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Review article: the management of heartburn in pregnancy

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SUMMARY

Heartburn is a normal consequence of pregnancy. The predominant aetiology is a decrease in lower oesophageal sphincter pressure caused by female sex hormones, especially progesterone. Serious reflux complications during pregnancy are rare; hence upper endoscopy and other diagnostic tests are infrequently needed. Gastro-oesophageal reflux disease during pregnancy should be managed with a step-up algorithm beginning with lifestyle modifications and dietary changes. Antacids or sucralfate are considered the first-line drug therapy. If symptoms persist, any of the histamine$_2$-receptor antagonists can be used. Proton pump inhibitors are reserved for women with intractable symptoms or complicated reflux disease. All but omeprazole are FDA category B drugs during pregnancy. Most drugs are excreted in breast milk. Of systemic agents, only the histamine$_2$-receptor antagonists, with the exception of nizatidine, are safe to use during lactation.

INTRODUCTION

Heartburn is estimated to occur in 30–50% of pregnancies, with the incidence approaching 80% in some populations.[1] Usually, heartburn during pregnancy resolves soon after delivery, however, sometimes it represents exacerbation of pre-existing gastro-oesophageal reflux disease. Most patients begin to note their symptoms late in the first trimester or second trimester of pregnancy with heartburn becoming more frequent and severe in the latter months of gestation. Although symptoms can be severe, oesophagitis is infrequent[2] and usually in patients with pre-existing disease. Reported risk factors for heartburn in pregnancy include gestational age, heartburn antecedent to the pregnancy and multiparity. Body mass index before pregnancy, weight gain during pregnancy, or race do not predict heartburn and older maternal age seems to have a protective effect.[3] Thus, heartburn is so common during pregnancy that patients and obstetricians both view it as a normal occurrence during a healthy pregnancy. Nevertheless, the challenge of heartburn during pregnancy is patient and doctor concerns about the potential teratogenicity of common antireflux medications and the approximate step-up therapy for troubling symptoms. This review will address the treatment of gastro-oesophageal reflux disease during pregnancy and breast feeding as well as briefly summarizing the pathogenesis of this syndrome, clinical presentation and diagnostic work-up. The literature search for this review used online databases PubMed and MEDLINE, and relevant manuscripts published in English between 1966 and 2005 were reviewed. The search terms used included gastro-oesophageal reflux disease, heartburn in pregnancy, heartburn in lactation, antacids, Gaviscon, sucralfate, histamine$_2$-receptor antagonists, proton-pump inhibitors and all the specific prescription drugs in the latter two drug classes. All abstracts were screened, potentially relevant articles were researched and bibliographies were reviewed.

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PATHOGENESIS

In the first trimester of pregnancy, basal lower oesophageal sphincter (LES) pressure may not change, but is less responsive to physiological stimuli (i.e. pentagastrin,

edrophonium chloride, methacholine or a protein meal) that usually increase LES pressure.[1, 4] In the later two trimesters, LES pressure gradually falls approximately 33–50% of basal values reaching a nadir at 36 weeks of gestation and rebounds to prepregnancy values 1–4 weeks postpartum.[5] Animal and human studies find that the increased circulating levels of progesterone during pregnancy mediate the LES relaxation, but oestrogen is a necessary primer.[1] The secondary role of increased abdominal pressure because of the enlarging gravid uterus is more controversial. All studies agree intra-abdominal pressure increases with pregnancy. It is unknown whether the normal compensatory response of the LES to increase to these changes is impaired during pregnancy.[1] Others have suggested that abnormal gastric emptying or delayed small bowel transit might contribute to heartburn in pregnancy.

