

# First-Trimester PPIs Linked to Birth Defects

BY HEIDI SPLETE

FROM THE ANNUAL DIGESTIVE DISEASE WEEK

NEW ORLEANS — Pregnant women who used proton pump inhibitors to treat their gastroesophageal reflux during the first trimester of pregnancy were more than twice as likely to have babies with cardiac defects than were pregnant women who did not use PPIs, based on a retrospective study of over 200,000 women.

Previous data have indicated a non-significant trend toward an association between use of proton pump inhibitors (PPIs) early in pregnancy and cardiac malformations, Dr. Andrew D. Rhim of the University of Pennsylvania in Philadelphia said in his presentation.

"Before this study, there were very limited human data [on risk], and this study suggests a possible increased risk of cardiovascular defects," Dr. Jennifer Niebyl of the University of Iowa, Iowa City, said in an interview. These results, however, are hampered by uncertainties surrounding the trimester of exposure and possible selection bias.

Last year, Dr. Niebyl and her colleagues published the results of a study of 3,458 women, which suggested that metoclopramide may be a safe option for pregnant

women (N. Engl. J. Med. 2009;360:2528-35). She advised that pregnant women avoid PPIs during the first trimester.

From a database of 208,951 pregnancies, Dr. Rhim and his colleagues identified 2,445 cases of cardiac malformations in newborns and compared them with 19,530 matched controls. All of the newborns were registered between 2000 and 2008 in the Health Improvement Network, a database of information collect-

ed by general practitioners in the United Kingdom.

"We found 130 instances of a PPI being prescribed within the first trimester" in the women who gave birth to infants with cardiac birth defects, Dr. Rhim said. After controlling for multiple variables including maternal BMI, smoking status, alcohol use, and use of other medications, the risk for cardiac birth defects remained significant. A history of either

cardiac malformations or diabetes in the mother was associated with a significantly increased risk of a cardiac defect in the baby, Dr. Rhim noted.

The researchers identified three types of defects: septal defects, left ventricular defects, and right ventricular defects. The frequencies of the three defects were comparable with those seen in the general population of the United Kingdom, said Dr. Rhim. ■

## Timing Is Key

MY TAKE

Although retrospective case-control studies can show associations, they cannot determine if the associations are causal. Moreover, such studies have major limitations, including selection bias, recall bias, and timing of exposures.

Timing is very important. For example, closure of the ventricular septum occurs by 6 weeks postconception, so an exposure that causes a ventricular septal defect (VSD) must occur before 6 weeks.

Another consideration is the animal reproduction data included by the manufacturers in their package inserts. None of the six PPIs available in the U.S. cause structural defects in animals. This is important because, with only two exceptions, all known human teratogens also are teratogenic in animals.

To my knowledge, no study has shown a significant association between PPIs and cardiac defects. Atrial septal defects and VSDs are among the most common cardiac defects, and VSDs are, overall, one of the most common birth defects.

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For patients with  
type 2 diabetes whose  
blood glucose control  
is not on track  
with orals alone

“YOU MAY WANT TO  
HAVE THE INSULIN  
TALK SOONER”



“By the time of diagnosis, up to 50% of patients' beta-cell function may have been lost.”<sup>4</sup>