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

Marlena S. Fejzo[a,c,*], Kimber W. MacGibbon[b], Patrick M. Mullin[c]

[a] University of California, Los Angeles, Department of Medicine, Los Angeles, CA, USA
[b] Hyperemesis Education and Research Foundation, Damascus, OR, USA
[c] Keck School of Medicine, University of Southern California, Department of Maternal-Fetal Medicine, Los Angeles, CA, USA

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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

* Corresponding author at: University of California, Los Angeles, Department of Medicine, Los Angeles, CA, 90095 USA.
E-mail addresses: mfejzo@mednet.ucla.edu, nvpstudy@usc.edu (M.S. Fejzo).

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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.

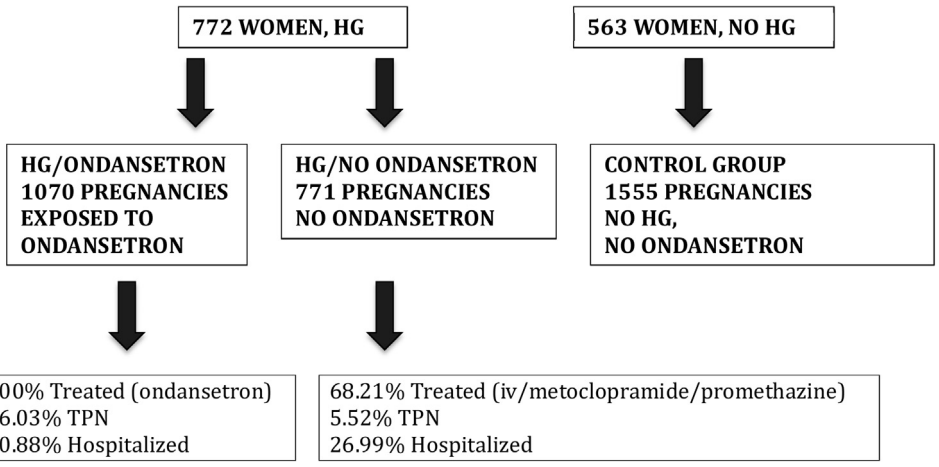

Fig. 1. Study Participants. 772 women with a history of HG, reported on 1070 pregnancies treated with ondansetron and 771 pregnancies that were not treated with ondansetron. 563 women that had normal or no nausea and vomiting in their pregnancies, reported on 1555 pregnancies that were not treated with any medication for nausea and vomiting. *Some pregnancies in the HG/Ondansetron group and the HG/No Ondansetron group have been exposed to other treatments for nausea/vomiting including but not limited to intravenous fluids, metoclopramide, promethazine, hospitalization, and/or TPN (total parenteral nutrition). The percentages reported for these treatments are with respect to live births only. The No HG/no ondansetron group was not exposed to any treatments for nausea/vomiting as they did not have nausea/vomiting severe enough to require any treatment. In this study, outcomes of the ondansetron exposure group (HG/ONDANSETRON) are compared to the two unexposed groups (HG/NO ONDANSETRON) and the CONTROL group (NO HG/NO ONDANSETRON).

Table 2A
Pregnancy outcome comparing women with a history of HG whose pregnancies were treated with ondansetron (O+) to women with a history of HG whose pregnancies were not treated with ondansetron (O−). Fisher's exact test was used for all categorical values where applicable.

	O+	%	O−	%	P-value	OR	95% CI
Pregnancies (N)	1070		771				
Outcome							
1–12 terminations	28	2.62	99	12.84	<0.01	0.18	(0.11, 0.28)
1–12 terminations (HG)[a]	27	2.52	67	8.69	<0.01	0.27	(0.17, 0.43)
13–20 terminations	9	0.84	5	0.65	0.84	1.3	(0.39, 4.60)
13–20 terminations (HG)[a]	8	0.75	3	0.39	0.33	1.93	(0.51, 7.29)
1–12 ectopic pregnancies	5	0.47	5	0.65	0.84	0.72	(0.16, 3.14)
1–12 miscarriages	40	3.74	236	30.61	<0.01	0.09	(0.06, 0.13)
13–20 miscarriages	24	2.24	14	1.82	0.64	1.24	(0.61)
21–36 stillbirths	7	0.65	4	0.52	0.95	1.26	(0.32, 5.90)
21–36 preterm birth	97	9.07	36	4.67	<0.01	2.03	(1.36, 3.11)
37–40+ stillbirth/neonatal death[b]	2	0.19	1	0.13	1	1.44	(0.07, 85.14)
37–40+ live birth	855	79.91	405	52.53	<0.01	3.59	(2.91, 4.44)
Other outcomes							
Total live births	952	88.97	441	57.2	<0.01	6.03	(4.73, 7.73)
Female	549	56.25	220	52.88	<0.01	2.64	(2.16, 3.23)
Male	427	43.75	196	47.11	<0.01	1.95	(1.58, 2.40)
Female:Male	1.29		1.12				
Birth Defects	33	3.47	15	3.4			
Heart Defect	5	NA	0	NA			
Ventricular septal defect	2	NA	0	NA			
Cleft lip/palate	1	NA	0	NA			
Club foot	0	NA	1	NA			

O+ (ondansetron exposure).
O− (not exposed to ondansetron).
NA = Not Applicable.
[a] Terminations due to HG.
[b] Neonatal death = death of baby within the first 28 days of life.

