

Safety of Ondansetron Use in Pregnancy

A Review of the Available Medical Literature

Prepared by Shaun D. Carstairs, M.D. FACMT FACEP

For Healthy Connections Homecare Services

Updated 09 September 2015

Up to 80% of expectant women experience some degree of nausea and vomiting in pregnancy (NVP) (1). For approximately 1/3 of these women, NVP can result in a significant clinical, psychological, and economic burden due to missed work time, increased visits to health care providers, and negative effects on family relationships (1-4). Moreover, severe NVP can result in dehydration and weight loss that require hospitalization. Rare complications can include Wernicke encephalopathy, splenic avulsion, esophageal rupture, pneumothorax, and acute tubular necrosis (3).

Various pharmacologic methods have been attempted for treatment of NVP, with varying success. Currently, limited data exist to guide the choice of antiemetic drugs for NVP. Although formal evaluation has been limited, available studies and clinical experience have supported the routine use of medications including pyridoxine, doxylamine, metoclopramide, and ondansetron (5-7). The combination of pyridoxine and doxylamine is currently recommended by the American College of Obstetricians & Gynecologists as first-line therapy for NVP. However, ondansetron, a 5-HT₃ receptor antagonist, has become one of the most frequently prescribed antiemetics in for the treatment of NVP in the United States. A number of publications have pointed to its efficacy in the treatment of NVP (8-10), including a recent double-blind randomized trial that I conducted that demonstrated superiority of oral ondansetron over the combination of oral pyridoxine and doxylamine for the treatment of NVP (11).

Although ondansetron is currently listed as pregnancy category B, concerns have recently been raised over the safety of ondansetron use in pregnancy (12), and specifically the possible increased risk of delivery of a child with birth defects. Per your

request, I have undertaken a review of the available literature on the subject, the results of which are summarized below.

Pre-clinical safety evaluation

In the late 1980's, a series of studies was undertaken to evaluate pre-clinical safety of ondansetron. These studies included: single dose, repeat dose, reproduction, genotoxicity, oncogenicity, local irritancy, and a hypersensitivity study. Ondansetron was found to have a very good safety profile; the only toxicity identified was central nervous system toxicity when near-lethal doses were administered. Ondansetron was not genotoxic and was not found to show reproductive or oncogenic potential (13).

Initial cohort studies

The first cohort studies to examine the safety of ondansetron in pregnancy were published in the mid-2000's. The first, from Canada, followed the outcomes of 176 women exposed to ondansetron in the first trimester of pregnancy and compared them to two other similarly sized groups of women who were not exposed to ondansetron during pregnancy (14). There were no statistical differences found between groups with respect to the incidence of miscarriages, stillbirths, major malformations gestational age at birth, and mean birth weights. However, given the small sample size, this study was only powered to detect a 5-fold increased risk of major malformations.

The second study, from Sweden, was a cohort study examining data from the Swedish Medical Birth Registry (15). A total of 65 women were exposed to ondansetron during pregnancy. No increased risk of malformations was found in fetuses exposed to ondansetron.

Larger studies

Over the last few years, several studies utilizing larger cohorts have examined the risk of ondansetron use during pregnancy. The first, in 2012, was a review of data from the National Birth Defects Prevention Study in the United States (16). A total of 4524 cases and 5859 controls were examined, and the authors looked specifically at 3 birth defect categories: orofacial clefts, neural tube defects, and hypospadias. No increased risk of neural tube defects or hypospadias was found. However, the authors found an increased risk (roughly two times) of cleft palate in infants exposed to ondansetron (odds ratio 2.37, 95% CI 1.18-4.76). A total of 11 cases of cleft palate were noted in infants who had been exposed to ondansetron, while a total of 514 cases were noted in unexposed offspring. The results are limited by the relatively small sample size, and the increased risk for cleft palate reported in this study has not been replicated in other studies.

