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Symptom profile of postpartum and non-postpartum manic episodes in bipolar I disorder: a within-subjects study

Running head: Postpartum and non-postpartum mania

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Abstract

The relationship of postpartum mania to episodes of mania occurring outside the perinatal period among women with bipolar disorder remains controversial. Previous studies have used between-subjects designs to compare the clinical presentations of these episodes meaning the differences, in part, may reflect between-group differences. To overcome this we have undertaken within-subject comparisons of the symptom profile of postpartum and non-postpartum manic episodes in 50 women with DSM-IV bipolar I disorder. For each woman detailed symptom information on a postpartum episode of mania and a comparison non-postpartum manic episode was collected. The occurrence of manic, psychotic and depressive symptoms in these episodes were compared. Postpartum manic episodes had a significantly higher incidence of perplexity and excessive self-reproach. Classic manic symptoms, specifically pressured speech and increased sociability, were significantly less frequent in postpartum manic episodes. Overall there were significantly fewer manic symptoms and significantly more depressive symptoms in the postpartum episodes than in the non-postpartum episodes. The mixed presentation of postpartum manic episodes suggests childbirth may act as a pathoplastic trigger in women with bipolar disorder. The differences in symptom profiles suggests further research is warranted into whether differences in treatment response exist among women experiencing postpartum and non-postpartum manic episodes.

Key words: bipolar disorder, postpartum mania, symptomatology

1. Introduction

The postpartum period has been well established as a time of increased vulnerability to relapse in women with bipolar disorder. The risk of admission in the postpartum is significantly greater for women with bipolar disorder than at any other point in their lives (Munk-Olsen et al., 2009). In particular, the risk of postpartum psychosis is dramatically elevated in bipolar disorder (approximately one in five deliveries) compared to the general population (approximately one in one thousand deliveries) (Jones and Craddock, 2001).

Previous studies have compared the clinical presentations of women with postpartum psychosis to women with episodes of psychosis and mania occurring outside of the postpartum period (Brockington et al., 1981; Oosthuizen et al., 1995; Wisner et al., 1994). As well as being key in establishing the relationship between postpartum psychosis and bipolar disorder, they have provided rich descriptions of the kaleidoscopic clinical presentation of postpartum psychosis characterised by confusion, manic symptoms, delusions, hallucinations and cognitive disorganisation. While these studies included women with a range of clinical diagnoses, only one previous study has specifically focused on comparing the clinical presentations of women with episodes of postpartum and non-postpartum mania (Ganjekar et al., 2013). Comparing two separate groups of women (30 in each group) the authors reported higher levels of ‘apparent sadness’, ‘lassitude’/lack of energy, labile emotional response, disorientation and perplexity among the women with postpartum mania. In comparison, typical manic symptoms including elated mood, ideas of grandeur and distractibility were more common in the non-postpartum mania group (Ganjekar et al., 2013). However, it is not possible to establish if the differences in presentation were a result of differences in the

nature of the underlying bipolar disorder between the two groups or reflect the postpartum context leading to differences in symptom presentation between the episodes.

In light of this, in a sample of women with bipolar I disorder, we have undertaken within-subject comparisons of the clinical presentation of postpartum and non-postpartum manic episodes. With women acting as their own controls the potential effects of between-group symptom heterogeneity are removed.

2. Methods

Participants were 50 women with bipolar I disorder recruited as part of our ongoing programme of research into the genetic and non-genetic determinants of bipolar disorder and related mood disorders (Bipolar Disorder Research Network, BDRN; bdrn.org). The research has UK National Health Service (NHS) Research Ethics Committee approval and local Research and Development approval in all participating NHS Trusts/Health Boards.

2.1. Recruitment of participants

Participants were recruited throughout the UK via systematic and non-systematic recruitment methods. Systematic recruitment involved screening for potential participants through UK National Health Service psychiatric services. Non-systematic recruitment involved advertisements for volunteers on the research team website and through the patient support organisation Bipolar UK.

BDRN inclusion criteria require participants to be aged 18 years or over, able to provide written informed consent, meet DSM-IV criteria for major affective disorder and for mood symptoms to have started before the age of 65 years. Individuals are excluded if they: (i) experienced affective illness only as a result of alcohol or substance dependence; (ii) experienced affective illness only secondarily to medical illness or medication; or (iii) are biologically related to another study participant. As a focus of research programme is genetic causes of affective disorders all participants were of UK White ethnicity.

