ABSTRACT
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. Gastrooesophageal 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 histamine2-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 histamine2-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. 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, histamine2-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.

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. 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. Animal and human studies find that the increased circulating levels of progesterone during pregnancy mediate the LES relaxation, but oestrogen is a necessary primer. 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. 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. 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.

Pathophysiology of gastroesophageal reflux

Disease during pregnancy

A limited number of studies have examined the role of the LES, esophageal motility, gastric emptying, and increased intra-abdominal pressure from the enlarged gravid uterus in promoting GERD during pregnancy. Several studies analyzed LES pressure during pregnancy. In an early manometric study, Nagler and LES pressure in 39 pregnant women -20 with heartburn and 19 without symptoms. Symptomatic patients were more likely than controls to have a hypotensive LES. Moreover, the LES pressure progressively decreased as the gestational period progressed and returned to normal after delivery. Lind and colleagues evaluated LES pressure in 20 pregnant patients, 11 with heartburn and 9 without heartburn, and in 10 nonpregnant asymptomatic adult controls. Symptomatic patients tended to have a lower LES pressure, but this trend was not statistically significant. LES pressures in symptomatic patients remained within the normal range but were lower than those of asymptomatic patients. Van Thiel and colleagues evaluated the LES in patients at 12, 24, and 36 weeks of gestation and at 4 weeks’ postpartum. LES pressure was lower than normal controls during pregnancy in their laboratory and decreased progressively from a mean of 11 mm Hg in the first trimester to 4 mm Hg at 36 weeks. Postpartum LES pressures averaged 20 mm Hg, normal values for their laboratory. Van Thiel and colleagues did not analyze the correlation between LES pressure and symptoms during pregnancy. In contrast, Fisher and co-worker, in a study of eight women, showed no difference in LES pressure in the late first trimester compared to 6 weeks after termination of pregnancy. Mean LES pressure was 22.0 ± 2.4 (SE) mm Hg versus 22.6 ± 2.3 mm Hg. These authors studied the response of LES pressure to pentagastrin, methacholine, edrophonium, and a protein meal. The effect of these agents on LES pressure was blunted during pregnancy compared to 6 weeks postabortion (Fig. 3). It has been long suspected that the decline in LES pressure during pregnancy was due to the sex hormones, estrogen and progesterone. The effect of these hormones was
studied in muscle strips from the opossum by evaluating the dose response curves of LES smooth muscle to acetylcholine and gastrin. The maximal LES muscle response was decreased by either estrogen or progesterone but was severely decreased by the combination of estrogen and progesterone (Fig. 4). In another study using opossum, LES pressure was measured at days 1, 5, and 12 during intramuscular administration of estrogen on days 1 to 7 and estrogen with progesterone on days 7 to 12. LES pressure was unchanged from baseline on days 1 and 7 but decreased on day 12 when combination therapy was given. Van Thiel and colleagues evaluated the effect of birth control pills-sequential estrogen and progesterone-on LES pressure and found no significant difference on days 18 to 20 when estrogen was taken alone, as compared to days 1 to 3 of the menstrual cycle when neither hormone was administered, but found a significant decrease in LES pressure on days 23 to 28 when both estrogen and progesterone were administered. An interesting study published as an abstract showed a decrease in LES pressure in five transsexual men taking estrogen and progesterone in combination compared to a control period before hormonal administration. A small effect occurred with progesterone but no change with estrogen alone. These data appear to show that LES pressure is decreased in the basal state during pregnancy, particularly during the third trimester. This effect is likely due to the combination of estrogen and progesterone but neither alone tude of distal esophageal contractions) is the most common motility abnormality seen in GERD. In a review of 100 patients with GERD undergoing esophageal manometry, ineffective motility occurred in 34% of patients compared to decreased LES pressure in 4%. Esophageal contraction abnormalities occur more frequently in patients with dysphagia and erosive esophagitis, which are uncommon clinical presentations of GERD during pregnancy. It is expected that esophageal contraction abnormalities would be rare during pregnancy, but few studies have analyzed esophageal peristalsis during pregnancy. Marrero and co-workers postulated that the increase in heartburn seen in patients during pregnancy was related to a decrease in esophageal clearance during the third trimester secondary to a rapid rise in gestational hormones. Marrero and co-workers could not document this. Nagler and Spiro found an increase in nontransmitted contractions in the distal esophagus in their early study. Another study demonstrated decreased contraction amplitude in the distal esophagus in six pregnant women compared to six In a study of healthy women in the authors’ laboratory, esophageal peristaltic wave amplitude or esophageal clearance rate did not change between the luteal and follicular phases of the menstrual cycle. Gastric emptying has not been extensively studied in pregnancy. Wald and associates demonstrated delayed mouth-to-cecum transit using breath hydrogen testing.
in 15 women in the third trimester compared to 4 weeks’ postpartum. Whether this delay was due to alterations of gastric or small bowel transit was not studied. A small study in 10 women found no difference in gastric emptying of solids in the first trimester compared to 6 weeks after therapeutic abortion. Increased abdominal pressure secondary to the enlarged gravid uterus is a potential mechanism for increasing reflux frequency. Spence and co-workers studied intragastric pressure during anesthesia in pregnant women compared to men, nonpregnant women, and children. Intragastric pressure in pregnancy was twice that of the control groups. The authors postulated that the elevated gastric pressure was caused by increased intra-abdominal pressure from the gravid uterus. In an attempt to reproduce the clinical milieu of a gravid uterus, Van Thiel and Wald studied cirrhotic patients with tense ascites (a clinical situation in which intra-abdominal pressure is likely to be increased) and demonstrated an increase in LES pressure that decreased after diuresis. They suggested that increased intra-abdominal pressure is unlikely to be a primary factor in the genesis of GERD in these patients. Whether increased intra-abdominal pressure affecting LES pressure occurs in pregnancy is not known.