The most methodologically sound study to date was done by Pasternak *et al.* and was published in the *New England Journal of Medicine* in 2013 (17). The authors, from Denmark, performed a nationwide cohort study of more than 600,000 pregnancies using data from the Medical Birth Registry and the National Patient Register from the years 2004-2011. They examined women exposed to ondansetron during the first trimester of pregnancy (through week 12) and studied the incidence of major birth defects as defined by EUROCAT. They excluded chromosomal aberrations (such as Down's syndrome) and known other causes of birth defects (such as fetal alcohol syndrome). The authors used logistic regression to estimate propensity scores as the probability of exposure to ondansetron and then matched each woman exposed to ondansetron to unexposed women

in a 1:4 ratio. The models were adjusted for hospitalization for hyperemesis gravidarum or nausea and vomiting as a proxy measure of severity and exposure to other antiemetics during pregnancy. No association was found between ondansetron exposure and the incidence of major birth defects (OR 1.12, 95%CI 0.69-1.82), preterm delivery (OR 0.90, 95%CI 0.66-1.25), low birth weight (OR 0.76, 95%CI 0.51-1.13), or SGA (OR 1.13, 95%CI 0.89-1.44).

A third study was published in 2013 in abstract form (18). The authors used data from the same database as Pasternak's *NEJM* study and looked at the years 1997-2010. Out of 897,018 total births, 1248 women redeemed a prescription for ondansetron. There were 58 congenital malformations (4.7%) in the ondansetron-exposed group, and 31357 malformations (3.5%) in the control group. The authors found an odds ratio of 1.3 (95%CI 1.0-1.7) for major malformations, most of which was due to an increased prevalence of heart defects (odds ratio 2.0, 95%CI 1.3-3.1). However, there are a number of concerns that I have with this data. The results from this study have, curiously, only been published in abstract form thus far and therefore it is not possible to determine their exact study methods, unlike the Pasternak study, the methods of which are clearly and meticulously delineated. Moreover, the confidence interval for risk of major malformations crosses 1, which is essentially a negative result.

In 2014, another Swedish cohort study was published that evaluated approximately 1.5 million births and examined 1349 infants reported to have been exposed to ondansetron in utero (19). No significantly increased risk was found for either total malformations (OR 0.95, 95%CI 0.72-1.26) or "relatively severe" malformations (OR 1.11, 95%CI 0.81-1.53). However, when the authors looked

specifically at cardiac malformations, they found a slightly increased risk compared with meclizine (OR 1.62, 95%CI 1.04-2.14). The majority of cardiac defects reported in this study were septal defects (17 of 19 total; OR 2.05, 95%CI 1.19-3.28).

Interpretation and Recommendations

The bulk of the published studies on ondansetron exposure in early pregnancy suggest that the risk of birth defects, preterm delivery, low birth weight, and SGA from ondansetron use is low. While one study suggested a slight increase in risk of development of cleft palate and two other studies suggested a very slight increase in risk of development of cardiac defects, the most methodologically sound study (which was also one of the largest by far) available did not demonstrate increased risk of any of the above adverse outcomes.

Based upon my interpretation of the available literature on the subject, I believe that the use of ondansetron in pregnancy is generally safe and is highly effective for the treatment of NVP. However, to minimize any potential risk to your patient population, I would suggest that ondansetron be used primarily as a second- or third-line agent for treatment of NVP. Initial treatment should include consideration of nonpharmacologic methods (e.g., ginger) as well as the combination of doxylamine and pyridoxine, which is the current first-line recommendation by ACOG for treatment of NVP. Other antiemetics that are generally recognized as safe in pregnancy, such as metoclopramide and promethazine, can be considered. Additionally, attempts should be made to avoid the use of ondansetron very early in pregnancy (i.e., prior to 8 weeks' gestation) to further minimize any potential risk (however small) of teratogenicity, since the fetal cardiovascular system forms very early in pregnancy (during the first 8 weeks).

Ondansetron has been designated FDA Pregnancy Category B and remains so -- the same category as metoclopramide (20). The most recent ACOG Practice Bulletin on Nausea and Vomiting of Pregnancy, published in September 2015, continues to list ondansetron as an effective treatment for nausea and vomiting of pregnancy and states that "the absolute risk to any fetus [from ondansetron] is low" (21). It also recommends that "early treatment of nausea and vomiting of pregnancy is recommended to prevent progression to hyperemesis gravidarum." The various risks to the mother and fetus from untreated or undertreated NVP and hyperemesis gravidarum are real and have been extensively documented, whereas the extremely small risk of birth defects potentially associated with use of ondansetron remains to be proven definitively. Ondansetron has been demonstrated in multiple studies to be an effective treatment for nausea and vomiting in pregnant women; if other methods have been tried unsuccessfully, the use of ondansetron should be considered.