CLINICAL PRESENTATION DURING PREGNANCY

The symptoms of heartburn during pregnancy do not differ from the classical presentation in the general adult population. Heartburn is the predominate symptom and worsens as pregnancy advances. Regurgitation occurs in about the same frequency as heartburn. The majority of patients report exacerbation of symptoms with eating and at bedtime.[2] Some patients will eat only one meal a day because of intense postprandial symptoms and others will need to sleep upright in a chair. Complications of gastro-oesophageal reflux disease (GERD) during pregnancy, especially oesophagitis and stricture formation, are rare. This observation should not be surprising since the reflux of pregnancy is generally of short duration without a background of chronic GERD.

DIAGNOSIS IN THE PREGNANT PATIENT

As in the non-pregnant patient, the initial diagnosis of GERD in pregnancy can reliably be made based on symptoms alone.[6] Barium radiographs are not necessary and should be avoided because of radiation exposure to the fetus. Oesophageal manometry and pH studies are rarely necessary during pregnancy but can be performed safely. Upper gastrointestinal (GI) endoscopy is the procedure of choice to evaluate intractable reflux symptoms or complications. This procedure can be safely performed without harm to the mother or fetus by carefully monitoring blood pressure and oxygen and judicious use of conscious sedation and fetal monitoring.[2, 7, 8] Midazolam and diazepam are category D, fentanyl is category C and meperidine and propofol are category B drugs during pregnancy (Table 1). Although not approved by the FDA for these indications during pregnancy, clinical experience suggests that these medications are safe with appropriate monitoring, particularly after the first trimester.[7, 8]

Table 1. FDA classification of drugs for pregnancy

FDA classification	Definition
Category A	Well controlled studies in humans show no fetal risk
Category B	Animal studies show no risks, but human studies inadequate or animal studies show some risk not supported by human studies
Category C	Animal studies show risk but human studies are inadequate or lacking or no studies in humans or animals
Category D	Definite fetal abnormalities in human studies but potential benefits may outweigh the risks
Category X	Contraindicated in pregnancy, fetal abnormalities in animals or humans. Risks outweigh benefits

MEDICAL TREATMENT OF GERD DURING PREGNANCY

The challenge of treatment during pregnancy is the potential teratogenicity of common antireflux medications. Lifestyle modification is the key for treating mild symptoms. Smaller meals, not eating late at night, elevation of the head of the bed and avoiding foods and mediations causing heartburn usually relieve the mild symptoms seen in early pregnancy. Chewing gum stimulates the salivary glands and can help neutralize acid. Abstinence from alcohol and tobacco are encouraged to reduce reflux symptoms and to avoid fetal exposure to these harmful substances.

For more troubling reflux symptoms, the doctor must discuss with the patient the benefits vs. the risk of drug therapy. Informed consent is appropriate. Nearly all medications are not tested in randomized-controlled studies in pregnant women because of ethical and medicolegal concerns. Most recommendations on drug safety arise from case reports and cohort studies by doctors, pharmaceutical companies or the FDA. Voluntary reporting by the manufacturer's suffers from

unknown duration of follow-up, absence of appropriate controls and possible reporting bias.[9]

Commonly used medications include antacids, sucralfate, histamine$_2$-receptor antagonists (H_2RAs), promotility drugs and proton-pump inhibitors (PPIs). The incidence of major fetal malformations in the general population ranges between 1% and 3%.[10] The FDA divides the safety of drugs during pregnancy into five categories (A, B, C, D and X) based on systemic absorption and reports of congenital defects in animals or humans (Table 1).[11]

The teratogeneic period ranges from day 31 (in a 28-day menstrual cycle) to day 71 from the last menstrual period,[10] essentially the first 10 weeks of gestation. This represents the critical period of organogenesis. Before day 31, exposure to a teratogen usually causes an all-or-none effect; either the fetus dies or survives without anomalies. Fetal cells are totipotential during this time period with respect to organogenesis; therefore, if a few cells die, the remaining cells can replace their function. Drugs that are not urgently required should be withheld until after the teratogeneic period, although drugs can still affect the fetus in later gestation. Drugs used for GERD during pregnancy and their FDA categories are summarized in Table 2.

