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Mania and depression in the perinatal period among women with a history of major depressive disorders

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Abstract

Background—Women with a history of major depressive disorder (MDD) have increased risks for postpartum depression, but less is known about postpartum mania in this population.

Objectives—To prospectively determine the frequency with which mania occurs in the postpartum among women who have a history of MDD, and to explore temporal relationships between onset of mania/hypomania and depression.

Methods—We administered the Structured Clinical Interview for DSM IV disorders (SCID) to pregnant women with a self-reported history of MDD to confirm diagnosis and exclude women with any history of mania/hypomania. Participants completed the Edinburgh Postnatal Depression Scale (EPDS) and Altman Self-Rated Mania scale (ASRM): once during the pregnancy (~26 weeks), and one week, one month, and three months postpartum.

Results—Among women ($N=107$) with a SCID-confirmed diagnosis of MDD, 34.6% ($n=37$) experienced mania/hypomania (defined by an ASRM score of ≥ 6) at 1 timepoint during the postpartum: and for just over half (20/37, 54%), onset was during the postpartum. The highest frequency of mania/hypomania (26.4%, $n=26$) was at one week postpartum. Women who experienced mania/hypomania at one week postpartum had significantly more symptoms of mania/hypomania later in the postpartum.

Conclusion—A substantive proportion of women with a history of MDD may experience first onset of mania/hypomania symptoms in the early postpartum, others may experience first onset during pregnancy. Taken with other recent data, these findings suggest a possible rationale for screening women with a history of MDD for mania/hypomania during the early postpartum period, but issues with screening instruments are discussed.

Keywords

postpartum; depression; mania; postnatal; hypomania; women

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Background

The perinatal period is a time of increased risk for all women to experience mental health problems – but those women who have a pre-existing history of mental illness are at particularly high risk. For example, while 10 – 15% of women in the general population experience postpartum depression (PPD) after a delivery (Howard, Boath, and Henshaw 2006), the chance for PPD among women with a history of major depressive disorder (MDD) may be as great as 50% (Di Florio et al. 2012; Payne et al. 2007; Wisner et al. 2001; Wisner et al. 2004). Further, 25 – 50% of women with a history of bipolar disorder (BD) experience postpartum mania or psychosis and women with a history of postpartum psychosis have a 54% chance of a recurrence (Blackmore et al. 2013; Jones and Craddock 2001). While considerable attention has been paid to documenting rates of PPD in various groups of women during the perinatal period, less data are available regarding the frequency with which women experience mania/hypomania during this period. While full-blown mania (indicative of BD type 1) is relatively likely to come to medical attention, hypomania (pathognomonic of BD type 2) is a condition which - according to an increasing body of evidence – is often under-diagnosed (Dubovsky et al. 2011; Hirschfeld, Lewis, and Vornik 2003; Kim et al. 2008). This under-diagnosis is thought to be due in large part to the fact that symptoms of hypomania rarely trigger individuals to seek assistance or investigation, and health professionals often fail to inquire about and identify symptoms of hypomania among those with depression (Sharma et al. 2008). Thus, many individuals who may actually meet criteria for BD2 have been diagnosed with depression alone (Sharma, Khan, and Smith 2005; Sharma et al. 2008; Sharma and Khan 2010), and some studies suggest that many individuals with treatment-resistant depression may have undiagnosed BD (Sharma, Khan, and Smith 2005). The identification of symptoms of hypomania is particularly important for those who have experienced depression for several reasons: first, for those with treatment-resistant depression, the identification of BD may allow for more effective treatment strategies to be implemented (Sharma, Khan, and Smith 2005); second, use of antidepressants in people with BD can trigger an episode of mania (Proudfoot et al. 2011); third, studies have shown that there is a higher risk of suicide among those with BD (Bostwick and Pankratz 2000; Sharma and Markar 1994); and last, some data suggest that women in the general population who experience mania/hypomania in the early postpartum period have increased risk for depression later on in the postpartum period (Glover et al. 1994; Hannah et al. 1993).

