GERD and Pregnancy

by Ryan D. Madanick and Philip O. Katz

INTRODUCTION AND EPIDEMIOLOGY

Heartburn, or pyrosis, is usually described as a burning sensation that radiates upward retrosternally from the epigastrium toward the neck. Heartburn is a common symptom that occurs frequently during pregnancy, in any trimester. Although “heartburn” and “gastroesophageal reflux disease (GERD)” have become integrally connected in the medical literature, the two terms have distinct connotations. Heartburn is a symptom that is considered highly sensitive and specific for GERD. GERD, on the other hand, is a disorder of abnormal gastroesophageal reflux and its associated complications, of which heartburn is the most common symptom. In the non-pregnant individual, GERD may present with extraesophageal complaints, including cough, hoarseness, vocal changes, and asthma, but the relationship between these symptoms and GERD has not been adequately evaluated in pregnant patients (1). Because of the close relationship between heartburn and GERD, most studies in this area address pregnancy-related heartburn in the absence of a stringent diagnosis of GERD.

In most women who experience heartburn during pregnancy, the symptoms begin during pregnancy, although less commonly the heartburn may represent a manifestation of underlying GERD. Heartburn may begin in any trimester. In a study of 60 pregnant women who experienced heartburn (2), the onset of heartburn was 52% in the first trimester, 40% in the second trimester, and 8% in the third trimester. Marrero, et al (3) confirmed in a larger study that the prevalence of heartburn increased with gestational age. Among 607 pregnant women attending an antenatal clinic, 22% experienced heartburn in the first trimester, 39% in the second, and 72% in the third, while only 14% of these women reported mild heartburn prior to their pregnancy. Severity also increased throughout pregnancy. By logistic regression analysis, significant predictors of heartburn were found to be increasing gestational age, heartburn before pregnancy, and parity. Maternal age was inversely correlated with heartburn. Race, prepregnancy body mass index, and weight gain in pregnancy did not correlate with the onset of heartburn. Despite its frequent occurrence during pregnancy, heartburn usually resolves after delivery (4).

PATHOPHYSIOLOGY

In the general population, a number of physiologic abnormalities work in concert to cause GERD, including a defective antireflux barrier, the lower esophageal sphincter (LES); impaired esophageal clearance of the refluxate; an altered mucosal barrier; and abnormalities in gastric function, including delayed gastric emptying (1). Increased intra-abdominal pressure as a result of the gravid uterus has been proposed as a possible contributing factor to the increased incidence of GERD in pregnancy. However this alteration does not explain the onset of GERD in the first and early second trimesters, before a change in intra-abdominal pressure is notable. Abnormalities in pregnancy vary with no unifying underlying pathogenetic defect supported in the literature (Table 1).
DIAGNOSIS

The presentation of GERD in pregnancy does not differ from that of the general population (5), and the diagnosis of GERD during pregnancy is made in much the same fashion as in nonpregnant patients. The cardinal symptom, heartburn, is highly accurate in diagnosing GERD, and in the absence of alarm symptoms such as dysphagia, weight loss or hematemesis, a presumptive diagnosis of GERD can be made in most patients who develop heartburn during pregnancy. The development of an esophageal stricture during pregnancy has been reported in only a single case report (6). Regurgitation, characterized by the return of gastric contents into the esophagus or mouth, further supports the diagnosis of GERD when present (1). Additional diagnostic testing is generally not required for the majority of patients with suspected GERD. Barium radiographs are relatively contraindicated during pregnancy because of their potential for teratogenicity. In the occasional patient who does require testing, upper endoscopy is the test of choice, but should be reserved for patients whose symptoms are refractory to medical therapy or who have suspected complications. Although midazolam is designated as category D and meperidine as category C during pregnancy, the medications are considered generally safe to use in low doses for endoscopy. If possible however, endoscopy should be delayed until after the first trimester (1,5). It is uncommon to require ambulatory pH monitoring during pregnancy, unless the diagnosis of GERD is in doubt.

MANAGEMENT

General/Lifestyle Modification

The safety of medical therapies in the nonpregnant patient is well-established. The focus of practitioners who care for pregnant patients with GERD must be the teratogenic potential of antireflux medications (Table 2). Concern about teratogenic potential leads many practitioners to avoid pharmacologic agents and pursue conservative care by initially recommending lifestyle modifications, especially for mild symptoms. It is important to instruct patients to elevate the head of the bed 6 inches and to avoid eating for 3 hours prior to bedtime. Chewing gum may also be of benefit for pregnant women with heartburn, as it stimulates salivary bicarbonate production. A specific chewing gum formulated with calcium carbonate (Surpass, Wrigley Healthcare) has been shown to improve heartburn symptoms, however it was withdrawn from the market in 2003. At least one additional calcium carbonate-based chewing gum (CHOOZ) is available commercially over the internet. Other lifestyle and dietary modifications are identical to those in nonpregnant patients, including maintaining a low-fat diet, avoiding alcohol and smoking, and eliminating medications that may exacerbate gastroesophageal reflux (Table 3). Following these basic lifestyle modifications is expected to resolve symptoms in up to 25% of patients with uncomplicated GERD (1). If it is feasible, pharmacotherapy should be withheld until after the critical period of organogenesis, which ends after the tenth week of gestation.