Women included in the current study all met DSM-IV diagnostic criteria for bipolar I disorder and had experienced a postpartum episode of mania with onset within 6 weeks of childbirth and a comparison non-postpartum manic episode where we had collected detailed symptom information for both episodes.

2.2. Psychiatric assessment

Participants were interviewed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990), which provides detailed information about lifetime psychopathology. In addition, women were asked pregnancy by pregnancy about mood episodes occurring in relation to the perinatal period. For the current study, women experiencing an episode of mania, lasting at least a week, within 6 weeks of delivery had a detailed SCAN assessment of this episode. Where women had experienced more than one past episode of postpartum mania, the episode they recalled as being the most severe was rated (worst postpartum manic episode (PPM)). As a comparison, a detailed SCAN assessment was also carried out for all women on their most severe non-postpartum episode of mania (worst non-postpartum manic episode (NPPM)).

Where available, information was also gathered from review of psychiatric and general practice case-notes. In all cases at least one of these additional case note sources was available. These data were combined with the interview data in order to establish the best-estimate main lifetime diagnosis according to DSM-IV criteria, and to rate other key lifetime clinical variables, for example age of illness onset.

All available data were used to rate presence/absence of a range of individual manic, depressive and psychotic symptoms occurring in women's PPM and NPPM episodes using a modified version of the Operational Criteria (OPCRIT) symptom checklist (McGuffin et al., 1991). Symptoms were rated present if they had occurred for a significant proportion of the episode. A small number of additional symptoms not included in OPCRIT, including symptoms previously reported in postpartum psychosis literature, such as perplexity, were also rated.

All diagnostic and clinical ratings were made by at least two members of the research team blind to each other's rating, and consensus was reached via discussion where necessary. Inter-rater reliability was formally assessed using 20 random cases. Mean kappa statistics were 0.85 for DSM-IV diagnosis and ranged between 0.81 and 0.99 for other key clinical categorical variables including all symptom ratings. Mean intra-class correlation coefficients were between 0.91 and 0.97 for key clinical continuous variables, such as age at illness onset. Team members involved in the interview, rating and diagnostic procedures were all research psychologists or psychiatrists.

2.3 Analysis

Analyses were carried out using Statistical Package for the Social Sciences (SPSS, version 23). Following descriptive parametric and non-parametric analyses of the sample clinical characteristics, McNemar tests were used to examine within-subjects comparisons of PPM versus NPPM episodes according to the presence of individual manic, depressive, psychotic and other symptoms and the overall presence of psychotic symptoms. Wilcoxon tests were used to examine within-subjects comparisons of PPM versus NPPM episodes according to the total number of manic, depressive and psychotic symptoms. Individual symptoms not present in either the PPM or NPPM episode in any participants were not included in the analyses.

3. Results

The mean age of the sample was 44 years (SD, 10.2; range, 22-68). The mean age of onset of bipolar disorder was 22 years (SD, 6.2; range 13-39). Due to the study design, all of the women had experienced at least two lifetime episodes of mania (median 5.5 episodes) and 48 out of the 50 had also experienced at least one lifetime episode of depression (median 4 episodes). The first episode of bipolar disorder occurred in a postpartum period, defined as up to six months after delivery, for 34% women, and outside of a postpartum period for the remaining 66%. The median number of deliveries and episodes of postpartum mania were two and one respectively (Table 1).

Within-subjects analyses of the PPM and NPPM episodes (Table 2) revealed the symptoms of pressured speech ($p=0.021$) and increased sociability ($p=0.013$) were significantly less

common in the PPM compared to NPPM episodes (78% vs. 94% and 52% vs. 74% respectively). In contrast, excessive self-reproach ($p=0.008$), and perplexity ($p<0.0001$) were significantly more common in the PPM episodes compared to NPPM episodes (16% vs. 0% and 44% vs 6%). A pattern was observed for all remaining manic symptoms to occur *less frequently* and all remaining depressive symptoms to occur *more frequently* in PPM episodes. Although these remaining individual symptom differences were not statistically significant, overall PPM episodes were characterised by significantly fewer manic symptoms ($p=0.014$) and significantly more depressive symptoms ($p=0.002$).

