Published in final edited form as:

Obstet Gynecol. 2016 May ; 127(5): 873–877. doi:10.1097/AOG.0000000000001375.

Ondansetron Use in Pregnancy

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Abstract

The American College of Obstetricians and Gynecologists recommends early treatment of nausea and vomiting of pregnancy to stop progression to hyperemesis gravidarum. Nausea and vomiting and hyperemesis gravidarum typically occur during the first trimester, the sensitive time for exposure to teratogens because organogenesis is occurring in the embryo. An efficacious treatment used widely across the United States for both nausea and vomiting of pregnancy and hyperemesis gravidarum is ondansetron. Recent studies have provided conflicting findings on the safety of ondansetron during pregnancy. There are numerous limitations in the current literature on ondansetron safety including exposure to the medication is not limited to sensitive windows of organogenesis, there is a lack of information on dosing and compliance, self-reports of exposure are commonly used, an inadequate accounting exists for other factors that may explain the relationship between ondansetron exposure and the adverse outcome, and there exists a lack of biologic plausibility by which ondansetron might cause harm. It is the authors' opinion that current data do not support a reluctance to treat women with ondansetron in clinical practice.

Nausea and vomiting is the most common pregnancy complication, occurring in up to 80% of pregnancies in the United States.¹ More than 59,000 pregnant women are hospitalized annually with hyperemesis gravidarum,² the severe form of nausea and vomiting of pregnancy.

Untreated and prolonged nausea and vomiting of pregnancy and hyperemesis gravidarum cause increased maternal stress and decreased quality of life and rarely may lead to Wernicke's encephalopathy, hyponatremia, malnutrition as well as other vitamin deficiencies.^{1,3} Nausea and vomiting of pregnancy and hyperemesis gravidarum have also been associated with an increased risk of preterm birth and small-for-gestational-age neonates.¹ The financial burden inflicted by nausea and vomiting of pregnancy and hyperemesis gravidarum is substantial, costing nearly \$2 billion in 2012 alone.⁴

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Financial Disclosure

The authors did not report any potential conflicts of interest.

Nausea and vomiting and hyperemesis gravidarum typically occur during the first trimester, the sensitive time for exposure to teratogens because organogenesis is occurring in the embryo. For treatment of mild-to-moderate nausea and vomiting of pregnancy and hyperemesis gravidarum, the American College of Obstetricians and Gynecologists recommends nonpharmacologic treatment, including prevention with a multivitamin and frequent, small meals. Early treatment of nausea and vomiting of pregnancy is recommended to stop progression to hyperemesis gravidarum.¹ For the estimated 10–15% of women who do not respond to lifestyle interventions, the American College of Obstetricians and Gynecologists recommends pyridoxine (vitamin B6) and the addition of doxylamine if necessary. This combination product was first marketed under the name Bendectin but was voluntarily withdrawn from the market in 1983 after legal costs soared as a result of unsubstantiated concerns of teratogenicity. In 2013 the U.S. Food and Drug Administration again approved this drug, this time marketed under the trade name Diclegis. Diclegis tablets are indicated for treatment of nausea and vomiting of pregnancy in women who fail conservative treatments.

Unfortunately, Diclegis is not indicated for treatment of hyperemesis gravidarum nor is it approved for intravenous administration, which is often necessary for persistent vomiting. When parenteral therapy is required, intravenous administration of Dramamine (dimenhydrinate), Phenergan (promethazine), or Reglan (metoclopramide) is commonly used after administration of intravenous replacement fluids. These medications are generally accepted as safe in pregnancy, but there are limited and nonconclusive efficacy data in regard to metoclopramide.¹ When these treatments fail, ondansetron is increasingly being used,⁵ but safety data are incomplete (ondansetron was classified as Pregnancy Category B by the prior U.S. Food and Drug Administration criteria).¹

Ondansetron has been found to be the most commonly used prescription oral antiemetic in pregnancy in the United States and was ranked as the fifth most commonly taken oral medication in pregnancy overall in the Slone Epidemiologic Center Birth Defects Study.⁵ Ondansetron has been shown to have fewer side effects with less sedation⁶ and superior antiemetic effects compared with alternatives.⁷ Many women who require treatment for nausea and vomiting of pregnancy are participating in activities that will be affected by drowsiness or dizziness (or both) often associated with alternatives. In regard to treatment of hyperemesis gravidarum, up to half of women treated in some emergency departments will receive intravenous ondansetron.⁸

PHARMACOLOGY OF ONDANSETRON

Ondansetron is a serotonin receptor antagonist that blocks the effects of serotonin. Ondansetron's primary indication is for treatment of nausea and vomiting associated with chemotherapy or surgery. It is available as a tablet, an oral disintegrating tablet, an oral solution, and intravenously, which makes it a useful candidate for treating women with intractable vomiting.

