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Bipolar disorder and psychotropic medication: Impact on pregnancy and neonatal outcomes

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Abstract

Objective: The hypotheses were: (1) pregnant women with bipolar disorder (BD) have less favorable pregnancy outcomes than unaffected women, and (2) psychotropic treated women with BD have better outcomes than unmedicated women.

Method: This prospective study included 174 mother-infant dyads. Women had BD without psychotropic exposure (BD-NP, n = 38), BD with psychotropic treatment (BD-P, n = 49), or neither psychotropic exposure nor major mood disorder (Comp, n = 87). Maternal characteristics were completed at 20 weeks gestation and evaluated for associations with delivery and birth outcomes. We performed multiple regressions on infant outcomes with adjustment for maternal age, race, employment status, use of illicit drugs and pre-pregnancy BMI.

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Contributors

Dr. Katherine Wisner was the Principal Investigator who supervised all aspects of the investigation including administrative oversight, data collection, analysis and manuscript preparation and finalization.

Dr. Dorothy Sit was the study psychiatrist who performed the psychiatric assessments and ensured that good clinical practice principles were followed for the care of our subjects with bipolar disorder and reviewed drafts of the manuscript.

Ms. Kelly O'Shea assisted with the data synthesis and analysis and drafted portions of the paper for publication and reviewed drafts of the manuscript.

Dr. Debra L. Bogen was the pediatrician who directed the collection and interpretation of infant outcomes and reviewed drafts of the manuscript.

Dr. Crystal T. Clark assisted with data synthesis, assisted in data interpretation and critiqued drafts of the manuscript.

Ms. Emily Pinheiro was the coordinator for the team's input to organize the manuscript drafts critically and she worked closely with the statistics team to coordinate finalization of the paper and present statistical findings to the clinical team.

Ms. Amy Yang performed the overall statistical analysis under the supervision of Dr. Ciolino.

Dr. Jody Ciolino is the statistician supervisor for the manuscript and the statistical evaluation.

Conflicts of interest

Dr. Sit received donations of study light boxes from Uplift Technologies for a study of light therapy for bipolar depression. Drs. Wisner, Bogen, Clark and Ciolino and Ms. Pinheiro, O'Shea and Yang have no conflicts to disclose.

Results: The BP-P, BP-NP and Comp groups varied significantly on sociodemographic characteristics. Women with BD were more likely to be less educated, unemployed, single, and use tobacco and illicit drugs than women in the Comp group. Compared to women with BD-NP, women with BD-P were more likely to be older and educated.

Approximately 10% of all infants were delivered preterm. No significant differences in outcome occurred for APGAR scores < 8, NICU admissions, sex or infant length. Infants of mothers with BD-NP had significantly smaller head circumferences (HC) than the other groups, adjustment for confounding variables mitigated this association.

Conclusions: The overall pregnancy outcomes for women with BD were similar to those in the Comp group. The reduced HC in women with untreated BD appears due to factors related to disadvantaged sociodemographic status, a higher proportion of female births, and/or a protective effect of medication in the BD-P group.

Keywords

Pregnancy; Postpartum; Newborn; Perinatal psychiatry; Psychopharmacology

1. Introduction

Bipolar disorder (BD) is a serious psychiatric condition that affects 1–2% of people in the United States. Inclusion of the more broadly defined bipolar spectrum disorders raises the prevalence to between 3% and 6.5% (Angst, 1998). The median age of onset of BD is during late adolescence (19.4 years in the Stanley Foundation Bipolar Network) (Post et al., 2003); therefore, women are at risk for episodes during their childbearing years. Forty to 70% of women with BD will suffer recurrent episodes post-birth (Reich and Winokur, 1970; van Gent and Verhoeven, 1992; Wisner et al., 2004). Postpartum psychosis, which occurs in 1–2 per 1000 births, is a strongly associated with genetic and clinical manifestations of BD (Jones and Craddock, 2007; Chaudron and Pies, 2003; Wisner et al., 1995).

BD is a chronic disease and continuous medication administration is the mainstay of treatment (Grunze et al., 2013). However, many pregnant women choose to discontinue pharmacotherapy or have difficulty finding a clinician who is comfortable prescribing medication during pregnancy. Although the volume of information available to physicians who treat pregnant women with unipolar depression has increased steadily over the past decade, data to inform decisions about the treatment of BD has not advanced similarly (Yonkers et al., 2004).

Relatively few investigations of pregnancy outcomes for women with BD have been published. Rusner et al. (2016) conducted a systematic review, rather than a meta-analysis, because of the substantial heterogeneity in nine eligible publications. They reported that adverse obstetrical outcomes (such as gestational hypertension and hemorrhage) occurred more frequently in women with BD, who also had increased rates of labor induction and caesarean section. Women with BD were more likely to have very small for gestational age (< third percentile) newborns.

