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Perinatal psychosis in mothers with a history of major depressive disorder

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Abstract

Purpose—While women with a history of major depressive disorder (MDD) have higher chances for postpartum depressive and manic episodes, little is known about their chance for postpartum psychosis (PPP). We prospectively assessed the frequency of perinatal psychotic symptoms among primiparous women with a history of MDD only (structured clinical interview was used to exclude women with pre-existing histories of mania or psychosis), and explored whether sex of the baby influenced these symptoms.

Methods—The presence of symptoms of psychosis was defined using previously established cutoff scores on five key items from the Positive and Negative Syndrome Scale (PANSS), which was administered during pregnancy, at 1 week, 1 month, and 3 months postpartum.

Results—Fourteen of 60 women (23%) scored above threshold for psychosis at one or more time-points, with six experiencing postpartum onset. There was a non-significant trend ($p = 0.073$) towards higher frequency of these symptoms among mothers of girls.

Conclusions—If controlled studies using diagnostic interviews confirm that psychotic symptoms are relatively common among women with MDD, monitoring for psychosis during the perinatal period may be indicated in this population. The potential effect of sex of the baby on mothers' chance for PPP requires further study.

Keywords

depression; pregnancy; postpartum; mental illness; psychosis

Background

Postpartum psychosis (PPP) is relatively rare (associated with ~1 in 1000 births in the general population) (Kendell *et al.* 1987; Sit *et al.* 2006), but as the most serious mental

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health event that can occur in the postpartum, it constitutes a medical emergency. Two in every 1000 women who experience PPP die by suicide (CEMD, 2001). And, though rare, risk of infanticide is elevated in the presence of PPP (Sit *et al.* 2006).

Onset of PPP is rapid and may occur as early as 2–3 days after delivery (Sit *et al.* 2006), with the mother experiencing features typical of any psychotic event (e.g. delusions, hallucinations, and conceptual disorganization) (Watkins and Newport 2009). Rapid hormonal changes, sleep deprivation, and high environmental stress in the early postnatal period are thought to contribute to PPP (Sit *et al.* 2006), but more specific identification of sub-groups of women at increased risk is critical in order to enable early intervention and management. Some risk factors are already known. For example, primiparous mothers are at higher risk to experience PPP than mothers who have previously been pregnant (Agrawal 1990; Videbech and Gouliaev 1995; Kirpinar *et al.* 1999; Blackmore *et al* 2006; Di Florio *et al.*, 2014). Also, women with a history of bipolar disorder (BD) have elevated risk (up to 27%) for PPP (Jones and Craddock 2001; Sit *et al.* 2006; Di Florio *et al.* 2014), and women who have experienced PPP have a 54% chance of recurrence following subsequent deliveries (Jones and Craddock 2001; Blackmore *et al.* 2013). Having a first-degree relative with schizophrenia or BD may also increase risk for PPP (Jones and Craddock 2001).

Though there is some reason to believe that women with a history of major depressive disorder (MDD) might have an increased risk for PPP, there are less data available on this topic. However, women with a history of MDD are known to have elevated risks for postpartum depression and mania (Di Florio *et al.* 2012; Inglis *et al.* 2013; Di Florio *et al.*, 2014), and a case study in 2010 described a woman with a history of MDD who went on to experience PPP (Ebeid *et al.*). Subsequently, a recent retrospective study of women with a history of recurrent MDD only, showed that 2% (20/1016) experienced mania/psychotic depression in the perinatal period (Di Florio e*t al.,* 2014).

Another potential risk factor for PPP relates to sex of the baby. Some evidence suggests that women who deliver female babies are more susceptible to PPP (Agrawal *et al.* 1990; Kendell *et al.* 1987; Okano *et al.* 1998), but others show no relationship between sex of the baby and PPP (Kendell *et al* 1981; Videbech & Gouliaev 1995), while still others have observed a trend towards mothers of male babies being more susceptible to PPP (Blackmore *et al.* 2006).

