



## Treatment of reflux disease during pregnancy and lactation

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### ABSTRACT

Gastroesophageal reflux disease (GERD) is frequently seen during pregnancy. In the medical treatment of pregnant women with GERD, alginate acid and sucralfate can be used. Calcium- and magnesium-based antacids can also be used, particularly for patients with preeclampsia. In particular, ranitidine -a histamine-2 receptor blocker- is preferred. In the case of non-responsiveness to the abovementioned treatments, proton pump inhibitors (PPIs), except omeprazole, can be given considering the benefit-harm ratio for the mother and fetus after the first trimester. In cases with GERD during the lactation period, drugs having minimum systemic absorption, such as sucralfate and alginate acid, are preferable but there is no data.

**Keywords:** Reflux, pregnancy, safety

### SAFETY OF DRUG TREATMENT IN PREGNANT PATIENTS WITH GERD?

"Heartburn" is a symptom that can be seen in 30%-50% pregnancies. It particularly develops at the end of the first trimester, in the second trimester, and it becomes more apparent in the last trimester (1-3). Basal lower esophageal sphincter (LES) pressure may not change in the first trimester. The reason for this is demonstrated to be the low response to physiological stimuli such as pentagastrin, edrophonium chloride, methacholine, and food with protein in the first trimester of pregnancy. The LES pressure may decrease to 33%-50% of basal values in the second trimester. During the second and third trimesters, a decrease in the LES pressure can be observed due to the elevated intra-abdominal pressure, increased progesterone, abnormal gastric discharge, or delayed intestinal transit (4).

### Antacids

In a previous retrospective case-controlled study on the use of antacids in pregnancy, no increase was detected in the development of congenital anomaly with aluminum hydroxide, sodium bicarbonate, magnesium

trisilicate, and calcium carbonate (5,6). Authors of this study reported that antacids having therapeutic doses of aluminum, magnesium, and calcium can be safely used during pregnancy (7).

In a European consensus meeting conducted in 2003 (Contemporary understanding and management of reflux and constipation in the general population and pregnancy: a consensus meeting), it was reported that the use of calcium-based antacids in pregnant women with GERD could be beneficial because it reduced the risk of hypertension and preeclampsia (8). Moreover, in a comprehensive randomized placebo-controlled study, it was demonstrated that the use of magnesium sulfate during pregnancy reduced eclampsia and maternal risk; it also caused no serious side effects in the short term. Antacids having sodium bicarbonate must be avoided because they can lead to metabolic alkalosis and increased fluid load both in the mother and the fetus (5).

Alginate builds a non-systemic strong barrier against acid and food reflux in the esophagus. In an open-labeled

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multi-centered study including 150 cases, the use of alginate for over 4 weeks yielded satisfying results both for physician and for patient, but fetal distress was observed in 3 fetuses (9). In another multi-centered (South Africa and United Kingdom) prospective study, a total of 144 women were given alginate therapy at a maximum dose of 80 mL/day for 4 weeks during their pregnancies. While side effects directly related to the drug, such as diarrhea and nausea, were observed only in 3 of the mothers using alginate, fetus-related perinatal morbidity and mortality rates were found to be similar to normal population incidences (10).

**Sucralfate**

Sucralfate is a sulfated disaccharide salt. It is absorbed from the gastrointestinal system at a minimal level and it exhibits a local mucosal protective effect. It inhibits the activity of pepsin and prevents the development of ulcers (5). The teratogenic effect of sucralfate has not been revealed, although it was used at a 50-times higher dose in animal models than in human subjects (9). In an Italian study conducted on the safety of sucralfate use in pregnancy, 42 women were administered 3x1 g/day doses of sucralfate for a month: no maternal or fetal side effects were reported (11). In a surveillance study in which 229101 pregnancies were examined between 1985 and 1992, birth defects were observed only in 5 out of 185 newborns that were exposed to sucralfate during the first trimester: this rate is below the expected rate of birth defects (5/185 vs. 8/185) (9).