NVP is not without its risks and can result in a significant clinical, psychological, and economic burden because of missed work time, increased health care visits, and adverse effects on family relationships. Severe NVP can require hospitalization due to dehydration, weight loss, and electrolyte disturbances. First-line agents such as doxylamine and pyridoxine are not always effective in the treatment of NVP, and the known risks associated with inadequately treated NVP or hyperemesis gravidarum must be balanced against the very small potential risks from ondansetron. Therefore, it is my belief that if first- and second-line methods for the treatment of NVP have failed and the health and well-being of the mother and the fetus are in question, it is reasonable and prudent to utilize ondansetron for the treatment of NVP.

References

1. Niebyl J. Nausea and vomiting in pregnancy. *N Engl J Med* 2010; 363:1544-50.
2. Ebrahimi N, Maltepe C, Einarson A. Optimal management of nausea and vomiting of pregnancy. *Int J Women's Health* 2010; 2:241-8.
3. Festin M. Nausea and vomiting in early pregnancy. *Clin Evid* 2009; 2009:pii 1405.
4. Lombardi D, Istwan N, Rhea D, O'Brien J, Barton J. Measuring outpatient outcomes of emesis and nausea management in pregnant women. *Manag Care* 2004; 13:48-52.
5. Badell M, Ramin S, Smith J. Treatment options for nausea and vomiting during pregnancy. *Pharmacotherapy* 2006; 26:1273-87.
6. Magee L, Mazzotta P, Koren G. Evidence-based review of safety and effectiveness of pharmacologic therapy for nausea and vomiting of pregnancy (NVP). *Am J Obstet Gynecol* 2002; 186:S256-61.
7. Matthews A, Dowswell T, Haas D, Doyle M, O'Mathúna D. Interventions for nausea and vomiting in early pregnancy. *The Cochrane Database of Systematic Reviews* 2010, Issue 9. Art. No.: CD007575. DOI: 10.1002/14651858.CD007575.pub2.
8. Siu S, Yip S, Cheung C, Lau T. Treatment of intractable hyperemesis gravidarum by ondansetron. *Eur J Obstet Gynecol Reprod Biol* 2010; 105:73-4.
9. Tincello D, Johnstone M. Treatment of hyperemesis gravidarum with the 5-HT3 antagonist ondansetron (Zofran). *Postgrad Med J* 1996; 72:688-9.
10. Sullivan C, Johnson C, Roach H, Martin R, Stewart D, Morrison J. A pilot study of intravenous ondansetron for hyperemesis gravidarum. *Am J Obstet Gynecol* 1996; 174:1565-8.
11. Oliveira L, Capp S, You W, Riffenburgh R, Carstairs S. Ondansetron compared with doxylamine and pyridoxine for treatment of nausea in pregnancy. *Obstet Gynecol* 2014; 124:735-42.
12. Koren G. Motherisk update. Is ondansetron safe for use during pregnancy? *Can Fam Physician* 2012; 58:1092-3.
13. Tucker M, Jackson M, Scales M, Spurling N, Tweats D, Capel-Edwards K. Ondansetron: pre-clinical safety evaluation. *Eur J Cancer Clin Oncol* 1989; 25:S79-93.
14. Einarson A, Maltepe C, Navioz Y, Kennedy D, Tan M, Koren G. The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. *BJOG* 2004; 111:940-3.

15. Asker C, Wikner B, Källén B. Use of antiemetic drugs during pregnancy in Sweden. *Eur J Clin Pharmacol* 2005; 61:899-906.

16. Anderka M, Mitchell A, Louik C, Werler M, Hernández-Diaz S, Rasmussen S. Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects. *Birth Defects Res A Clin Mol Teratol* 2012; 94:22-30.

17. Pasternak B, Svanström H, Hvild A. Ondansetron in pregnancy and risk of adverse fetal outcomes. *N Engl J Med* 2013; 368:814-23.

18. Andersen J, Jiminez-Solem E, Andersen NL, et al. *Ondansetron use in early pregnancy and the risk of congenital malformations -- a register based nationwide control study*. International Society of Pharmaco-epidemiology. Montreal, Canada; 2013. Abstract 25, Pregnancy session 1.

19. Danielsson B, Wikner BN, Källén B. Use of ondansetron during pregnancy and congenital malformations in the infant. *Reprod Toxicol* 2014; 50:134-7.

20. Zofran® Prescribing Information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020007s040,020403s018lbl.pdf. Accessed 09 September 2015.

21. Practice Bulletin No. 153: Nausea and Vomiting of Pregnancy. *Obstet Gynecol* 2015; 126:e12-24.