There are a few studies that have investigated the frequency with which symptoms of hypomania occur during the postpartum among women in the general population. The rate with which women experience symptoms of hypomania in the first few days postpartum has ranged between 9 and 19% in different studies (Glover et al. 1994), (Lane et al. 1997), (Webster et al. 2003), (Hasegawa 2000), (Heron et al. 2009), and at 6 weeks postpartum the rate with which women experience these symptoms ranges between 7–9% (Glover et al. 1994), (Lane et al. 1997).

Among individuals initially diagnosed with MDD, up to 50% eventually manifest manic or hypomanic episodes consistent with a diagnosis of BD (Goldberg, Harrow, and Whiteside 2001). Although two studies have retrospectively assessed mania/hypomania in the

postpartum among women initially ascertained for the presence of postpartum depression (Sharma et al. 2008; Sharma and Khan 2010), at the time of initiation of this study, none had either prospectively examined the incident symptoms of mania/hypomania during the perinatal period in women with a history of MDD alone, or explored the temporal relationships between symptoms of depression and mania/hypomania during this period.

Purpose

To prospectively determine the frequency with which mania/hypomania occurs in the postpartum among women who have a history of MDD alone, and to explore temporal relationships between onset of mania/hypomania and depression. We expected a peak in the frequency of symptoms of mania/hypomania in the early postpartum period (~1 week), and sought to test the hypotheses that: among women with a history of MDD, as compared to those who did not experience mania/hypomania in the early postpartum, those who did would:

1. have more symptoms of depression later on in the postpartum
2. have fewer symptoms of mania/hypomania later on in the postpartum

Methods

Women were eligible to participate in the study if they were: pregnant, English-speaking and had a history of MDD without mania/hypomania - as confirmed by Structured Clinical Interview for the DSM IV (SCID) (First et al. 2002). Potential participants (women with a self-reported history of depression) were recruited from the local community (events for pregnant women, internet advertisements, posters, and the Reproductive Mental Health Program at BC Women's Hospital), and after consenting the SCID was administered by a trained clinician to confirm a history of MDD and to rule out a pre-existing lifetime history of manic/hypomanic episodes.

Eligible participants provided demographic information, and at four time-points (T1 - during pregnancy - after 15 weeks gestation (immediately after completing the SCID); T2 - one week postpartum; T3 - one month postpartum; and T4 - three months postpartum), provided information regarding their use of psychotropic medications and psychiatric hospitalizations, and completed two measures of mood: the Altman Self-Rated Mania Scale (ASRM), and the Edinburgh Postnatal Depression Scale (EPDS). Women who: had a pregnancy ending in miscarriage, stillbirth or termination; or only completed the enrollment (T1) visit were excluded from data analysis. All women were provided with mental health referrals/resources where appropriate. The study was approved by the University of British Columbia Research Ethics Board (H06-70145).

The ASRM is a self-administered five-item questionnaire that has been validated for use with individuals who have bipolar disorder, depression, schizophrenia and schizoaffective disorder (Altman et al. 1997). Each item represents a major domain of mania as defined by the DSM-IV (Altman et al. 1997) (e.g. feeling more self-confident than usual, feeling more talkative than usual). Each item is rated on a 5 point anchored Likert scale, generating total

scale scores ranging from 0 to 20. A total score ≥ 6 indicates symptoms of mania/hypomania with a sensitivity of 85% and specificity of 87% (Altman et al. 1997), but does not distinguish between mania and hypomania.

The EPDS is a self-administered, 10-item questionnaire, which has been validated in both prenatal and postnatal populations of women (Cox, Holden, and Sagovsky 1987; Murray and Cox 1990). Each item is rated on a 4 point anchored Likert scale, and total scale scores range from 0 to 30. Scores of ≥ 15 and ≥ 13 during the prenatal and postpartum periods respectively, indicate probable major depression (Cox, Holden, and Sagovsky 1987; Matthey et al. 2006).

