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Research paper

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.

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.

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).

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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 multiparous. 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, antipsychotics, 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. unipolar 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 ($N = 55$), anticonvulsants ($N = 28$), 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