Smoking and risk of postpartum psychosis in women with bipolar disorder

Arianna Di Florio M.D., Ph.D (1),
Holly Morgan (1),
Lisa Jones Ph.D. (2),
Liz Forty Ph.D.(1),
Katherine Gordon-Smith Ph.D. (1,2),
Nick Craddock F.R.C.Psych, Ph.D. (1),
Ian Jones M.R.C.Psych, Ph.D. (1)*

(1) Institute of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University
(2) Department of Psychiatry, School of Clinical and Experimental Medicine, University of Birmingham

*Corresponding Author:
Prof. Ian Jones
Institute of Psychological Medicine & Clinical Neurosciences
MRC Centre for Neuropsychiatric Genetics and Genomics
Cardiff University
Hadyn Ellis Building
Maindy Road
Cathays
Cardiff CF24 4HQ
UK

Email: JonesIR1@cf.ac.uk
Tel: +44 029 20687066
ABSTRACT (will be modified according to journal):
OBJECTIVES: 1) to test the hypothesis that a lifetime history of regular smoking is inversely associated with episodes of postpartum psychosis in bipolar women, consistent with findings for another pregnancy-related disorder, pre-eclampsia and in contrast to other mental disorders 2) to test whether the association is specific for postpartum psychosis or if it extends to postpartum bipolar depression.

METHODS: Information in relation to pregnancy, childbirth and lifetime history of regular smoking were gathered retrospectively for 662 parous women with DSM-IV bipolar I disorder by interview and case-notes review. Analyses controlled for a number of clinical and socio-economic confounders.

RESULTS: There was a negative association between smoking and postpartum psychosis (OR: 0.36, 95%CI 0.246-0.517, p<0.01). The association was specific for psychosis and did not extend to postpartum bipolar depression (OR: 0.80, CI 95%: 0.53-1.22, p=0.31).

DISCUSSION: This study generates new hypotheses of a biological link between smoking and postpartum psychosis. Research in this area needs to take into account the potential effect of many confounders and reporting bias.

BACKGROUND

Bipolar disorder is a leading cause of disability among women below 45\(^1\). A striking and clinically important feature of bipolar disorder is the very high risk of mood/psychotic episodes in the first few weeks following childbirth. We recently reported that more than 70% of mothers with bipolar disorder experience at least one episode in relationship to pregnancy or childbirth and more than 30% experience a severe manic or psychotic episode following delivery - postpartum psychosis\(^2\). Severe postpartum episodes have long-term implications for the wellbeing of the woman, her family and wider society. Suicide is a leading cause of maternal death in the UK\(^3\) for which bipolar disorder is a major risk factor.

Knowing as much as possible about episodes in relation to childbirth is of great importance not only for the clinical management of women at risk, but also for improving our understanding of the pathogenesis of a broader spectrum of mood disorders\(^4\). A strategy that may help in this task is to investigate the overlapping risk and possible protective factors between bipolar postpartum psychosis and other non-psychiatric peripartum conditions. For example, a link between postpartum psychosis and eclamptic disorders is of particular interest and has been recognised for over 160 years\(^5\).

Smoking in pregnancy increases the risk of many adverse outcomes, including poor placental function, low birth weight, intrauterine growth restriction, prematurity, miscarriage and perinatal death\(^6\). Perhaps surprisingly, however, smoking has been found in a number of studies to be protective for the development of preeclampsia\[^6\]. Smoking is also robustly associated with a broad range of mental disorders. Co-occurrence rates of smoking among individuals with bipolar disorder range from 30%
to 70%\textsuperscript{7}, and nicotine dependence rates are about 3 to 5-fold the rates observed in the general population\textsuperscript{8}.

Given the relationship between postpartum psychosis and preeclampsia we aimed to: 1) test the hypothesis that smoking is inversely associated with postpartum affective psychosis, consistent with findings for pre-eclampsia and in contrast to other mental disorders; and 2) test whether the association is specific for postpartum affective psychosis or if it compared against postpartum bipolar depression.
METHODS

Sample
The sample was drawn from our study on the clinical and genetic determinants of bipolar disorder, conducted within the Bipolar Disorder Research Network (bdrn.org) framework and described in detail elsewhere. In brief, participants were recruited between 1998 and 2012 using both systematic and non-systematic methods across the United Kingdom.

Participants were excluded from the original studies if they had: i) a lifetime diagnosis of intravenous drug dependency; ii) only experienced affective illness as a result of alcohol or substance dependence; and iii) only experienced affective illness secondary to medical illness or medication.

Participants were included in the current analyses if they had i) a lifetime diagnosis of DSM–IV bipolar I disorder ii) at least one full term delivery iii) complete information on smoking habits and perinatal mood episodes. As we were interested in mood episodes occurring in the reproductive years, women with age of onset of bipolar disorder in the post-menopausal period were excluded. A cut-off of 50 years old was set.