In a retrospective study of Western Australian women with mixed psychiatric diagnoses (BD, $n = 56$; schizophrenia, $n = 44$, non-psychotic serious mental illness = 38) who presented to an antenatal psychiatric clinic, Nguyen et al. (2013) reported that smoking and substance use were significantly greater than in the general obstetrical population. The women with mental illness were also more likely to experience pre-eclampsia and gestational diabetes and have newborns that were less likely to have APGAR scores 8.

In another Australian study, Jablensky et al. (2005) compared reproductive outcomes for women with BD ($n = 1301$ births) to women without a psychiatric diagnosis in ($n = 3,129$) in Australia with record linkage methodology. Women with BD were more likely to be unmarried, have a partner with unskilled employment and be multi-parous. They were significantly more likely to develop placenta previa, antepartum hemorrhage or other adverse effects due to the use of alcohol, tobacco and drugs of abuse compared to the non-psychiatrically ill group. However, no data on psychotropic exposure was presented.

In a Swedish population database study, Boden et al. (2012) investigated the risks of adverse pregnancy and birth outcomes for *both* treated ($n = 320$) and untreated ($n = 554$) pregnant women with BD. Treated pregnant women filled a prescription for lithium, anti-psychotics, or anticonvulsants. Women with BD were compared with all other women giving birth ($n = 331,263$). The major finding was that both groups of women with BD had an increased rate of planned cesarean delivery, preterm birth, and infants with microcephaly, small for gestational age status and neonatal hypoglycemia. The odds ratios (OR) varied from 1.8 to 2.1 and, importantly, the analyses of variance in outcomes did not reveal significant differences between treated and untreated women with BD, except that microcephaly remained more frequent in the *un-medicated* women with BD (OR 1.68; 95% CI 1.07 to 2.62).

A challenge in studies that evaluated the impact of medications upon reproductive outcomes is separating the effects of the disorder from that of the drugs. Psychotropic agents treat the symptoms of BD, but the disorder itself is associated with another set of exposures that also affect offspring development, such as maternal interpersonal, financial and legal problems and high-risk behaviors (Yonkers et al., 2004). Maternal decompensation can result in psychosis and attempted or completed suicide (Yonkers et al., 2004). Viguera et al. (2007) reported that the recurrence risk was 2.3 times greater after discontinuation of mood stabilizer treatment (53 of 62, 85.5%) than with continued treatment (10 of 27, 37.0%).

A method to differentiate the effects of drug versus disease exposure is to compare women who are psychotropic-treated versus those who are *un-medicated*. However, the demographic and disease characteristics of women who take medication differ from those who do not (Jablensky et al., 2005; Boden et al., 2012; Driscoll et al., 2017). These characteristics also affect reproductive outcomes and complicate the interpretation of the impact of the medication as a sole exposure. Another challenge is that multiple classes of medications are used to treat BD, and polypharmacy is common. Lithium, anticonvulsants, atypical antipsychotics, antidepressants, benzodiazepines and a variety of other agents are prescribed for pregnant women (Driscoll et al., 2017).

To complement the retrospective and database studies, we conducted a secondary analysis from a prospective observational study of pregnancy outcomes for women with BD. The aim of this investigation was to define maternal and infant outcomes in both psychotropic-treated and *un-medicated* women with BD compared to those of healthy pregnant women. Our hypotheses were: (1) pregnant women with BD will have less favorable outcomes than unaffected women, and (2) psychotropic treated women with BD will have better outcomes than untreated women with BD.

2. Patients and methods

2.1. Study subjects

Pregnant women participated in one of two prospective studies (Antidepressant Use during Pregnancy-ADUP, R01-MH60335; and Antimanic Use during Pregnancy-AMUP, R01-MH07592; Principal investigator: K.L.W.) funded by the National Institute of Mental Health. The two studies were identical except for the diagnosis of BD vs. uni-polar depression. Study participants were between the ages 18 and 44 years, English-speaking, and recruited in Pittsburgh, PA between July 2006 and March 2011. Recruitment methods included self-referral, physician and community health center referral and advertising.

Subjects were recruited from multiple sources: the greater Pittsburgh community, a rural regional medical center, and an academic perinatal specialty program.

Women were not eligible to participate if they were diagnosed with an active substance use disorder or were exposed to prescription drugs designated as category D or X by the U.S. Food and Drug Administration (FDA) at the time of enrollment. Although these FDA categories have been eliminated (U.S. Department of Health and Human Services, 2014), they were active during the period of study. The University of Pittsburgh Institutional Review Board approved the research protocol, and all women provided written informed consent.

