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Postpartum Depression in Women with the *FMR1* Premutation

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Abstract

Background—Psychiatric disorders in women with the *FMR1* premutation are common and include attention deficit hyperactivity disorder, anxiety, depression, and eating disorders. This pilot study explored the risk factors for postpartum depression (PPD) in women with the premutation.

Methods—We conducted a chart review of 50 women premutation carriers with major depressive disorder who had children. Of these, 7 women had a history of major depressive episodes in the postpartum period. The PPD and non-PPD groups were characterized descriptively based on women's age at the time of the psychiatric evaluation, race, ethnicity, education level, IQ, CGG repeat size, comorbid psychiatric conditions, parity, and number of children with fragile X syndrome (FXS). Exact logistic regression was used to analyze the relationship between the number of children with FXS and the risk of PPD.

Results—The PPD and non-PPD groups were similar on all variables examined, with the exception of the number of affected children. Each of the 7 women with PPD had at least one child with FXS, whereas a third of the women without PPD had no affected children. For each additional affected child, the risk of PPD increased by 158% (exact odds ratio 2.58, 95% CI 0.99–7.59). Further studies are needed to replicate these findings and to better characterize PPD in female premutation carriers.

Keywords

female carriers; *FMR1* premutation; fragile X syndrome (FXS); major depressive disorder; postpartum depression

BACKGROUND

Fragile X syndrome (FXS), previously known as the Martin-Bell syndrome, is the most common inherited cause of intellectual disability, with a prevalence of 1 in 4,000 males and 1 in 8,000 females [1, 2]. Individuals affected by FXS have various cognitive impairments, ranging from learning disabilities to severe mental retardation. The characteristic physical

phenotype consists of a long narrow face, prominent ears, and macroorchidism in males [3]. Behavioral manifestations include hyper-arousal, social anxiety and withdrawal, communication deficits, unusual responses to sensory stimuli, and stereotypic behaviors [4]. FXS is caused by full mutations of the fragile X mental retardation (*FMR1*) gene, leading to gene inactivation and a failure to synthesize the corresponding protein, the fragile X mental retardation protein (FMRP). The role of FMRP is not fully understood, although the protein is known to be important in normal brain development [4].

The *FMR1* gene is composed of CGG trinucleotide repeats. The number of CGG repeats determines the extent of the clinical involvement. A neurotypical person generally has less than 45 CGG repeats, while individuals with the “gray zone” have 45–54 repeats, and carriers of the *FMR1* premutation have 55–200 CGG repeats. The full mutation is characterized by more than 200 CGG repeats [1]. *FMR1* premutations are present in about 1 per 130–260 women and 1 per 250–800 men in the general population [5]. When premutations are maternally transmitted, they are unstable and can become full mutations [6]. A neurodegenerative movement disorder has recently been described in premutation carriers, fragile X-associated tremor/ataxia syndrome (FXTAS). FXTAS affects 17% of male carriers in their 50's, up to 75% of male carriers in their 80's, and up to 16% of female carriers [7–9]. Approximately 20% of women carrying the *FMR1* premutation develop primary ovarian insufficiency (POI) [10]. Female premutation carriers may also develop thyroid disease, hypertension, peripheral neuropathy, migraines, and fibromyalgia, and often report chronic paresthesias, muscle pain, and tremor [8]. Recent studies have revealed a significantly higher lifetime prevalence of major depressive disorder (MDD), panic disorder, posttraumatic stress disorder, and specific phobia in carriers of both genders with FXTAS, and a higher lifetime prevalence of social phobia in those without FXTAS, compared to the general population [11].

