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Gastroesophageal Reflux (GERD) Medications in Pregnancy

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Gastroesophageal reflux disease (GERD) is the movement of acidic gastric contents into the lower esophagus. Often described as heartburn or “acid indigestion,” reflux occurs in approximately two thirds of all pregnancies. Almost everyone experiences gastroesophageal reflux at some time, although in some individuals reflux is frequent or severe enough to require daily medication. There is also a growing percentage of women with GERD prior to pregnancy who will require maintenance medications throughout gestation. The origin of GERD is multifactorial, but the predominant factor is a decrease in lower esophageal sphincter pressure. Since mechanical factors and female sex hormones, especially progesterone, play a role in GERD (Baron and Richter, 1992), heartburn is more common during the last months of pregnancy, when the growing fetus presses against the stomach and hormones are at high levels. This RISK//NEWSLETTER will present information on the reproductive risks of GERD medications.

Mild heartburn may be treated with lifestyle and dietary modifications. Good posture while eating and avoiding lying down after meals may reduce the occurrence of heartburn. Smoking should also be avoided because it increases stomach acidity.

Antacids

Antacids are commonly used by many women during pregnancy. Available without a prescription, they neutralize stomach acid to provide temporary relief. A variety of antacids are available. The most common antacids on the market are: Mylanta (calcium carbonate and magnesium hydroxide); Maalox (magnesium hydroxide and aluminum hydroxide); Tums (calcium carbonate); and Roloids (calcium carbonate and magnesium hydroxide). Although there is little empiric data on human exposure to antacids, they are a common exposure in pregnancy, and as such are unlikely to significantly increase the risk for birth defects at therapeutic doses.

Aluminum Hydroxide

Animal studies of aluminum hydroxide at oral doses up to 64 times the human dose did not show significant maternal or developmental toxicity (Domingo et al., 1989; Gomez et al., 1990; Colomina et al., 1994). Therefore, at usual human doses, aluminum hydroxide is not likely to increase the risk for birth defects.

Calcium Carbonate

In an animal study done by Shackelford et al. (1993), rats were given up to 1.25% dietary calcium carbonate before mating and during organogenesis. Dietary calcium was not found to have adverse effects of the offspring. Severe hypercalcemia, a potentially life-threatening condition, was reported in

a pregnant woman with excessive ingestion of absorbable calcium antacid. She was treated and the child was delivered a month later with an uncomplicated neonatal course (Kleinman et al., 1991). Even with toxic levels of calcium carbonate in the mother, teratogenic effects were not seen in the fetus. Therefore, calcium carbonate is unlikely to significantly increase the risk for birth defects.

Magnesium Hydroxide

In one study, magnesium hydroxide was administered to 27 pregnant women in the third trimester without adverse effects (Rudnicki et al., 1991). Although limited information is available, this data does not support an association between magnesium hydroxide and birth defects.

Histamine-2 Receptor Blockers (H2RA)

Histamine-2 Receptor Blockers (H2RA) treat the discomfort of heartburn and acid indigestion by blocking histamine, which decreases acid secretion. They are also commonly used during pregnancy, and they are available both over the counter and by prescription at higher doses. The majority of reproductive information for H2RAs regards cimetidine and ranitidine.

Cimetidine (Tagament)

Cimetidine has weak antiandrogenic effects in animals and antiandrogenic effects in humans, causing impotence and oligospermia (Sawyer et al., 1981). While no studies have examined these possible antiandrogenic effects in human pregnancy, two studies found that cimetidine adversely affects male androgenization and neuroendocrine programming in rats (Anand and Van Theil, 1982; Parker et al., 1984). It is theoretically possible that use in pregnant women may adversely affect adult sexual behavior and development of male progeny. Other animal studies showed no difference in masculinity between those animals taking cimetidine from their controls (Hoie et al., 1994; Shapiro and Bitar, 1991; Shapiro et al., 1988; Walker et al., 1987). It remains unclear what significance, if any, these findings may have on human exposures.

A prospective study of 10 women exposed to cimetidine in the first trimester reported 2 therapeutic abortions and 8 normal births (Koren and Zemlickis, 1991). A retrospective study of 460 newborns exposed to cimetidine in the first trimester found no increase in major birth defects, but slightly more heart defects were observed than expected (Briggs et al., 1998). Other studies have not shown an increase in heart defects. The manufacturer reported three newborns with congenital birth defects (congenital heart defect, clubfoot, and mental retardation, respectively) after in utero exposure to cimetidine. No pattern was seen in these infants and the defects were not attributed to the use of cimetidine (Briggs et al., 1998). While limited, this data does not suggest an association between cimetidine and birth defects.

Cimetidine is also used at term to prevent maternal Mendelson's syndrome. There are several reports of women exposed late in pregnancy, without reported teratogenic effects in the newborns (e.g., Carazza et al., 1982). Glade et al. (1980) reports transient neonatal liver toxicity in a newborn exposed to cimetidine at term. This has not been reported in any subsequent studies.

Famotidine (Pepcid)

Animal studies have shown no adverse effects when given famotidine at doses as high as 2,000 mg/kg/day, much higher than the recommended human dose (Shibata et al., 1983; Burek et al., 1985). There is little information in the medical literature on the effects of famotidine in human pregnancy. In a retrospective study of 33 newborns exposed to famotidine in the first trimester, 2 major birth defects were seen; there was no pattern to these defects (Briggs et al., 1998). The number of exposures is too small to make a risk assessment. Famotidine does not have antiandrogenic effects.