There were no significant differences between the two episodes when comparing the frequency of individual psychotic symptoms, the total number of psychotic symptoms or the overall presence/absence of psychotic symptoms (Table 2 and Table 3). Combined analyses of all types of visual hallucinations, auditory hallucinations and delusions respectively found that visual and auditory hallucinations of any type were more common in the PPM episodes with the difference almost reaching statistical significance for visual hallucinations occurring in 20% of PPM episodes compared to 8% of NPPM episodes (Table 3).

4. Discussion

Using a within-subjects analysis we have investigated differences in the symptom profile of postpartum and non-postpartum episodes of mania in a group of women with bipolar I disorder. The hallmarks of postpartum psychosis have been previously described in the literature in case series, retrospective and prospective studies (Kamperman et al., 2017; Klompenhouwer et al., 1995; McNeil, 1986) with a smaller number of studies including a separate comparison group of women with non-postpartum mania and/or psychosis

(Brockington et al., 1981; Ganjekar et al., 2013; Oosthuizen et al., 1995; Wisner et al., 1994).

In a narrowly-defined sample our robust study design has enabled us to remove the potential bias of other between-group differences and to establish whether the unique features of postpartum mania observed in our sample of women with bipolar disorder are in fact specifically related to the postpartum context thus building on previous research.

We found specific manic symptoms (pressured speech and increased sociability) were significantly *less* frequent in postpartum episodes whereas the depressive symptom excessive self-reproach (excessive guilt) was significantly *more* frequent in the postpartum. Overall PPM episodes were characterised by significantly *fewer* manic symptoms and *more* depressive symptoms. Perplexity was also significantly *more* frequent in postpartum mania than in mania unrelated to the postpartum period. The overall presence of psychotic symptoms was not significantly different between the episodes (70% and 66% of PPM and NPPM episodes) however there was a trend for visual hallucinations to occur more frequently in PPM episodes almost reaching statistical significance.

These findings suggest women with bipolar disorder are likely to experience more mixed features of mania with perplexity during postpartum manic episodes compared to episodes at other times in their lives. This is agreement with the most comparable previous study to ours by Ganjekar et al. (2013) in India, where the authors also found differences in symptom profile between two separate groups of women experiencing postpartum mania and non-postpartum mania. In both studies perplexity was significantly associated with postpartum mania which is in agreement with previous studies reporting a greater severity of confusion

(Brockington et al., 1981) and ‘cognitive disorganisation’ (Wisner et al., 1994) among women with more broadly-defined postpartum psychosis.

Our finding that typical manic symptoms, pressured speech and increased sociability, were significantly less common in postpartum mania is also in agreement with Ganjekar et al. who reported elation, ideas of grandeur and elated mood to be less common in their postpartum group. Differences between the two studies in the specific manic symptoms occurring less frequently in postpartum mania may, in part, reflect differences in the tools used to assess symptomatology but also cultural variations in psychopathology. Ganjekar et al., (2013) also found that depressive symptoms, specifically ‘apparent sadness’ and ‘lassitude’/lack of energy were more frequent in postpartum mania suggesting dysphoria is a common feature of these episodes. Similarly we found the depressive symptom excessive self-reproach, defined as extreme feelings of guilt and unworthiness, to be significantly more common in postpartum mania.

We found visual hallucinations to be more than twice as common in postpartum manic episodes than in non-postpartum manic episodes. A *post-hoc* power calculation revealed our analysis of this variable was under powered (69%) and a larger sample size would be needed to demonstrate statistical significance of our observed effect size. This finding is in concordance with a recent Dutch study examining the phenotypical characteristics of postpartum psychosis in a cohort of 130 women (Kamperman et al., 2017) where the prevalence of visual hallucinations was even higher at 34% than in our study (21%). Their cohort may represent more severe episodes, however, as all women included were admitted

to a mother-baby unit, whereas women in our sample may or may not have received inpatient treatment.