**Metoclopramide**

Metoclopramide, which is a dopamine-2 receptor antagonist, prevents gastroesophageal reflux by increasing the LES pressure. In addition, it is effective in the treatment of GERD because it increases the esophageal acid clearance and accelerates gastric drainage.

Metoclopramide rapidly passes through the placenta and the plasma concentration of the fetus can reach 60%–70% of the maternal plasma concentration (7). However, although the dose was 12-250 times higher in animal studies than in human studies, no teratogenic effect was observed (12). Further, in human subjects, no metoclopramide-related congenital malformation or fetal toxicity has been reported yet. In the Michigan Medicaid Surveillance Study, a major birth defect was observed only in 10 (5.2%) out of 992 newborns that were exposed to metoclopramide in the first trimester (expected: 8/992) (9). In the study of Sørensen et al. (13), in which they compared 309 newborns with exposure to metoclopramide during conception or pregnancy with the control group including 13327 cases, no increase was detected in congenital malformation (OR: 1.1, 95% CI: 0.60-2.06), low birth weight (OR: 1.79, 95% CI: 0.83-3.86), or preterm labor risk (OR: 1.02, 95% CI: 0.62-1.67). Similarly, in a retrospective cohort study examining 81703 single births, Matok et al. (14) found no increase in the risks of congenital malformation, preterm labor, perinatal mortality, low birth weight, and low APGAR score with exposure to metoclopramide during the first trimester.

**Histamine-2 (H2) Receptor Blockers**

H2 receptor blockers are the safest and most widely used drugs in pregnant women with heartburn that do not respond to lifestyle modifications and antacids. All H2 receptor blockers are in FDA pregnancy category of B. Cimetidine and ranitidine have been used in pregnancy for about 30 years owing to their high safety profiles. On the other hand, specific safety studies have been conducted only for ranitidine (5). Although animal studies have revealed that cimetidine exhibited anti-androgenic action and caused reduction in the sizes of testis, prostate, and seminal vesicle, no anti-androgenic effect associated with H2 receptor blockers was demonstrated in any newborns in the human data (15). According to the data of the Michigan Medicaid Surveillance Study, in 229101 pregnancies examined between 1985 and 1992, major congenital malformation was observed in 20 (4.3%) out of 460 newborns that were exposed to cimetidine in the first trimester and in 23 (4.5%) out of 560 newborns that were exposed to ranitidine in the first trimester. These data were found to be similar to the results of newborns without the exposure to H2 receptor blockers (4.3%) (9). Similarly, in the multi-centered international study of Ruigómez et al. (16), it was demonstrated that the use of cimetidine (RR: 1.2, 95% CI: 0.6-2.3) or ranitidine (RR: 1.4, 95% CI: 0.8-2.4) during pregnancy did not cause an increase in the risk of non-genetic congenital malformation.

Data on the safety of famotidine and nizatidine are fewer than those on the safety of ranitidine and cimetidine. While fetal toxicity or teratogenicity associated with famotidine was not reported in animal studies, it was revealed that the rates of abortus, low birth weight, and fetal loss increased when nizatidine was used in rabbits at a dose 300 times higher than the dose recommended for human subjects (17,18).

In a meta-analysis examining the data of 4 studies on the safety of all the H2 receptor blockers in pregnancy (2398 exposure to H2 receptor blockers vs. no exposure to 119892 H2 receptor blockers), no increased risk was detected for spontaneous abortus (OR: 0.62, 95% CI: 0.36-1.05), preterm labor (OR: 1.17, 95% CI: 0.94-1.47), or growth retardation according to gestational age (OR: 0.28, 95% CI: 0.06-1.22) (19).

**Proton Pump Inhibitors**

Proton pump inhibitors (PPI) are the most effective drugs used in the treatment of reflux symptoms and esophagitis. However, the use of PPIs in pregnancy is not as common as H2 receptors, and data on the safety of these drugs in pregnancy are more restricted.