Purpose

The goals of this study were first, to prospectively examine the frequency with which symptoms of psychosis occur in a cohort of primiparous women with a history of MDD alone, and second, to determine whether the sex of the baby influences the risk of women experiencing these symptoms. Specifically, we aimed to test the hypothesis that mothers of female babies would have a higher rate of symptoms of psychosis.

Methods

Primiparous women with singleton pregnancies who had a history of MDD only (without psychosis, mania or hypomania) as confirmed by the Structured Clinical Interview for the

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DSM IV (SCID) (First *et al.* 2002) were eligible to participate. Women were recruited during pregnancy between March 10, 2007 and October 17, 2013, through events for pregnant women, internet advertisements, posters, and the Reproductive Mental Health Program at BC Women's Hospital. A trained clinician administered the SCID to confirm a history of MDD and rule out a history of mania, hypomania, or psychosis.

Participants were interviewed at four time-points (T1 – during the pregnancy after 15 weeks gestation; T2 – one week postpartum; T3 – one month postpartum; and T4 – three months postpartum). At T1 (mean = 32 weeks gestation), participants provided demographic information and a family history; at all time-points they provided information about their use of psychotropic medication and psychiatric hospitalizations. At each time-point, a trained clinician administered the Positive and Negative Symptom Scale (PANSS) to assess psychosis symptomatology.

The PANSS is a well-validated instrument (completed by a clinically trained rater, on the basis of a 30–45 minute semi-structured interview) that measures the presence and severity of 30 psychiatric symptoms (Kay *et al.* 1987). Each symptom is rated on a 7-point scale; a score of 1 means the symptom is not present, and a score of 7 means that it is present to an extreme degree, thus total scores range from 30 to 210. Five of the PANSS items can be used to assess the presence and severity of psychosis, using specific cut off scores for each of these items (delusions ≥ 3, conceptual disorganization ≥ 4, hallucinations ≥ 3, suspiciousness ≥ 5, unusual thought content ≥ 4). This approach was used to establish the presence of relapse of psychosis in a randomized clinical trial of relapse prevention in first episode psychosis (Hui et al 2013 Chen *et al.* 2010)

All PANSS raters participated in training and underwent inter-rater reliability testing throughout the course of the study. Krippendorf's alpha for inter-rater reliability was calculated for each of the five PANSS items (delusions, conceptual disorganization, hallucinations, suspiciousness, and unusual thought content). Alpha values were 0.75, 0.88, 1.00, 1.00, and 0.94 for each item respectively, indicating substantial to very good agreement.

All data were analyzed using SPSS. We determined the frequency with which women experienced psychotic symptoms (as defined by scoring above cut-off on one or more of these five PANSS items) at one or more time-points, and the frequency with which women experienced psychotic symptoms at each time-point. Given that even after transformation, the data were not normally distributed, a non-parametric rank test, the Mann-Whitney U test, was conducted on the total PANSS scores to assess the relationship between sex of the baby and frequency of postpartum-onset psychosis. Then, a Fisher's exact test was performed to compare number of women with PANSS scores above cut-off for psychosis with male versus female infants among women who experienced postpartum-onset psychosis.

The study was approved by the University of British Columbia Research Ethics Board (H06-70145).

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Results

We recruited 103 primiparous women with a self-reported lifetime history of MDD, of whom 43 were excluded from analyses due to carrying twin pregnancies (n=2) or having a history of psychosis/psychotic features (n=27), or mania/hypomania (n=14).

The sociodemographic characteristics of the 60 remaining women (mean age 28.1, range 18 to 38) are shown in Table 1.

No participants were hospitalized for psychiatric reasons during the course of the study. However, 14/60 women (23.3%) scored above threshold for psychosis on one or more of the five PANSS items at one or more time-points during the perinatal period, with 3/60 (5%) scoring above threshold during pregnancy only, 6/60 (10%) scoring above threshold only in the postpartum and 5/60 (8.3%) scoring above threshold in the pregnancy as well as the postpartum (see Table 2 for more details). The item on which women most frequently surpassed the cut-off score was conceptual disorganization, with 15% (9/60 women) scoring above cut-off (Table 2).