Our within-subject analysis, which has found similar differences between postpartum and non-postpartum mania to previous between-subjects analysis, supports the suggestion that the perinatal context may exert a pathoplastic influence on the way manic symptoms are expressed. Childbirth may specifically modify the presentation of manic episodes with a number of neurobiological factors including hormonal, immunological and circadian changes potentially playing a role.

Most obviously the perinatal period is a time of major hormonal fluctuations with oestrogen and progesterone levels rapidly dropping after birth. As proposed in relation to postpartum depression, women may have differential sensitivity to rapid hormonal changes following childbirth rather than abnormalities in absolute concentrations of these hormones (Schiller et al., 2015). It is therefore possible that among women with bipolar disorder sensitivity to childbirth related hormonal changes may lead to differences in the presentation of manic episodes in the postpartum compared to other manic episodes in their lives. Similarly, pregnancy and the immediate postpartum period are also times of naturally heightened immune responsiveness. Recent evidence has highlighted a potential role of immune system dysregulation in the pathogenesis of postpartum psychosis (Bergink et al., 2013) which may contribute to a pathoplastic impact on the symptom profile of postpartum mania.

Sleep disruption in the immediate postpartum may play a role in the differing presentations observed in postpartum and non-postpartum episodes of mania. The fact that sleep loss as a

symptom is an integral part of the manic syndrome makes investigations into the role of sleep disruption in mania difficult. For example, in our sample reduced need for sleep was common, being present in 83% and 94% of the postpartum and non-postpartum episodes respectively. Further research with detailed within-subject comparisons of the symptom profile of manic episodes where the absence or presence of a clear period of acute sleep deprivation prior to episode onset is evident would help to establish the role that acute sleep disruption may play in the presentation of manic episodes, and would have obvious relevance for postpartum episodes where sleep disruption is often severe.

Unique external/environmental characteristics of the postpartum period and may also account for some of the observed differences in our sample. For example the lower occurrence of increased sociability in postpartum manic episodes could be the result of women being in hospital in the immediate days following childbirth and/or the tendency for women to focus on their baby and immediate family during this period. Changes in women's treatment regimes during the perinatal period are also an important consideration. Unfortunately we did not collect detailed treatment information and so could not explore whether the occurrence of specific symptoms was associated with any types of medications or whether or not women were admitted to hospital.

There are further limitations to consider when interpreting our findings. First, the assessments of the postnatal and non-postnatal episodes were retrospective, although they were supplemented by contemporaneous medical case-notes where available. Large scale prospective studies detailing the presentation of manic episodes across the lifespan would be ideal but costly. Second, although we obtained detailed information on a range of manic,

depressive and psychotic symptoms, there are other aspects that we did not examine for example the presence of anxiety, mood instability/lability, obsessional thoughts and some specific delusions including religious delusions. Third, conservatively correcting for the number of independent comparisons performed using the Bonferroni method results in perplexity being the only variable to show a statistically significant difference between the PPM and NPPM episodes ($p=0.042$). Fourth, due to the sample size we were unable to stratify and carry out the within-subjects analyses separately in women whose postpartum episode of mania was or was not their first illness episode, or in women whose postpartum episode did or did not occur in the immediate postpartum (days) which may or may not reveal different patterns. Our findings therefore require replication in independent and larger samples using a similarly robust within-subjects design.

Our findings support the suggestion that childbirth has a pathoplastic impact on the presentation of manic episodes among women with bipolar disorder. The differences in the symptom profiles of postpartum manic and non-postpartum manic episodes we observed could be important for clinicians in making assessments in the postpartum period. The mixed presentation of manic episodes following childbirth compared to episodes occurring at other times in women's lives also suggests further research is warranted into whether differences also exist in the speed of onset, length of episode and treatment response between postpartum and nonpostpartum episodes of mania. The findings could further inform guidance on the management women with bipolar disorder during pregnancy and in the postpartum period.

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Conflicts of interest

None.

