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Obstetrical and neonatal outcomes after benzodiazepine exposure during pregnancy: Results from a prospective registry of women with psychiatric disorders

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ABSTRACT

Objective: The goal of this analysis was to examine the effect of benzodiazepine use during pregnancy on maternal and neonatal outcomes in a cohort of women with psychiatric disorders.
Methods: 794 evaluable women from the Massachusetts General Hospital National Pregnancy Registry for Psychiatric Medications were followed across pregnancy ($N = 144$ exposed to benzodiazepines and $N = 650$ unexposed). Data obtained through maternal report and medical records included maternal outcomes (cesarean section, preeclampsia) and neonatal outcomes (birth weight, breathing difficulty, feeding difficulty, head circumference, 5-minute Apgar score, muscular and/or extrapyramidal symptoms, NICU admission, prematurity).
Results: In adjusted analyses, infants exposed to benzodiazepines *in utero* were more likely to be admitted to the NICU (OR: 2.02, 95% CI: 1.11, 3.66) and to have small head circumferences (OR: 3.89, 95% CI: 1.25, 12.03) compared to unexposed infants. Other neonatal adverse effects such as respiratory distress or muscular symptoms including hypotonia were not observed. There were no significant differences in adverse obstetrical outcomes.
Conclusions: Infants exposed to benzodiazepines during pregnancy had an increased risk of NICU admissions and small head circumferences. Confounding from psychiatric symptoms and other variables cannot be ruled out as contributors to these findings.

1. Introduction

It is estimated that 33.3% of women will meet criteria for an anxiety disorder during their lifetimes, a rate 50–80% higher that of men [1–4]. Importantly, women during the reproductive years are at risk for anxiety disorders, and the prevalence during pregnancy is notable, making treatment considerations for the mother and baby of great clinical consideration. Studies demonstrate that > 10% of women experience symptoms of anxiety during pregnancy, particularly during the first trimester [5,6].

Prior studies indicate that anxiety symptoms during pregnancy may impact both the mother and the fetus. Adverse effects may include appetite and sleep disruption, increased risk of substance abuse, and increased risk of postpartum depression and anxiety [6–10]. Furthermore, research has shown that exposure to maternal anxiety may increase the risk of adverse neonatal outcomes including low birth weight [11–13], preterm birth [11,14,15], and low Apgar scores [16] as well as obstetric complications such as cesarean section delivery [13] and preeclampsia [17]. However, results have been conflicting or imprecise [16,18–21].

Benzodiazepines are commonly used to treat anxiety disorders, anxiety symptoms in the context of other psychiatric disorders, seizures, and insomnia. The effects of benzodiazepines are mediated through the neurotransmitter gamma-aminobutyric acid (GABA) in the central nervous system. One recent study found that 3.9% of American women with private insurance used a benzodiazepine during pregnancy [22]. In the past few decades numerous concerns have been raised regarding exposure to benzodiazepines across pregnancy [21,23,24]. Early case reports and case series suggested a relationship between maternal benzodiazepine use proximal to delivery and increased risk of neonatal outcomes including apnea and hypotonia [25–28]. Studies using the Swedish Medical Birth Register have found at least a 38%

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increased risk of having an infant with neonatal outcomes such as preterm birth, low birth weight, respiratory distress, hypoglycemia, CNS diagnosis, and low Apgar scores among women who filled a prescription for a benzodiazepine during the second or third trimester of pregnancy [29,30]. The Omega Study, a prospective cohort of women attending prenatal care clinics in Washington State, found at least a 3-fold increase in the risk of preterm birth, low birth weight, low Apgar scores, admission to the Neonatal Intensive Care Unit (NICU), and respiratory distress after exposure [31]. A limited number of studies, however, have controlled for indication in their assessment of neonatal outcomes related to use of benzodiazepines, raising the question of the impact of underlying illness on maternal and infant findings presented above. Recently, Yonkers et al. (2017) sought to disentangle the risks of benzodiazepine use and psychiatric indications of panic disorder and generalized anxiety disorder in a cohort study, and did not find increased risks of obstetrical or neonatal complications associated with the anxiety disorders, but did observe an increased risk of C-section, low birth weight, and need for ventilatory support in the neonatal period associated with antenatal benzodiazepine use. [21] However, the impact of confounding variables, such as comorbid disorders and severity of illness, remains difficult to ascertain in the limited number of studies that have included control groups with psychiatric illness.

Rigorous data regarding the safety of benzodiazepines during pregnancy remain relatively sparse. The goal of this analysis was to examine the impact of benzodiazepine use during pregnancy with respect to neonatal and obstetrical outcomes among a population of women with serious psychiatric illnesses using data collected prospectively from the National Pregnancy Registry for Psychiatric Medications. The use of prospectively gathered data from this registry allows for the examination of outcomes associated with benzodiazepines using an appropriate comparison group of women with serious psychiatric disorders.

