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Ondansetron in pregnancy and risk of adverse fetal outcomes in the United States

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ABSTRACT

This is an analysis of fetal outcome in pregnancies exposed to ondansetron to treat Hyperemesis Gravidarum (HG). In this retrospective cohort study, U.S. data on outcome were collected on 1070 pregnancies exposed to ondansetron and compared to outcomes in two control groups: 771 pregnancies in women with a history of HG with no ondansetron exposure and 1555 pregnancies with neither a history of HG nor ondansetron exposure. Ventricular septal defects were reported in 2/952 of infants in the HG/Ondansetron-exposure group and 4/1286 in the No HG/No Ondansetron-exposure group. Cleft palate was reported in 1/952 live births in the HG/Ondansetron and 2/1286 in the No HG/No Ondansetron-exposure groups. Women with a history of HG who took ondansetron reported less miscarriages and terminations, and higher live birth rates. The overall results do not support evidence of teratogenicity of ondansetron.

1. Introduction

Ondansetron is a serotonin 5-HT3 receptor antagonist which is commonly prescribed off-label in the United States to treat the symptoms of nausea and vomiting of pregnancy [1]. To our knowledge, there are only 2 peer-reviewed published articles of ondansetron exposure in pregnancy, which have included, at minimum, 1000 pregnancies. A Danish study of 1233 first trimester exposures concluded that ondansetron was not associated with a significantly increased risk of adverse fetal outcomes [2]. A Swedish study of 1349 exposures also found no significantly increased risk for a major malformation, but did find an increased risk for a cardiac septal defect.[3] Herein we report on the fetal outcomes of 1070 exposures to ondansetron for the treatment of HG in the United States.

2. Material and methods

2.1. Sample and settings

This retrospective cohort study is part of a larger investigation evaluating the genetics and epidemiology of Hyperemesis Gravidarum (HG). Eligible patients were primarily recruited through advertising on the Hyperemesis Education and Research Foundation Web site at www.HelpHer.org between 2007 and 2014. The inclusion criteria for women with a history of HG were a diagnosis of HG in a singleton pregnancy and treatment with IV fluids and/or total parenteral nutrition/nasogastric feeding tube. Participants with a history of HG were asked to submit their medical records. Minors (under 18 years) were not included in the study because few teens are expected to fit the study criteria for controls of having had two pregnancies.

Each women with a history of at least one pregnancy affected with HG and treated with IV fluids was asked to recruit one acquaintance with at least 2 pregnancies lasting beyond 27 weeks to participate as a control. Because this study is part of a genetic and epidemiology study comparing women with a history of HG

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to controls, the requirement of 2 pregnancies for controls was to help ensure controls would not be misclassified. Albeit rare, some women may have normal nausea/vomiting in one pregnancy and HG in another, and therefore, selecting controls with a minimum of 2 pregnancies with normal or no NVP helps minimize enrollment of those types of controls. Controls were eligible if they experienced either no nausea/vomiting in pregnancy or normal nausea/vomiting that did not interfere with their daily routine, no weight loss due to nausea/vomiting and no medical attention in any pregnancy due to nausea. Women with a history of HG and controls living outside the United States were excluded due to added time and costs to consent by phone and enroll participants. This study has been approved by the Institutional Review Board at UCLA, IRB # 09-08-122-01A.

2.2. Study procedures

Participants were asked to complete an online survey regarding detailed information on symptoms, treatments, including ondansetron, and outcomes, including birth defects. The majority of participants, both women with a history of HG and controls, joined the study and began the survey during their pregnancies and were automatically prompted to complete the survey on fetal outcome following their due date. Participants were prompted every six months to update the survey. Participants were asked to fill out the survey for all past, current, and "future" pregnancies (pregnancies that occurred when participants were prompted to update the survey). Survey questions can be found in Appendix A.

2.3. Statistical analyses

Respondents were categorized according to their exposure to ondansetron and responses to variables. To evaluate differences amongst the groups Fisher's exact tests were used for categorical variables (ie ethnicity, education, termination, miscarriage, etc.) and unpaired *t*-tests were used for numerical variables (ie age). Logistic regression was performed in order to derive estimated odds ratios.