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Table 1. Clinical characteristics of the sample (n=50)

		Range
Age at interview, years, mean (SD)	43.7 (10.2)	22-68
Age of onset of impairment, mean (SD)	22.2 (6.2)	13-39
Lifetime number of episodes of mania, median (IQR)	5.5 (5)	2-26
Lifetime number of episodes of depression, median (IQR)	4 (4)	0-55
First episode postpartum, n (%)	17 (34)	-
Number of deliveries, median (IQR)	2 (1)	1-8
Number of episodes of postpartum mania, median (IQR)	1 (0)	1-3

Table 2. Symptom profile of worst postpartum manic episode (PPM) and worst non-postpartum manic episode (NPPM) in 50 women with bipolar I disorder

	PPM n (%)	NPPM n (%)	p
<i>Manic symptoms</i>			
Elevated mood	47 (94)	47 (94)	1.000
Irritable mood	34 (68)	35 (70)	1.000
Thoughts Racing	41 (82)	47 (94)	0.109
Pressured speech	39 (78)	47 (94)	0.021
Distractibility	38 (76)	40 (80)	0.774
Excessive activity	45 (90)	46 (92)	1.000
Increased self esteem	34 (68)	39 (78)	0.302
Reckless activity	21 (42)	30 (60)	0.093
Reduced need for sleep	41 (82)	47 (94)	0.070
Increased sociability	26 (52)	37 (74)	0.013
Total number manic symptoms; mean, median (IQR)	7.32, 7.5 (3)	8.30, 9 (3)	0.014
<i>Depressive symptoms</i>			
Dysphoria	17 (34)	9 (18)	0.077
Loss of pleasure	2 (4)	0 (0)	0.500
Diurnal variation	1 (2)	0 (0)	1.000
Suicidal ideation	6 (12)	2 (4)	0.219
Excessive self-reproach (excessive guilt)	8 (16)	0 (0)	0.008
Poor concentration	2 (4)	1 (2)	1.000
Slowed activity	2 (4)	1 (2)	1.000
Loss of energy/tiredness	1 (2)	0 (0)	1.000
Agitated activity	4 (8)	1 (2)	0.375
Total number depressive symptoms; mean, median (IQR)	0.86, 0 (2)	0.28, 0 (0)	0.002
<i>Affective psychotic symptoms</i>			
Grandiose delusions	25 (50)	20 (40)	0.359
Delusions of guilt	1 (2)	0 (0)	1.000
Nihilistic delusions	3 (6)	0 (0)	0.250
Other secondary delusions	9 (18)	14 (28)	0.267
Persecutory delusions	10 (20)	7 (14)	0.581
Mood congruent visual hallucinations	6 (12)	2 (4)	0.125
Mood congruent 2 nd person auditory hallucinations	6 (12)	1 (2)	0.125
Abusive accusatory persecutory voices	2 (4)	0 (0)	0.500
<i>Non-affective psychotic symptoms</i>			
Delusions of influence	16 (32)	20 (40)	0.481
Delusions of passivity	1 (2)	1 (2)	1.000
Bizarre delusions	2 (4)	0 (0)	0.500
Other primary delusions	0 (0)	1 (2)	1.000
Primary delusional perception	1 (2)	0 (0)	1.000
Non affective visual hallucinations	5 (10)	3 (6)	0.625
Non affective auditory hallucinations	2 (4)	4 (8)	0.687
Non affective hallucinations in any other modality	3 (6)	0 (0)	0.250
Total number affective and non-affective psychotic symptoms; mean, median (IQR)	1.84, 1.5 (3)	1.46, 1 (2)	0.230
<i>Other symptoms</i>			
Bizzare Behaviour	5 (10)	3 (6)	0.687
Catatonia	0 (0)	1 (2)	1.000
Speech Difficult to Understand	1 (2)	1 (2)	1.000
Restricted Affect	2 (4)	1 (2)	1.000
Inappropriate Affect	1 (2)	0 (0)	1.000
Perplexity	22 (44)	3 (6)	<0.0001

IQR=interquartile range

Table 3. Comparison of the overall occurrence of visual hallucinations, auditory hallucinations, delusions and any psychotic symptoms in the worst postpartum manic episode (PPM) and worst non-postpartum manic episode (NPPM) in 50 women with bipolar I disorder

	PPM n (%)	NPPM n (%)	p
Visual hallucinations	10 (20)	4 (8)	0.070
Auditory hallucinations	7 (14)	4 (8)	0.579
Delusions	33 (66)	33 (66)	1.000
Any psychosis	35 (70)	33 (66)	0.839