For this analysis, women with BD (any subtype) were derived from AMUP. Healthy pregnant women were included from both the AMUP and ADUP studies. Women with singleton pregnancies were included. For women enrolled across multiple pregnancies, we included only the first pregnancy. We created three non-overlapping groups based on diagnosis and psychotropic medication exposure in our study population:

1. Bipolar Disorder with psychotropic treatment (BD-P; $N = 49$) — presence of BD and treatment with psychotropics during the entirety of pregnancy or for the majority of each of the three trimesters.
2. Bipolar Disorder with no psychotropic (BD-NP; $N = 38$) — presence of BD without psychotropic treatment at any point during pregnancy.
3. Comparison (Comp; $N = 87$) — no exposure to any psychotropic medication or to BD or a major mood disorder during pregnancy.

We used the broad category of psychotropic drug exposure because polypharmacy and frequent individual agent changes were common in this sample. The following exposures to

drugs within psychotropic classes occurred at some point in the pregnancies of the 49 women with BD-P: antidepressants ($N = 62$), antipsychotics ($N = 55$), anti-convulsants ($N = 28$), benzodiazepines ($N = 20$), lithium ($N = 13$), and other psychotropics ($N = 9$).

2.2. Assessments

Descriptive data for the study sample included baseline maternal mood assessments, demographic characteristics, smoking status, alcohol intake, parity, illicit substance use) at 20 weeks gestation. Pre-pregnancy body mass index (BMI) was calculated from the mother's pre-pregnancy weight and height. Depression severity was assessed with the 29-item Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (Williams and Terman, 2003) (SIGH-ADS). Functional measures included the Global Assessment Scale (GAS) from the Structured Clinical Interview for DSM-IV and the SF-12 Health Survey (Ware et al., 1996), which yields summary scores for the mental and physical components. Manic symptoms were evaluated with the Mania Rating Scale (MRS) derived from the Schedule for Affective Disorders and Schizophrenia Research Diagnostic Interview (Endicott and Spitzer, 1978). The MRS is a discrete measure with the distribution of scores heavily weighted toward zero because 5 of the 11 items on the scale require at least one other manic symptom to permit assigning a score other than zero.

Advanced practice nurses or obstetricians who were blind to maternal exposure group reviewed delivery records for maternal and infant outcomes including method of delivery, gestational age of newborn, birth weight, length, and head circumference, APGAR score at 5 min, admission to a neonatal intensive care unit (NICU), and neonatal complication signs on the infant subscale of the Peripartum Events Scale (PES) (O'Hara et al., 1986). The infant subscale of this measure includes 11 items (pH correction, volume expansion, transfusion/exchange transfusion, hypoglycemia, hyperbilirubinemia, hypocalcaemia, sepsis, meconium aspiration pneumonitis, other, other life-threatening, and given medications). Due to the relatively low occurrence of problems, the infant subscale was divided into 0 versus 1 problems for analysis. Similarly, maternal PES subscale scores representing past obstetric complications (i.e., preterm birth, hemorrhage) medical risk factors (i.e., diabetes, hypertension), obstetric risk factors (i.e., abnormal fetal presentation, fever) and delivery complications (i.e., hemorrhage, anesthesia complications) were totaled and dichotomized into 0 versus 1, again due to the low frequency of occurrence across all groups of women.

2.3. Statistical methods

Simple descriptive statistics (frequency and percent for categorical variables, mean and standard deviation for continuous variables) were used to summarize demographic characteristics and clinical measures. Pearson's Chi-Squared test was applied to assess associations between group and categorical measures. Fisher's Exact test was used when expected cell counts were less than 5 for a given cross tabulation. Continuous variables were compared across groups using one-way ANOVA for normally distributed data and Kruskal-Wallis tests when statistical assumptions (i.e., normality) were questionable. Post-hoc comparisons employed Benjamini and Hochberg corrections (Benjamini and Hochberg, 1995) for baseline health status and functioning scores that differed significantly between groups. We also performed multiple regressions on infant outcomes with adjustment for the

potential confounding effects of maternal age, race, employment status, use of illicit drugs and pre-pregnancy BMI. All analyses assumed a 5% level of significance and were performed using R: A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria, Version 3.3.2).

3. Results

3.1. Participant characteristics

The flow of the study sample is displayed in Fig. 1 and characteristics in Table 1. The overall group of women with BD were significantly less educated and more likely to be unemployed, single, and use tobacco and illicit drugs than women in the Comp group. Women with BD-P were significantly more likely to be older (mean age 28.5 ± 5.8 vs. 24.6 ± 5.5 years) and more highly educated than women with BD-NP. Across all three groups, 21.5% of women reported alcohol use.

