (1.13,78.41)
6	ESR1	rs11155820	152245902	G	0.21/0.07	0.04	3.77 (0.97,14.73)
6	ESR1	rs2273206	152424003	T	0.08/0.23	0.05	0.31 (0.09,1.04)

PPD: postpartum depression; CHR: chromosome; POSITION: SNP location on UCSC genome browser hg18; A1: reference allele; fA1 PPD/CTRL: frequency of allele A1 in PPD cases and controls; OR (95% CI): odds ratio and 95% confidence interval

as the basis of each test, rather than the individual SNP.[32] It relies on permutation to derive empirical *p*-values that are adjusted for the many SNPs within a set (e.g., all 5 SNPs in the HTR2A region) by taking account of the linkage disequilibrium between these SNPs. Using analysis parameters for linkage disequilibrium (r2 threshold=0.5) and significance thresholds (*p*-value threshold=1.0) and permutation of the dataset 100,000 times, we tested all 12 genes. Bonferroni correction was then implemented to control for the number of set tests (i.e., 12 set tests, significance threshold of p=0.004).

Environmental factors. Data were inputted into a Microsoft Access database and analyzed using SAS v9.2 (SAS Institute Inc., Cary, North Carolina). Level of statistical significance (two-sided) was established *a priori* at 0.05. Univariate logistic regression models were examined to explore a potential association between each demographic, clinical and psychosocial variable and the presence of postpartum depression. A multivariable model was constructed using forward stepwise regression

RESULTS

Demographics. From October 2007 through November 2008, 71 participants enrolled in the study. Sixteen participants failed to appear for their follow-up appointment, five participants recruited as cases were not confirmed to have depression by the SCID, one participant recruited as a control was found to have depression by the SCID, and one failed to have her blood drawn, leaving 48 participants enrolled for full analysis (24 cases and 24 controls). Participant ages ranged from 18 to 39 years old (mean age 27.7 years) with varying ethnic backgrounds. The characteristics of the sample are shown in Table 1.

Genetic findings. Table 2 shows the result of nominally significant allelic association tests for 77 deoxyribonucleic acid (DNA) variants in 12 genes hypothesized to play a role in PPD. No variant met an experiment-wide Bonferroni-corrected *p*-value threshold of 0.00065. Supplemental Table 2 shows *p*-values for all variants after both permutation and incorporation of genetic ancestry covariates. The strongest findings were for three SNPs in the serotonin 2A receptor (HTR2A) and the most associated SNP was rs6311, with a *p*-value of 0.002 and an odds ratio of 0.25. The T allele of this SNP was found to be protective against PPD, occurring in PPD at a frequency of 0.19, compared against 0.49 in controls. The frequency of this allele in eleven HapMap populations representing most continental populations was 0.429 (range 0.31–0.58). Two additional SNPs in HTR2A showed nominal association, with the interrogated alleles of intronic SNP rs2070040 (p=0.003) conferring risk and the non-synonymous SNP rs6314 (His452Tyr) conferring protection from PPD (p=0.008). Interestingly none of these three SNPs were correlated (i.e., in linkage disequilibrium) with each other (Supplemental Table 3). Haplotypic analysis of the three HTR2A SNPs provided additional evidence for association (p=0.003, omnibus test, 5 *df*), with the rs6314-rs2070040-rs6311 haplotype C-A-C having estimated frequencies of 0.52 in cases and 0.25 in controls (data not shown). Also noted were nominally significant associations with FK506 binding protein 5 (FKBP5), a gene associated with MDD and antidepressant response,[33,34] and also with two intronic SNPs separated by 178kb within the estrogen receptor gene (ESR1). A set-based analysis was carried out to interrogate the variation within each gene in aggregate, allowing us to test the hypothesis that multiple variants within a gene may independently contribute to the association. HTR2A was the only gene showing association of the 12 tested when correcting for the number of genes tested, showing a *p*-value of 0.0009

after 100,000 permutations of the data (Supplemental Table 4).

