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Update on Proton Pump Inhibitors During Pregnancy

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GERD

Gastro-esophageal reflux disease (GERD) is a chronic disease characterized by repeated or prolonged exposure of the lining of the esophagus to the acidic contents of the stomach. Common symptoms include heart burn and acid regurgitation. Approximately 22% of pregnant women will suffer from reflux during the first trimester, 39% develop it by the second trimester, and up to 72% of women develop it by the third trimester (Tytgat et al, 2003).

GERD rarely causes serious complications during pregnancy, but symptoms may be unpleasant and require treatment. There is a common treatment protocol for pregnant women outlined in the literature. GERD is typically treated with dietary and lifestyle changes, along with periodic use of over-the-counter calcium and magnesium based antacids (Tytgat et al., 2003). If this approach is not effective, the H₂-blocker ranitidine is often tried concurrently with antacids (Katz et al., 1998; Richter, 2003). Proton pump inhibitors are generally reserved for more severe cases.

Proton pump inhibitors are effective treatments for conditions such as GERD because they block enzymes in the wall of the stomach that produce acid. A variety of GERD medications were reviewed in the June 1999 (RISK//NEWSLETTER 7(5)); this newsletter serves as an adjunct to that issue.

This newsletter will focus on the proton pump inhibitors omeprazole (Prilosec), lansoprazole (Prevacid), rabeprazole (Aciphex), pantoprazole (Protonix), and esomeprazole magnesium (Nexium).

Omeprazole (brand name: Prilosec)

Omeprazole was approved by the FDA in 1989. Currently, it is the best studied proton pump inhibitor for use during pregnancy. A reproductive study in rats and rabbits found no teratogenic effect in fetal development after administering doses up to 250-500 times greater than the recommended human dose (Lalkin et al., 1998). There was a slight increase in fetal loss at the top doses.

Although there are individual case reports of congenital anomalies, controlled studies have not found an increased risk of major malformations. A prospective cohort study by Lalkin et al. (1998) described 113 pregnancies exposed to omeprazole compared to a control group taking H₂-blockers and a control group with no prescription GERD medications. Eighty-five percent of the women took omeprazole during the first trimester, while 15% continued use through delivery.

There were no significant differences in the number of congenital anomalies, miscarriages, mean birthweight, or premature delivery between the three groups. Based on the small sample size, this study had an 80% power to identify a 5-fold increased risk.

Two databases, one from England and the other from Italy, were combined in a study published in 1999 that was designed to assess the incidence of congenital malformations in women who had received a

prescription for an acid-suppressing drug including omeprazole during the 1st trimester (Ruigomez et al., 1999). Omeprazole was taken in 134 pregnancies, resulting in 139 live births. There was no significant increase in the rate of malformations.

A review of the Swedish medical birth registry by Kallen (2001) identified 955 infants exposed to omeprazole during pregnancy. Eighty-six percent of the infants were exposed only during the first trimester. Specific data on dose and timing was not available. The authors found no significant increase in congenital anomalies, low birth weight, low Apgar scores, or perinatal survival.

Most recently, a multicenter prospective case controlled study by Diav-Citrin et al. (2005) identified 295 women exposed to omeprazole during pregnancy. Seventy-nine percent of exposures occurred during the first trimester only. The median dose was 20 mg (20-40 mg) and median duration of use was 22 days (4-47 days). The incidence of congenital anomalies in the study population was not greater than the observed frequency in the control group. This sample size was noted to have an 80% power to detect a 2.72-fold increase of major malformations. There were also no significant differences in the rates of miscarriage, ectopic pregnancies, stillbirths, or preterm deliveries. There was a significant 60 g reduction in the median birth weight in the exposed group which has not been replicated in other studies.

Brunner et al. (1998) identified nine cases of maternal exposure to omeprazole: four women were treated during the first trimester and of those, three women continued taking omeprazole until delivery. Five women were treated during the third trimester only. There were no congenital anomalies reported. Brunner et al. followed-up with the children on an average of 5 years (2-12 years) and reported normal development in all nine children.

Lansoprazole (brand name: Prevacid)

Lansoprazole was approved by the FDA in 1995. A reproductive study in rats and rabbits by Schardein et al. (1990) found no adverse effect on fertility and no increased incidence of congenital anomalies after administering doses 16 to 40 times the recommended human doses.

The largest study sample size on lansoprazole consisted of only 62 pregnancies exposed to lansoprazole, 55 of which were during the first trimester (Diav-Citrin et al., 2005). The median dose was 30 mg (30-60 mg) and the median duration of use was 14 days (7-32 days). The incidence of congenital anomalies in the study population was not greater than the observed frequency in the control group. This sample size had an 80% power to identify a 4.75-fold increase risk of major malformations. There were no significant differences in the rates of miscarriages, ectopic pregnancies, stillbirths, or the rate of preterm deliveries.

Rabeprazole (brand name: Aciphex)

Rabeprazole was approved by the FDA in 1999. In preclinical studies reported by the manufacturer, no teratogenic effects were seen in rats or rabbits at 8-13 times the human dose (Product information, Aciphex, 1999). Administered doses of 195 times the human dose during late pregnancy and lactation in rats decreased weight gain of the pups. Currently there are no studies evaluating the safety of rabeprazole use during pregnancy in humans.

Pantoprazole (brand name: Protonix)

Pantoprazole was approved by the FDA in 2000. A reproductive study by the manufacturer in rats and rabbits found no adverse effects in fetal development after administering doses 16 to 88 times greater than the recommended human dose. (Product information, Protonix, 2001).

Diav-Citrin et al. (2005) prospectively followed 53 pregnancies exposed to pantoprazole. Forty-seven exposures occurred during the first trimester. All women took 40 mg omeprazole daily for a median duration of 14 days (7-23 days). There were no significant differences in the rates of miscarriages,

ectopic pregnancies, stillbirths, or rate of preterm deliveries. The incidence of congenital anomalies in the study population of 48 infants was not greater than the observed frequency in the control group. This study had an 80% power to identify a 4.9-fold increase risk of major malformations.

Esomeprazole (brand name: Nexium)

Esomeprazole was approved by the FDA in 2001. An animal study by the manufacturer found no adverse effects in fertility or embryo development after administering oral doses to rats up to 57 times the human dosage and oral doses to rabbits up to 35 times the human dose (Product information, Nexium, 2001).

There are no human studies specific to esomeprazole. However, due to the chemical similarities to omeprazole, studies on the latter should have some relevance. Omeprazole is a racemate, meaning it contains two compounds (isomers) with the same chemical components but different spatial dispositions which leads to different pharmacological properties (Kendall 2003). Esomeprazole is one of isomers of omeprazole.

Summary

During pregnancy, dietary changes and limited use of antacids and/or ranitidine is typically the primary treatment for GERD. Proton pump inhibitors are typically reserved for pregnant women with moderate/severe gastrointestinal symptoms for which the former treatments are ineffective. As a class, current data does not suggest that proton pump inhibitors represent an increased risk for major malformations. However, only omeprazole has several human studies for better confirmation. Chronic use throughout pregnancy is not well studied.

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