Women in the BD-P group tended to have a higher pre-pregnancy BMI than women in the Comp and BD-NP groups, although the difference was not statistically significant. Parity was similar in the three groups. Women did not significantly differ with respect to obstetric risk factors across the three groups; however, general medical problems were more prominent in the BD-P (65.3%) versus the Comp (41.4%, $p = 0.037$) and BD-NP (44.7%, $p = 0.134$) groups. Specifically, hypertension affected 8.2% of women in the BD-P group compared with 1.2% of the Comp and none in the BD-NP groups, respectively (overall p -value = 0.049; pairwise comparisons were not significant).

The completion of the PES outcome measure was achieved in 65% of women. Due to this relatively high rate of missing data, we compared the women's demographics for those with missing compared to completed PES data. Women with missing PES data had a significantly higher level of education ($p = 0.04$) and a lower rate of reported alcohol use ($p = 0.039$). This finding suggests that women with relatively more risk factors were included in the results compared to the overall sample enrolled, which is encouraging because of the generally positive outcomes observed even in this subset. Women in Comp group had a significantly lower rate of missing data (20%) than women in the BD-P (47%) or the BD-NP (41%) groups; however, the PES completion rates of BD groups did not differ from each other.

3.2. Health and functional status

As expected, women in the Comp group had significantly lower depressive symptom levels, higher functional status, better physical and mental health and fewer symptoms of hypomania than either group of women with BD (Table 2). However, the mean symptom levels between groups of women with BD did not differ significantly for any symptom scores, although the BD-P group tended to endorse poorer mental health on the SF-12 ($p = 0.060$) (Table 3).

3.3. Pregnancy outcomes

The gestational age at delivery and method of delivery were similar across the three groups of women. Approximately 10% of the infants were delivered preterm overall, and the proportions of late (34–37 weeks) and early (< 34 weeks) preterm births were similar across groups.

No significant differences in outcomes occurred across the three groups for APGAR scores < 8, NICU admissions, sex or infant length. Although the frequency of neonatal signs did not significantly differ, more than twice as many newborns of mothers with BD-P (16.3%) had neonatal signs versus infants of mothers from the Comp (6.9%) and BDNP (5.3%) groups.

Infants of mothers in the BD-NP group had significantly smaller HC than the other two groups (post-hoc comparison p -values = 0.05 for both when compared to the Comp and BD-P groups). According to the World Health Organization (World Health Organization. 2018), the average HC at term birth is 34.2 cm. The mean HC in our Comp and BDP groups were 34.5 and 34.6 cm, respectively; however, the mean HC of infants in the BD-NP group was 1 cm less at 33.5 cm. The HC in this group was also more variable (standard deviation = 2.1 in BD-NP versus 1.8 and 1.6 in Comp and BD-P, respectively). Mean newborn length did not differ between BD-NP and the other two groups. Mean birthweight did not significantly differ ($p = 0.079$), but tended to be lower in the BD-NP group (3230 ± 610 g) than the BD-P (3304 ± 560 g) or the Comp (3487 ± 592 g) groups. However, none of the infant outcomes remained significantly different across the three groups in the multiple regression models adjusting for the potential confounding effects of maternal age, race, employment status, use of illicit drugs and pre-pregnancy BMI.

4. Discussion

Similar to previous studies, we found that the three groups of pregnant women varied with respect to sociodemographic characteristics. Women with BD, whether medicated or not, were significantly more likely to be single, unemployed and to use tobacco and illicit drugs than women in the Comp group. Comparing women in the BD-P to the BD-NP group, the former were more often white, older, and more educated; however, they also had more medical comorbidity and rated their mental health more poorly than women in the BD-NP group. These findings suggest that two factors (more resources with access to mental health care and greater severity of disease) contributed to engaging in pharmacotherapy during pregnancy in women with BD. These observations create challenges in attempting to disentangle the effect of medication and disease exposure, which is an issue inherent in non-randomized observational studies (Bosco et al., 2010).