Environmental findings. Environmental predictors for PPD are listed in Table 3. The strongest predictors for PPD included distressed relationship, as measured by the Dyadic Scale (OR=16.7; 95% CI 3.6–78.0, p=0.0003), and self-reported history of depression (OR=16.4, 95% CI: 1.89–143, p=0.01). Very or extremely difficult pregnancy was also a strong predictor for PPD (OR=9.30, 95% CI: 1.78–49.0) as well as classifying caring for the baby as very or extremely difficult (OR=4.85, 95% CI: 1.10–21.0). Results of the MOS Social Support Survey revealed that the depressed women scored significantly lower on all domains of emotional/informational support, tangible support, affectionate support, and positive social support (p<0.005 all measures).

Other predictors for PPD that showed a trend towards significance included family history of depression (p=0.11), family history of depression, anxiety or bipolar disorder (P=0.06), family history of alcohol abuse (p=0.10), history of ever having depression during pregnancy (p=0.10), or history of ever having depression after pregnancy (p=0.14).

A multivariate model constructed using forward stepwise regression included distressed relationship, difficulty with pregnancy, and difficulty caring for the baby, all of which were independently statistically associated with presence of PPD (Table 3).

DISCUSSION

The results of this pilot investigation revealed promising statistical associations of postpartum depression with a variety of genetic and psychosocial factors. For several of these predictor variables, our findings served to confirm the results of previous investigations, but others are relatively new and may merit further study. Analysis of select candidate genes revealed DNA variations at several loci, which may be relevant to the pathogenesis of postpartum depression, most notably the 5HT2A serotonin receptor. Three of the five HTR2A SNPs (rs6311, rs2070040, rs6314) were found to have statistically significant associations with PPD even after correcting for ancestry. This finding was further supported following permutation tests. Nominal associations were discovered for genes involved in glucocorticoid response (FKBP5), estrogen activity (ESR1) and, to a lesser extent, progesterone effects (PGR). Other notable candidate genes that were not found to be associated with PPD in this investigation included BDNF, SLC6A4, and COMT. The length polymorphism of the serotonin transporter, 5-HTTLPR, showed no association (p=0.15).

The nominally significant association found between PPD and the 5HT2A receptor in this investigation is consistent with previous evidence suggesting that alterations in serotonergic activity in the central nervous system (CNS) may be underlying reproductive depression. For example, l-tryptophan is a precursor essential for the production of serotonin which competes with other amino acids for active transport into the CNS. During the immediate postpartum period, there is an abrupt increase in amino acids competing for transport across the blood brain barrier, resulting in a net decrease of CNS tryptophan concentrations and a relative serotonin deficiency.[35] Serotonergic antidepressants appear to be more effective than other medication classes for the treatment of major depression in women, as well as those suffering from PMDD.[12,36–38] In addition, l-tryptophan depletion studies have also revealed that premenopausal women responding to SSRIs were particularly sensitive to relapse in comparison to men or postmenopausal women.[39] Both research and anecdotal evidence suggest that SSRIs are more effective than other antidepressants for postpartum depression, though few randomized controlled trials have been published.[40] This matches similarly to our findings related to the 5HT2A serotonin receptor.

Further supporting some our findings is the complex and reciprocal relationship between serotonin and estrogen hypothesized to influence PPD. In spite of evidence linking serotonergic abnormalities with reproductive depression, only limited genetic evidence has been published in the postpartum population. Sanjuan et al[15] longitudinally examined the role of the serotonin transporter gene (SLC6A4) within the context of tryptophan depletion in a postpartum population. The authors reported a significant association between depressive symptoms and SLC6A4 expression at the eight-week postpartum time point, but not during the immediate postpartum period or 32 weeks later. This was the only candidate gene that was studied. Costas et al[18] examined 44 candidate genes within the context of depressive and anxious symptoms experienced by a postpartum population. The authors reported a strong association between anxiety scores and one SNP in SLC6A4, but depressive symptoms were not as closely correlated. Comasco et al[16] reported an association between PPD and the serotonin transporter linked polymorphic region (5-HTTLPR) but this finding was limited to subjects with a prior history of mental disorders, and a similar vulnerability was not evident in women without a history of mental illness. To our knowledge, this is the first time an association between HTR2A and PPD has been reported. The T allele for the most associated SNP, rs6311, showed a protective pattern of association. Interestingly, the same protective T allele was previously reported to protect against suicidal behavior.[41] This SNP, which is upstream of HTR2A, has been reported to influence promoter activity.[42,43]