All participants were aged 18 years or over and provided written informed consent. This study received Multi-Region Research Ethics Committee (MREC) approval and local Research and Development approval in all participating NHS Trusts and Health Boards.

Procedures and diagnostic criteria
Participants were interviewed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN), which provides detailed information about lifetime psychopathology. Psychiatric case-notes, where available, were also reviewed.

Due to the longstanding interest of our group in postpartum mood disorders, detailed information on pregnancies and the postpartum periods were available for women participants.

Best-estimate lifetime diagnoses were made according to DSM-IV criteria and key clinical variables, such as age at onset and number of episodes, were rated. In cases where there was doubt, diagnostic and clinical ratings were made by at least two members of the research team blind to each other’s rating. Inter-rater reliability was formally assessed using 20 cases. Mean kappa statistics were 0.85 for DSM-IV diagnoses and ranged between 0.81 and 0.99 for other key clinical categorical variables; mean intra-class correlation coefficients were between 0.91 and 0.97 for key clinical continuous variables. Team members involved in the interview, rating and diagnostic procedures were all research psychologists or psychiatrists.

The DSM-IV post-partum onset specifier covers episodes within 4 weeks of childbirth, but may be too narrow for depressive episodes. We therefore used a broader definition and included episodes occurring within 6 weeks postpartum. Postpartum affective psychosis was defined as any episode of mania, mixed, affective psychosis within 6 weeks after childbirth. Postpartum depression was defined as an episode of major depression within 6 weeks postpartum.

Only live births were considered. Multiparae could have experienced both postpartum psychosis and postpartum depression. A hierarchical approach was therefore used
and women who reported both postpartum affective psychosis and postpartum depression were included in the postpartum affective psychosis group. We did not have detailed information about smoking status in each pregnancy, but at interview women were asked if they had ever been a regular tobacco smoker during their lifetime. On the basis of this question the sample was divided into those who had ever been a regular smoker (here referred to as the smokers group), and a group who denied ever being a regular smoker (here referred to as the non-smokers group). Information on age at first regular smoking and whether this was before or after the onset of bipolar disorder was also collected.

**Statistical analyses**

Statistical analyses were performed using R version 2.13.0 (Copyright 2011 by The R Foundation for Statistical Computing). Bivariate analyses were conducted using t test for normally distributed continuous variables, rank test for those not normally distributed and Chi-squared test for nominal variables. We used binary logistic regression to test the hypothesis of an association between smoking and postpartum psychosis or depression while taking into account statistically significant confounders. Nested models were compared using the likelihood ratio test. As there were multiparae who had a history of both postpartum depression and psychosis, we conducted further pregnancy-by-pregnancy analyses 1) including only first deliveries and 2) using mixed-effects regression models (lme4 package), including the individual woman as random effect.
RESULTS

Sample description
Complete information was available for 667 parous women with bipolar I disorder. In our sample 293 (44.3%) women were non-smokers and 369 (55.7%) admitted to have been regular smokers at some point in their lives.

Clinical and socio-demographic comparisons between smokers and non-smokers are reported in table 1. The majority of smokers (N= 272, 75.8%) started smoking regularly before the onset of impairing bipolar symptoms. Their mean age at onset of bipolar disorder was 21.7 years (s.d. 8.42), while mean age at first regular smoking was 16.8 years (s.d. 5.85).
Table 1. Clinical and socio-demographic comparisons according to smoking status

<table>
<thead>
<tr>
<th></th>
<th>NON SMOKERS</th>
<th></th>
<th>SMOKERS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Age at interview</td>
<td>49</td>
<td>21-79</td>
<td>47</td>
<td>22-76</td>
</tr>
<tr>
<td>Age at impairment(^a)</td>
<td>22</td>
<td>8-48</td>
<td>20</td>
<td>4-49</td>
</tr>
<tr>
<td>Deliveries</td>
<td>2</td>
<td>1-7</td>
<td>2</td>
<td>1-7</td>
</tr>
<tr>
<td>Admissions</td>
<td>2</td>
<td>0-30</td>
<td>3</td>
<td>0-25</td>
</tr>
<tr>
<td>N (%)</td>
<td>293 (44.3%)</td>
<td></td>
<td>369 (55.7%)</td>
<td></td>
</tr>
</tbody>
</table>

More than one episode/year of illness

<table>
<thead>
<tr>
<th>Number of medical comorbidities</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>0-10</td>
<td>1</td>
<td>0-10</td>
</tr>
</tbody>
</table>

Postpartum episodes \(^a\)