In this study, we attempted to explore characteristics of postpartum depression (PPD) in women with the premutation. We looked into the possible etiologic implications of various biological and psychosocial factors. In particular, we were interested to observe whether the presence of the premutation and/or the stress of raising children with developmental disabilities contributed to the occurrence of major depressive episodes (MDEs) in the postpartum period in female carriers. The prevalence of MDD in the postpartum period is 12–13% of live births [12]. The DSM-IV-TR recommends using the specifier “with postpartum onset” for the first 4 weeks postpartum [13], however the widely accepted working definition extends to a year after delivery [14]. Among 2,252 women with recurrent MDD, 5% had an MDE during pregnancy, while 30% had an episode in the first six months postpartum [15]. Depression or anxiety during pregnancy, prior PPD episodes, a history of premenstrual dysphoric disorder, recent stressful life events (including child care stress), poor social support, single marital status, poor relationship with the spouse/partner, intimate partner violence, low socioeconomic status, and obstetric or pregnancy complications increase the PPD risk [12, 16, 17]. Medical conditions may contribute or confound the picture and should be ruled out [18]. Roberts et al. found higher rates of lifetime MDD, lifetime panic disorder, and current agoraphobia in female carriers than in the general population [19]. The increased MDD prevalence was associated with CGG repeat length,

but not with child or other demographic variables, and only 11% of MDEs were thought to be linked to challenges of raising a child with FXS [19]. To our knowledge, this is the first descriptive study that explores the PPD contributory factors in female *FMRI* premutation carriers.

METHODS

We conducted a retrospective review utilizing data collected through a comprehensive study of premutation carriers performed at the Medical Investigation of Neurodevelopmental Disorders (M.I.N.D.) Institute of the University of California, Davis. The study protocol was reviewed and approved by the Institutional Review Board at the University of California, Davis. Participants were selected from a larger cohort of carriers evaluated at the M.I.N.D. between September 2007 and May 2012. All participants gave informed consent. Most carriers were identified through cascade testing from families with a member with FXS. Participants received a full evaluation consisting of genetic testing, a detailed history and physical examination, a comprehensive neuropsychological test battery, and a psychiatric assessment, based on the Structured Clinical Interview for DSM IV-TR (SCID) [20]. SCIDs were administered by experienced psychiatric researchers and focused on the mood, anxiety, and substance use modules, as well as the psychotic symptom screener.

Fifty three women premutation carriers met criteria for MDD but only 50 had children. The 50 charts were subsequently reviewed for history of PPD. Additional information collected included: the women's age at the time of the evaluation, race, ethnicity, education level, full scale intelligence quotient (IQ), CGG repeat size, other SCID diagnoses (comorbid psychiatric conditions), parity (number of children), and number of children affected by FXS, if any. For women who met the criteria for the PPD diagnosis, we also noted the age when the postpartum episodes occurred, whether these episodes were linked to the birth of children with FXS, and if they had sought any treatment. The IQ scores were determined using the Wechsler Adult Scale of Intelligence-Third Edition [21]. Measurements of CGG repeat size were obtained as described in detail in Tassone et al. [22].

Descriptive statistics (means, standard deviation, and range for the continuous variables and frequencies and percentages for categorical ones) were used to summarize the demographic and clinical characteristics of the sample. Exact logistic regression was used to characterize the relationship between the number of children with FXS and the risk for PPD. All analyses were implemented in SAS Version 9.3 (SAS Institute, 2002–2010, Carey, NC, USA).

RESULTS

Participants' demographic and clinical characteristics including age, education level, IQ, CGG repeat size, parity, number of children with FXS, and number of psychiatric comorbidities are summarized in Table 1, stratified by PPD presence. Of the 50 carriers with MDD, 7 (14%) had PPD. Most women were Caucasian, with the exception of one American Indian and one Hispanic participant (both of these women were in the non-PDD group).

The two groups were similar age-wise. The mean participant age at the time of the SCID interview was 60.5 years old (range 39 to 87) for the non-PPD group and 58.3 years old

(range 41 to 71) for the PPD group. In each group, about a third of the women had completed high school or obtained a GED, and approximately 60% had at least a partial college education. Women without PPD had a mean IQ score of 105.1, similar to those with PPD (mean IQ score, 104.1). Women in each group had on average three children (between one and ten in those without PPD, and between one and five for those with PPD). All women with PPD, but only two thirds of those without PPD, had at least one affected child. On average, each woman with PPD had two children with FXS (mean 1.7, standard deviation 0.7), whereas each mother without PPD had only one affected child (mean 0.9, standard deviation 0.9). The results of the exact logistic regression revealed that for each additional affected child, the odds for PPD increased by 158% (exact odds ratio = 2.58, 95% confidence interval 0.99–7.59). Although this confidence interval contains 1, it lies almost entirely to the right of 1, so a true association is likely to exist between the number of affected children and the risk of PPD.

