

# USE OF ONDANSETRON (ZOFRAN) IN PREGNANCY: AN UPDATE

**Concerns Over Fetal Defects From Zofran Use During Pregnancy:** important facts to know.

1. No medications are FDA-approved for treating hyperemesis gravidarum.
2. Most research studies, large and small, find little if any increase (e.g. 3 in 10,000) in the number of birth defect cases after ondansetron (Zofran) use in early pregnancy. (See table below.)
3. Other concerns about Zofran safety involve giving a large, single dose (32 mg IV) or multiple serotonin antagonist meds simultaneously, neither of which are usually prescribed for HG.
4. About 3% of all babies in the US are born with major birth defects and 70% of pregnant women take at least one prescription medication during pregnancy.
5. About 15% of over 2.3 million pregnancies take Zofran during pregnancy. (Taylor, 2017)
6. Fetal anomalies such as septal defects and orofacial clefts are associated with genetic mutations, maternal diabetes, *poor prenatal nutrition/weight gain*, and high maternal weight prior to pregnancy.
7. Congenital cardiac defects affect 1% of all births and are defined as structural heart problems present at birth and are believed to occur before 10 weeks gestation. They range from minor (septal) to complex. Research finds the risk of cardiac defects (septal) in babies exposed to Zofran to be small or not existent.
8. Prematurity and other health problems associated with HG and resulting malnutrition may necessitate greater medical care and thus subsequent diagnosis of more cardiac septal defects in children.
9. Cleft defects are structural defects of the mouth, and a common birth defect affecting up to 12 per 10,000 infants. A few studies find a very *small* increase in the incidence of oral clefts after use of Zofran.
10. Research finds lower termination rates with medication usage for HG, suggesting many babies born to HG mothers would not be here without medications that effectively minimize nausea and vomiting.
11. GSK did not market Zofran for HG. The 2012 settlement GSK accepted to avoid further litigation focused on 3 other drugs. Zofran's small contribution to the settlement reimbursed the US government for health care charges arising from the use of Zofran off-label. The MDL lawsuit is being dismissed.
12. **When thinking about risk**, it is important to consider that the small potential for increased risks of birth defects found in a few studies on ondansetron are much lower than the risk, for example, of miscarriage after an amniocentesis (which occurs in 1 in 200 to 1 in 400 cases). Few studies consider malnutrition as a cause and thus compare the rates of defects in HG without ondansetron vs HG and ondansetron. Further, the risks from malnutrition, chronic dehydration, or termination of a wanted pregnancy are higher than the possible small risks with medication usage.



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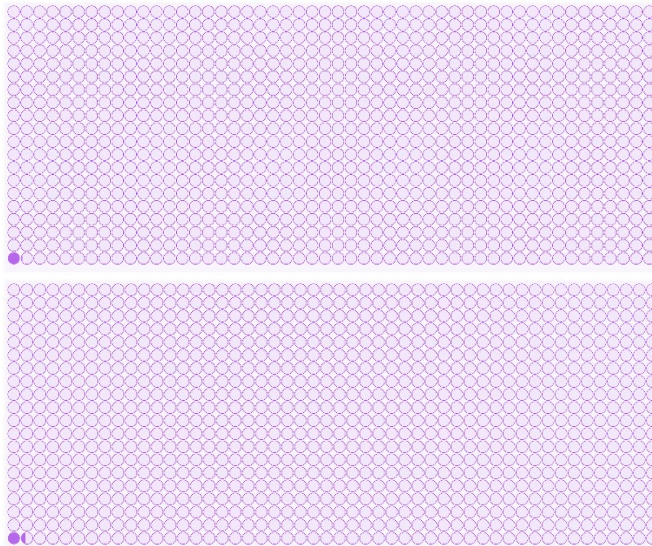
13. Another weakness in many studies is that we do not know the exact week of exposure, and in some, if the prescribed medication was actually taken. If patients are concerned about the as yet unconfirmed risk, they may want to wait until after 9-12 weeks gestation before starting ondansetron treatment.

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*“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.”*

*Obstet Gynecol. 2016 May;127(5):873-7.*

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**Oral clefts - unexposed to Zofran  
11/10,000 pregnancies**

**Oral clefts - exposed to Zofran  
14/10,000 pregnancies**

Graphic of Huybrechts' data (Huybrechts et al., JAMA (2018)) created by Brian Cleary PhD, Irish Medicines in Pregnancy Service, Rotunda Hospital/Royal College of Surgeons in Ireland.

