Antiemetic medications in pregnancy: a prospective investigation of obstetric and neurobehavioral outcomes

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OBJECTIVE: The study goal was to examine the impact of commonly prescribed antiemetic medications in pregnancy on neurobehavioral and obstetric outcomes.

STUDY DESIGN: Five hundred thirty-three women accounting for 550 live births (17 multiple gestations) enrolled before 16 weeks' gestation participating in an observational longitudinal study of stress and pharmacologic exposure in pregnancy at Emory Women's Mental Health Program were included in this study. Maternal report of exposure to medications was documented by weeks of use. Obstetric and neonatal data were obtained from medical records. The Neonatal Behavioral Assessment Scale was completed by certified raters at age 7 days. The Child Behavior Checklist (CBCL) was completed by the mother between 17 and 66 months of age. Comparison of groups was conducted using χ^2 and Wilcoxon rank-sum tests. Spearman correlation analysis was used for CBCL percentile scores to evaluate duration of exposure.

RESULTS: The exposed group (n = 143) was comprised of children whose mothers received promethazine or ondansetron during pregnancy. Unexposed children (n = 407) were used for comparison. Neonatal Behavioral Assessment Scale data 7 days (range, 2–77) was available on 345 infants (exposed n = 102; unexposed n = 243), and a total of 247 CBCLs (exposed n = 51; unexposed n = 196) at 29 (range, 17–66) months of age. No significant differences were seen using Neonatal Behavioral Assessment Scale and CBCL. Statistically significant differences were seen in gestational age at delivery (0.3 weeks) and birthweight (110 g).

CONCLUSION: No clinically significant adverse neurobehavioral effects or obstetric outcomes were identified. This is reassuring as promethazine and ondansetron are commonly prescribed during pregnancy.

Key words: antiemetics, neurobehavior, ondansetron, promethazine

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Nausea and vomiting is a common problem occurring in up to 70-85% of all pregnancies.[1,2] Pharmacotherapy with antiemetic medication is used for these symptoms in approximately 10-15% of such pregnancies.[3,4] The most commonly prescribed antiemetics include promethazine and ondansetron.

Promethazine, a neuroleptic medication belonging to the phenothiazine family, has been used for decades as an antiemetic in pregnancy. It is a potent antihistamine that also acts as an antagonist at both serotonergic (5-HT_{2A}, 5-HT_{2C})[5] and dopaminergic receptors (D_2).[6] Promethazine is considered a weak antipsychotic, but tardive dyskinesia has been reported. Ondansetron is a centrally acting serotonin antagonist that binds the 5-HT_3 receptors[7] that was initially used as an antiemetic for patients receiving chemotherapy. It has also been used as a psychotropic agent, as an adjunct to haloperidol in patients with schizophrenia[8] and to treat psychotic symptoms in patients with advanced Parkinson's Disease.[9] Given this evidence that both promethazine and ondansetron may possess antipsychotic efficacy, albeit limited, it is perhaps relevant that our group recently found that prenatal exposure to several antipsychotic medications was associated with impaired neurobehavioral development at 6 months of age.[10] There is limited neurobehavioral data on the potential impact of prenatal exposure to

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antiemetic medications, such as promethazine and ondansetron.

Previous studies have focused on the potential teratogenicity of these medications. Only 2 studies have examined the neurologic effects of promethazine exposure in pregnancy on offspring. It is reassuring that both investigations did not identify any adverse effects. The first study used an existing database, the authors identified 32 mothers who attempted suicide by overdose with promethazine.[11] The second study used longitudinal follow-up to evaluate the child behavior in 127 offspring and reported no adverse somatic effects.[12] A recently published review of 1849 women treated with ondansetron did not reveal an increase in adverse pregnancy outcomes, but offspring neurobehavioral aspect was not evaluated.[13]

The primary aim of the current study was to examine the impact of in utero exposure to promethazine and ondansetron in a well characterized cohort of women followed throughout pregnancy.