All data were analyzed using SPSS. In addition to applying descriptive statistics to demographic variables, we tested hypotheses one and two using a T test and a Mann Whitney U test, respectively. Specifically, to allow for potential differences in timing of symptom emergence, for hypothesis one, we used the highest EDPS score from T3 or T4 as the outcome, and for hypothesis two we used the highest ASRM score from T3 or T4. For hypothesis one, after assessing the EPDS outcome data for normality of distribution, and discovering it to be skewed, we used a natural Log transformation, followed sequentially by a square transformation, log 10 transformation and finally a square root transformation, the last of which produced a normal distribution. We then applied an independent T-test to investigate whether women who experienced mania/hypomania (as defined by a score of ≥ 6 on the ASRM) at one week postpartum (T2) had more symptoms of depression later on in the postpartum compared to those who did NOT experience mania/hypomania at T2. For hypothesis two, the ASRM outcome data remained skewed after transformation (natural Log, square, log 10 and square root transformations were performed), so to investigate whether women who experienced mania/hypomania (as defined by a score of ≥ 6 on the ASRM) at one week postpartum (T2) experienced fewer symptoms of mania/hypomania later on in the postpartum compared to those who did NOT experience mania/hypomania at T2 we applied a Mann Whitney U test.

Finally, we conducted several exploratory, post-hoc chi-square tests: to investigate the relationship between antidepressant medication use and ASRM scores at each timepoint; and second to investigate if experiences of mania/hypomania during the postpartum were more common among primiparous women, or women whose MDD involved any psychotic features/psychosis NOS.

For all statistical tests, a significance threshold (α) of $p < 0.006$ was applied (to allow for the eight tests we performed at a nominal overall significance level of 0.05).

Results

Demographics

We recruited 125 women with a self-reported lifetime history of depression; of whom 11 were excluded as a result of SCIDs revealing a pre-existing lifetime history of mania/hypomania, two were excluded due to pregnancy loss/termination, and five were excluded as they only completed T1 before being lost to follow up.

The remaining 107 women were all included in the study and each had a SCID-confirmed diagnosis of MDD with no lifetime history of manic/hypomanic episodes. Of these women, the majority had completed some post secondary education and were married or living with a partner (Table 1). Seventy-six women self-reported comorbid psychiatric conditions: anxiety (n=60, 56%), attention deficit disorders (n=11, 10%), PTSD (n=6, 6%), eating disorder (n=5, 5%), OCD (n=4, 4%), borderline personality disorder (n=2, 3%), and premenstrual dysphoric disorder (n=1, 1%). A detailed three-generation family history was taken for all participants, except for one. Participants' relevant family history of psychiatric disorders in first-degree family members is described in Table 1.

No women were hospitalized for psychiatric reasons during the study time-period. With regard to the threshold for mania/hypomania, 34.6% (n=37) of participants had scores above cut-off at one or more of the three postpartum timepoints: just over half of these women (20/37, 54%), or 18.7% of total number of participants scored above cut-off at one or more time point in the postpartum, but not during the pregnancy (T1). Eleven women (10.3%) scored above cut-off at all time points (T1–T4); 4.7% (n=5) scored above cut-off at T1 only; and 5.6% (n=6) scored above cut-off at T1 and at least one other but not all time points. As expected, there was a peak in the frequency of mania/hypomania symptoms at T2 (~1 week postpartum), when 23/87 (26.4%) had scores above cut-off. In the postpartum, 34.6% (n=37) of participants had scores above cut-off for mania/hypomania and 24.3% (n=26) had scores above cut-off for depression at one or more of the three time points (T2, T3, and T4) (see Table 2).

An independent t-test showed that the mean scores of the transformed EPDS T3/T4 data did not differ significantly between those who scored above and below the cut off for mania/hypomania at T2 ($t = 2.02$ (84) $p = 0.047$).

A Mann Whitney U test showed that the mean ASRM scores at T3/T4 differed significantly between those who scored above (mean rank = 66.78) and below (mean rank = 35) cut off for mania/hypomania at T2 ($Z = -5.271$, $p < 0.000$), reflecting more symptoms of mania/hypomania during the later postpartum among women who scored above cut off for mania/hypomania at T2.