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*“In this large, multicenter cohort study, there was **no association** between ondansetron exposure during pregnancy and increased risk of fetal death, spontaneous abortion, stillbirth, or major congenital malformations compared with exposure to other antiemetic drugs.”*

*JAMA Network Open. 2021 Apr;4(4):e215329.*

## ZOFRAN RESEARCH SUMMARY

CITATION	PARTICIPANTS	SUMMARY OF FINDINGS
<p>Anderka et al., <i>Clinical and molecular teratology</i> (2012)</p>	<p>514 Mothers who took Zofran in United States.</p>	<p>“Nausea and vomiting of pregnancy was not observed to be associated with an increased risk of birth defects, but possible risks related to three treatments (i.e. proton pump inhibitors, steroids and ondansetron), which could be chance findings, warrant further investigation.”</p> <p>Note: The increased risk was very small statistically.</p>
<p>Pasternak et al., <i>New England Journal of Med</i> (2013)</p>	<p>1970 Mothers who took Zofran during the first trimester in Denmark.</p>	<p>“Receipt of ondansetron was NOT associated with - significantly increased risk of spontaneous abortion - significantly increased risk of stillbirth - any major birth defect, preterm delivery, delivery of a low-birth-weight infant, or delivery of a small-for-gestational-age infant.”</p> <p>“Ondansetron taken during pregnancy was not associated with a significantly increased risk of adverse fetal outcomes.”</p>
<p>Colvin et al., <i>BioMed Research International</i> (2013)</p>	<p>251 Mothers who took Zofran during pregnancy in Western Australia, 2002–2005.</p>	<p>“Our study did not detect any adverse outcomes from the use of ondansetron in pregnancy but could not conclude that ondansetron is safe to use in pregnancy.”</p>
<p>Danielsson et al., <i>Reproductive Toxicology</i> (2014)</p>	<p>1349 Infants of women who took ondansetron in early pregnancy between 1998-2012 in Sweden.</p>	<p>“No statistically significantly increased risk for a major malformation was found... The teratogenic risk with ondansetron is low but an increased risk for a cardiac septum defect is likely.”</p> <p>Note: There were 17 septum (cardiac) defects out of 1349 (&lt;1%) women exposed to Zofran (aka cases) compared to their control group where 315 septum defects were identified out of 41,388 (&lt;1%) pregnancies exposed to meclizine. In both cases and controls approximately 99% of exposed babies did NOT have a cardiac septum defect.</p>



<p>Carstairs., <i>Obstet Gynecol</i> (2016)</p>	<p>423 records across all databases</p>	<p>“Data from the various studies were conflicting: whereas the three largest studies showed no increased risk of birth defects as a whole (36 malformations, 1,233 exposed compared with 141 malformations and 4,932 unexposed; 58/1,248 exposed compared with 31,357/895,770 unexposed; and 38/1,349 exposed compared with 43,620/1,500,085 unexposed... two of these studies demonstrated a slightly increased risk of cardiac defects.”</p> <p>“The overall risk of birth defects associated with ondansetron exposure appears to be low. There may be a small increase in incidence of cardiac abnormalities...”</p>
<p>Fejzo et al., <i>Reproductive Toxicology</i> (2016)</p>	<p>1070 HG pregnancies exposed to ondansetron compared to 771 HG pregnancies unexposed and compared to 1555 pregnancies with no HG and no ondansetron exposure.</p>	<p>“The overall results do not support evidence of teratogenicity of ondansetron.”</p>
<p>Huybrechts et al., <i>JAMA</i> (2018)</p>	<p>88,467 1st trimester ondansetron exposures compared to 1,727,947 unexposed babies</p>	<p>“ondansetron was not associated with cardiac malformations or congenital malformations overall after accounting for measured confounders but was associated with a small increased risk of oral clefts.”</p>
<p>Parker et al., <i>Obstet Gynecol</i> (2018)</p>	<p>Included 2 cohorts: 6,751 and 5,873 control mothers and 14,667 and 8,533 case mothers who reported first-trimester nausea and vomiting of pregnancy were included.</p>	<p>“there was no increased risk associated with first-trimester use of ondansetron ... compared with no treatment, although modest associations with cleft palate and renal agenesis-dysgenesis warrant further study.” “...these findings may be the result of chance”</p>
<p>Zambelli-Weiner et al., <i>Reprod Toxicol</i> (2019)</p>	<p>Early exposure to ondansetron occurred in 76,330 mother-child pairs (8.8%), and early exposure to medical administration of ondansetron occurred in 5557 mother-child pairs (0.64%).</p>	<p>First trimester exposure to ondansetron was associated with increased risk of cardiac (OR: 1.52 95% CI: 1.35–1.70) and orofacial cleft defects (OR: 1.32 95% CI: 0.76–2.28) in offspring.</p> <p>Note: The increased risk was very small statistically &amp; the study was <b>FUNDED by plaintiffs in an ondansetron lawsuit.</b></p>
<p>Huybrechts et al., <i>JAMA</i> (2020)</p>	<p>23,877 (1.3%) received at least one ondansetron injection during the first trimester.</p>	<p>Overall, these findings suggest that ondansetron is not a major teratogen.</p>
<p>Dormuth et al., <i>JAMA Netw Open</i> (2021)</p>	<p>456,963 pregnancies from US, UK, Canada exposed to Zofran</p>	<p>“In this large, multicenter cohort study, there was no association between ondansetron exposure during pregnancy and increased risk of fetal death, spontaneous abortion, stillbirth, or major congenital malformations compared with exposure to other antiemetic drugs.”</p>