Medical Therapies (See Table 4)

Antacids

Antacids should be considered the first line of therapy for symptom relief in pregnant women with heartburn. Antacids containing aluminum, magnesium and calcium have no FDA classification and are generally considered safe for use during pregnancy, although there are limited data regarding fetal safety. However aluminum-containing antacids, especially when taken in high doses, have the potential to cause fetal neurotoxicity. During the last several weeks of pregnancy, magnesium-containing antacids should be avoided because of the tocolytic property of magnesium. (continued on page 35)
Antacids that contain sodium bicarbonate are not considered safe during pregnancy because of the risk for maternal or fetal metabolic alkalosis and fluid overload. Algic acid (Gaviscon®) is usually combined with antacids to cause buffering of gastric acid and works by forming a raft-like barrier to the reflux of gastric contents into the esophagus. It provides adequate relief of heartburn symptoms that develop during pregnancy (5), but has been implicated in adverse fetal outcomes, including fetal distress. Magnesium trisilicate, the compound found in Gaviscon Regular Strength Tablets, can cause fetal nephrolithiasis, hypotonia, respiratory distress and cardiovascular impairment when used long-term in high doses (7). Calcium-based compounds are therefore the preferred first choice of antacids through all trimesters, with magnesium-based compounds (except magnesium trisilicate) a safe option except near the end of pregnancy.

### H₂-Receptor Antagonists (H₂-RAs)

For patients whose symptoms do not respond to antacid therapy, the next option in therapy is H₂-receptor antagonists (H₂-RAs). The primary limitation of these drugs is their onset of action, which is not rapid enough for immediate symptom relief, such as in the postprandial period. H₂-RAs are FDA pregnancy category B, although nizatidine was previously considered a category C drug based on animal studies. Several registries have confirmed in retrospective analyses that exposure to H₂-RAs during pregnancy does not appear to increase the rate of major fetal malformations over controls, with rates ranging between 3.1% and 7.4%. In their prospective cohort study, Magee, et al (8) reported that there was no increased risk of major fetal malformations (2.1% vs 3.5%) or other adverse gestational outcomes in 178 patients exposed to H₂-RAs during pregnancy (88% during the first trimester) when compared with matched controls. Larson, et al (9) conducted a small study of the effectiveness of ranitidine in pregnancy, and found that ranitidine needed to be taken...
twice a day to gain a statistically significant improvement in heartburn control versus placebo, with a mean reduction of heartburn intensity of 44.2% versus placebo. Because of weak antiandrogenic properties in cimetidine, there is a theoretical risk of impaired sexual development in male children whose mothers used cimetidine during gestation. There are no reports of this defect occurring in humans. Most of the H2-RA data in human studies is with cimetidine and ranitidine, with limited data on famotidine and nizatidine.

**Proton Pump Inhibitors**

Proton pump inhibitors (PPIs) are the most effective medical therapy currently available to control GERD symptoms and complications. However, their safety in pregnancy is not as well documented as the H2-RAs, and subsequently they should only be used for patients who have severe symptoms that are refractory to other treatments. There are no studies regarding pregnant women with severe GERD complications (Barrett’s esophagus, esophageal stricture), but PPI use may also be considered if women are known to harbor one of these conditions prior to gestation. Because animal studies have shown teratogenic effects at large doses, omeprazole is classified as FDA pregnancy category C, but the remainder of the PPIs are category B. A meta-analysis of five cohort studies demonstrated a relative risk of 1.18 (95% CI 0.72–1.94 P = NS) for major fetal malformations among 593 PPI-exposed pregnancies (10). An overall rate of malformations among the exposed pregnancies in this meta-analysis was 2.8% (10). A recent multicenter prospective cohort study followed 295 pregnancies exposed to omeprazole, 62 to lansoprazole, and 53 to pantoprazole (233, 55, and 47 within the first trimester, respectively) (11). The rates of major congenital abnormalities was 3.6%, 3.9%, and 2.1% respectively, and these rates did not differ from the control group, whose rate of major congenital abnormalities was 3.8%. These studies suggest that PPIs do not necessarily result in a significant increase in major fetal abnormalities. Nonetheless their use in pregnancy should be approached with caution. When a pregnant woman’s symptoms do not respond to antacids, most still recommend a trial of an H2-RA before a PPI, based on the more extensive experience with H2-RAs during pregnancy. For women of childbearing age who are taking a PPI prior to pregnancy, it is worthwhile to review the indications for the PPI and the possible teratogenic risks, and re-assess the need for chronic therapy prior to any planned pregnancy.