Women who were above cut-off for mania/hypomania were no more likely to be using antidepressants than women who were below the cut-off for mania/hypomania (T1: $\chi^2 = 3.57$, $p = 0.06$; T2: $\chi^2 = 0.78$, $p = 0.38$; T3: $\chi^2 = 2.21$, $p = 0.14$; T4: $\chi^2 = 3.83$, $p = 0.05$, see Table 3).

Comparisons of demographic variables between women (n=20) who scored above cutoff for mania/hypomania for the first time during postpartum, and those who scored below cutoff for mania/hypomania at all timepoints (n=65) are presented in Table 1. Neither primiparous women nor women who had a history of psychosis were more likely to score above cutoff for mania/hypomania ($p = 0.652$, $.601$ respectively).

Discussion

This represents one of the first studies to prospectively investigate symptoms of mania/hypomania in the perinatal period among women with a lifetime history of MDD. More than a third of participants scored above cut-off for mania/hypomania on the ASRM at one or more of the postpartum study timepoints, with just over half of them (or 18.7% of total number of study participants) experiencing first onset of mania/hypomania in the postpartum. The highest frequency of mania/hypomania was at one week postpartum. Primiparous women, and those whose history of MDD involved psychotic features were no more likely to experience mania/hypomania than other women. Our data are broadly in line with previous work suggesting that BD (and in particular BD2) may be under diagnosed (Azorin et al. 2012; Sharma et al. 2008; Sharma and Khan 2010).

Importantly, as women with any lifetime history of mania/hypomania had been excluded, these data suggest that for women with a history of MDD, the postpartum period may be a period of vulnerability for a first onset of mania/hypomania symptoms. These data are consistent with previous studies demonstrating an increased risk for psychiatric problems in the postpartum (notably PPD and postpartum psychosis) (Di Florio et al. 2012; Jones and Craddock 2001; Payne et al. 2007; Wisner et al. 2004), but also add support to the findings of a recent study by Sharma et al who found that 6.5% of women with MDD had their first experience of hypomania during the postpartum period (Sharma et al. 2013). As compared to the data reported by Heron et al (Heron et al. 2009), the rate of mania/hypomania in the early postpartum in our study population was higher (26.4% vs. 11.7%). Perhaps this difference reflects a genuinely higher risk for mania/hypomania in the postpartum among women with a history of MDD than among women with no such history, but it is important to note that direct comparisons cannot be made between the two studies because the tools used to assess mania/hypomania differed. However, in this study, women who scored above cut-off for mania/hypomania were no more likely to be taking antidepressants than those women who scored below cut-off, making it unlikely that the data presented here relate to antidepressant-induced mania/hypomania.

Previous studies in the general population have suggested that experiencing hypomania during the early postpartum period increases a woman's chances for developing depression later on (Glover et al. 1994; Hannah et al. 1993). However, our data offered no support for this, suggesting instead that among women with a history of MDD, mania/hypomania symptoms at one week postpartum predicted mania/hypomania later on in the postpartum. One (of several) possible explanations for these data is that some women experienced an episode of mania/hypomania that lasted ~12 weeks – this possibility is compatible with recent work showing that 25% of mania episodes last more than 15 weeks (Solomon et al. 2010). Future studies over longer periods of time would be needed to see if early postpartum mania/hypomania symptoms predict onset of PPD over a longer timeframe.

During pregnancy 20.6% of women met criteria for mania/hypomania according to the ASRM. Prior to completing the ASRM, but at the same study visit, all women completed the SCID, during which they were asked about mania/hypomania, as follows: "In the last month has there been a period of time when you were feeling so good, "high," excited, or hyper