ONDANSETRON SAFETY

There is disagreement in the literature regarding the teratogenic risk of ondansetron use during pregnancy, particularly with regard to cardiac defects and cleft palates. The current dispute arose largely because of the publication of two large, retrospective studies^{9,10} and one abstract, which reported results that conflicted with the earlier studies.¹¹ None of these studies reported any significant association between ondansetron and “any major birth defect.”

Interpreting the Literature: Optimal Study Design

To identify the literature contributing to the controversy of ondansetron’s safety in pregnancy, we performed a literature search in November 2015 in PubMed using the search terms “pregnancy,” “ondansetron,” and “malformation.” We limited our search to original research conducted in humans that included study populations after 2003. This time point was chosen to refer to the most recent and likely relevant literature as well as to assess the time period when ondansetron became most frequently used.⁵ This literature search identified four relevant studies.^{9–12} A final study conducted by Andersen et al was included because it was referenced by multiple opinion papers as well as in Danielsson et al.

To test the teratogenicity of a drug, double-blind placebo-controlled randomized clinical trials (RCTs) are the gold standard design. However, ethical and liability concerns over fetal and maternal risk typically preclude RCTs to test the teratogenicity of an agent, and the rare occurrence of fetal malformations makes RCTs less practical. Observational studies, including cohort and case–control designs, are the next highest quality study design. Given the infrequent occurrence of drug-specific malformations of interest, retrospective cohort designs are often used. In these retrospective cohort studies, a large population—typically ascertained from a perinatal database—is used to identify cases of the outcome and retrospectively determine drug use earlier in pregnancy.

Description of Previous Studies

Two of the primary research studies that largely inform the debate over the safety of ondansetron during pregnancy used a retrospective cohort design. Owing to their large samples and rigorous design, these two studies are the least biased in assessing the effect of ondansetron on embryonic and fetal malformations.^{9,10}

We conclude that the strongest evidence comes from a study by Pasternak et al,⁹ which used the Danish National Birth Registry linked with the National Prescription Registry (2004–2011) to assess the risk of ondansetron on adverse fetal outcomes. In the 441,511 pregnancies, 1,233 were exposed to ondansetron in the first trimester as determined by filled prescription data. A similar rate of 2.9% for any major birth defects was seen in those women exposed (36/1,233) and those unexposed (141/4,932) to ondansetron in the first trimester. Pasternak et al used propensity score matching to best account for any residual factors that potentially influence the relationship between ondansetron use and birth defects including maternal age, place of birth, marriage status, education, household income, pregnancy history, medical history, and health care utilization. This was the only study to

account for maternal medical history, including diabetes mellitus of any type, which is known to increase risk of congenital heart defects. After propensity score adjustment, exposed pregnancies had no statistically significant increase in the risk of any major birth defect (adjusted odds ratio [OR] 1.12, 95% confidence interval [CI] 0.69–1.82), still-birth, spontaneous abortion, preterm delivery, low birth weight, or small for gestational age. There were no neonates with a cleft palate in women exposed to ondansetron.

In 2014, Danielsson et al¹⁰ published results of a retrospective Swedish cohort of 1,501,434 pregnancies, including 1,349 exposed to ondansetron in the first trimester. Exposure was determined from self-report for 435 women and extracted from a prescription registry for 914. Malformations were identified using the Medical Birth Register, the Birth Defect Register, and diagnoses on hospital discharge. Like Pasternak et al,⁹ they found no significant risk of major malformations (adjusted OR 0.95, 95% CI 0.72–1.26). However, after accounting for self-reported year of delivery, maternal age, parity, smoking status, and body mass index, they found an increased risk of cardiovascular defects (adjusted OR 1.62, 95% CI 1.04–2.14). This finding is based on cardiac defects in 19 of the 1,349 neonates (1.4%) exposed to ondansetron. This association was stronger when the analyses focused specifically on septal defects (ventricular, atrial, or both), which occurred in 17 of 1,349 (1.3%) exposed compared with 10,474 of 1,458,697 (0.7%) unexposed women. The analysis of Danielsson et al was less rigorous than that of Pasternak et al; they adjusted for fewer confounders with simpler methods and performed fewer sensitivity analyses.