While omeprazole, rabeprazole, and esomeprazole are FDA category-C agents, others are FDA category-B medications. Dose-related mortality developed in the embryos of pregnant rabbits and rats at the doses of omeprazole used in human beings, but no teratogenicity was observed (20). Moreover, no increase was found in the risk of congenital malformation in a meta-analysis

examining 5 studies (a total of 534 births) about the safety of omeprazole exposure (RR: 1.05, 95% CI: 0.59-1.85) (21).

In animal studies in which lansoprazole was used at a dose 40 times higher than that recommended for human subjects, impaired fertility or fetal toxicity was not detected (22). In a study comparing 62 cases with lansoprazole exposure to a control group, while the frequency of congenital anomaly was 3.9% in the lansoprazole group, it was 3.8% in the control group (23).

The safety of using rabeprazole, pantoprazole, and esomeprazole—which are newer PPIs—in pregnancy was proven in some animal experiments (9). In the meta-analysis conducted by Gill et al. (24) in 2009, including 6 prospective and retrospective cohort studies concerning the safety of omeprazole, pantoprazole, and lansoprazole were included. According to the results of this meta-analysis, no increase was found in the risk for congenital malformation, preterm labor, or spontaneous abortion due to in utero exposure to PPIs. Moreover, in another recent study, it was confirmed that there was no increase in the risk for congenital malformation due to the use of lansoprazole, omeprazole, or pantoprazole in the first trimester (OR: 1.06, 95% CI: 0.89-1.33). In addition, it was also revealed in this study that no increase occurred in the risk for preterm labor, perinatal mortality, or low birth weight due to exposure to PPIs during the third trimester.

In the population-based study of Pasternak et al. (25), in which the safety of PPIs including omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole was considered, it was reported that the risk of birth defect did not increase with the use of these agents in the first trimester.

#### RECOMMENDATIONS

- In the first stage, alginic acid, which is known to be safe, can be used (Level of evidence: 3b).
- In pregnant women with preeclampsia, calcium- and magnesium-based antacids should be preferred due to their effect of lowering the blood pressure (Level of evidence: 3b).
- In cases in which antacid therapy is inadequate, ranitidine is the preferred H<sub>2</sub> receptor blocker (Level of evidence: 2a).
- In particular, in pregnant women with reflux accompanied by nausea, metoclopramide can be preferred (Level of evidence: 2b).
- If no response is obtained to the abovementioned therapies, PPIs, except omeprazole, can be given considering the benefit–harm ratio for mother and fetus after the first trimester (Level of evidence: 3a).

#### SAFETY OF DRUGS IN PATIENTS WITH GERD DURING LACTATION PERIOD?

Data on the use of GERD drugs during the lactation period are very limited and are restricted to the studies and anecdotes on the metabolite level.

The passage of aluminum or magnesium hydroxide into breast milk could not be determined. The data on the passage of sucralfate into breast milk are insufficient. However, minimal absorption of the agent suggests that the passage into breast milk will also be at the minimal level (15).

Metoclopramide passes into breast milk. However, no neonatal side effect was observed in mothers using up to a dose of 45 mg/day (7).

Metabolized ranitidine passes into breast milk at a higher rate than in plasma, but its effect on infants is unknown. Although cimetidine passes into breast milk, its use during the lactation period is reported to be safe by the American Academy of Pediatrics. It passes into breast milk at a lesser rate than famotidine, ranitidine. In spite of the fact that the passage of nizatidine into breast milk is low (0.1%), it was reported to cause growth retardation in animal models (9,26).

There are no data on the passage of omeprazole into breast milk. In one case report, satisfactory results were obtained in a case with refractory GERD during the lactation period, and no neonatal side effect was observed. Although the fact that lansoprazole passes into breast milk is unknown, its use is not recommended. On the other hand, in the only case report on the use of pantoprazole, 0.14% of the weight-normalized maternal dose was detected in the infant (7.3 µg), but no side effect was found in the infant (27,28).

#### RECOMMENDATIONS

- Data on the safety of medications that can be used for patients with GERD during the lactation period are not available. Some drugs with minimum systemic absorption, such as sucralfate and alginic acid, can be used (Level of evidence: 5).

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