that other people thought you were not your normal self or you were so hyper that you got into trouble?” with follow-up questions addressing duration of those feelings. While it may seem contradictory that women may score above threshold for mania/hypomania on the ASRM and simultaneously not endorse the presence of mania during the SCID, there are key issues that are relevant to considering this observation. First, whereas the ASRM simply asks respondents to rate their internal feelings, the SCID asks whether these internal state changes were noted by others. Importantly, both SCID and ASRM are potentially confounded in this regard by pregnancy (particularly a first pregnancy, as is the case for half of the women in this study). Specifically, in the SCID, it may be difficult for others to determine whether or not a pregnant woman is “her normal self” given that she is in the throes of the unfamiliar experience of a first pregnancy, and any changes may be explained by hormones and/or pregnancy. Similarly, the ASRM asks women to compare how they feel to “usual”, which is difficult to anchor given the novel life experience. Second, to be classified by the SCID as having experienced mania/hypomania, symptoms must have been present for a minimum threshold number of days, while the ASRM does not ask about duration. Thus, the discrepancy between SCID and ASRM could arise from either or both of these potential sources. As we know that in ~50% of cases PPD actually begins during the pregnancy, the issue of whether or not some women with postpartum mania/hypomania actually experience symptom onset during the pregnancy is an important issue that should be explicitly explored in future research.

Limitations

There are several factors to consider when evaluating potential confounders to accurately characterizing the rate of mania/hypomania for this population. First, although the ASRM cut-off we used has been shown (in a population of subjects that included those with depression) to have a sensitivity of 85% and a specificity of 87% for identifying the presence of clinician-confirmed mania (Altman et al. 1997), the ASRM is not a diagnostic instrument. This is relevant to considering possible explanations for why 11 women scored above threshold for mania/hypomania at all timepoints: perhaps these women are just dispositionally “happy”, perhaps there were periods of time that we did not capture during which they were euthymic, or, given that research suggests that 45% of cases of PPD have onset during pregnancy (Josefsson et al. 2001), perhaps the symptoms were real, started during the pregnancy and continued into the postpartum. Second, the ASRM does not provide information that facilitates distinctions to be made between those experiencing mania and those experiencing hypomania. However, given that mania is relatively more likely to come to medical attention and to be associated with hospitalization, and that none of the participants in this study were hospitalized for psychiatric reasons during the study, we might speculate that most of the symptoms that were identified were more likely to be associated with hypomania rather than mania (Dubovsky et al. 2011; Hirschfeld, Lewis, and Vornik 2003; Kim et al. 2008). The fact that no participants were hospitalized for psychiatric reasons during the study, also suggests that it is unlikely that missing individual data points occurred as a result of acute exacerbations of illness (and thus it is less likely that we have dramatically underestimated incidence of mania or severity of symptoms).

Additionally, for women that missed a study visit (T2, T3, or T4), it is more likely that they might have had symptoms of depression that prevented them from engaging in that study visit rather than symptoms of mania/hypomania (which would potentially increase activity, sociability, etc.). However, it is possible that the five women who were excluded from the study as a result of loss to follow up after enrollment were lost as a result of psychiatric hospitalization, thus it is possible that the incidence of mania/hypomania is marginally higher than reflected by the data presented here. Last, there are no screening instruments that have been validated in the specific population of perinatal women with MDD. The instruments available include the Highs and the ASRM; the former of which has been suggested to underestimate, and the latter to overestimate the frequency and symptoms of mania in the postpartum period (Smith et al. 2009). For this study, we selected the ASRM because unlike the Highs, it has been validated in a population of individuals with MDD, but this remains an important caveat. The fact that there were no hospitalizations among study participants (and thus no dramatically negative outcomes were predicted by the ASRM in this study) could bring the utility of the ASRM in this population into question. However, it is important to note that: a) the absence of “marked impairment in social or occupational functioning” constitutes one of the criteria that defines a hypomanic episode, that would be indicative of BD2, and b) the women in this study were only followed over the first three months postpartum, and thus outcomes over the longer term were not evaluated.

Last, generalizability is limited by the fact that the majority of women who participated were married/partnered (96.3%) and had some post secondary education (84%). Future Canadian studies focusing on women with more diverse backgrounds are warranted.

Conclusions

This is one of the first studies to prospectively examine the frequency of mania/hypomania during pregnancy and the postpartum in a population of women with a history of MDD in whom previous experience of mania had been ruled out. Our findings emphasize the importance of screening women with a history of MDD for mania/hypomania during the early postpartum period. Clinical practice guidelines recommend that all healthcare practitioners who come into contact with pregnant or postpartum women screen for symptoms of current depression (for example using the EPDS); our data suggest that, particularly for women with a history of MDD, perhaps screening for mania is also warranted in the perinatal period (Breedlove and Fryzelka 2011; Kaminsky et al. 2008).