Overall, the maternal and infant outcomes were comparable to general population data across the sample. Similar to the national average (Center for Disease Control and Prevention, 2018), approximately 10% of the infants in all groups were delivered preterm. Our first hypothesis, pregnant women with BD would have less favorable outcomes than women in the Comp group, was true in this sample only for the subgroup of non-psychotropic-treated women with BD. The second hypothesis, women with BD-P would

have better outcomes than women with BD-NP, was supported for a significantly higher mean HC and a trend toward higher mean birthweight. Our finding of a 1 cm smaller mean HC of infants from the maternal *un-medicated* BD group is consistent with previous studies (Jablensky et al., 2005; Boden et al., 2012). Head growth, a measure of fetal brain development (Harris, 2015), was affected more than length and weight in the off-spring of women with BD-NP in this sample. Application of multiple regression models adjusting for maternal age, race, employment status, illicit drug use and pre-pregnancy BMI resulted in non-significant differences between the Comp and both BD group for all infant outcomes. The interpretation is that the less optimal demographic and clinical characteristics in the BD-NP group appear to be driving the association between adverse outcomes in *un-medicated* women with BD compared to women with BD-P. Similar to our findings, Boden et al. (2012) also reported that infants of mothers with untreated BD had newborns with significantly smaller HC compared to those with treated disorder (adjusted OR = 1.68, 1.07–2.62). In the same study, the HC of infants born to women with psychotropic-treated BD compared to healthy women did not significantly differ. Birthweight and length also did not significantly differ after adjustment, which suggests a specific effect on fetal head growth rather than a reduction in body growth, in nonpsychotropic treated women with BD, similarly due to less optimal sociodemographic characteristics as in our study.

This collection of studies demonstrate that non-psychotropic treated women with BD comprise a high-risk obstetrical population with a specific risk for giving birth to newborns with smaller HC. Infants born to women with BD-P had comparable HC to infants born to women in the Comp group although their mothers had more medical comorbidity (including hypertension) during pregnancy. One explanation is that favorable factors associated with pharmacotherapy such as older maternal age, higher educational status and additional health professional contact during pregnancy act to reduce the effects of BD on head growth. Another possibility is that the rate of male births differs between groups (Comp 61.4%, BD-P 50%, BD-NP 42.9%). Although the difference is not significant, the average HC of males is about 1 cm. larger than females; therefore, the mean will be higher in groups with more male infants, such as the Comp group in this sample.

However, this reasoning does not clarify why HC was affected to a greater degree than birth weight or length. Another possibility is that pharmacotherapy has a direct role in improving outcomes. Psychotropic drugs act to decrease the effects of stress by reducing symptoms of anxiety and depression. Although the depressive and manic symptom levels did not differ between women with BD-P and BD-NP, women with BD-P had more severe disease which was likely controlled to some extent by pharmacotherapy. Substantial life stress during pregnancy exposes the fetus to maternal hypothalamic-pituitary-adrenal axis (HPA) hormone activation, which is associated with less favorable growth outcomes, and in particular smaller HC (Lou et al., 1994), especially if the stress is elevated in mid- to late- pregnancy (Henrichs et al., 2010). Antipsychotic treatment may regulate the HPA axis and immune system through pharmacological action via Dopamine receptor D2 antagonism. Handley et al. (2016) found that the anti-psychotic drug haloperidol significantly lowered cortisol, the inflammatory marker interleukin-6 levels and hippocampal resting cerebral blood flow compared to placebo treatment.

Although non-significant, the observation that more than twice as many newborns of mothers with BD-P had neonatal signs versus infants in the other two groups suggests that exposure to psychotropic medications may affect the adaptation of newborns (Sadowski et al., 2013), similar to the increase in neonatal adaptation signs associated with SSRI antidepressants (Moses-Kolko et al., 2005).

The strengths of this study include prospective assessment of the women in three groups (BD-P, BD-NP, and no exposure to BD or P), blinded review of maternal and neonatal status by obstetrically trained clinicians, exclusion of women with exposure (at baseline) to illicit substances through urine drug screen and focused interview. Limitations are the relatively small sample size inherent in prospective studies compared to large-scale database investigations. Broadly inclusive psychotropic exposure, as opposed to specific drugs, was utilized due to the complex regimens and polypharmacy inherent in treating BD. The difficulty in studying this population of psychiatrically ill pregnant women is reflected in the 34.5% loss to follow-up and the lack of other published prospective studies.

In summary, psychotropic drug treatment did not significantly increase the risk for adverse pregnancy and birth outcomes in women with BD after adjustment for confounding factors. Maternal socio-demographic factors and behavioral factors associated with non psychotropic treated status of women with BD were the drivers for the occurrence adverse outcomes in this sample, as was also concluded by Jablensky et al. (2005). The finding of reduced HC compels mechanistic investigation because microcephaly predicts reduced brain growth, particularly forebrain development, which is associated with reduced cognitive achievement (McElrath et al., 2010). Elucidation of the factor (s) influencing fetal head growth offers the potential to develop focused interventions to protect it.