Methods

Participants were enrolled before conception or during early gestation, no later than 16 weeks estimated gestational age, in a prospective observational study of the impact of maternal stress, mental illness, and pharmacologic exposures during pregnancy. The study was conducted under the auspices of the Emory Women's Mental Health Program, a tertiary referral center for neuropsychiatric illness in pregnancy. Participants were referred to the Emory Women's Mental Health Program by primary care physicians, obstetric care providers, mental health care providers, and self-referral. By design, the inclusion criteria for the primary investigation were broad, and only women with an active eating disorder or substance use disorder were excluded from participation. All participants provided written informed consent and the study was approved by the Emory Institutional Review Board.

The overall study design relevant to the current study included enrollment before 16 weeks' gestation, follow-up visits during pregnancy at 4-8 week intervals to gather information on stress, symptoms of depression and anxiety, and documentation of exposures (prescription, over the counter, and environmental). After delivery, each subject was interviewed to obtain information on labor and delivery, and release of information for medical records was obtained. At 7 days of age, corrected for gestational age at delivery, a certified rater blind to course and exposures during pregnancy conducted a home visit to complete the Brazelton Neonatal Behavioral Assessment Scale (NBAS) to evaluate neonatal behavior.[14]

NBAS was developed in 1973 by Brazelton and Nugent.[14] It is a widely used research instrument. The scale produces a total of 47 scores. These scores are used to generate scores for 10 separate domains (Table 3) that provide a measure of a variety of areas including neurologic, social, and behavioral. In addition, reflexes, response to stress, startle reactions, cuddliness, motor maturity, ability to habituate to sensory stimuli, and hand-mouth coordination are all assessed. There are no clear normative values and the NBAS is typically used in comparing different groups.

The mothers completed the Child Behavior Checklist (CBCL) to evaluate areas of problem behavior in offspring between 17 and 66 months of age.[15] The CBCL has 11 subscales including, delinquent behavior, aggressive behaviors, withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, externalizing problems (includes delinquent and aggressive behaviors), internalizing problems (includes withdrawn, somatic complaints, and anxiety/depressed problems), and total problems (includes externalizing, internalizing, social, thought, and attention problems).[15] The scores are adjusted for age and gender to produce a T score. T scores >65 are considered to be a vulnerable range although >70 (2 standard deviations above the normal level) is considered clinically meaningful. All data was coded and entered into a research database.

Inclusion in the current analysis was limited to participants who, by the time of data sequestration, had delivered a live infant, and for whom the following data collection had been completed: (1) abstraction of obstetric records; (2) prospective documentation of medication exposure recording the daily dose of all agents on a week-by-week basis across the entirety of gestation; (3) neonatal evaluation completed up to 2 months of age (NBAS) and/or maternal rating of behavior (CBCL) from 17-66 months of age; and (4) signed consent for continuing use of data by the investigative team for further examination on the effects of exposures during pregnancy.

Women were grouped based on antiemetic exposure status as determined by maternal self-report during serial prospective prenatal visits: (1) antiemetic exposed group: any exposure to ondansetron or promethazine during pregnancy; and (2) unexposed group: no reported exposure to antiemetic agents.

Statistical analysis

All statistical analyses used SAS v9.3 (The SAS Institute, Cary, NC). The exposed group was compared with the unexposed group using the χ^2 test and Wilcoxon rank-sum test for categorical and numeric data, respectively. In particular, each CBCL variable had raw scores, "*t* scores", and percentile scores available. Both *t* scores and percentile scores were analyzed via Wilcoxon rank-sum test. Within the exposed group, the CBCL percentile scores were further analyzed for evidence of association with duration of antiemetic exposure in weeks via Spearman correlation analysis (Figure). An unadjusted alpha = .05 significance level was used for all comparisons and correlations despite the multiple testing, so as not to compromise Type II (false-negative) error when screening for potentially harmful associations in this observational study.

Results

A total of 533 women qualified for the present analysis. These women accounted for a total of 550 children (17 twin pregnancies). The overall sample was homogeneous with respect to race, marital status, socioeconomic status,