PPD episodes occurred when women were, on average, 28.4 years old; all followed the birth of affected infants, even though the children were diagnosed with FXS years later (between ages 3 and 12). Two of the women with PPD had had MDEs prior to the postpartum episode; the other five experienced the lifetime onset of MDD in the postpartum period. We also inquired whether women had sought treatment for PPD; most, but not all, had done so. One participant poignantly discussed her difficulties in getting help at the time, as she struggled to raise her two children, one of whom had FXS: “My mother told me I had to just snap out of it”. She had limited family support and remained untreated for two years, until her MDE eventually remitted.

The number of CGG repeats was similar across the two groups, with an average of 93.6 (range 55 to 165) for women without PPD and 94 repeats (range 76 to 115) for those with PPD. Psychiatric comorbidities were common in our sample; two thirds of the women met criteria for at least two other disorders. Four women in the non PPD group had no additional diagnosis. Other psychiatric diagnoses included: dysthymia, generalized anxiety, panic disorder, social phobia, specific phobia, obsessive-compulsive disorder, posttraumatic stress disorder, eating disorders (anorexia, bulimia, binge eating disorder), substance abuse/dependence (alcohol, cannabis, nicotine, or stimulants), and somatoform disorders. One participant reported a historical diagnosis of attention deficit hyperactivity disorder, and another one also met clinical criteria for dementia.

DISCUSSION

To date, multiple studies have investigated psychiatric manifestations in *FMRI* carriers. However, this is the first study to explore PPD risk factors in female premutation carriers. Using a biopsychosocial lens, we aimed to elucidate whether women carriers were more predisposed to developing PPD due to their genetic vulnerability or other biological factors (as illustrated by CGG repeat size or psychiatric comorbidities), or due to psychosocial stressors (e.g., number of children or children affected by FXS).

Our most salient finding was the fact that PPD episodes were linked to having children with FXS. All women with PPD had at least one affected child (on average, two) whereas less

than two thirds of those without PPD had children with FXS (on average, one). All PPD episodes occurred after female carriers had a baby who was eventually diagnosed with FXS. Also, all the women with PPD but two experienced the lifetime onset of MDD in the postpartum period. Previous research has indicated higher depressive symptoms in mothers of children with FXS than in mothers of children with mental retardation due to another cause [23], as well as lower well-being levels in mothers of children with FXS [24]. Abbeduto et al. showed a significant correlation between the number of disabled children and depressive symptoms in mothers of individuals with FXS, Down syndrome, and autism [24]. On the other hand, Roberts and colleagues did not find an association between child variables (number of affected children, behavioral problems) and MDD in a sample of 93 female *FMRI* carriers [19]. Almost half of the women studied by Roberts et al. had had mood episodes before giving birth to their first affected child, however these authors did not specifically comment on postpartum presentations.

The PPD working definition refers to MDEs during the first year after giving birth to a baby. The average age when concerns are first noted in an affected child is 11.6 months, with the FXS diagnosis being made by a professional almost two years later [25]. Even though, in our study, mothers with PPD reported that their children's diagnosis was not confirmed until years later (in one case, when the affected son was 12 years old), parents had noticed subtle or more overt developmental delays well before their children received a formal diagnosis of FXS. Some children had seizures, hypotonia or other sensorimotor impairments, language delays, learning disabilities, and autistic features. Mothers often had to fight the healthcare and educational systems to obtain the necessary diagnostic evaluations and interventions, further increasing the immense stress of raising children with developmental disabilities. Our findings suggest that premutation carrier mothers of children with FXS may be at higher risk of PPD than female carriers without affected children. For each additional child with FXS, the risk of PPD more than doubled (exact odds ratio, 2.58). Our study was not adequately powered to find a significant association; larger studies are required in order to confirm our results.