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References

- Angst J, 1998 The emerging epidemiology of hypomania and bipolar II disorder. *J. Affect. Disord* 50 (2–3), 143–151. [PubMed: 9858074]
- Post RM, et al., 2003 A re-evaluation of the role of antidepressants in the treatment of bipolar depression: data from the Stanley Foundation Bipolar Network. *Bipolar Disord.* 5 (6), 396–406. [PubMed: 14636363]
- Reich T, Winokur G, 1970 Postpartum psychoses in patients with manic depressive disease. *J. Nerv. Ment. Dis* 151 (1), 60–68. [PubMed: 5426650]
- van Gent EM, Verhoeven WM, 1992 Bipolar illness, lithium prophylaxis, and pregnancy. *Pharmacopsychiatry* 25 (4), 187–191. [PubMed: 1528958]
- Wisner KL, et al., 2004 Prevention of postpartum episodes in women with bipolar disorder. *Biol. Psychiatry* 56 (8), 592–596. [PubMed: 15476689]

- Jones I, Craddock N, 2007 Searching for the puerperal trigger: molecular genetic studies of bipolar affective puerperal psychosis. *Psychopharmacol. Bull* 40 (2), 115–128. [PubMed: 17514190]
- Chaudron LH, Pies RW, 2003 The relationship between postpartum psychosis and bipolar disorder: a review. *J Clin Psychiatry* 64 (11), 1284–1292. [PubMed: 14658941]
- Wisner KL, Peindl KS, Hanusa BH, 1995 Psychiatric episodes in women with young children. *J Affect Disord* 34 (1), 1–11. [PubMed: 7622734]
- Grunze H, et al., 2013 The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. *World J. Biol. Psychiatry* 14 (3), 154–219. [PubMed: 23480132]
- Yonkers KA, et al., 2004 Management of bipolar disorder during pregnancy and the postpartum period. *Am. J. Psychiatry* 161 (4), 608–620. [PubMed: 15056503]
- Rusner M, Berg M, Begley C, 2016 Bipolar disorder in pregnancy and childbirth: a systematic review of outcomes. *BMC Pregnancy Childbirth* 16 (1), 331. [PubMed: 27793111]
- Nguyen TN, et al., 2013 Obstetric and neonatal outcomes of pregnant women with severe mental illness at a specialist antenatal clinic. *Med. J. Aust* 199 (3 Suppl), S26–S29.
- Jablensky AV, et al., 2005 Pregnancy, delivery, and neonatal complications in a population cohort of women with schizophrenia and major affective disorders. *Am. J. Psychiatry* 162 (1), 79–91. [PubMed: 15625205]
- Boden R, et al., 2012 Risks of adverse pregnancy and birth outcomes in women treated or not treated with mood stabilisers for bipolar disorder: population based cohort study. *BMJ* 8 (345).
- Viguera AC, et al., 2007 Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. *Am. J. Psychiatry* 164 (12), 1817–1824 quiz 1923. [PubMed: 18056236]
- Driscoll KE, et al., 2017 Mood symptoms in pregnant and postpartum women with bipolar disorder: a naturalistic study. *Bipolar Disord.* 19 (4), 295–304. [PubMed: 28665044]
- U.S. Department of Health and Human Services, 2014 U.S.F.D.A. Pregnancy and Lactation Labeling (Drugs) Final Rule. Available from: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>.
- Williams JBW, Terman M, 2003 Structured Interview Guide For the Hamilton Depression Rating Scale With Atypical Depression Supplement (SIGH-ADS). New York State Psychiatric Institute, New York.
- Ware J Jr., Kosinski M, Keller SD, 1996 A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med. Care* 34 (3), 220–233. [PubMed: 8628042]
- Endicott J, Spitzer RL, 1978 A diagnostic interview: the schedule for affective disorders and schizophrenia. *Arch. Gen. Psychiatry* 35 (7), 837–844. [PubMed: 678037]
- O'Hara M, Varner M, Johnson S, 1986 Assessing stressful life events associated with childbearing: the peripartum events scale. *J. Reprod. Infant. Psychol* 4 (1–2), 85–98.
- Benjamini Y, Hochberg Y, 1995 Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. R. Stat. Soc. B* 57 (1), 289–300.
- World Health Organization, 2018 Child growth standards. Available from: http://www.who.int/childgrowth/standards/hc_for_age/en/.
- Bosco JL, et al., 2010 A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. *J. Clin. Epidemiol* 63 (1), 64–74. [PubMed: 19457638]
- Center for Disease Control and Prevention, 2018 Reproductive health: maternal and infant health: Preterm birth. Available from: <https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm>.
- Harris SR, 2015 Measuring head circumference: Update on infant microcephaly. *Can. Fam. Phys* 61 (8), 680–684.
- Lou HC, et al., 1994 Prenatal stressors of human life affect fetal brain development. *Dev. Med. Child. Neurol* 36 (9), 826–832. [PubMed: 7926332]
- Henrichs J, et al., 2010 Maternal psychological distress and fetal growth trajectories: the Generation R Study. *Psychol. Med* 40 (4), 633–643. [PubMed: 19656431]