3. Results

A total of 772 women with a history of HG reported on 1070 pregnancies exposed to ondansetron (HG/Ondansetron) and 771 pregnancies that were not exposed to ondansetron (HG/No Ondansetron). Over 90% of women who took ondansetron reported a first trimester exposure. While by definition, 100% of the HG/Ondansetrong group was treated for HG with ondansetron, 50.88% were hospitalized and 16.03% required total parenteral nutrition to treat their HG. Among the group with a history of HG who were not treated with ondansetron, 68.21% were treated with other common methods (iv fluids and/or metoclopramide and/or promethazine), 26.99% were hospitalized, and 5.52% were treated with total parenteral nutrition. An additional 563 women who did not have HG in any pregnancy (Controls) reported on 1555 pregnancies that were not exposed to ondansetron, nor any medication/treatment for nausea/vomiting of pregnancy (Fig. 1).

3.1. Demographic characteristics

Women with a history of HG and controls were primarily white (87% vs 92%), born on average in 1976 for women with a history of HG and 1975 for controls, and gave birth to their first child on average in 2003 for women with a history of HG and 2002 for controls. 61% of women with a history of HG attended college and 62% of controls, and 19% of women with a history of HG had an advanced degree compared to 18% of controls (Table 1).

Table 1
Demographic characteristics comparing women with a history of HG (HG) to women who did not have a history of HG (Controls). An unpaired *t*-test was used for numerical values (age) and a Fisher's exact test for categorical values (ethnicity and education). The age range at the study start date (2007) for women with HG was 12–49 (the girl who was 12 joined the study in 2014 when she was 19). The age range in 2007 for the control group was 18–48.

Demographic characteristics			
Demographic characteristics	HG	Control	p-value
N	772	563	
Ethnicity (% white)	87%	92%	$p < 0.01$
*Mean maternal age (median,IQR)	31 (29, 8)	32 (32, 8)	$p < 0.01$
Attended college (%)	61%	62%	$p = 0.73$
Advanced degree (%)	19%	18%	$p = 0.67$
1st Child (Average year born)	2003	2002	$p < 0.01$

IQR = interquartile range.
* Mean and median age at study start date (2007).

3.2. Outcome

Pregnancy outcomes comparing the HG/Ondansetron to the HG/No Ondansetron group are shown in Table 2A. Pregnancy outcomes comparing the HG/Ondansetron to the No HG/No Ondansetron (Control) group are shown in Table 2B.

3.2.1. Women with a history of HG who took ondansetron were less likely to report termination of the pregnancy than women with a history of HG who did not take ondansetron

There were no significant differences in reports of pregnancy termination between women with a history of HG who took ondansetron (HG/Ondansetron) and Controls who did not have HG. In pregnancy week 1–12, women with a history of HG who took ondansetron were significantly less likely to report termination of the pregnancy ($p < 0.01$; OR = 0.18, 95% CI = 0.11–0.28) than those with a history of HG who did not take ondansetron (HG/No Ondansetron). The women with a history of HG who took ondansetron were also significantly less likely to report a termination in weeks 1–12 due to HG (2.52%) compared to women with a history of HG who did not take ondansetron (8.69%) ($p < 0.01$; OR = 0.27 (0.17, 0.43). Among HG/No Ondansetron that terminated their pregnancy due to HG, 54% reported their reason for termination was not being offered any medication for their nausea, 15% were unable to endure symptoms any longer, and 8% reported one of either A) declined treatment, B) nothing worked, C) feared for life, or D) doctor recommended termination.

3.2.2. Women with a history of HG who took ondansetron were less likely to report a miscarriage

The HG/Ondansetron group was significantly less likely ($p < 0.01$; OR = 0.09, 95% CI = 0.06–0.13) to report a miscarriage in weeks 1–12 (3.74%) compared to the HG/No Ondansetron group (30.61%). The HG/Ondansetron group was also significantly less likely $p < 0.01$; OR = 0.29, 95% CI = 0.20–0.42 to report a miscarriage in weeks 1–12 than the Control group (11.77%). Late miscarriages (weeks 13–20) were not significantly different in any group.

3.2.3. Women with a history of HG who took ondansetron and women with a history of HG who did not take ondansetron were equally at an increased risk for preterm birth

Preterm birth (21–36 weeks) was significantly more common in the HG/Ondansetron group (9.07%) than the HG/No Ondansetron (4.67%) and Control groups (4.50%). However, when adjusted for live births only, there was no significant difference between HG/Ondansetron and HG/No Ondansetron groups for preterm birth.