Nizatidine (Axid)

Nizatidine was given orally to rats and rabbits at doses as high as 1500mg/kg/day and no teratogenic effects were seen (Morton , 1987). In contrast, the manufacturer reports animal studies with congenital malformations at doses of 20mg/kg and 50mg/kg. These malformations included cardiac defects, neural tube defects and cutaneous edema (Briggs et al., 1998). There is no human epidemiologic data on the effects of nizatidine during pregnancy, and its risk is therefore undetermined. One case report of a woman exposed to nizatidine in the second trimester shows that she delivered a healthy infant (Briggs et al., 1998). Unlike cimetidine, nizatidine is not an androgen antagonist (Neubauer et al., 1990).

Ranitidine (Zantac)

Animal studies on ranitidine have not shown an increased risk for malformations. A prospective study of 13 women exposed to ranitidine during the first trimester reported 10 normal births, 2 spontaneous abortions and one infant born with a hemangioma on the right upper eyelid (Koren and Zemlickis, 1991). A retrospective study of 516 newborns exposed to ranitidine in the first trimester reported no increase in malformations nor pattern to those noted (Briggs et al., 1998).

Most data on ranitidine is regarding use near delivery to prevent Mendelson's syndrome. There have not been reports of adverse effects in newborns exposed to ranitidine near delivery (summarized in Briggs et al., 1998). While limited, the data does not support an association between the drug and congenital defects. Antiandrogenic effects have not been seen with the use of ranitidine (Parker et al., 1984).

Proton Pump Inhibitors (PPIs)

Proton pump inhibitors decrease the stomach's production of acid more completely than the H2RA's by stopping the stomach's acid pump, which is the final step of acid secretion. PPIs are a relatively new class of GERD treatment, and as such, less information is available.

Lansoprazole (Prevacid)

Animal studies on lansoprazole in rabbits and rats did not find evidence that lansoprazole impairs fertility or teratogenicity at 16 to 80 times the human doses, respectively (Schardein et al., 1990; Briggs et al., 1998). There have been no reports on the effects of lansoprazole use during human pregnancy, and as such its risk is undetermined.

Omeprazole (Prilosec)

Animals given up to 345 times the recommended human dose of omeprazole did not show teratogenic effects, although there was a slight increase in miscarriage and fetal mortality (Briggs et al., 1990). A case report of a woman who used omeprazole in three pregnancies, including one in the first trimester, showed that she delivered three healthy infants (Harper et al., 1995). Several case reports exist of adverse outcomes after omeprazole use. The FDA has received 11 voluntary reports of birth defects following pregnancy exposure to omeprazole use, including four cases of anencephaly and one case of hydranencephaly after use in the second trimester (Briggs et al., 1998). Tsirigotis et al. (1995) describes a woman who ingested 20mg of omeprazole daily during two consecutive pregnancies and subsequently terminated them because of anencephaly and clubfoot, respectively. While these case reports of anencephaly suggest a pattern of defects, without background information on these pregnancies, the potential confounding factors inherent in case reports make it difficult to attribute the cause to omeprazole.

In a recent prospective cohort study of 113 women exposed to omeprazole, 101 throughout organogenesis (89%) and 15% throughout pregnancy, no association was found between in utero exposure and malformations, birth weight, gestational age at delivery, preterm deliveries, or neonatal complications (Lalkin et al., 1998). Although the case reports may be concerning, the lack of

teratogenicity in animals and the recent prospective human studies show that omeprazole is unlikely to significantly increase the risk for birth defects.

Prokinetic Agents

Prokinetic agents hasten emptying of the stomach contents, resulting in less acid secretion available for reflux. Some agents also increase the “tone” of the lower esophageal sphincter, making it more difficult to open.

Cisapride (Propulsid)

Animal studies in rats show impaired fertility at 25 times the human dose. At 12 to 100 times the human dose in rats and rabbits, respectively, an increase in IUGR and neonatal death was noted (Briggs et al., 1998). In a prospective study, 129 pregnant women were exposed to cisapride, including 88 during organogenesis. There were no differences in birthweight, gestational age at delivery, and rates of livebirths, spontaneous abortions, fetal distress, and major or minor malformations among those exposed to the drug and those used in the control group. This suggests that cisapride is not likely to pose a significant teratogenic risk (Bailey et al., 1997).

Metoclopramide (Reglan)

Manufacturer’s information on mice, rats, and rabbits given doses up to 250 times the human dose, showed no evidence of fetal harm (Briggs et al., 1998). In a retrospective study of 192 newborns exposed to metoclopramide in the first trimester, 10 (5.2%) major birth defects were seen (Briggs et al., 1998). In a study by Nageotte et al. (1996) 80 women with hyperemesis used metoclopramide during pregnancy. Three women who used metoclopramide in the second trimester delivered infants with birth defects; there was no pattern to the defects, making it even less likely that metoclopramide was a causal factor. Five case reports of women exposed to metoclopramide in early pregnancy did not show teratogenic effects (Briggs et al., 1998).

Summary

Little empiric data is available on most GERD treatments in pregnancy, despite their frequent exposure. The lack of human studies on GERD medications in pregnancy makes it difficult to provide an accurate teratogenic risk assessment. As with any medication, the lowest possible dose should be taken to relieve discomfort. Pregnant women with GERD should speak to their doctors about the best treatment for their GERD, and consider weighing the need for treatment with the options and information available on use during pregnancy.

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