ONLINE EXCLUSIVE

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Q/ How safe and effective is ondansetron for nausea and vomiting in pregnancy?

EVIDENCE-BASED ANSWER

A/ **ORAL ONDANSETRON IS MORE EFFECTIVE** than a combination of pyridoxine and doxylamine for outpatient treatment of nausea and vomiting in pregnancy (strength of recommendation [SOR]: **B**, randomized controlled trial [RCT]).

For moderate to severe nausea and vomiting, intravenous (IV) ondansetron is at least as effective as IV metoclopramide and may cause fewer adverse reactions (SOR: **B**, RCTs).

Disease registry, case-control, and cohort studies report a slight increase in the risk of cardiac defects with ondansetron use in first-trimester pregnancies, but no major or other birth defects are associated with ondansetron exposure (SOR: **B**, a systematic review of observational trials and a single retrospective cohort study).

A specialty society guideline recommends weighing the risks and benefits of ondansetron use before 10 weeks' gestational age and suggests reserving ondansetron for patients who have persistent nausea and vomiting unresponsive to first- and second-line treatments (SOR: **C**, expert opinion).

Evidence summary

Efficacy. A 2014 double-blind RCT compared ondansetron with pyridoxine plus doxylamine (standard care) for outpatient treatment of nausea and vomiting in pregnancy.[1] The 36 patients had an average gestational age of 8 weeks and received either 4 mg oral ondansetron plus placebo or 25 mg pyridoxine plus 12.5 mg doxylamine 3 times daily for 5 days. Nausea and vomiting severity was measured using 2 separate 10-cm visual analog scales (VAS) with scores ranging from 0 to 10 (worst nausea or vomiting imaginable). Researchers determined that a VAS score reduction of 2.5 cm was clinically significant.

Patients treated with ondansetron described greater improvements in nausea (mean VAS change –5.1 cm vs –2 cm; $P = .019$) and vomiting (mean VAS change –4.1 cm vs –1.7 cm; $P = .049$). No patient required hospitalization. The researchers didn't report on adverse effects or birth outcomes. The study was limited by the small sample size and a high rate (17%) of patients with missing data or who were lost to follow-up.

IV ondansetron vs metoclopramide: Similar efficacy, fewer adverse effects

A 2014 double-blind RCT compared IV ondansetron with IV metoclopramide (standard care) for treating hyperemesis gravidarum.[2] The 160 patients had an average gestational age of 9.5 weeks and intractable nausea and vomiting severe enough to cause dehydration, metabolic disturbance, and hospitalization. Patients received either 4 mg ondansetron or 10 mg metoclopramide IV every 8 hours for 24 hours. The primary outcomes were number of episodes of vomiting over 24 hours and self-reported sense of well-being rated on a 10-point scale.

No differences were found between the ondansetron- and metoclopramide-treated

groups in terms of vomiting over 24 hours (median episodes 1 and 1; P = .38) or sense of well-being (mean scores 8.7 vs 8.3; P = .13). Patients treated with ondansetron were less likely to have persistent ketonuria at 24 hours (relative risk [RR] = 0.3; 95% confidence interval [CI], 0.1-0.8; number needed to treat [NNT] = 6). They also were less likely to feel drowsy (RR = 0.3; 95% CI, 0.1–0.8; NNT = 6) or complain of dry mouth (RR = 0.4; 95% CI, 0.1-0.9; NNT = 8). The study didn't report birth outcomes or adverse fetal effects.

Oral ondansetron outperforms oral metoclopramide in small study

A 2013 double-blind RCT compared ondansetron with metoclopramide (standard care) for controlling severe nausea and vomiting.[3] The 83 patients, with an average gestational age of 8.7 weeks, had more than 3 vomiting episodes daily, weight loss, and ketonuria. They received either 4 mg oral ondansetron or 10 mg oral metoclopramide for 2 weeks as follows: 3 times daily for 1 week, then twice daily for 3 days, then once daily for 4 days. Patients rated nausea severity using a 10-cm VAS from 0 to 10 (severe nausea) and recorded the number of vomiting episodes.

Women treated with ondansetron had significantly lower VAS scores on Days 3 and 4 of treatment (5.4 vs 6, P = .024 on Day 3; 4.1 vs 5.7, P = .023 on Day 4). They also had fewer episodes of vomiting on Days 2, 3, and 4 (3.7 vs 6, P = .006 on Day 2; 3.2 vs 5.3, P = .006 on Day 3; and 3.3 vs 5, P = .013 on Day 4). The study was limited by the small sample size.

Safety. A 2016 systematic review examining the risk of birth defects associated with ondansetron exposure in pregnancy found 8 reports: 5 birth registries, 2 case-control studies, and 1 prospective cohort study.[4] Investigators compared rates of major malformations—cleft lips, cleft palates, neural tube defects, cardiac defects, and hypospadias—in 5101 women exposed to ondansetron in the first trimester with birth defect rates in more than 3.1 million nonexposed women.

No study demonstrated an increased rate of major malformations associated with ondansetron exposure except for 2 disease registry studies with nearly 2.4 million patients that reported a slight increase in the risk of cardiac defects (odds ratio [OR] = 2; 95% CI, 1.3-3.1; OR = 1.6, 95% CI, 1-2.1). Comparisons of other birth defect rates associated with ondansetron exposure were inconsistent, with studies showing small increases, decreases, or no difference in rates between exposed and nonexposed women.

Exposure vs nonexposure: No difference in adverse outcomes

A 2013 retrospective cohort study looked at 608,385 pregnancies among women in Denmark, of whom 1970 (0.3%) had been exposed to ondansetron.[5] The study found that exposure to ondansetron compared with nonexposure was associated with a lower risk for spontaneous abortion between 7 and 12 weeks' gestation (1.1% vs 3.7%; hazard ratio [HR] = 0.5; 95% CI, 0.3-0.9).

No significant differences between ondansetron exposure and nonexposure were found for the following adverse outcomes: spontaneous abortion between 13 and 22 weeks' gestation (1% vs 2.1%; HR = 0.6; 95% CI, 0.3-1.2); stillbirth (0.3% vs 0.4%; HR = 0.4; 95% CI, 0.1-1.7); any major birth defect (2.9% in both exposed and nonexposed women; OR = 1.12; 95% CI, 0.69-1.82); preterm delivery (6.2% vs 5.2%; OR = 0.9; 95% CI, 0.7-1.3), low birth weight infant (4.1% vs 3.7%; OR = 0.8; 95% CI, 0.5-1.1); and small-for-gestational-age infant (10.4% vs 9.2%; OR = 1.1; 95% CI, 0.9-1.4).

Recommendations

The American College of Obstetricians and Gynecologists (ACOG) states that insufficient data exist regarding the safety of ondansetron for the fetus.[6] ACOG recommends individualizing the use of ondansetron before 10 weeks of pregnancy after weighing the risks and benefits. ACOG also recommends adding ondansetron as third-line treatment for nausea and vomiting unresponsive to first- and second-line treatments.

Editor's takeaway

Higher-quality studies showed ondansetron to be an effective treatment for hyperemesis gravidarum. Lower-quality studies raised some concerns about adverse fetal effects.

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Oral ondansetron is more effective than pyridoxine plus doxylamine for outpatient treatment of nausea and vomiting in pregnancy.

Although the adverse effects were rare and the quality of the evidence was lower, the cautionary principle suggests that ondansetron should be a second-line option. JFP

References

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