Maternal education level and IQ scores did not correlate with PPD history, as expected since previous literature has shown similar results [26, 27]. Most women in our sample had a high school or partial college education, consistent with general characteristics of premutation carriers [11, 19]. Five women without PPD and only one of those with PPD had graduate degrees (MA/MS/MD/PhD). PPD episodes occurred when women were about 28 years old, on average. Female carriers with PPD may have greater difficulty in pursuing higher education, either due to caregiving obligations, or to the timing of MDEs in the context of their careers. We should note that, although we did inquire about age at the time of the PPD episodes during SCID interviews, we did not specifically compare ages of MDD onset in the two groups. Most, but not all, women with PPD had sought psychiatric treatment at the time, and untreated depression could definitely affect academic performance.

Previous studies explored multiparity as a risk factor for PPD; some failed to demonstrate a convincing association [15, 26]. However a 20-year retrospective review of over 2 million births confirmed that multiple gestations were associated with PPD [28]. In our sample, parity was similar across the PPD and non-PPD groups.

We also investigated whether CGG repeat sizes would influence the risk of PPD. We observed similar values in the PPD and non-PPD groups. Roberts et al. suggested that there may be a nonlinear association between CGG repeat length and MDD, placing women with midsize repeats at greater risk [19]. Other authors found a significant nonlinear positive association of repeat size with POI: women with CGG repeats in the 80–99 range appeared to be at higher risk, whereas those with over 100 repeats had a lower risk of ovarian dysfunction [29]. Seltzer et al. reported that women carriers with medium size CGG repeats (90–105) had more anxiety and depressive symptoms in response to above-average numbers of negative life events in the preceding year compared to women with lower or higher repeat sizes [30]. Nevertheless, mothers with midsize CGG repeats who had experienced below-average numbers of negative life events in the previous year had the lowest levels of anxiety and depressive symptoms, pointing to an intriguing differential susceptibility [30]. Our sample was too small to test this hypothesis, although the overall average CGG repeat size was 93.7 (in medium range).

Most women in our study had on average three lifetime psychiatric diagnoses besides MDD, which was true for both the PPD and non-PPD group. Co-occurring conditions may enhance the PPD risk or pose additional treatment challenges. For example, panic disorder during pregnancy or a personal or family history of panic disorder predicts PPD after adjusting for lifetime depression and risk factors [31]. In premutation carriers, the burden of additional psychiatric disorders may compound the genetic vulnerability and thus exacerbate the severity or frequency of mood episodes. MDD severity was documented during SCID interviews, but not specifically for the postpartum episodes. Studies are still needed to explore the succession of mood and anxiety disorders over carriers' lifetimes. These studies would help us understand if, for example, a lifelong struggle with social phobia (which may be present in a third of carriers without FXTAS [10]) might contribute to PPD development, due to insufficient social support.

Socioeconomic stressors are known PPD risk factors [17, 28]. Life events (death of a loved one, divorce, job loss, a child's diagnosis of FXS, learning about the premutation carrier status, caring for elderly parents) in the context of MDD were noted in the interviews, but the timing of the stressor relative to pregnancies was not always available. Association of life events with PPD episodes in female carriers could be targeted in further studies, especially since these are established risk factors. Exploring the financial, professional, and marital status or social supports of female carriers would provide more information about risk and protective factors for PPD. Additionally, Black women appear to be at higher risk for PPD, whereas Asians may have a lower risk than Caucasian mothers [28]; most of our participants were Caucasian, thus a more ethnically diverse sample is desirable for future studies.

Finally, even though the SCID is the gold standard in psychiatric epidemiology [32], this may introduce a recall bias, given that older women (our oldest participant was 87) were asked to remember events from decades earlier. However we are confident that our participants accurately reported information related to postpartum periods, due to the emotional salience of such events. Another bias of our study could be participant selection, since carriers assessed at the M.I.N.D. Institute generally tend to be more resourceful,

having learned about our research studies through internet searches or online newsletters, or being ascertained from families of children with FXS.