An earlier case–control study by Anderka et al¹¹ found no increased risk of cardiac defects in women exposed to ondansetron; however, investigators did find an increased risk of cleft palate (adjusted OR 2.37, 95% CI 1.18–4.76) associated with ondansetron use in the first trimester using the National Birth Defects Prevention Study (1997–2004), a finding contrary to those of Danielsson et al and Pasternak et al. Because teratogens are typically associated with a specific birth defect or a collection of birth defects, the heterogeneity of this finding of cleft palate taken with the other associations with cardiac defects weakens the argument of causation. The association found is based on cleft palates seen in 11 of the 55 neonates exposed to ondansetron and 514 of the 4,479 who were not exposed. The high prevalence (20%) of cleft palate among exposed fetuses is striking, particularly because an increase in cleft palate was not reported in either Danielsson et al or Pasternak et al, which included many more exposed women. Recall bias in the study of Anderka et al is a particular concern because exposure to ondansetron was based on maternal recall of first-trimester medication use at 6 weeks to 2 years postpartum. It is possible that mothers of neonates with birth defects were more likely to report exposure to hypothesized teratogens. This study was further limited by a small number of exposed fetuses and low response rates.

A third, significantly smaller, retrospective study conducted by Colvin et al¹² in western Australia also found no statistically significant increased risk of any major birth defects attributed to ondansetron use in the first trimester (OR 1.2, 95% CI 0.6–2.2). The study population was small (only 211 neonates were exposed in the first trimester) and private prescriptions for ondansetron not subsidized by the Australian government could not be quantified.

One year after the Pasternak et al publication, Andersen et al¹³ conducted a similar study using the same registries as Pasternak et al,⁹ adding 15 women exposed to ondansetron (n = 1,248 exposed) by including an additional 7 years of data (1997–2010). It is critical to note that although this study is frequently cited, it was published only as an abstract and never as a peer-reviewed article. The abstract lacks critical information such as the total number of heart defects in the study. Andersen et al found a significantly increased risk of cardiac malformations, but because of this lack of peer review and incomplete information, it is inappropriate to use these findings in any critical assessment of ondansetron.

BASIS AND RELIABILITY OF RESULTS

It is difficult to interpret the results of these studies and integrate any change into practice as a result of the issues described subsequently and contradictory findings.

Rare Birth Defects and Exposure to Ondansetron

Teratogens are typically related to distinct birth defects or a constellation of birth defects. However, even with large cohorts, few cases of specific defects are identified. If individual heart defects were analyzed separately to account for the various mechanisms of effects (ie, atrial septal defects separate from ventricular septal defect), event rates would decrease even further. At the same time, exposure to ondansetron in the aforementioned cohorts was infrequent (0.3%⁹–0.09%¹⁰) compared with much higher estimated use in the United States (estimated 3% in the first trimester⁵). Small numbers of exposed pregnancies with the outcome of interest limit statistical power. In both Danielsson et al¹⁰ and Pasternak et al⁹ there were only 19 and 13 cases, respectively, of cardiac defects in neonates of women exposed to ondansetron. It is difficult to base any strong conclusions on such low event rates.

Limiting to Sensitive Exposure Window

Teratogen exposure is relevant during the period of organogenesis, yet, in previous studies, the majority of the women began ondansetron after the heart is fully formed at approximately 8 weeks of gestation. Only Pasternak et al⁹ tested the effect of limiting the exposure window to 2–8 weeks or 4–10 weeks of gestation and confirmed their null findings.

Medication Compliance and Dosing

Whether the medication was truly ingested is difficult to prove. This bias can be greater when medication use is self-reported, which occurred in the studies of Danielsson et al¹⁰ and Anderka et al.¹¹ Furthermore, ondansetron use was analyzed as a binary variable (any use compared with no use) in the primary analyses of all three major studies,^{9–11} which disregards essential information pertaining to dosage, route of administration, frequency, and precise gestational timing of exposure when analyzed as “during the first trimester.”