**DIAGNOSIS**

The classic presentation of substernal burning occurring postprandially in the supine position or on bending over (heartburn) is a 90% sensitive and specific symptom for the diagnosis of GERD. The presence of regurgitation, the effortless return of gastric contents into the esophagus or mouth, makes the diagnosis even more certain, and no further diagnostic studies are required whether or not the patient is pregnant. When symptoms are difficult to treat and esophagitis or complications of GERD are suspected, EGD is the procedure of choice because barium radiographs are to be avoided in pregnancy. EGD, if indicated, appears to be safe in pregnancy; conscious sedation with meperidine and midazolam or diazepam are likely safe, particularly after the first trimester (although not approved by the Food and Drug Administration [FDA]). Cappell and Sidhom determined the safety of upper endoscopy in a retrospective study of 20 pregnant women collected over a 7-year period. Procedures were performed for a range of indications with equal frequency in each trimester. Sixty-five percent of the patients received meperidine and 20% midazolam or diazepam. Premature delivery or fetal distress did not occur. Apgar scores at delivery were uniformly 8 or higher. In a further study of 83 pregnant patients undergoing EGD at eight different centers over a 14-year period, a high diagnostic yield was obtained, particularly in patients with gastrointestinal bleeding.** No significant complications occurred, and EGD did not induce
labor. Ninety-five percent delivered healthy infants, a rate equal to age-matched controls. Birth weight was comparable to controls as were Apgar scores and fetal heart rate. In a mailed survey of physicians conducted under the auspices of the American Society for Gastrointestinal Endoscopy, information on 73 upper endoscopies from pregnant women was collected. Thirty-five percent received meperidine or diazepam. No fetal or maternal complications were reported. It should be noted that midazolam and diazepam are designated as category D, and meperidine (and fentanyl) are category C during pregnancy (Table 1). Cauter formed endoscopies on 38 pregnant patients with symptomatic GERD and found hyperemia, mucosal edema, or both in 28 of 38. This would be the equivalent of grade I esophagitis by current grading standards. Only one patient had mucosal erosions (grade II esophagitis), whereas the remaining nine had a normal endoscopy. The subject of endoscopy during pregnancy is considered in detail in another article elsewhere in this issue. The authors reserve endoscopy for a medically refractory patient (see treatment later) and prefer not to perform endoscopy until after the first trimester. Ambulatory pH monitoring is safe during pregnancy and can be used to confirm the diagnosis of GERD in difficult cases and atypical presentations and to monitor therapy in the rare pregnant patient with symptoms refractory to conventional therapy. pH monitoring is the best test to identify reflux. A small study with pH monitoring suggested that reflux is more common immediately preterm compared to the postpartum period.