Antacids

Antacids are fast and effective at relieving the symptoms of heartburn and are preferred by patients as a result of the immediate symptom relief provided. About 30–50% of women will only require antacids to ease their

Table 2. FDA classification of drugs used for gastro-oesophageal reflux disease in pregnancy

Drugs	FDA class	Comments
Antacids		
Aluminium-, calcium- or magnesium-containing antacids	None	Most are safe for use during pregnancy and for aspiration prophylaxis during labour because of minimal absorption
Magnesium trisilicates	None	Avoid long-term, high-dose therapy in pregnancy
Sodium bicarbonate	None	Not safe for use in pregnancy as causes fluid overload and metabolic alkalosis
Mucosal protectant		
Sucralfate	B	No teratogenicity in animals. Generally regarded as acceptable for human use because of minimal absorption
Histamine$_2$-receptor antagonist (H_2RA)		
Cimetidine	B	A prospective, controlled study suggests acceptable for use in humans
Ranitidine	B	Same as above. Ranitidine is the only H_2RA whose efficacy during pregnancy has been established
Famotidine	B	Same as cimetidine, but paucity of safety data in humans
Nizatidine	B	Not recommended during pregnancy. In animals, spontaneous abortion, congenital malformations, low birth weight and fewer live births have been reported. Little data in humans
Promotility agents		
Cisapride	C	Embryotoxic and fetotoxic in animals. Recent prospective controlled study in humans suggests acceptable in pregnancy, but drugs recently removed by FDA for fatal cardiac arrhythmias
Metoclopramide	B	No teratogeneic effects in animals or humans reported
Proton-pump inhibitors		
Omeprazole	C	Embryotoxic and fetotoxic in animals. Case reports in human suggest similar concerns. Acceptable for use for aspiration prophylaxis in labour
Lansoprazole	B	No fetal teratogenicity or harm. Limited human pregnancy date Use is acceptable for aspiration prophylaxis during pregnancy
Rabeprazole	B	No fetal teratogenicity or harm. Limited human pregnancy date Use is acceptable for aspiration prophylaxis during pregnancy
Pantoprazole	B	No fetal teratogenicity or harm. Limited human pregnancy date Use is acceptable for aspiration prophylaxis during pregnancy
Esomeprazole	B	No fetal teratogenicity or harm. Limited human pregnancy date Use is acceptable for aspiration prophylaxis during pregnancy

heartburn of pregnancy. Only limited data exist concerning the effects of antacids on the fetus with no controlled trials of efficacy. Magnesium-, aluminium-, or calcium-containing antacids are not teratogeneic in animal studies,[12] although 15–30% of magnesium and a smaller percentage of aluminium preparations are absorbed after reacting with hydrochloric acid.

One retrospective, case–controlled study in the 1960s[13] reported a significant increase in major and minor congenital malformations in infants exposed to antacids during the third trimester of pregnancy. However, analysis of individual antacids (aluminium hydroxide, sodium bicarbonate, magnesium trisilicate and calcium carbonate) found no association with increased congenital anomalies. A recent European consensus conference recommended calcium/magnesium-based antacids for pregnant women because of their safety profile.[14] These experts found that calcium-based antacids had the added benefit of increasing calcium supplementation to prevent the hypertension and pre-eclampsia associated with pregnancy. In addition, a large, randomized placebo-controlled trial found that magnesium sulphate supplementation reduces the risk of eclampsia by 50% compared with placebo, and may also reduce the risk of maternal death, with no serious short-term side-effects.[15]

