Is Ondansetron Safe in Pregnancy? A Recommendation Based on Literature Review

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Abstract

Objective: Nausea and vomiting in pregnancy is a common problem primary care physicians and their patients face. Ondansetron is often used but new research calls this into question. We completed a literature search and review to make an evidence-based recommendation on use of ondansetron during early pregnancy (< 12 weeks).
Methods: We performed a literature search using the PICO method to find research studies on effects of ondansetron use in early pregnancy. We analyzed these studies for their results in odds ratios and their power in sample size. We present an evidence-based recommendation based on the analysis of these study results and comparing the powers of each study to determine the strength of the evidence.
Results: Our literature search found four research studies, which had varying degrees of strength based on their power. Each study also had different results of risk and types of congenital malformations that occur with use of ondansetron in early pregnancy.
Conclusions: We recommend avoiding use of ondansetron in early pregnancy and discussing the potential increased risk of congenital malformations with pregnant patients before its use. Level B recommendation.

Key words: Pregnancy; Zofran; Ondansetron; Congenital malformation

Introduction

A 22-year-old female presents with 2 weeks of nausea and vomiting and positive urine pregnancy test. Dating ultrasound shows a viable intrauterine pregnancy at 6 weeks. Prescriptions for prenatal vitamins and prescriptions for doxylamine succinate and pyridoxine hydrochloride are given at this initial visit. At follow up, she reports continued nausea and vomiting with 3 lb. weight loss despite compliance with the medications. She asks if there is anything else to help her nausea and vomiting. She has ondansetron at home from a previous prescription but was not sure if it was safe to use during pregnancy. She tells you she has seen commercials advertising lawsuits against GlaxoSmithKline, manufacturers of Zofran, due to congenital heart defects.[1] She has friends that have used ondansetron during pregnancy but wants to know if it can really cause any harm to her baby. How do you counsel this patient?

As of April 2013, there is only one FDA approved medicine for nausea and vomiting in pregnancy (NVP) and that is doxylamine-pyridoxine. Often it does not control symptoms of hyperemesis gravidarum and physicians and patients alike turn to unapproved medications like ondansetron to prevent weight loss and malnutrition. According to Dr. Koren in his article in American Journal of Obstetrics and Gynecology, "The use of ondansetron for nausea and vomiting in pregnancy has increased from 50,000 monthly prescriptions in 2008 to 110,000 at the end of 2013, despite unresolved issues regarding fetal safety and Food and Drug Administration warnings about serious dysrhythmias."[2] We sought to complete a literature search for studies regarding the safety of ondansetron and analyze them to form an evidence-based recommendation to better care for our prenatal patients and their children.

Methods

With the help of the MAHEC librarians we completed a literature search using the PICO method with the following inputs: Problem – pregnancy, Intervention – Zofran/ondansetron exposure, Comparison – no exposure, Outcome – congenital malformations/birth defects. Of the eight articles resulted, four were research studies dated between January 2012 and December 2014. We analyzed those research studies and compared power based on sample size (Table 1) to determine the strength of their results.

Results

We analyzed the studies based on the effect of the power on the results. Power in statistics is the ability of a study to truly reject the null hypothesis. The higher the power of the study, the less likely a rejection of the hypothesis is false; in other words, the more likely that the impact of the intervention is real. A high population will show small but important impacts that might not show up in a smaller population. The concern of increasing the power in a study is that it might lead to a type 1 error, or showing an impact when there is not one.

Table 1. Comparison of Research Studies on Risk of Congenital Malformations and Use of Ondansetron

Study	Sample Size (*n*)	Results
Danielsson, et al. 2014[3]	1349	Risks for a cardiovascular defect & notably cardiac septal defect were increased & statistically significant
Pasternak, et al. 2013[4]	1233	Ondansetron taken during pregnancy was not associated with a significantly increased risk of adverse fetal outcomes.
Ferreira, et al. 2012[5]	7	Teratogenicity associated with the use of ondansetron has so far not been shown in humans.
Anderka, et al. 2012[6]	4524 (all medications used for NVP) 5859 unexposed (control)	Significantly increased risk of cleft palate with ondansetron.

The Ferreira study with *n* of seven is small and case-based.[5] Given the small population size, there is not much power in this study; thus, a greater sampling of the population is needed to determine if the results are applicable to the general population. The next 3 studies attempted to increase the power of the study to gain a better understanding of the impact of ondansetron in pregnancy. The Anderka study looked at all women with nausea and vomiting in pregnancy.[6] It did indicate cleft palate associated with ondansetron. However, only a small cohort of 51 patients received the medication, reducing its power. The Pasternak study had 1233 patients and was a retrospective study that looked at adverse neonatal outcomes.[5] The study defined adverse outcomes as an increased risk of spontaneous abortion or stillbirth. However, the study did not contribute information on specific birth defects and morbidity to a fetus. The Danielsson study, with 1349 patients, was significantly powered to detail birth defects associated with ondansetron use.[3] The stronger power of the study and specific outcomes measure lead us to concentrate on these results. The caveat is they reviewed several million cases to come up with the cases needed to achieve a

sufficient power. This leads us to conclude that there is a possibility of type 1 error or that the impact of the intervention, though real, is small.

Conclusions

Large prospective trials when dealing with safety of medications in pregnancy are usually not done due to ethical concerns, so we felt that a recommendation should be made from what retrospective data is presented in these studies.

Based on this review, there are rare but possible congenital malformations caused by the use of ondansetron in pregnancy, with the strongest evidence for cardiac septal defects. Embryologically, the endocardial tubes fuse to make the primitive heart tube around 21 days. At 37 days the heart walls are formed and by 8 weeks the basic anatomical cardiac development is completed. This period seems most crucial to heart development and likely when it is most vulnerable to chemical effects of medications. Fetal heart rate continues to change up until 15 weeks gestation where it levels off around 145 bpm, indicating further physiological development.[7] Based on embryology, it seems prudent to avoid use of ondansetron until after 10 weeks gestation and preferably after 15 weeks.

Therefore, we make the recommendation to avoid use of ondansetron in management of nausea and vomiting in early pregnancy (< 12 weeks), and to use only after a discussion with the patient of the potential increased risk of congenital malformations, especially cardiac septum defects. During the first trimester, ondansetron should be reserved for hyperemesis where dehydration and malnutrition become a threat to the mother and baby (Level B recommendation).[8]

We do suggest the use of other means for treating nausea including ginger, pressure bands, frequent fluids, small meals, or snacks before getting out of bed to be implemented first. A combination of pyroxidine 25 mg 4 times daily and doxylamine 12.5 mg twice daily is inexpensive and can be helpful for significant hyperemesis.[9]

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