<table>
<thead>
<tr>
<th>Postpartum affective psychosis</th>
<th>125</th>
<th>42.5</th>
<th>86</th>
<th>23.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postpartum depression</td>
<td>65</td>
<td>22.1</td>
<td>96</td>
<td>25.7</td>
</tr>
<tr>
<td>No postpartum episodes (^a)</td>
<td>104</td>
<td>35.4</td>
<td>191</td>
<td>51.2</td>
</tr>
</tbody>
</table>

\(^a\) p<0.01
Smokers were more likely to be less educated (p<0.01), younger at the first impairment due to bipolar disorder (p<0.01) and less likely to have ever had a professional occupation (p<0.01). Number of medical comorbidities (including cancer, liver, kidneys, heart, lungs, neurological and thyroid disorders) did not differ between smokers and non-smokers.

**Association between smoking and postpartum affective psychosis**

A history of postpartum psychosis was overrepresented in non-smokers (N=124, 42.3%) compared to smokers (N=85, 23.0%). There was a negative association therefore between smoking status and postpartum affective psychosis (OR:0.38, 95%CI 0.259-0.555, p<0.01).

Many variables could influence the association between smoking and postpartum psychosis, including number of deliveries, severity of bipolar disorder, education and socio-economic status. When we limited the analyses to women recruited systematically through the National Health Service, to account for possible selection bias, the association with smoking remained statistically significant and with similar effect size (OR: 0.40, 95%CI 0.181-0.864; p<0.02).

Because our study was retrospective and considered multiple pregnancies from the same woman, we hypothesised that smoking may reduce fertility and thus the number of live births. A reduced number of deliveries compared to non-smokers could go some way to explain the protective effect of smoking on postpartum episodes. Women with fewer children would have less chance to develop a postpartum episode than those with more children. However, smoking status was not associated with number of deliveries (p=0.75).

Course of illness and medications may also bias the association between postpartum psychosis and smoking. When analyses were limited to women who had their first lifetime episode of bipolar disorder within 6 weeks after childbirth, history of postpartum psychosis remained overrepresented in non-smokers (N=57, 35.4%) compared to smokers (N= 25, 11.7%), with an even stronger effect (OR: 0.24, 95%CI% 0.137-0.422; p<0.01).

In the multivariable model, age at impairment and education remained associated with smoking (respectively, p=0.02 and p<0.01).

Women with postpartum affective psychosis were older at first episode of bipolar disorder causing impairment than women with no postpartum episodes, so we controlled our analyses for age at first impairment.

In the multivariable model, the negative association between smoking and postpartum affective psychosis remained significant (OR: 0.36, 95%CI 0.246- 0.517, p<0.01 after correcting for age at first impairment  figure 1.
Association between postpartum bipolar depression and smoking

A history of postpartum bipolar depression but not postpartum psychosis was reported by 96 (26.0%) smokers and 65 non-smokers (22.2%). There was no statistically significant association between bipolar postpartum depression and smoking (OR 0.82, CI 95% 0.54-1.24, p=0.31).

Pregnancy-by-pregnancy analyses

To account for women who had more than one delivery and a history of both postpartum affective psychosis and depression (N=14), we used mixed effect regression models, with postpartum mood episodes as outcome variable and individual woman as random effect. When only first deliveries were considered, smoking remained significantly associated with postpartum affective psychosis (p<0.01) and not associated with postpartum depression (p=0.51).
DISCUSSION

In a large retrospective sample of mothers with bipolar I disorder we found that postpartum affective psychosis was underrepresented among smokers. The negative association was strong and specific for postpartum affective psychosis and did not extend to postpartum depression.

The percentage of women who had ever been regular smokers in our sample (56%) was in the range reported in the literature for people with bipolar disorder (30-70% for current smoking, although studies have been conducted after 2004 and there is a dearth of information on secular trends of smoking in bipolar disorder). Although women with a history of postpartum affective psychosis were less likely to have ever smoked regularly than women with bipolar disorder without postpartum psychosis, the rates of ever-regular smokers were still higher than in the general female population (16.5% in the US and 19% in the UK according to recent surveys (www.cdc.gov/tobacco and ash.org.uk).

The findings are particularly intriguing as they are consistent with the protective effect of smoking on preeclampsia (typical relative risk, 0.68; 95% confidence interval, 0.67-0.69).

Our results need to be interpreted in the light of the following limitations:

1. We had information on lifetime smoking, but not on smoking during pregnancy. The prevalence of smoking in pregnancy has been decreasing during the past decades. A registry-based Swedish study found that while 67% of women with affective psychosis smoked during pregnancy in years 1973–1977, the proportion was more than halved by 2000-2002 at 24% and 10% reporting that they quit smoking in early pregnancy. However, smoking in pregnancy is under-reported in the general population with more than 20% of self-reported quitters being active smokers according to urinary cotinine concentration. Studies investigating the risk of pre-eclampsia in women who quit smoking before pregnancy are not consistent. The protective effect observed in smokers was maintained in quitters in some studies, but not in others.