**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. 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.
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.\(^7,8\)

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, histamine2-receptor antagonists (H2RAs), 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).

HEARTBURN FRIENDLY MENU

BREAKFAST:
- 2 eggs
- Apple slices
- Whole wheat toast
- Milk

SNACK:
- Yogurt with a sliced peach

LUNCH:
- Small corn tortillas with beans, lettuce, low-fat cheese
- Watermelon
- Milk

SNACK:
- Carrot and celery sticks with hummus dip
- Whole grain crackers
- Grapes

SUPPER:
- Spinach salad with Ranch dressing
- Grilled chicken thigh
- Baked sweet potato
- Water

SNACK:
- Cereal with milk, half a banana with peanut butter

The teratogenic period ranges from day 31 (in a 28-day menstrual cycle) to day 71 from the last menstrual period, 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 teratogenic 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
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 teratogenic in animal studies,\textsuperscript{[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\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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 (Carafate) contains aluminum. Aluminum is believed to be toxic to the fetus, resulting in increased perinatal mortality and impaired memory after parenteral administration to pregnant laboratory animals. Little aluminum is absorbed, however, from oral administration of aluminum-containing medication. Sucralfate, therefore, appears to be
safe because little systemic absorption occurs. was evaluated in the treatment of heartburn associated with Sucralfate 1 g three times daily was compared to dietary and lifestyle modifications. Symptoms were evaluated before therapy and at days 15 and 30. Sucralfatetreated patients had significantly greater remission of heartburn (90% versus 43%) and of regurgitation (83% versus 27%) compared to controls. The only side effect was diarrhea in one patient. No teratogenic effects were observed from sucralfate absorption in a study of 183 newborns exposed in utero to sucralfate during the first trimester.” Studies performed in mice, rats, and rabbits at doses up to 50 times the recommended human dose have demonstrated no fetal harm. Sucralfate is designated category B by the FDA.

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, H2RAs 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]

**Histamine2-receptor antagonists**

The H2RAs are the most commonly used and safest medications for the pregnant woman with heartburn not responding to lifestyle modification and nonabsorbable 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 H2RA 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 H2RAs were matched with 178 women with no exposure with similar maternal
age, smoking and alcohol history. 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 H2RAs 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. 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 H2RAs 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 H2RAs 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. 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 H2RA 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. Famotidine and nizatidine. There are much less reported safety data with these latter H2RAs than cimetidine and ranitidine. Animal studies with famotidine revealed no fetal toxicity or teratogenicity. However, pregnant rabbits with the equivalent of 300 times the recommended human dose of nizatidine encountered abortions, low fetal weights and fewer live fetuses. On the contrary, rat studies found no adverse effects on the fetal pups.

In the Michigan Medicaid Surveillance Study, 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. 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 H2RAs 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 H2RAs, 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 nonpregnant heartburn patient, PPIs should only be used during pregnancy in women with well-defined complicated GERD, not responding to lifestyle changes, antacids and H2RAs (Figure 1). 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 reports34 and small case series21, 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 linkage27, 28, 37 or by direct interview with the mother.36, 38 A total of 593 infants were exposed to PPIs, most (534) received.
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 nonsignificant 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. Human data on the safety of lansoprazole in pregnancy are more limited. In one non-observational cohort study, 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. Two birth defects were observed; one atrial septal defect and one undescended testes. In a Danish study published in 1999, 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, 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.
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 H2RAs are excreted in human breast milk. Cimetidine and ranitidine reach concentrations in breast milk four to seven times the doses present in maternal serum. In contrast, famotidine only reaches a mean milk:plasma concentration of 1.78, 6 h after ingestions. Small amounts of nizatidine are excreted into human breast milk. In the only animal studies assessing H2RA safety during lactation, pups reared by lactating rats ingesting nizatidine experienced growth.