The numbers of women delivering male and female babies who scored above threshold for psychosis (on one or more item, including the conceptual disorganization item) are shown in Table 3. Among women with postpartum-onset psychosis, the Mann-Whitney U test found no significant difference (p = 0.348) between the mean PANSS scores on these five items for the women who delivered girls (mean rank = 32.96) and the woman who delivered a boy (mean rank = 28.74). The Fisher's Exact Test demonstrated a non-significant trend (p=0.073) towards higher risk for postpartum onset of symptoms of psychosis among women with female babies.

After considering the possibility that the conceptual disorganization item could potentially be confounded by natural phenomena related to the perinatal period, we explored the consequences of excluding women who only scored above cut-off on this item. This reduced the proportion of women scoring above cut-off for psychosis to 15% (9/60). It resulted in no change in the number of women with a history of only a single episode of depression who scored above threshold at one or more time-point during the perinatal period (n=3), but reduced the number of women with a history of recurrent depression who scored above threshold from 11 to six, with three of them experiencing postpartum onset. Removing conceptual disorganization had no effect on the number of mothers of female babies who experienced perinatal (n = 6) and postpartum (n = 5) onset of symptoms of psychosis. Among mothers of male babies, removing conceptual disorganization reduced the number of women who experienced symptoms of psychosis at some point in the perinatal period from eight to three, with one woman experiencing symptoms with postpartum onset.

Discussion

In this study we explored the frequency with which psychotic symptoms occurred during the perinatal period among women with a history of MDD alone. Data suggest that 0.1–0.2% of women from the general population and up to 27% of women with a history of BD experience clinically defined PPP (Kendell *et al.* 1987; Di Florio *et al.* 2013, Jones and

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Craddock 2001). Our data, showing that 23% of women with a history of MDD only experienced symptoms of psychosis in the perinatal period, are in line with findings that this is a time of increased risk for psychiatric disorders (Mannion and Slade 2014), and that a history of mental illness further exacerbates risk (Paffenbarger 1964; Jones and Craddock 2001).

Important differences between the current study and that of Di Florio preclude a fully meaningful comparison of data (e.g. classification of postpartum psychosis, characteristics of participants' histories of depression), but the two studies revealed rather different frequencies of psychosis among women with a history of MDD alone (Di Florio *et al.*, 2014), and thus exploration of possible explanations is important. While Di Florio et al used stringent clinical diagnostic criteria to determine the presence of psychosis, we applied the PANSS. The PANSS is not a diagnostic instrument, but specific cut-off scores for five of its items have previously been used (in the context of evaluating relapse rates in patients with a history of first episode psychosis) to assess presence of psychosis (Hui et al. 2013, Chen *et al.* 2010). Though each cut off is anchored on the identification of clearly defined symptoms that have been deemed to be clinically significant (see Table 2), they have not been specifically validated to assess psychosis in women with a history of MDD, and it is important to consider whether they could potentially be confounded by the perinatal period. While the rating of items like hallucinations and delusions using the PANSS in the perinatal period seems theoretically sound, it is possible that the rating of conceptual disorganization may be confounded by pregnancy/postpartum. Specifically, the anchor that defines the threshold on this item is: "Able to focus thoughts when communications are brief and structured, but becomes loose or irrelevant when dealing with more complex communications or when under minimal pressure." It could be argued that the profound life change of a first pregnancy and delivering one's first child – for example, lack of sleep and the disruptions to normal interaction that are associated with a newborn could present with challenges that could be rated on this item but that may in fact be unrelated to psychosis.

When we removed the item conceptual disorganization, the percentage of women above threshold for symptoms of psychosis on the PANSS decreased to 15% (9/60) in the perinatal period (Table 3), and the most frequently occurring symptom became delusions (which was the most frequently occurring symptom of psychosis in a population of individuals with pre-existing psychotic illness, Chen et al, 2010). Removing the conceptual disorganization item had no effect on the frequency of symptoms of psychosis during the perinatal period among participants with a history of single episode MDD, but decreased the frequency of symptoms of psychosis among women with a history of recurrent MDD (Table 3). Research in a larger sample of women is warranted to further explore the magnitude of having a history of recurrent MDD versus a single episode of depression on a woman's risk for PPP.