Confounding by Indication and Disease Severity

The issue of confounding by indication and severity of nausea and vomiting of pregnancy was not always adequately addressed. For example, women experiencing nausea and vomiting of pregnancy and hyperemesis gravidarum may share some characteristic that

increases risk for birth defects. In other words, is the defect a sequelae of the nausea and vomiting of pregnancy and hyperemesis gravidarum or did the treatment lead to this outcome? This concept extends to the severity of the ailment. Pasternak et al⁹ attempted to account for confounding by indication and severity by adjusting for exposure to other antiemetics and for hospitalization resulting from nausea and vomiting of pregnancy and hyperemesis gravidarum in addition to propensity score matching. Danielsson et al¹⁰ attempted to evaluate confounding by indication using self-reported meclizine-treated women as a comparator. Only Pasternak et al⁹ accounted for a previous pregnancy with the same outcome (eg, birth defect), attempting to assess the effect of family history.

Biologic Plausibility

Very little evidence of biologic plausibility exists for the association between ondansetron and birth defects, although ondansetron crosses the placenta as do most medications with low molecular weight (less than 500 Daltons). Investigators have hypothesized the mechanism to be related to QT prolongation and subsequent cardiac arrhythmia in a sensitive embryonic heart.¹⁰ However, to date, no evidence has supported this suggestion. Animal studies, although imperfect predictors of human teratogenicity, do not support teratogenicity of ondansetron even when a dose 70 times the human dose is given to pregnant rabbits and rats at the time of organogenesis.¹⁴

Genetic and Medical Predisposition to Septal Defects

A key element not addressed in any previous study is the critical role that genes or maternal diseases may play in early heart development. Research has demonstrated that three transcriptional genes (*GATA4*, *NKX2.5*, and *TBX5*), when mutated, contribute to both atrial and ventricular septal defects.¹⁵ Additionally, an estimated half of all neonates born with trisomy 21 have heart defects with even higher incidences for those born with trisomy 13 or 18.¹⁶ This relationship between chromosomal abnormalities and congenital heart defects was also not properly addressed by Danielsson et al¹⁰ but was appropriately excluded in both Pasternak et al⁹ and Anderka et al.¹¹ Maternal diabetes increases fetal risk for cardiac malformations; this and other maternal medical disorders must be considered in any assessment of potential teratogens. As stated earlier, Pasternak et al⁹ adjusted for diabetes but Danielsson et al¹⁰ did not.

WEIGHING THE RISKS AND BENEFITS OF ONDANSETRON USE DURING PREGNANCY

The guiding clinical principle for treatment of nausea and vomiting of pregnancy and hyperemesis gravidarum is avoidance of unnecessary medications. When medication is necessary, use of the safest and most efficacious medication at the lowest effective dose for the shortest period (as is generally suggested for all medications) is ideal. When nonpharmacologic therapies fail, the first-line outpatient pharmacologic treatment should be monotherapy with oral pyridoxine followed by a combination pyridoxine and doxylamine because these have the best safety profile. If these fail, ondansetron can be considered based on our assessment of the literature relating to safety and its efficacy. In an RCT comparing doxylamine and pyridoxine combination therapy with orally administered ondansetron,

ondansetron was found to be superior in reducing both nausea and vomiting in pregnancy.¹⁷ Ondansetron has also been compared with metoclopramide in the treatment of hyperemesis gravidarum and was found to be more effective at reducing vomiting when administered orally.⁷ Clearly, additional safety data with ondansetron are needed.

As for inpatient intravenous therapy for hyperemesis gravidarum, no study has reported teratogenicity of intravenous ondansetron. When ondansetron was compared with metoclopramide for the treatment of hyperemesis gravidarum through the intravenous route, both demonstrated similar efficacy, with ondansetron having an overall preferable profile in regard to adverse effects.⁶ Given the existing evidence for ondansetron efficacy and safety, in addition to the biases noted, it is our opinion that intravenous ondansetron can also be considered as therapy in women with hyperemesis gravidarum. In these severe cases, intravenous ondansetron can be considered for short-term treatment at the same point as alternatives with electrocardiographic monitoring for those with electrolyte abnormalities. It is not our assertion that ondansetron use is conclusively safe, but rather that its use in treatment of nausea and vomiting of pregnancy and hyperemesis gravidarum is guided on the principle of absence of harm to date and presence of efficacy.

These recommendations are all based on the strongest current evidence and are subject to change as more research is conducted. These approaches are applicable before and after organogenesis, but clearly the potential risks are fewer after organogenesis and short-term treatment is always preferable. In the face of recent questioning of the safety of ondansetron use in pregnancy, it is the authors' opinion that current data do not support a reluctance to treat women with ondansetron in clinical practice. The maternal benefit of treatment for nausea and vomiting of pregnancy and hyperemesis gravidarum with ondansetron outweighs the risks.

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