<table>
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<tr>
<th>Drugs</th>
<th>Safety</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Antacids</td>
<td>Yes</td>
<td>Not concentrated in breast milk</td>
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<tr>
<td>Sucralfate</td>
<td>Yes</td>
<td>Minimal, if any, excretion in breast milk</td>
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<td>H2RA</td>
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<td>Cimetidine</td>
<td>Yes</td>
<td>American Academy of Pediatrics classified as compatible with breast feeding</td>
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<td>Ranitidine</td>
<td>Yes</td>
<td>Excreted in breast milk in concentrations similar to cimetidine</td>
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<td>Famotidine</td>
<td>Yes</td>
<td>Lowest concentrations in breast milk of all H2RAs</td>
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<tr>
<td>Nizatidine</td>
<td>No</td>
<td>Growth depression in pups of lactating rats</td>
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<td>Proton-pump inhibitors</td>
<td>No</td>
<td>Little known of excretion in breast milk. Growth depression in pups of lactating rats receiving omeprazole and rabeprazole</td>
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GERD, gastro-oesophageal reflux disease; H2RA, histamine2-receptor antagonist.

Retardation. The effects of H2RAs in breast milk on the nursing human infant are unknown. In 1994, the American Academy of Pediatrics classified cimetidine as compatible with breast feeding. The present review also suggests that ranitidine and famotidine are
safe and the latter H2RA 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 lowmolecular 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. H2RA) from another class.

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**Pregnancy and heartburn**

Many women have heartburn when they are pregnant. It may be painful for you but it will not hurt your baby.

**What is heartburn?**

Heartburn is when food and stomach acid backs up into your throat. The acid from your stomach causes a burning feeling.

**Signs you might have heartburn**

- A burning feeling in your chest after eating a meal
- A burning feeling in your chest when you lie down or bend over
- A sour or bitter taste in your throat when you lie down or sleep

**Tips that might help relieve and prevent heartburn**

- Eat 5 or 6 small meals throughout the day instead of fewer, larger meals.
- Eat slowly.
- Chew your food well.
- Drink liquids and soups 1 hour before, or after meals, rather than with meals.
- Wait 1 hour or more after eating meals before you lie down.
- Sleep with your head and upper body raised higher than your stomach.
- Wear loose fitting clothing.

**Foods and Heartburn**

<table>
<thead>
<tr>
<th>Eat less of these:</th>
<th>Drink less of these:</th>
</tr>
</thead>
<tbody>
<tr>
<td>greasy foods</td>
<td>coffee or tea</td>
</tr>
<tr>
<td>fried foods</td>
<td>soft drinks</td>
</tr>
<tr>
<td>spicy foods</td>
<td></td>
</tr>
<tr>
<td>chocolate</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eat more of these:</th>
<th>Drink more of these:</th>
</tr>
</thead>
<tbody>
<tr>
<td>oven-baked foods</td>
<td>water</td>
</tr>
<tr>
<td>crackers</td>
<td>milk</td>
</tr>
<tr>
<td>fresh fruit</td>
<td></td>
</tr>
<tr>
<td>fresh veggies</td>
<td></td>
</tr>
</tbody>
</table>

**Antacids for heartburn during pregnancy**

If you take an antacid, take your prenatal vitamin at the opposite time of day.

**Safe for you**

- Tums™
- Maalox™
- Gaviscon™
- Riopan™

**NOT safe for you**

- Baking soda
- Alka Seltzer™
- Eno™

**Talk to Your Doctor...**

- If your heartburn gets worse
- Before taking any medications for your heartburn (some are NOT safe in pregnancy)
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 H2RAs 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 H2RAs, with the exception of nizatidine, are safe to use during lactation.

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