If a woman on chronic antisecretory therapy becomes pregnant during therapy with a PPI, she should be reassured that even though PPI exposure during the first trimester appears to be safe, most would recommend discontinuing the drug at least through the first trimester. Therefore, the need for continued therapy throughout pregnancy should be addressed with the

(continued on page 39)
patient as soon as possible so she may make the choice
to discontinue the drugs at this critical time.

Promotility Agents

Promotility agents have played a decreased role in the
management of GERD in the non-pregnant patient since
potent antisecretory agents have become widely
accepted as safe and effective in healing esophagitis and
controlling symptoms. Cisapride has been removed
from the market in the United States, and should not be
considered an option in the management of GERD in
pregnancy. Although metoclopramide is categorized as
an FDA class B drug and is used in hospitalized
patients, it has significant neurologic side effects,
including drowsiness, dystonic reactions, and akathisia.
Its principal use in pregnancy is for refractory nausea
and vomiting of pregnancy (5). We do not recommend
metoclopramide as a treatment for reflux symptoms
unless all other options have been exhausted. Tegaserod
is an FDA class B drug, but its safety during pregnancy
in humans is not well documented. Its use for refractory
GERD is still under investigation, and it cannot cur-
cently be recommended for GERD during pregnancy.

Sucralfate

Sucralfate is a poorly absorbed cytoprotective agent
that contains an aluminum salt. As previously dis-
cussed, aluminum can cause fetal toxicity, but is likely
to be safe during pregnancy because of its poor sys-
temic availability. It is therefore classified as an FDA
class B drug. No human studies are available in the
English literature, although there is one Italian study
showing improvement in symptoms.

GERD Therapy During Lactation

Most women who develop reflux symptoms during
pregnancy experience relief of their symptoms (4).
However some women, especially those with pre-existent
GERD, will still require ongoing therapy after
delivery, during lactation. Certain medications may be
transmitted through the breast milk to the nursing infant
and the safety of these medications on the newborn is
of utmost concern. Antacids, even those containing alu-
minum, are considered to be safe during lactation. All
H2-RAs, and probably all PPIs, are excreted in breast
milk. H2-RAs are considered to be safe, however one
animal study suggested that nizatidine caused growth
retardation in nursing pups (12). Nizatidine is therefore
the only H2-RA not recommended for use by lactating
mothers. The concentration of PPIs in breast milk and
the safety of PPIs on the nursing infant have not been
adequately investigated. PPIs are also not recom-
ended for use during lactation. Those women who
require continued GERD therapy post-partum should
avoid PPIs during lactation or discontinue nursing.

SUMMARY

Management of the pregnant patient with GERD con-
tinues to be a clinical challenge. Though likely safe,
antisecretory therapy should be used with caution early
in pregnancy. Traditional approaches—antacids, sucral-
fate and lifestyle modifications—are still the standard
recommendation. A safe, perhaps endoscopic therapy
would be welcomed by patients with chronic GERD.

References
1. Katz PO, Castell DO. Gastroesophageal reflux disease during
2. Castro LP. Reflux esophagitis as the cause of heartburn in preg-
3. Marrero JM, Goggin PM, de Caestecker JS, Pearce JM, Maxwell
1992;99: 731-734.
954-970.
5. Richter JE. Review article: the management of heartburn in preg-
due to reflux oesophagitis in pregnancy. *Brit J Obstet Gynaecol*,
7. Lewis JH, Weingold AB. The committee on FDA-related matters
for the American College of Gastroenterology. The use of gas-
trointestinal drugs during pregnancy and lactation. *Amer J Gas-
troenterol*, 1985; 80: 912-923.
of first trimester exposure to histamine H3-blockers: a prospective
9. Larson JD, Patatanian E, Minner PB, Rayburn WF, Robinson MG.
Double-blind, placebo-controlled study of ranitidine for gastro-
esophageal reflux symptoms during pregnancy. *Obstet Gynecol*,
10. Nikfar S, Abdollahi M, Moretti ME, Magee LA, Koren G. Use of
proton pump inhibitors during pregnancy and rates of major mal-
11. Dian-Citrin O, Arnon I, Schechtman S, Schaefer C, Van Tornin-
gen MR, Clementi M, DeSanitis M, Robert-Gnansia E, Valit E,
Malm H, Ornay A. The safety of proton pump inhibitors in preg-
nancy; a multicentre prospective controlled study. *Alim Pharma-
12. Obermeyer BD, Bergstrom RF, Callaghan JT, Knadder MP, Goli-
chowsk A, Rubin A. Secretion of nizatidine into human breast
milk after single and multiple doses. *Clin Pharmacol Therap*,
1990; 47: 724-730.