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Table 1

Demographic Information

Characteristic		% (n)
Annual household income	<20,000	9.3 (10)
	20,000 – 40,000	17.8 (19)
	41,000 – 60,000	17.8 (19)
	61,000 – 80,000	16.8 (18)
	81,000 – 100,000	11.2 (12)
	>100,000	19.6 (21)
	Unsure	7.5 (8)
Education ^a	Highest level of education: < grade 12	8 (8)
	Highest level of education: grade 12	8 (8)
	Highest level of education: post secondary	84 (88)
Marital Status	Married/living with a partner	96.3 (103)
	Single	3.7 (4)
Reproductive History	First Pregnancy ^b	49.0 (52)
	First live born	62.6 (67)
	Have one pre-existing child	23.4 (25)
	Have two pre-existing children	10.3 (11)
	Have three pre-existing children	3.7 (4)
History of PPD ^c	Previous history of PPD	51.9 (28)
	No previous history of PPD	44.4 (24)
	Unsure if previously had PPD	3.7 (2)
Self-reported comorbid disorder ^d	Anxiety	56.1 (60)
	Posttraumatic Stress Disorder	5.6 (6)
	Eating disorder	4.7 (5)
	Attention deficit/hyperactivity disorder	10.3 (11)
	Borderline personality disorder	2.8 (2)
	Premenstrual dysphoric disorder	0.9 (1)
	Obsessive compulsive disorder	3.7 (4)
Reported First degree family member condition ^e	Postpartum psychosis	0 (0)
	Postpartum depression	4.7 (5)
	Schizophrenia/schizoaffective disorder	4.7 (5)
	Bipolar disorder	7.5 (8)

^aData missing for three participants^bData missing for one participant^cData only for those 54 participants who had more than one pregnancy^dParticipants sometimes reported more than one comorbid disorder

^eData missing for one participant

Table 2

EPDS and ASRM scores for all time points

	EPDS				ASRM			
	<i>n</i>	Range (0 – 30)	Mean (SD)	% 15 at T1 13 at T2-T4	<i>n</i>	Range (0 – 20)	Mean (SD)	% 6
T1	107	0 – 21	7.75 (4.829)	10.3	107	0 – 18	3.11 (3.454)	20.6
T2	87	0 – 21	6.79 (5.149)	16.1	87	0 – 12	3.54 (3.413)	26.4
T3	102	0 – 23	6.01 (4.702)	9.8	102	0 – 16	3.16 (3.531)	19.6
T4	102	0 – 20	6.21 (4.306)	8.8	102	0 – 14	3.20 (3.252)	22.5

Table 3

Participants categorized according to scores above or below the cut-off of 6 on the ASRM and for use of antidepressants at each time point.

		ASRM ≥ 6 % (n)	ASRM <6 % (n)
T1 n=106 ^a	Using antidepressants	7.5 (8)	15.1 (16)
	Not using antidepressants	12.3 (13)	65.1 (69)
T2 n=87	Using antidepressants	4.6 (4)	19.5 (17)
	Not using antidepressants	21.8 (19)	54 (47)
T3 n=101 ^b	Using antidepressants	6.9 (7)	16.8 (17)
	Not using antidepressants	11.9 (12)	64.4 (65)
T4 n=102	Using antidepressants	9.8 (10)	17.6 (18)
	Not using antidepressants	12.7 (13)	59.8 (61)

Note: Antidepressants used by women in this study included: Sertraline, Fluoxetine, Venlafaxine, Citalopram, Paroxetine, Bupropion, and Escitalopram. Two women were not included in the numbers presented here as a result of taking mood stabilizing medications: one^a, due to a history of epilepsy, was taking Valproic Acid and Topiramate at T1 and was above cut-off on the ASRM; another^b was taking Topiramate at T3 and was above cut-off on the ASRM.