Alginates form a strong, non-systemic barrier in the stomach, preventing reflux of acid and food into the oesophagus. They are usually combined with antacids and marketed under the general label of Gaviscon. Recently, a form of Gaviscon with less sodium per dose was studied in an open-label multicentre study in 150 pregnant women over 4 weeks. Overall, the investigator's and women's rating of efficacy was 'very good' or 'good' in 88% and 90% of women, respectively, with most women (57%) reporting symptom relief within 10 min.[16] However, 10 adverse events were reported in 10 fetuses (three episodes of fetal distress) and others report that Gaviscon compounds containing magnesium trisilicate can cause fetal nephrolithiasis, hypotonia, respiratory distress and cardiovascular impairment if used long-term and at high doses.[11]

Antacids containing sodium bicarbonate should be avoided during pregnancy because they cause maternal or fetal metabolic alkalosis and fluid overload. Antacids should be taken at a different time than supplemental iron, because normal gastric acid facilitates the absorption of iron.

Sucralfate

Sucralfate, an aluminium salt of a sulphated disaccharide, inhibits pepsin activity and protects against ulcers. It is poorly absorbed from the GI tract, exerting its mucosal protection through a local, rather than systemic action. Each gram of sucralfate contains 207 mg of aluminium.[16] The potential fetal toxicity of sucralfate relates to its aluminium content.

Sucralfate is the only non-absorbable drug that has been studied in a randomized-controlled study during pregnancy. In an Italian study,[17] 42 women were given sucralfate 1 g three times daily and compared with 24 women given information on dietary and lifestyle modifications. Sucralfate-treated patients had a higher frequency of remission of heartburn and regurgitation symptoms at 1 month than controls (90% vs. 43% and 83% vs. 27%, respectively). No maternal or fetal adverse events were reported.

In several animal models, sucralfate did not affect fertility and was not teratogeneic with doses up to 50 times those used in humans.[16] Likewise, human fetal toxicity has not been reported. For example, in a surveillance study of 229 101 pregnancies in Michigan Medicaid patients evaluated between 1985 and 1992, 185 newborn babies were exposed to sucralfate in the first trimester. Five birth defects were observed, whereas eight were expected.[16] Therefore, sucralfate is an FDA category B drug.

Promotility drugs

Metoclopramide. Metoclopramide, an antidopaminergic drug, improves GER by increasing LES pressure, improving oesophageal acid clearance and promoting gastric emptying. Its major use in pregnancy is for the treatment of nausea and vomiting. Reproductive studies in animals in doses up to 250 times the recommended human dose reveal no evidence of impaired fertility or fetal toxicity.[18] Congenital malformations or fetal toxicity because of metoclopramide have not been reported in humans. In the Michigan Medicaid Surveillance Study,[16] 10 (5.2%) major birth defects were reported in 992 newborns exposed to metoclopramide during the first trimester (eight were expected). Metoclopramide is designated a category B drug during pregnancy.

Cisapride. Cisapride promotes the release of acetylcholine from the myenteric plexus, thereby increasing LES pressure, improving acid clearance and promoting

gastric emptying. The drug is toxic to the fetuses of rats and rabbits at doses 112 times the recommended human dose, resulting in lower birth weights and decreased survival.[19]

Human reports suggest cisapride is safe during pregnancy. In a prospective, multicentre study, the outcome of 129 Canadian women who took cisapride during pregnancy between November 1996 and November 1998 were compared with a control group.[20] The mean daily cisapride dose was 25 mg (range: 5–120) and the mean length of exposure was 4.6 weeks (range: 0.14–41). Most women took cisapride during the first trimester (88%), 3% of women took it throughout their pregnancy. Most women were also taking multiple other antireflux medications, including antacids, H_2RAs and PPIs. Investigators found no differences in rates of major or minor congenital malformations in the cisapride group compared with the matched controls. In 1998, an observational cohort study described the outcome of 12 pregnancies in women taking cisapride during the first trimester in England.[21] The outcomes included two elective abortions, one lost to follow-up and 10 normal term babies. In two other cases, cisapride was taken during the second or third trimesters and healthy babies were born.

