# *Scary Science: Ondansetron Safety in Pregnancy—Two Opposing Results From the Same Danish Registry*

**A critical review of several recent papers published on ondansetron use in pregnancy**

**Abstract:** While perceived safe in pregnancy, several recent studies raise concerns about both fetal and maternal safety of ondansetron. Until more data are available, it should not be a first-line medication for morning sickness.

In February 2013, the *New England Journal of Medicine* published an article by Pasternak et al reporting that ondansetron is not associated with increased malformation rates when used for morning sickness.[1] This was based on retrospective analysis of data from the Danish Birth Registry collected between 2004 and 2011, and linked to the National Prescription Register to identify prescriptions of the drug. Each woman exposed to ondansetron (n = 1970) was matched to 4 unexposed control cases.

Of note, the mean age of exposure was 10 gestational weeks, which means that half of the cases were exposed to ondansetron at later than 10 gestational weeks, when malformations could not be produced any more. This can cause a bias toward the null, that is, dilute an existing risk because of inclusion of cases that were not exposed during embryogenesis.

On August 27, 2013, this study by Pasternak was presented again at the International Society of Pharmacoepidemiology in Montreal. Back-to-back with this study, Andersen et al[2] from Denmark presented a study using the same registries. This study covered more years (1997–2010) and more pregnant women (897,018 versus 608,835) using the same national registries as in Pasternak's study. Of major concern, Andersen's study detected a 2-fold increased risk of cardiac malformations with ondansetron {odds ratio = 2.0 (95% confidence interval [CI], 1.3–3.1)} leading to an overall increased risk of major malformations of 30%. To rule out confounding by indication, Andersen et al also examined metoclopramide taken for morning sickness, finding no increased teratogenic risk.

The fact that the same large registry can be manipulated to yield such opposing results is very concerning. We are witnessing exponential rise in use of prescription database linkage to birth registries. None of these were designed specifically to address fetal drug safety, and there may be flaws in the quality and completeness of the data. The example of the Danish data shows that in addition to these potential flaws, human decisions can shape the results in any direction. This is scary.

Ondansetron, a potent antiemetic agent, is a 5-HT3 receptor antagonist blocking the effect of serotonin, which was designed originally for cancer chemotherapy-induced nausea and vomiting. The drug is labeled also for use for nausea and vomiting associated with radiation therapy, anesthesia, and surgery. However, because of 30 years without an FDA-approved drug for morning sickness in the United States, increasing numbers of American women suffering from nausea and vomiting of pregnancy (NVP) have been managed with ondansetron. As of April 2013, the doxylamine–pyridoxine combination (Diclegis) has been approved by the regulatory agency.

## FETAL SAFETY

The fetal safety of the drug has been first addressed by Einarson et al[3] in 2004 through a prospective controlled cohort study of 176 women, mostly American, in whom we could not detect an increased teratogenic risk. However, this sample size could rule out only a 5-fold increased risk of major malformations and not any specific malformation. In February 2013, Pasternak et al[1] published the article cited above, further suggesting that the drug may be safe. However, the opposing results of analysis of the same Danish database by a different group of researchers call for caution.

Of potential importance, a recent large control study by the Sloan epidemiology unit and the Centers of Disease Control and Prevention has detected a 2-fold increased risk for cleft palate associated with ondansetron taken for NVP in the first trimester of pregnancy [odds ratio = 2.37 (95% CI, 1.28–4.76)].[4]

## MATERNAL SAFETY

In June 2012, the FDA issued a warning of possible serious QT prolongation and *Torsade the Pointe* among people receiving ondansetron.[5] As a result, the FDA requires strict follow-up of patients receiving ondansetron, to rule out long QT, electrolyte imbalance, congestive heart failure, or taking concomitant medications that prolong the QT interval.[5] In the context of NVP, quite a few women with severe NVP may have electrolyte abnormalities (hypokalemia or hypomagnesemia). Presently, counseling of women who receive ondansetron for morning sickness reveals that these FDA precautions are not being followed.

## SEROTONIN SYNDROME

Serotonin syndrome is life-threatening disorder of excessive serotonergic activity typically occurring when 2 or more serotonin-modifying agents are used simultaneously, although it may also occur with a single agent.[6] From January 1, 1998 to December 30, 2002, Health Canada received 53 reports of suspected serotonin syndrome. Serotonin syndrome was most often reported with the use of selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and venlafaxine.

The clinical presentation is characterized by the triad of cognitive or behavioral changes (confusion, agitation, lethargy, coma), autonomic instability (hyperthermia, tachycardia, diaphoresis, nausea, vomiting, diarrhea, dilated pupils), and neuromuscular changes (myoclonus, hyperreflexia, tremor).[6]

Critically, serotonin syndrome has also been reported with the concomitant use of 5-HT3 receptor antagonists (eg, ondansetron, dolasetron, granisetron).[7,8] Because a large number of pregnant women are on selective serotonin reuptake inhibitors and up to

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90% experience morning sickness, a possible interaction with ondansetron leading to serotonin syndrome must be considered. Because the paramount challenge of treating pregnant women with medications is fetal, and maternal safety ondansetron should be used cautiously only after drugs with better safety record, which have been labeled to use in pregnancy (eg doxylamine–pyridoxine) have been tried.

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## REFERENCES

1. Pasternak B, Svanström H, Hviid A. Ondansetron in pregnancy and risk of adverse fetal outcomes. *N Engl J Med.* 2013;368:814–823.
2. Andersen JT, Jimenez-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.
3. Einarson A, Maltepe C, Navioz Y, et al. The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. *BJOG*. 2004;111:940–943.
4. Anderka M, Mitchell AA, Louik C, et al. 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.
5. FDA Drug Safety communication: Abnormal heart rhythms may be associated with use of Zofran (ondansetron). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm271913.htm.
6. Mason PJ, Morris VA, Balcezak TJ. Serotonin syndrome presentation of 2 cases and review of the literature. *Medicine (Baltimore)*. 2000;79:201–209.
7. Turkel SB, Nadala JG, Wincor MZ. Possible serotonin syndrome in association with 5-$HT_3$ antagonist agents. *Psychosomatics*. 2001;42:258–260.
8. Sorscher SM. Probable serotonin syndrome variant in a patient receiving a selective serotonin reuptake inhibitor and a 5-$HT_3$ receptor antagonist. *J Psychopharmacol.* 2002;16:191.