Given that no women were hospitalized over the course of the study, our data could be interpreted two ways. First our data could simply reflect the idea that psychosis exists as a continuum (Mannion and Slade 2014), and that contrary to the suggestion of Chen *et al*, these symptoms are not necessarily clinically significant. Alternatively, these data could support Ebeid *et al*'s suggestion (2010) that cases of PPP may frequently go undiagnosed

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and untreated. Clearly, future studies involving confirmatory diagnostic interviews are needed in this population.

Our finding that sex of the baby did not significantly alter the frequency with which women experienced symptoms of psychosis is consistent with findings by Videbech and Gouliaev (1995), and Kendell (1981). Categorical analysis revealed a positive trend, but no significant association between female babies and frequency of symptoms of psychosis. Agrawal (1990), who found a significant positive correlation between female birth and PPP occurrence, speculated that disappointment in sex of the baby may have been a stressor that contributed to triggering PPP. Further research is necessary to explore how sex of the baby may affect a woman's chance of experiencing PPP; a meta-analysis of existing studies may be beneficial as a first step.

Limitations

A number of factors must be considered in evaluating the accuracy of characterizing the rate of PPP in this population. First, the PANSS was developed and validated for use in a population of individuals with schizophrenia, most of whom were inpatients. While the positive scale has not been validated for use in a population with a history of major depression, or in a population of individuals during the perinatal period, we are not aware of any scale assessing symptoms of psychosis that has been validated for use specifically during the perinatal period.

Second, at T1, both the SCID and the PANSS were administered, and some women simultaneously scored above threshold for psychosis on the PANSS whilst the SCID revealed no psychotic features. The key issue relevant to reconciling these observations is that the SCID relies on participant self-report of symptoms, whilst the PANSS ratings of all items except hallucinations is dependent on rater impressions (no women were rated above threshold on hallucinations at this time-point in the PANSS, see Table 2). Thus, it is entirely possible that, for example, a participant's thought content may be observed by the rater to be unusual, and classified as such, whilst the participant herself reports no current psychotic symptoms.

Third, we interviewed women at four discrete time points throughout the perinatal period. The PANSS addresses behaviour, mood, and thoughts during the interview and the week preceding it. Since PPP often manifests rapidly, and in some cases may have passed without treatment, we may have missed symptoms or episodes of psychosis, particularly between the one-week and one-month postpartum visits, as women are at highest risk during the first month postpartum (Sit *et al.* 2006). Further, some women missed one or more study visits (11 participants missed the one week timepoint), perhaps in some cases because of psychiatric symptoms. Thus it is possible that the true frequency with which women experienced symptoms of psychosis was actually higher.

Fourth, the sample size used to address whether sex of the baby influenced occurrence of psychosis was small. Further research in larger populations, or a meta-analysis of all

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previous studies are needed to elucidate whether sex of the baby may be a risk factor for PPP among women with a history of MDD.

Finally, all of the women in this study were primiparous, most were married/living with a partner (91.7%) and had completed some post-secondary education (88.5%), and thus our data are not generalizable beyond these constraints. Further studies involving women with more diverse backgrounds would be beneficial.

Conclusions

Our findings support previous findings suggesting that MDD may increase a woman's chance of experiencing symptoms of psychosis in the perinatal period. Given that existing recommendations that health-care practitioners screen pregnant or postpartum women for symptoms of depression (Breedlove and Fryzelka 2011) were based on data demonstrating that this timeframe was associated with increased risk for women, these data suggest a need for additional research to determine whether there is a possible rationale for screening of women with a history of MDD for symptoms of psychosis. If confirmed in controlled studies using diagnostic interviews, these data could inform clinicians' discussions of perinatal psychiatric risks for women with a history of MDD and may facilitate early intervention and treatment to prevent maternal and infant harm.

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Table 1

Demographic information for participants overall.