Cisapride is designated a category C drug in pregnancy because of its toxicity in animals. In July 2000, Janssen Pharmaceutical removed cisapride from the market and it now is only available in a limited-access program. High cisapride blood levels, because of other drugs interfering with its metabolism by the cytochrome P-450 3A4 enzyme, caused serious cardiac arrhythmias in more than 400 cases, including 80 fatalities.[22]

Histamine$_2$-receptor antagonists

The H_2RAs are the most commonly used and safest medications for the pregnant woman with heartburn not responding to lifestyle modification and non-absorbable medication. All four drugs (cimetidine, ranitidine, famotidine and nizatidine) are FDA approved category B drugs for pregnancy.

Cimetidine and ranitidine. Cimetidine and ranitidine have had considerable use in pregnancy over the last 30 years with an excellent safety profile. Only ranitidine's efficacy has been specifically studied during pregnancy. In a double-blind, placebo-controlled, triple-crossover study, Larson *et al.*[23] compared ranitidine once or twice daily with placebo in pregnant heartburn subjects not responding to antacids and lifestyle modification. Twenty women at least 20 weeks gestation were studied assessing symptom response and antacid use by daily diaries. In the 18 women completing the 4-week study, only ranitidine 150 mg b.d. reduced symptoms and antacid usage compared with baseline values ($P < 0.001$) or with placebo ($P < 0.001$). The average heartburn reduction was 55.6% (95% CI: 34.8–76.5) compared with baseline and 44.2% (95% CI: 15.4–72.9) when compared with placebo. No adverse pregnancy outcomes or drug reactions were noted.

In animal studies, cimetidine has a weak antiandrogenic effect in animals, as evidenced by a reduction of the size of testes, prostate glands and seminal vesicles.[24] Ranitidine has no antiandrogenic activity in animals.[25] Neither H_2RA has reports of human sexual defects in infants.

To date, the safety of cimetidine and ranitidine has been assessed in over 2000 pregnancies in database studies not sponsored by the manufacturers. In the surveillance study of 229 101 pregnancies in the Michigan Medicaid recipients between 1985 and 1992,[16] 460 newborns were exposed to cimetidine and 560 newborns were exposed to ranitidine during the first trimester. Twenty (4.3%) major birth defects were observed with cimetidine and 23 (4.5%) with ranitidine, a rate similar (4.3%) to that reported in women taking no medications during their pregnancies. In a 1996 prospective cohort study, 178 women exposed during pregnancy to H_2RAs were matched with 178 women with no exposure with similar maternal age, smoking and alcohol history.[26] Among these subjects, 71% took ranitidine, 16% cimetidine, 8% famotidine and 5% nizatidine. The outcomes of both groups were similar in terms of live births, spontaneous or elective abortions, gestational age at delivery, birth weight or major malformation. The latter rate was 2.1% in subjects exposed to H_2RAs vs. 3.0% in the non-exposed cohorts.

The Swedish Medical Birth Registry in 1998 reported on 553 babies delivered by 547 women using various acid-suppressing medications in early pregnancy.[27] Seventeen infants had congenital defects (3.1%, 95% CI: 1.8–4.9) compared with the expected rate of 3.9% in the Registry among women not taking any medications. Of the 17 infants, 10 had been exposed to PPIs, six to H_2RAs and one to both class of drugs. Two birth defects (5.7%) in 35 infants exposed to cimetidine and six defects (3.8%) in 156 infants exposed to ranitidine were reported. Overall, the odds ratio for malformations after

H_2RAs was 0.46 (95% CI: 0.17–1.20) in contrast to 0.91 (95% CI: 0.45–1.84) for infants exposed to PPIs, early during pregnancy. Finally, two databases, one from England and another from Italy, were combined in a study published in 1999, which compared the incidence of congenital malformations in infants and women receiving cimetidine, ranitidine or omeprazole during the first trimester of pregnancy with unexposed control women.[28] The relative risk of malformation (adjusted for maternal age and prematurity) were similar among all three drugs: cimetidine (1.3%, 95% CI: 0.7–2.6), ranitidine 1.5 (95% CI: 0.9–2.6) and omeprazole 0.9 (95% CI: 0.4–2.4).