Effective pharmacological and psychosocial treatments exist for PPD; therefore, an adequate evaluation and discussion of treatment options are very important [13, 33]. Depressed mothers may be less responsive to their infants, experience more parenting stress, and view their infants more negatively [34], further reinforcing dysfunctional attachment patterns. Untreated depression in the postpartum period poses serious safety risks to the baby, mother, and other children in the family, especially if there is limited social support and poor access to resources for the children with FXS. Furthermore, maternal depression may lead to poor child adjustment. Research has shown that the level of maternal support and child emotional regulation during frustrating tasks predict later social skills in children with developmental delays [35]. These findings emphasize the need to promptly identify and address PPD in premutation carriers, especially those with affected children.

DNA testing for *FMR1* mutations and premutations is available and should be considered in women with a family history of FXS, mental retardation, learning disability, language delay, developmental delay, autism spectrum disorders or behaviors (gaze avoidance, repetitive behaviors, hand-flapping, hand biting, touch avoidance), ataxia, tremor, FXTAS, or unidentified movement disorders [36]. Both the American College of Obstetricians and Gynecologists and the American College of Medical Genetics recommend testing for diagnostic purposes, carrier detection, and in the prenatal setting [37, 38]. All women identified as premutation carriers should be referred for genetic counseling to appropriately convey risks of allele expansion and to discuss possible future fragile X-associated diseases [39]. Women carriers who become aware of genetic risks may utilize coping strategies such as positive interpretation and problem solving [40], which could be protective against developing PPD or other psychiatric illnesses later in life.

In summary, complex biopsychosocial factors contribute to the development of PPD in women with the *FMR1* premutation. This pilot study suggests that carrier mothers of children with FXS are at higher risk for PPD than female carriers without affected children. Further research with larger, ethnically diverse samples is needed to replicate our findings and to better characterize PPD in women premutation carriers, as well as to identify potential protective factors, such as coping style or social support.

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PRACTICE TIPS

- DNA testing for *FMRI* premutations and genetic counseling should be considered in women who have a family history of FXS, intellectual disabilities, autism spectrum disorders, ovarian insufficiency, or FXTAS.
- Female premutation carriers have a 50% chance of passing the premutation on to their children of either gender. The maternally transmitted premutation can expand into a full mutation, causing FXS in the affected child.
- Among women premutation carriers, mothers of children with FXS have a higher risk of developing postpartum depression than those who do not have children with FXS.
- Prompt identification and treatment of postpartum depression in women premutation carriers is imperative. Untreated maternal depression may pose safety risks to the infant, mother, and other family members and contribute to poor adjustment of affected children.

Table 1

Demographic and clinical characteristics of the participants.

	Without PPD (<i>n</i> = 43)	With PPD (<i>n</i> = 7)
Age	60.5 ± 10.5	58.3 ± 10.9
Education¹		
< High School	2 (5%)	0 (0%)
High School/GED	14 (34%)	2 (29%)
Partial College	10 (24%)	3 (43%)
BA/BS	10 (24%)	1 (14%)
MA/MS/MD/PhD	5 (12%)	1 (14%)
IQ²	105.1 ± 12.7	104.1 ± 11.4
Parity	3.0 ± 1.6	2.6 ± 1.3
CGG repeats³	93.6 ± 26.9	94 ± 13.4
Affected children (at least one)		
Yes	28 (65%)	7 (100%)
No	15 (35%)	0 (0%)
Comorbidities⁴	2.4 ± 1.5	2.7 ± 1.0

PPD = postpartum depression

¹ Missing data = 2 in the non-PPD group² Missing data = 6 in the non-PPD group³ Missing data = 3 in the non-PPD group⁴ Number of additional psychiatric disorders, besides major depressive disorder

Results for age, IQ, parity, CGG repeats, and comorbidities are presented as mean ± standard deviation; the other results are presented as number and percentage of total.