2. Materials and methods

The Massachusetts General Hospital National Pregnancy Registry for Psychiatric Medications (NPRPM) is a prospective cohort study that remotely follows pregnant women with histories of psychiatric morbidity who are exposed and unexposed to psychiatric medications during pregnancy. The analyses presented here were based on data from participants who were followed between November 14, 2008 and March 19, 2018 ($N = 1231$). The study protocol is approved through the Massachusetts General Hospital Institutional Review Board. Participants in the NPRPM give verbal informed consent at the time of the initial phone call after all procedures have been explained and immediately prior to the baseline interview. All subjects are sent a copy of the phone consent document. Written consent is obtained prior to procurement of maternal and pediatric medical records.

Details of the methodology for this Registry have been published elsewhere [32]. Briefly, subjects are recruited primarily through consultations at the MGH Center for Women's Mental Health and external healthcare provider referral. All pregnant women are eligible for inclusion in the Registry if they are 18–45 years old. The primary aim of the Registry is to quantify the reproductive safety of psychiatric medications. Manufacturers of psychiatric medications provided support for the NPRPM; however, this research was conducted independently by the researchers at Massachusetts General Hospital.

Medication exposure and obstetric and neonatal outcome data were obtained through maternal report and medical record review. Participants were interviewed at three time points during the study: at enrollment, seven months of pregnancy, and 3 months postpartum. Women were asked to report detailed medication usage information at each interview, including all medications taken, dose, and the timing of use across pregnancy. Participants were also asked to authorize release of obstetric, labor and delivery, and newborn pediatric medical records following delivery. Trained research coordinators used a standard neonatal/maternal outcome report form to abstract information, a process which was then repeated by a senior study investigator.

Exposure for these analyses was defined as participant report of any use of a benzodiazepine anytime during pregnancy. For secondary analyses of outcome prevalence rates by trimester, exposure was defined as use 1) during the first trimester only 2) during the second and/or third trimester only and 3) across the full pregnancy (first trimester plus second or third trimester). Benzodiazepines studied include alprazolam, clonazepam, diazepam, lorazepam, and temazepam. The comparison group includes women who remained unexposed to benzodiazepines during the full pregnancy.

A number of maternal and neonatal outcomes were examined in relation to benzodiazepine use. The outcomes were collected as part of a standard outcome report form used in the Registry. The maternal outcomes assessed were cesarean section delivery and preeclampsia. Neonatal outcomes include birth weight, breathing difficulty, feeding difficulty, small head circumference, low 5-minute Apgar score, muscular extrapyramidal symptoms, NICU admissions, and prematurity. Outcome information was obtained through maternal report and medical record review. The medical record was considered the gold standard and used as the primary source of the outcomes. Agreement between medical records and maternal report was assessed. When kappa values for agreement were above 0.7, maternal report was considered an adequate substitute for missing medical record information.

All outcomes were examined as binary yes/no variables. Low birth weight was defined as an infant born weighing < 2500 g. High birth weight was defined as birth weight > 4000 g. Small head circumference was defined as head size at birth less than the 3rd percentile on the CDC growth chart [33]. Low Apgar scores were those < 7 at 5 min. Prematurity was defined as gestational length < 37 weeks. NICU admissions, cesarean section and preeclampsia were collected and analyzed as yes/no.

Breathing difficulty, feeding difficulty, and muscle symptoms were only assessed in the medical records and were defined based on FDA extrapyramidal symptom criteria from 0 to 1 month of life [34]. Infants were considered to have difficulty breathing when the medical records contained notation of breathing related procedures or if they experienced breathing related issues such as respiratory distress, tachypnea, apnea, or persistent pulmonary hypertension. Difficulty feeding was defined by record of conditions such as acid reflux or gastroesophageal reflux disease (GERD), procedures such as nasogastric intubation, or notation of “feeding problems in the newborn.” An infant met criteria for abnormal muscle movements if they had abnormally increased or decreased muscle tone (hypertonia/hypotonia), acute dystonic reactions (muscle spasms of the neck, eyes, tongue or jaw, or torticollis), akathisia or motor restlessness, or akinesia or sluggish reflexes.

A number of binary and continuous covariates were examined. Covariates were provided by maternal report and were measured before or concurrently with benzodiazepine use and before the outcomes occurred. All predictors were analyzed as displayed in Table 1. The chronicity of illness was calculated as the difference between the participant's current age and age at first symptoms onset divided by the participant's current age.

2.1. Data analyses

All analyses were completed using STATA/SE version 14.2. Chi-squared tests with one degree of freedom were used to compare outcome prevalence between the exposed and unexposed groups. When any cell size was < 5, two-tailed Fisher's Exact tests with one degree of freedom were used.

Crude and adjusted logistic regression models were used to examine the relationship between any use of a benzodiazepine during pregnancy and the outcomes of interest. To adjust for confounding, a propensity score predicting exposure (any benzodiazepine use) was created using hypothesized confounders selected *a priori*. Maternal age, diagnosis of