A significant difference remained between the HG groups and the Control group ($p < 0.01$).

3.2.4. *Women with a history of HG who took ondansetron were significantly more likely to report a live birth than either HG/No ondansetron or controls ($p < 0.01$)*

Overall, 88.97% of women with a history of HG who took ondansetron reported a live birth compared to 57.20% of women with a history of HG who did not take ondansetron (OR = 6.03, 95% CI = 4.73–7.73) and 82.70% of Controls (OR = 1.69, 95% CI = 1.33–2.15). Female pregnancies were also significantly increased ($p < 0.01$) in the HG/Ondansetron exposure group compared to the other groups.

3.2.5. *Birth defects (major and minor) are equally reported in the HG groups, regardless of ondansetron exposure, but are increased compared to the control group*

Among 952 live births in the HG/Ondansetron group, there were 33 birth defects reported (3.47%) which was similar ($p = 1.0$) to the rate in the HG/No Ondansetron group where 15 birth defects were

Table 2B
Pregnancy outcome comparing women with a history of HG whose pregnancies were treated with ondansetron (O+) to women with no history of HG whose pregnancies were not treated with ondansetron (O−). Fisher's exact test was used for all categorical values where applicable.

	O+	%	O−	%	P-value	OR	95% CI
Pregnancies (N)	1070		1555				
Outcome							
1–12 terminations	28	2.62	41	2.64	1	0.99	(0.59, 1.66)
1–12 terminations (HG)[a]	27	2.52					
13–20 terminations	9	0.84	8	0.51	0.44	1.64	(0.56, 4.90)
13–20 terminations (HG)[a]	8	0.75					
1–12 ectopic pregnancies	5	0.47	4	0.26	0.57	1.82	(0.39, 9.19)
1–12 miscarriages	40	3.74	183	11.77	<0.01	0.29	(0.20, 0.42)
13–20 miscarriages	24	2.24	22	1.41	0.15	1.6	(0.85, 3.01)
21–36 stillbirths	7	0.65	8	0.51	0.84	1.27	(0.39, 4.03)
21–36 preterm birth	97	9.07	70	4.5	<0.01	2.11	(1.52, 2.95)
37–40+ stillbirth/after	2	0.19	3	0.19	1	0.97	(0.08, 8.47)
37–40+ live birth	855	79.91	1216	78.2	0.32	1.11	(0.91, 1.35)
Other outcomes							
Total live births	952	88.97	1286	82.7	<0.01	1.69	(1.33, 2.15)
Female	549	56.25	638	48.7	<0.01	1.51	(1.29, 1.78)
Male	427	43.75	672	51.3	0.1	0.87	(0.74, 1.03)
Female:Male	1.29		0.95				
Birth Defects	33	3.47	24	1.87			
Heart Defect	5	NA	8	NA			
Ventricular septal defect	2	NA	4	NA			
Cleft lip/palate	1	NA	2	NA			
Club foot	0	NA	0	NA			

O+ (ondansetron exposure).
O− (not exposed to ondansetron).
NA = Not Applicable.
[a] Terminations due to HG.

reported out of 441 live births (3.40%). None of the birth defects were unique to the HG groups. The types of defects found in the HG/Ondansetron and the HG/No Ondansetron groups were also seen amongst the Controls. Thus, a specific birth defect linked to HG was not identified.

3.2.6. Reports of major birth defects including heart defects, ventricular septal defects, cleft lip/palate, and clubfoot are not increased in the ondansetron group compared to the control group

Reports of major birth defects including heart defects and cleft lip/palate were similar in the HG/Ondansetron group (5 heart defects, 1 cleft lip/palate) compared to the Control group (8 heart defects, 2 cleft lip/palates) (Table 2B). There were no reports of clubfoot in the HG/Ondansetron, nor in the Control group. However in the HG/No Ondansetron group, there was one report of clubfoot, but no reports of either heart defects, or cleft lip/palate.

4. Discussion

This well-controlled study shows no statistically significant increase in the overall reporting of major and minor birth defects in women with a history of HG exposed to ondansetron (%) compared to women with a history of HG who did not take ondansetron (3.40%). Birth defects were reported in 1.87% of infants from pregnancies with no HG and no ondansetron exposures. This study suggests a history of HG, and not ondansetron exposure, may be associated with an increased risk of birth defects, although we cannot rule out the possibility of over-reporting in the HG groups. The same is true for preterm birth. Women with a history of HG, regardless of ondansetron exposure, were equally likely to have an increased risk of preterm birth and were at a significantly higher risk than the non-HG control group. Of particular importance, this study finds similar levels of cardiac defects, cleft lip/palate, or clubfoot when comparing 1070 exposures to ondansetron to 1555 unexposed fetuses. Thus, the overall results do not support evidence of teratogenicity of ondansetron.

