UAMS Journal Club Summary
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Safety of Ondansetron Use in Treatment of Nausea and Vomiting in First Trimester Pregnancy

Clinical Bottom Line

Although there has been controversy that ondansetron is not safe for use in pregnancy, newer data on ondansetron use indicates that it can be used in early pregnancy without significant increases in negative effects on pregnancy outcomes, especially after the first 10 weeks of pregnancy. We suggest still trying other options for nausea control, and using shared decision in choosing whether or not to add ondansetron for those who cannot control their nausea and vomiting with other medication options.

PICO Question

Does ondansetron significantly increase the risk of negative pregnancy outcomes when compared with the use of other antiemetics?
P – Patients pregnant in the first trimester with nausea and vomiting
I – Administration of Ondansetron
C – Administration of an alternative antiemetic
O – Adverse pregnancy outcomes

Background

Up to 80% of women experience nausea and vomiting during the course of their pregnancy, and up to 25% of these women use ondansetron for treatment. The safety of ondansetron in pregnancy is unclear, as studies have yielded mixed results on different outcomes. Early studies did demonstrate signals toward harm, specifically in regard to congenital malformations, but more recent studies have shown that this may not be the case. This becomes especially true when considering that few studies have directly compared ondansetron to other commonly used antiemetics. Altogether, this evidence has left an unclear picture as to the safety of the use of Ondansetron in pregnancy.

Trial 1

Dormuth CR, Winquist B, Fisher A, et al. Comparison of Pregnancy Outcomes of Patients Treated With Ondansetron vs Alternative Antiemetic Medications in a Multinational, Population-Based Cohort. *JAMA Netw Open.* 2021;4(4):e215329. doi:10.1001/jamanetworkopen.2021.5329

Link: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2779055

The Basics:

This was a multicenter, retrospective cohort study of female patients aged 12 to 55 years who were pregnant between April 2002 and March 2016 that included data collected from 5 Canadian provinces, the IBM MarketScan Research Database from the US, and the United Kingdom's Clinical Practice Research Datalink. The goal of this study was to compare pregnancy outcomes of patients who received ondansetron with those who received an alternative antiemetic for treatment of nausea and vomiting during pregnancy.

Inclusion Criteria:
Patients were included if they had a spontaneous abortion, induced abortion, stillbirth, or live birth within the set time period, and they had a dispensation or prescription for ondansetron or another antiemetic during their pregnancy.

Exclusion Criteria:
Patients were excluded if they did not have continuous drug and medical coverage for at least 1 year before pregnancy outcome was recorded. Live births with chromosomal abnormalities, genetic syndromes, congenital virus infections, and other anomalies with known causes were excluded from analysis in regard to the congenital malformations cohort.

Primary Outcomes:
Fetal death

Secondary Outcomes:
Spontaneous abortion, stillbirth, major congenital malformations

Results:
After pooling data from multiple resources, a total of 163,810 pregnancies with exposure to ondansetron and 306,766 pregnancies with exposure to other antiemetics were used in the final analysis. Ondansetron use in pregnancy was not associated with an increased risk of fetal death (HR, 0.91; 95% CI, 0.67-1.23), stillbirth (HR, 0.97; 95% CI, 0.79-1.20), or major congenital malformations (OR, 1.06; 95% CI, 0.75-2.31). From this data the authors concluded that there was no association between exposure to ondansetron during pregnancy and an increased risk of fetal death, spontaneous abortion, stillbirth, or major congenital malformations when compared to exposure to other antiemetic medications.

Limitations/Bias:
Limitations of this trial included lack of analysis of certain congenital malformations due to the rarity of the condition as well as limitations in data collection. As the exposure was determined by written or filled prescriptions, it is not certain whether the medications were actually taken by the patient. With this being a retrospective analysis, there also was no blinding in this study.

Trial 2
Huybrechts KF, Hernández-Díaz S, Straub L, et al. Association of Maternal First-Trimester Ondansetron Use With Cardiac Malformations and Oral Clefts in Offspring. *JAMA.* 2018;320(23):2429–2437. doi:10.1001/jama.2018.18307

Link: https://jamanetwork.com/journals/jama/fullarticle/2718793

The Basics:
This was a retrospective cohort study that utilized the 2000-2013 nationwide Medicaid Analytic extract to evaluate the association between ondansetron exposure during the first trimester of pregnancy and the risk of congenital malformations. The cohort consisted of 1 816 414 pregnancies contributed by 1 502 895 women enrolled in Medicaid from 3 months before the last menstrual period through 1 month or longer after delivery; infants were enrolled in Medicaid for at least 3 months after birth. Primary outcomes were cardiac malformations and oral clefts diagnosed during the first 90 days after delivery. Secondary outcomes included congenital malformations overall and subgroups of cardiac malformations and oral clefts.

Inclusion Criteria:
Pregnant women from the years 2000-2013 that were aged 12 through 55 years and were required to have Medicaid coverage from 3 months before the date of the last menstrual period to 1 month after delivery. They were also required to have filled at least one ondansetron prescription during the first 3 months of pregnancy to be considered exposed.

Exclusion Criteria:
Pregnant patients with exposure to a known teratogenic medication (i.e., warfarin, antineoplastic agents, lithium, isotretinoin, misoprostol, thalidomide) during the first trimester (n = 3562) and pregnancies with a chromosomal abnormality (n = 3156) were excluded. Additionally women who did not retain Medicaid for at least 1 month following delivery or infants who did not have Medicaid coverage during entire first 3 months of life were excluded.

Primary Outcomes:
Cardiac malformations and cleft palate.

Secondary Outcomes:
Specific subgroups of cardiac malformations and oral clefts (ie, palate, lip, or lip and palate) were evaluated along with congenital malformations overall.

Results:
Among 1,816,414 pregnancies (mean age of mothers, 24.3 years), 88,467 (4.9%) were exposed to ondansetron during the first trimester. Overall, 14,577 of 1,727,947 unexposed and 835 of 88,467 exposed infants were diagnosed with a cardiac

malformation, for an absolute risk of 84.4 (95% CI, 83.0 to 85.7) and 94.4 (95% CI, 88.0 to 100.8) per 10,000 births respectively. The absolute risk of oral clefts was 11.1 per 10,000 births (95% CI, 10.6 to 11.6; 1921 unexposed infants) and was 14.0 per 10,000 births (95% CI, 11.6 to 16.5; 124 exposed infants). The risk of any congenital malformation was 313.5 per 10,000 births (95% CI, 310.9 to 316.1; 54,174 unexposed infants) and was 370.4 (95% CI, 358.0 to 382.9; 3277 exposed infants). The adjusted relative risk (RR) for cardiac malformations was 0.99 (95% CI, 0.93 to 1.06) and the adjusted risk difference (RD) was −0.8 (95% CI, −7.3 to 5.7 per 10,000 births). For oral clefts, the adjusted RR was 1.24 (95% CI, 1.03 to 1.48) and the RD was 2.7 (95% CI, 0.2 to 5.2 per 10,000 births). The adjusted estimate for congenital malformations overall was an RR of 1.01 (95% CI, 0.98 to 1.05) and an RD of 5.4 (95% CI, −7.3 to 18.2 per 10,000 births).

Limitations/Bias:
The major limitation/bias of this study is that the data is collected only from pregnancies of women who have Medicaid as their primary medical coverage, so this could introduce possible confounding factors related to socioeconomic status. Additionally, this only examines pregnancies where an ondansetron prescription was filled; it is not known how many of these prescriptions were taken.