In summary, cimetidine and ranitidine have not been associated with an increased risk of congenital malformations. Ranitidine is the only H_2RA with documented efficacy in pregnancy. Some authorities have recommended that cimetidine not be used during pregnancy because of possible feminization as observed in some animals and non-pregnant humans.[29]

Famotidine and nizatidine. There are much less reported safety data with these latter H_2RAs than cimetidine and ranitidine. Animal studies with famotidine revealed no fetal toxicity or teratogenicity.[30] However, pregnant rabbits with the equivalent of 300 times the recommended human dose of nizatidine encountered abortions, low fetal weights and fewer live fetuses.[31] On the contrary, rat studies found no adverse effects on the fetal pups.[32]

In the Michigan Medicaid Surveillance Study,[16] two (6.1%) of 33 fetuses exposed to famotidine during the first trimester of pregnancy developed major birth defects compared with the expected prevalence of one. The small size was too small to draw firm conclusions, however. With nizatidine there is only a single case report of a woman delivering a healthy baby after taking the drug during 14–16 weeks of gestation.[16]

Although few reports are available, famotidine appears safe during pregnancy. Although nizatidine was previously classified as category C, the FDA recently reclassified it as a category B drug. However, the conflicting animal data are troublesome and suggest that other H_2RAs may be safer during pregnancy.

Proton-pump inhibitors

Proton-pump inhibitors are the most effective drug therapy for symptom control and healing of oesophagitis. The PPIs have not been as extensively used in pregnancy as the H_2RAs, or is their efficacy proven in pregnancy, and the data about total safety are more limited. Omeprazole is categorized as a class C drug by the FDA because of fetal toxicity. The other PPIs are categorized as class B drugs. However, unlike the non-pregnant heartburn patient, PPIs should only be used during pregnancy in women with well-defined complicated GERD, not responding to lifestyle changes, antacids and H_2RAs (Figure 1).

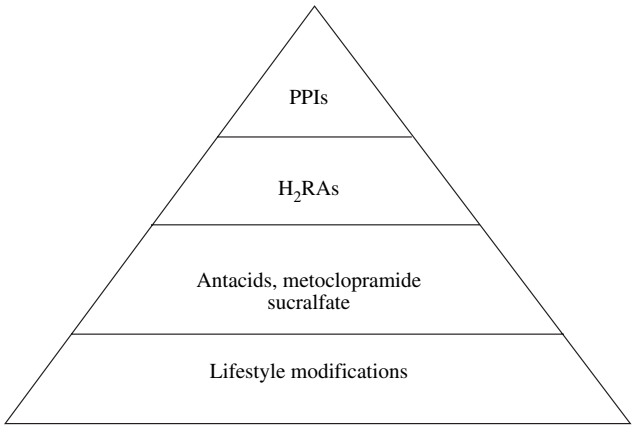

Figure 1. The pyramid of medical therapy for gastro-oesophageal reflux disease (GERD) in the pregnant woman with heartburn. Unlike the non-pregnant patient, step-up therapy is preferred and proton-pump inhibitors (PPIs) reserved for the women with well-defined complicated GERD not responding to lifestyle changes, antacids or histamine$_2$-receptor antagonists (H_2RAs).

Omeprazole. Omeprazole, the first of the PPIs, is classified as a class C drug in pregnancy because at doses similar to those used in humans, omeprazole produced dose-related embryonic and fetal mortality in pregnant rats and rabbits.[33] No teratogenicity was observed.

The FDA has received reports of at least 12 birth defects in pregnant women exposed to omeprazole, including anencephaly and hydroencephaly.[16] However, other case reports[34] and small case series[21, 35] have found no infant congenital malformations in mothers taking 20–60 mg omeprazole/day, even in the first trimester of pregnancy.