The positive correlation of PPD with an estrogen receptor in the present investigation is also of note, particularly when one considers the complex and reciprocal relationship that exists between this reproductive hormone and serotonin. At the present time, the evidence of polymorphisms in the ESR1 gene influencing reproductive depression is limited to a preliminary investigation in women suffering from PMDD.[44] While there are few studies of estrogen receptor polymorphisms in PPD, there is literature supporting an association between ESR1 variants and depression.[45–48] Although there are data from studies supporting functional interactions between estrogen and 5-HT2A receptor function in animals[49] and in human imaging studies,[50–52] we did not detect evidence of genetic interaction via analysis of epistasis between ESR1 and HTR2A (data not shown).

In terms of environmental factors affecting PPD, a statistical comparison of psychosocial variables revealed strong associations with postpartum depression and distressed relationships, as evidenced by total scores of less than 13 on the Dyadic Adjustment Scale. This particular vulnerability was also evident in the results of the MOS Social Support Survey, where depressed women scored significantly lower on all five domains. Distressed relationships are likely correlated with unplanned pregnancies which was also a predictor of PPD found in this study. As a distressed relationship was the most statistically significant risk factor for PPD in the investigation, this variable served as the primary predictor for the construction of a subsequent model where other risk factors were considered in stepwise fashion. The final model revealed three specific variables that were strongly and independently associated with PPD: distressed relationship, difficult pregnancy, and difficulty caring for the baby.

The perceived lack of social support has been associated with PPD in several other investigations but, as all of these studies were either retrospective or cross-sectional in nature, a causal relationship between this risk factor and depression is difficult to determine.[19,20,53,54] A previous history of mood disorders was also strongly predictive of the PPD phenotype, as women with a diagnosis of depression in the past were much more likely to suffer from PPD following the index pregnancy. A history of diagnosed anxiety disorders was much less common in the study population, preventing comparisons between groups.

Our study has several limitations. First and foremost, the statistical power of this investigation was limited by the small size of the study population. As a result, our preliminary results should be interpreted with caution and await future confirmation through the completion of a similar investigation featuring a much larger population (which the authors are pursuing at the present time). Due to this limitation in statistical power, we were unable to assess the association of relatively uncommon events such as rare genetic polymorphisms. The small sample size also precluded us from systematically analyzing potential gene-environment interactions, which would have important implications in regards to PPD prevention, identification, and treatment strategies.

This investigation featured an analysis of a limited number of candidate genes, most of which had been previously implicated in the pathogenesis of mood disorders. While a genome-wide association study (GWAS) would be more comprehensive, the small sample size would make this approach unacceptably underpowered. It is quite likely that other polymorphisms may also be influencing the PPD phenotype, and future investigations should be encouraged to employ a broader array of candidate genes.

Our patient population could also be viewed as homogenous, consisting primarily of urban nonwhite women with lower socioeconomic status, and results may not necessarily be generalizable to other demographic samples. As this investigation was cross-sectional in nature, there is a possibility that results from demographic and clinical surveys may have been influenced by patient recall bias as well. It should also be noted that the *a priori* cutoff we used for depressed status (EPDS>14) was conservative by design and considerably higher than that employed in most perinatal depression screening studies.[1] This cutoff was chosen to minimize the inclusion of individuals with dysthymia or minor depression (i.e., false positives) and increase the likelihood that our PPD cases were consistent with DSM-IV-TR criteria for major depressive illness of at least moderate severity.

CONCLUSION

The results of this preliminary investigation suggest that genetic polymorphisms in HTR2A, the gene encoding the 5HT2A receptor, may be associated with postpartum depression. Several psychosocial factors were also implicated, including a previous history of depression, perceived difficult pregnancy, and the presence of a distressed relationship after delivery. As this investigation featured a limited number of research subjects, the relative influence of these genetic and environmental factors in the pathogenesis of postpartum depression merits further study.

SUPPLEMENTAL MATERIAL

Supplemental Tables 1–4 and Figure 1 can be accessed by visiting http://innovationscns.com/wp-content/uploads/El-Ibiary_Supplemental_Tables.pdf.

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