- Handley R, et al., 2016 Effects of antipsychotics on cortisol, interleukin-6 and hippo-campal perfusion in healthy volunteers. *Schizophr. Res* 174 (1–3), 99–105. [PubMed: 27112637]
- Sadowski A, et al., 2013 Pregnancy outcomes following maternal exposure to second-generation antipsychotics given with other psychotropic drugs: a cohort study. *BMJ Open* 3 (7).
- Moses-Kolko EL, et al., 2005 Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. *JAMA* 293 (19), 2372–2383. [PubMed: 15900008]
- McElrath TF, et al., 2010 Factors associated with small head circumference at birth among infants born before the 28th week. *Am. J. Obstet. Gynecol* 203 (2), 138 e1–8. [PubMed: 20541727]

Fig. 1.

Study subject flow ADUP = Antidepressant Use during Pregnancy AMUP = Antimanic Use During Pregnancy BD-P = Bipolar Disorder with Psychotropic Treatment BD-NP = Bipolar Disorder without Psychotropic Treatment Comp = Unmedicated Women without Bipolar Disorder.

Characteristics of pregnant women in study of effects of psychotropic medications on pregnancy and neonatal outcomes.

Table 1

Characteristic	Total (N = 174)	Comparison (N = 87)	Bipolar with Psychotropic (N = 49)	Bipolar without Psychotropic (N = 38)	p-value	Group1 vs Group2	Group1 vs Group3	Group2 vs Group3
Age	28.1 (5.9)	29.3 (5.7)	28.5 (5.8)	24.6 (5.5)	< 0.001	0.690	< 0.001	0.005
Race					0.248			
White	124 (71.3%)	65 (74.7%)	37 (75.5%)	22 (57.9%)				
Black	42 (24.1%)	19 (21.8%)	9 (18.4%)	14 (36.8%)				
Other	8 (4.6%)	3 (3.5%)	3 (6.1%)	2 (5.3%)				
Hispanic	2 (1.32%)	1 (1.16%)	1 (2.94%)	0 (0.00%)	0.677			
Education level					< 0.001	< 0.001	< 0.001	< 0.016
< High school	18 (10.3%)	6 (6.9%)	3 (6.1%)	9 (23.7%)				
High school	35 (20.1%)	16 (18.4%)	7 (14.3%)	12 (31.6%)				
Some college	47 (27.0%)	7 (8.1%)	27 (55.1%)	13 (34.2%)				
College	44 (25.3%)	33 (37.9%)	8 (16.3%)	3 (7.9%)				
Graduate school	30 (17.2%)	25 (28.7%)	4 (8.2%)	1 (2.6%)				
Employed	87 (51.5%)	62 (72.1%)	16 (34.8%)	9 (24.3%)	< 0.001	< 0.001	< 0.001	0.429
Marital status					< 0.001	< 0.001	< 0.001	0.215
Single	72 (41.4%)	21 (24.1%)	25 (51.0%)	26 (68.4%)				
Married/cohabitating	95 (54.6%)	63 (72.4%)	20 (40.8%)	12 (31.6%)				
Divorced/separated	6 (3.5%)	3 (3.5%)	3 (6.1%)	0 (0.0%)				
Widowed	1 (0.6%)	0 (0.0%)	1 (2.0%)	0 (0.0%)				
Smoked tobacco	39 (22.7%)	7 (8.1%)	16 (34.0%)	16 (42.1%)	< 0.001	< 0.001	< 0.001	0.591
Drank alcohol	37 (21.5%)	21 (24.1%)	8 (17.0%)	8 (21.1%)	0.631			
Used illicit drugs	27 (15.8%)	4 (4.6%)	12 (26.1%)	11 (28.9%)	< 0.001	< 0.001	< 0.001	0.963
Weeks of gestation					0.989			
< 34 weeks	5 (2.8%)	3 (3.5%)	1 (2.0%)	1 (2.6%)				
34–37 weeks	12 (6.9%)	6 (6.9%)	4 (8.2%)	2 (5.3%)				
> = 37 weeks	157 (90.2%)	78 (89.7%)	44 (89.8%)	35 (92.1%)				
Parity					0.218			
1	64 (37.9%)	37 (43.0%)	16 (33.3%)	11 (31.4%)				