A recent meta-analysis assessed the risks of congenital fetal malformations in women using PPIs in the first trimester of pregnancy.[36] Five studies met the inclusion criteria, all were cohort studies ascertaining pregnancy outcomes with either registry linkage[27, 28, 37] or by direct interview with the mother.[36, 38] A total of 593 infants were exposed to PPIs, most (534) received

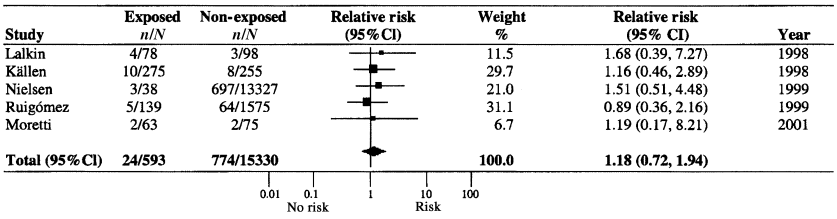

Figure 2. Individual and summary relative risk for studies including all proton-pump inhibitor exposures (from Ref.,[36] with permission).

omeprazole. The summary relative risk for all major malformations among any PPI exposure was 1.18 (95% CI: 0.72–1.94), a non-significant relative risk ($P = 0.7$). For the four studies where data for only omeprazole could be extracted (Figure 2), the summary relative risk was 1.05 (95% CI: 0.59–1.85), also indicating a non-significant relative risk for malformations.

Although the weight of evidence suggests omeprazole is safe in pregnancy, the FDA has not changed its class C rating. With the advent of newer PPIs, especially esomeprazole, omeprazole is currently infrequently prescribed. However, the drug is now over-the-counter at a 20 mg dose and cheaper than prescription PPIs.

Lansoprazole. Animal studies using doses of lansoprazole up to 40 times the recommended human dose have found no evidence of impaired fertility or fetal toxicity.[39]

Human data on the safety of lansoprazole in pregnancy are more limited. In one non-observational cohort study,[21] six pregnant patients taking lansoprazole during the first trimester delivered seven healthy newborns. Lansoprazole was the only acid-suppressing drug exposure in 13 infants reported to the Swedish Medical Birth Registry.[27] Two birth defects were observed; one atrial septal defect and one undescended testes. In a Danish study published in 1999,[37] 38 patients had taken PPIs during the first trimester of pregnancy (35 omeprazole, three lansoprazole). The prevalence of major birth defects, low birth weight and prematurity were no different than in pregnant controls not receiving any medications. In a study published this year,[40] 295 pregnancies exposed to omeprazole, 62 to lansoprazole and 53 to pantoprazole were compared with 868 pregnant controls for the development of congenital abnormalities. As with other studies, the rate of congenital abnormalities did not differ between the exposed and control groups: omeprazole nine of 249 (3.6%), lansoprazole two of 51 (3.9%) and pantoprazole one of 48 (2.1%) vs. controls 30 of 792 (3.8%). No differences were found when exposure was limited to the first trimester.

The lack of teratogenicity in animals is reassuring, accounting for the FDA class C risk category for lansoprazole use during pregnancy. However, the data on safety in human pregnancies are limited and avoidance of this PPI and all PPIs, especially during the first trimester, is the safest course. If lansoprazole is required, or if inadvertent exposure occurs early in gestation, the fetal risk seems to be low.

Newer PPIs

Based on product information from the individual manufacturers, the newer PPIs (rabeprazole, pantoprazole and esomeprazole) have been shown safe in various animal studies. No reports describing the use of these newer PPIs during human pregnancies are available.[16]

SAFETY OF MEDICAL TREATMENTS FOR GERD DURING LACTATION

The heartburn of pregnancy typically resolves shortly after delivery, although some women still experience symptoms postpartum requiring treatment. All systemic antireflux medications are excreted in breast milk and could harm the infant. Therapeutic options must be explained and discussed with women who require treatment but who want to breastfeed.