Characteristic		**Total, of all participants % (*n*)**
Sex of baby	Female	41.7 (25)
	Male	58.3 (35)
Type of MDD history	Single episode	26.7 (15)
	Recurrent	73.3 (45)
Annual household income	<$20,000	13.3 (8)
	$20,000 – $40,000	15.0 (9)
	$41,000 – $60,000	20.0 (12)
	$61,000 – $80,000	11.7 (7)
	$81,000 – $100,000	11.7 (7)
	>$100,000	26.7 (16)
	Did not provide information	1.7 (1)
Highest level of Education	< grade 12	6.7 (4)
	grade 12	3.3 (2)
	post-secondary	90.0 (54)
Marital Status	Married/living with a partner	91.7 (55)
	Partnered	3.3 (2)
	Single	5.0 (3)
History of psychiatric illness reported in first-degree family member	Postpartum psychosis	0 (0)
	Bipolar disorder	3.3 (2)
	Schizophrenia	3.3 (2)
Total		60

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Table 2

Proportion/number of the total sample (n=60) who had ratings above cut-off for each of the five items assessing psychosis on the PANSS at each time point.

PANSS Item	T1% (*n*)	T2% (*n*)[1]	T3% (*n*)[2]	T4% (*n*)[3]	Above cut off at one or more time-points[^] % (*n*)
Conceptual disorganization[a]	10.0 (6)	4.1 (2)	6.8 (4)	0.0 (0)	15.0 (9)
Delusions[b]	5.0 (3)	0.0 (0)	1.7 (1)	1.8 (1)	8.3 (5)
Hallucinations[c]	0.0 (0)	2.0 (1)	1.7 (1)	3.6 (2)	6.7 (4)
Suspiciousness[d]	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Unusual thought content[e]	1.7 (1)	0.0 (0)	1.7 (1)	0.0 (0)	3.3 (2)
Two of the above items[*]	3.3 (2)	0.0 (0)	1.7 (1)	0.0 (0)	5.0 (3)
Total number of women above cut-off on one or more item	13.3 (8)	6.1 (3)	10.2 (6)	5.4 (3)	23.3 (14)
Total number of women above cut-off on one or more item, excluding conceptual disorganization	6.7 (4)	1.7 (1)	5.0 (3)	5.0 (3)	15.0 (9)

[a]**The minimum threshold anchor for this item was** "Able to focus thoughts when communications are brief and structured, but becomes loose or irrelevant when dealing with more complex communications or when under minimal pressure."

[b]**The minimum threshold anchor for this item was** "Presence of one or two delusions which are vague, uncrystallised and not tenaciously held. Delusions do not interfere with thinking, social relations, or behavior."

[c]**The minimum threshold anchor for this item was** "One or two clearly formed but infrequent hallucinations, or else a number of vague abnormal perceptions which do not result in distortions of thinking or behaviour."

[d]**The minimum threshold anchor for this item was** "Patient shows marked distrustfulness, leading to major disruption of interpersonal relations, or else there are clear-cut persecutory delusions that have limited impact on interpersonal relations and behavior."

[e]**The minimum threshold anchor for this item was** "Ideas are frequently distorted and occasionally seem quite bizarre."

[1]Data missing for 11 women.

[2]Data missing for one woman.

[3]Data missing for four women.

[*]Three women scored above threshold simultaneously for two of the five items on the PANSS during the perinatal period. The items that co-occurred were conceptual disorganization and delusions (3.3%, 2/60), and conceptual disorganization and unusual thought content (1.7%, 1/60). **No women in this study had more than two items above cut-off.**

[^]Some women scored above threshold on the same item at more than one time-point

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Table 3

Numbers of women who experienced perinatal or postpartum symptoms of psychosis by sex of baby and type of history of MDD

Characteristic		**Women who experienced psychosis at some point in the perinatal period *n***	**Women who experienced postpartum onset psychosis *n***
Sex of baby	Female (n=25)	6	5
	Male (n=35)	8	1
Type of MDD history	Single episode (n=15)	3	2
	Recurrent (n=45)	11	4
Total		14	6