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Characteristic	Total (N = 174)	Comparison (N = 87)	Bipolar with Psychotropic (N = 49)	Bipolar without Psychotropic (N = 38)	p-value	Group1 vs Group2	Group1 vs Group3	Group2 vs Group3
2	60 (35.5%)	32 (37.2%)	14 (29.2%)	14 (40.0%)				
3 +	45 (26.6%)	17 (19.8%)	18 (37.5%)	10 (28.6%)				
Method of delivery					0.940			
Caesarean	43 (24.7%)	21 (24.1%)	13 (26.5%)	9 (23.7%)				
Vaginal	131 (75.3%)	66 (75.9%)	36 (73.5%)	29 (76.3%)				

Relation of Maternal Pre-pregnancy Body Mass Index (BMI), Infant and Maternal Outcomes to Mother's Exposure to Psychotropic Medications during Pregnancy.

Table 2

Characteristic	Total (N = 174)	Comparison (N = 87)	Bipolar with Psychotropic (N = 49)	Bipolar without Psychotropic (N = 38)	p-value
Pre-pregnancy BMI	26.6 (6.4)	25.8 (5.8)	28.4 (6.9)	26.2 (6.7)	0.088
Pre-pregnancy BMI 30 +	40 (25.8%)	15 (18.3%)	16 (37.2%)	9 (30.0%)	0.060
Five-minute Apgar < 8	2 (1.2%)	2 (2.3%)	0 (0.0%)	0 (0.0%)	0.717
NICU	12 (6.9%)	7 (8.1%)	2 (4.1%)	3 (7.9%)	0.729
Baby gender					0.166
Female	70 (46.4%)	27 (38.6%)	23 (50.0%)	20 (57.1%)	
Male	81 (53.6%)	43 (61.4%)	23 (50.0%)	15 (42.9%)	
Infant outcome signs	16 (9.2%)	6 (6.9%)	8 (16.3%)	2 (5.3%)	0.150
Length cm	50.5 (3.2)	51.0 (3.1)	50.0 (3.1)	50.4 (3.7)	0.309
Weight gm	3373 (593)	3487 (592)	3304 (560)	3230 (610)	0.079
Head circumference cm [£]	34.3 (1.9)	34.5 (1.8)	34.6 (1.6)	33.5 (2.1)	0.036
Past obstetric history	47 (27.0%)	26 (29.9%)	10 (20.4%)	11 (28.9%)	0.468
Medical risk factors [£]	85 (48.9%)	36 (41.4%)	32 (65.3%)	17 (44.7%)	0.023
Obstetric risk factors	81 (46.6%)	42 (48.3%)	24 (49.0%)	15 (39.5%)	0.611
Indication for admission to labor and delivery	130 (74.7%)	63 (72.4%)	38 (77.6%)	29 (76.3%)	0.777
Delivery complications	44 (25.3%)	20 (23.0%)	11 (22.4%)	13 (34.2%)	0.358

[£] Significant at alpha = 0.05 level. Pairwise comparison results were described in the results section.

Table 3

Baseline health status and functioning of women with or without exposure to psychotropic medications and bipolar disorder during pregnancy.

Measures	Total (N = 174)	Comparison (N = 87)	Bipolar with psychotropic (N = 49)	Bipolar without psychotropic (N = 38)	p-value	Group1 vs Group2	Group1 vs Group3	Group2 vs Group3
GAS	76.9 (15.3)	88.6 (7.45)	63.0 (10.3)	65.0 (11.0)	< 0.001	< 0.001	< 0.001	0.590
MRS > 0⁺	34 (21.0%)	8 (9.41%)	11 (26.2%)	15 (42.9%)	< 0.001	0.039	< 0.001	0.194
SF12 Mental	47.2 (13.4)	55.5 (5.91)	34.1 (13.9)	39.6 (11.3)	< 0.001	< 0.001	< 0.001	0.060
SF12 Physical	48.4 (9.3)	51.6 (7.0)	46.3 (11.1)	42.5 (9.1)	< 0.001	0.010	< 0.001	0.166
SIGH-ADS-29	12.3 (8.7)	6.27 (3.3)	18.8 (9.0)	18.7 (7.2)	< 0.001	< 0.001	< 0.001	0.997
HAM-d-17	7.52 (6.3)	3.25 (2.2)	12.3 (6.7)	11.9 (5.4)	< 0.001	< 0.001	< 0.001	0.925

⁺ An extremely non-normal distribution required dichotomization for modeling.