2. The retrospective data collection, confounding factors, recall and selection bias may limit the validity of our results. However, we assessed and controlled the association between smoking and several suspected confounders, including recruitment methods. The association between smoking and psychosis was neither anticipated nor hypothesized when the original study was designed and sample was collected. We minimized recall bias by collecting data from multiple sources, including case-notes. The reporting of episodes at interview was in agreement with the medical records and the recollection of episodes in relation to childbirth has been shown to be excellent.

3. There is no consensus on the definition of who is a smoker. In this study we recorded whether women had ever been regular smokers according to what was reported during the face-to-face interview. Information on occasional smokers, on the amount and the time pattern of smoking was not collected. We also did not collect information on the actual nicotine exposure that is influenced by factors such as type of cigarette, depth of inhalation and individual differences in the metabolism of smoking products.
There are several possible explanations for the lower rates of postpartum affective psychosis in smokers.

Smoking is common in bipolar disorder. Potential mechanisms responsible for this association include shared risk factors as well as common disease pathways (for a review see\textsuperscript{7}). Sparse evidence points towards a self-medication hypothesis for nicotine addiction in individuals with bipolar disorder. Nicotine has in fact positive effects on cognition and reverses the cognitive side effects of anti-psychotic drugs. Smoking and bipolar disorder also share common environmental risk factors, including childhood adverse events and co-morbidity with alcohol and substance misuse\textsuperscript{7}.

It is possible that women with bipolar disorder and psychotic episodes in relation to childbirth represent a distinctive subgroup with a less severe course of illness and a better psychosocial context. However, in our analyses the negative association between smoking and postpartum affective psychosis remained significant after adjusting for recruitment, disease severity, education and occupation, suggesting that, this is not the sole explanation for the association. It is still possible that there were other confounding psychosocial factors and clinical variables that we did not explore.

Another particularly intriguing hypothesis is that of a specific effect of smoking on the biological pathways involved in postpartum affective psychosis. Given the paradoxical protective effect of smoking on the risk of pre-eclampsia\textsuperscript{6}, it is possible that pre-eclampsia and postpartum affective psychosis share common disease pathways. Clinical\textsuperscript{21,22}, molecular/pharmacological\textsuperscript{23} studies have shown possible similarities between the pathogenesis of eclampsia and that of postpartum affective psychosis. The mechanisms underpinning the protective effect of smoking on pre-eclampsia, however, are still unknown. Possible explanations include alterations in the thromboxane A2 and nitric oxide metabolism or the suppression of the immune system\textsuperscript{6,24,25}. Interestingly, immune dysfunction has also been implicated in the pathogenesis of postpartum affective psychosis\textsuperscript{26}.

The specificity of the association between smoking and postpartum affective psychosis that did not extend to postpartum bipolar depression suggests that psychotic episodes occurring in the postpartum identify a distinctive subgroup of women with bipolar disorder. Childbirth may trigger separate disease pathways, leading to affective psychosis or to non-psychotic depression.

The hypothesis of a separate pathogenesis for postpartum affective psychosis and non-psychotic depression is consistent with our previous findings of a parity effect on affective psychosis, but not on non-psychotic bipolar depression. Despite the high prevalence in mothers with bipolar disorder\textsuperscript{2}, there is a paucity of information on risk factors for bipolar postpartum depression and further studies are needed to identify them. We hypothesise that bipolar postpartum psychosis and bipolar postpartum depression do not lie on a continuum of severity, but represent two distinct disease entities that may help identify two different subgroups of women with bipolar disorder. Recently it has been shown that peripartum risk of relapse differs in women with a history of affective psychosis limited to the postpartum period compared to those with episodes outside the childbirth period\textsuperscript{27}. In our sample, however, only 6 women had
episodes limited to the childbirth period and the median period of observation after the first episode in these women was 3 years, much lower than the 25 years period in the whole sample.

This study generates new hypotheses of a biological link between smoking and postpartum psychosis that need to be tested in further rigorous longitudinal studies. Research in this area needs to take into account the potential effect of many confounders and reporting bias. A possible cost-effective strategy to indirectly test the hypothesis of an immediate protective effect of smoking on postpartum psychosis is to analyse data from clinical controlled trials on the effectiveness of interventions for smoking cessation in pregnancy.

CONCLUSION
There is a strong, specific and inverse association between smoking and postpartum affective psychosis. Our findings open a new venue for research in the childbirth trigger of severe episodes of bipolar disorder.