Drug safety during lactation has been assessed in animal studies and human case reports (Table 3). Aluminium and magnesium hydroxide antacids are not concentrated in breast milk and, thus, are safe during lactation. Neither Gaviscon nor sucralfate have been studied during lactation, but are presumed safe because of limited maternal absorption.

All H_2RAs are excreted in human breast milk. Cimetidine and ranitidine reach concentrations in breast milk four to seven times the doses present in maternal serum.[41] In contrast, famotidine only reaches a mean milk:plasma concentration of 1.78, 6 h after ingestions.[42] Small amounts of nizatidine are excreted into human breast milk.[43] In the only animal studies assessing H_2RA safety during lactation, pups reared by lactating rats ingesting nizatidine experienced growth

Table 3. Safety of GERD medications during lactation

Drugs	Safety	Comments
Antacids	Yes	Not concentrated in breast milk
Sucralfate	Yes	Minimal, if any, excretion in breast milk
H_2RA		
Cimetidine	Yes	American Academy of Pediatrics classified as compatible with breast feeding
Ranitidine	Yes	Excreted in breast milk in concentrations similar to cimetidine
Famotidine	Yes	Lowest concentrations in breast milk of all H_2RAs
Nizatidine	No	Growth depression in pups of lactating rats
Proton-pump inhibitors	No	Little known of excretion in breast milk. Growth depression in pups of lactating rats receiving omeprazole and rabeprazole

GERD, gastro-oesophageal reflux disease; H_2RA, histamine$_2$-receptor antagonist.

retardation.[44] The effects of H_2RAs in breast milk on the nursing human infant are unknown. In 1994, the American Academy of Pediatrics classified cimetidine as compatible with breast feeding.[45] The present review also suggests that ranitidine and famotidine are safe and the latter H_2RA may be preferred because of the lower concentration in human breast milk. Nizatidine should be avoided in the breast feeding mother because of the single animal study.[44]

Little is known about PPI excretion in breast milk or infant safety in lactating women. PPIs probably are excreted in human milk, because of their relatively low-molecular weight. This was confirmed in the only report of PPI use during breast feeding.[46] During the day, the patient fed her infant son just before taking omeprazole at 8:00 AM, refraining from nursing for 4 h, and then expressed and discarded her breast milk at noon. At 3 weeks postpartum, blood and milk samples were obtained at 8:00 AM, and then every 30 min for 4 h. Breast milk levels of omeprazole began to rise at 9:30 AM and peaked at 11:00 AM at 58 mM, considerably lower value than simultaneous maternal level of 950 mM. The infant was doing well at 1 year. However, rats administered omeprazole at 35–345 times and rabenprazole at a dose of 195 times the recommended human dose during late pregnancy and lactation had decreased body weight gain of their pups.[33, 47] Therefore, PPIs are not recommended for use by lactating mothers. Women with severe GERD symptoms can either take PPIs and discontinue nursing or use a GERD medication (i.e. H_2RA) from another class.

CONCLUSION

Heartburn is a normal consequence of pregnancy, occurring in nearly two-thirds of women. The predominant cause is a decrease in LES pressure caused by female sex hormones, especially progesterone. Serious reflux complications (i.e. oesophagitis) during pregnancy are uncommon; therefore upper endoscopy and other diagnostic tests are usually not needed. Symptomatic GERD during pregnancy should be managed with a step-up algorithm beginning with lifestyle modifications and dietary changes (Figure 1). Antacids or sucralfate are considered the first-line medical therapy. If symptoms persist, any of the H_2RAs can be used. Proton-pump inhibitors are reserved for women with intractable symptoms or complicated reflux disease. All but omeprazole are FDA category B drugs during pregnancy. Most drugs are excreted in breast milk. Of the systemic agents, only the H_2RAs, with the exception of nizatidine, are safe to use during lactation.

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