This study is in line with the findings of a study with a similar exposure size (1233 exposures) in a Danish cohort, [2] where it was concluded that ondansetron taken during pregnancy was not associated with a significantly increased risk of adverse fetal outcomes including heart defects and cleft palate. The findings are in contrast to a Swedish study of similar exposure size (1349) [3] which found a low but significant increased risk for cardiac septal defects but not cleft palate, and a US-based study that reported an increased risk for cleft palate but not heart defects [4]. In our study, the number of cardiovascular defects among women with a history of HG exposed to ondansetron was similar to the control group, the number reported in both the Danish study and the Swedish study, and consistent with the reported national average [5]. However, it is important to note that in our study, no cardiovascular defects were reported by the women with a history of HG that did not take ondansetron. This may be because there were only 441 live births in the HG/No Ondansetron group, compared to 952 and 1286 in the other two groups, and/or it may be due to under-reporting in the HG/No Ondansetron group.

This study also shows women who took ondansetron for the treatment of HG were significantly less likely to report termination of their pregnancies due to HG and significantly less likely to report a spontaneous abortion in the first 12 weeks of pregnancy. Consequently, women taking ondansetron were more likely to report a live birth. Only 3 out of 35 (8.6%, data not shown) women who took ondansetron and subsequently terminated, reported that the medication was effective. This is in contrast to a reported effectiveness of 65% (682/1047) by the group of women in this study who took ondansetron and reported a live birth. Our previous study on reported effectiveness of ondansetron, and a recent clinical trial show ondansetron to be one of the more effective treatments for HG [6,7]. Perhaps ondansetron treatment, when effective, may play a role in preventing termination due to HG. However, this study cannot determine whether women who take ondansetron are subsequently less likely to miscarry or vice versa. Of note, the Danish study also found women exposed to ondansetron had a decreased risk of spontaneous abortion and an increased risk of preterm birth.

Our study suggests preterm birth risk may be linked to HG and not ondansetron exposure since both HG/Ondansetron and HG/No Ondansetron had an equally increased risk of preterm birth.

Admittedly, this report has some limitations. In order to increase compliance, and matching of demographic characteristics, controls were recruited by women with a history of HG. Factors such as ethnicity, maternal age, age of first child, and education, were close, but not perfectly matched between women with a history of HG and controls. In addition, there may be other unforeseen factors that are attributed to the self-selection of the control group. However, the number of heart defects in both the HG/Ondansetron group and the control group were well in the range of expectation compared to several other reports including the national average, suggesting any bias in the control group is not likely to have a meaningful impact on the number of reported major birth defects.

In addition, the controls were required to have at least 2 pregnancies that went beyond 27 weeks (in order to confirm no HG in at least 2 pregnancies). Therefore, controls were likely to begin filling out the survey later in pregnancy or beyond, compared to women with a history of HG. This introduces the possibility of recall bias and may explain the greater number of major and minor birth defects overall reported in both HG groups compared to the control group. However, it is unlikely that major birth defects (heart defects and cleft lip/palate, club foot) would be under-reported by controls. And, if they were, it would bias toward finding less of these birth defects in controls than women with a history of HG, which was not the case. With respect to minor birth defects, there may be under-reporting of minor defects that are missed if there is too short a follow-up time for more recently enrolled study participants. However, there is no reason to believe that this problem would be unique to any specific group in this study since women with a history of HG and controls are enrolled simultaneously.

Another potential problem is that while most participants enter the study while they are pregnant, the gestational age was not noted. Differences in gestational age when joining the study could have an effect on rate of termination, miscarriage, and livebirth. Despite this, the control group, which is required to have at least 2 pregnancies lasting beyond 27 weeks, reported a similar termination rate, live birth rate, and a significantly higher (11.77%) early miscarriage rate than the HG/Ondansetron group. If there was bias, one would expect the control group to have lower miscarriage and termination rates and significantly more live births than the HG/Ondansetron group. There is no reason to believe that the HG/Ondansetron group and HG/No Ondansetron group joined the study at different times because the clinical criteria for participation in the study was intravenous-fluid treatment, not medication.

5. Conclusions

These results do not support a teratogenic risk for ondansetron. While women with a history of HG have an increased risk of reporting a child with a birth defect, ondansetron exposure does not appear to be associated with this increased risk. Additionally, women with a history of HG who took ondansetron were significantly less likely to report termination of their pregnancy due to HG, significantly less likely to report a miscarriage, and, as a result, significantly more likely to report a live birth.

Conflict of interest

The authors report no conflict of interest.

Transparency document

The Transparency document associated with this article can be found in the online version.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.reprotox.2016.04.027.

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