DRUG SAFETY CONCEPTS

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Treating Gastro-Oesophageal Reflux Disease During Pregnancy and Lactation

What are the Safest Therapy Options?

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Abstract

Gastro-oesophageal reflux and heartburn are reported by 45 to 85% of women during pregnancy. Typically, the heartburn of pregnancy is new onset and is precipitated by the hormonal effects of estrogen and progesterone on lower oesophageal sphincter function. In mild cases, the patient should be reassured that reflux is commonly encountered during a normal pregnancy: lifestyle and dietary modifications may be all that are required.

In a pregnant woman with moderate to severe reflux symptoms, the physician must discuss with the patient the benefits versus the risks of using drug therapy. Medications used for treating gastro-oesophageal reflux are not routinely or vigorously tested in randomised, controlled trials in women who are pregnant because of ethical and medico-legal concerns. Safety data are based on animal studies, human case reports and cohort studies as offered by physicians, pharmaceutical companies and regulatory authorities.

If drug therapy is required, first-line therapy should consist of nonsystemically absorbed medications, including antacids or sucralfate, which offer little, if any, risk to the fetus. Systemic therapy with histamine H_2 receptor antagonists (avoiding nizatidine) or prokinetic drugs (metoclopramide, cisapride) should be re-

served for patients with more severe symptoms. Proton pump inhibitors are not recommended during pregnancy except for severe intractable cases of gastro-oesophageal reflux or possibly prior to anaesthesia during labour and delivery. In these rare situations, animal teratogenicity studies suggests that lansoprazole may be the best choice. Use of the least possible amount of systemic drug needed to ameliorate the patient's symptoms is clearly the best for therapy. If reflux symptoms are intractable or atypical, endoscopy can safely be performed with conscious sedation and careful monitoring the mother and fetus.

Gastro-oesophageal reflux and its main symptom heartburn, is a very common manifestation of several physiological changes that occur in the gastrointestinal tract during pregnancy. Gastro-oesophageal reflux is reported by 45 to 80% of women who are pregnant,[1,2] and the symptomatology of this disorder is essentially identical during pregnancy and in the nonpregnant state, although the aetiology may differ. The medical therapies available for treating the pregnant patient with heartburn, especially if severe, may be limited due to the potential teratogenic risks of some drugs. This article will review the treatment options available to the physician for this common malady of pregnancy. The recommendations for treatment made apply equally well to the patient receiving treatment for gastro-oesophageal disease who becomes pregnant. An extensive MEDLINE search of the English literature assessing the drugs used for gastro-oesophageal reflux during pregnancy was used as the basis for material for the review.

1. Epidemiology

Typical gastro-oesophageal reflux in pregnancy is new onset, although some women will experience heartburn before pregnancy and will notice either a continuation or an exacerbation during gestation. Heartburn can occur anywhere within, or throughout the 3 trimesters of pregnancy. In a study of 88 pregnant women, Castro[3] observed that the majority of symptoms of gastro-oesophageal reflux occurred within the first and second trimesters, with few new symptoms encountered in the third trimester (52.6, 40 and 8.3% respectively). However, other studies have reported reflux symptoms increasing in frequency and severity as gestational age increases, particularly in the third trimester.[4,5] Nevertheless, symptoms usually resolve post partum. There is a tendency for heartburn to recur in subsequent pregnancies.[6]

Few studies have looked at the association of heartburn and ethnicity in pregnant women. One study[7] noted a higher incidence of heartburn in Caucasians when compared with Nigerians (78.8 *vs* 9% respectively) while Bainbridge et al.[8] found no difference in the incidence of heartburn between Caucasian Europeans and Asians. Marrero et al.[4] studied 607 women during various stages of pregnancy via a questionnaire, and found there was an increased risk of heartburn with increasing gestational age, presence of prepartum heartburn and parity, but not race.

1.1 Clinical Features

The spectrum of gastro-oesophageal reflux in pregnancy is similar to that in the general population. Heartburn and regurgitation are the predominant symptoms. Other common complaints include indigestion, epigastric pain, waterbrash, anorexia, nausea and vomiting. Likewise, the common precipitating factors in the general population also aggravate the heartburn of pregnancy such as eating before bedtime, ingestion of fatty or spicy foods, caffeinated beverages, mints, chocolate and sometimes inadvertent use of drugs that decrease lower oesophageal sphincter pressure (e.g. calcium antagonists, anticholinergics). Complications of gastro-oesophageal reflux, including oesophagitis, with or without bleeding and stricture formation, are rare in pregnancy. Reflux symptoms are typically limited to the pregnancy and no adverse effects on the mother or fetus have been reported.[9]

1.2 Pathophysiology

Although the exact mechanism is unknown, the pathophysiology of gastro-oesophageal reflux in pregnancy is probably multifactorial including hormonal effects on lower oesophageal sphincter function, and mechanical factors.

Most studies have found that lower oesophageal sphincter pressure decreases during the course of a pregnancy. For example, Van Thiel et al.[10] demonstrated that resting lower oesophageal sphincter pressures were lower than normal during all 3 trimesters of pregnancy, reaching a nadir at 36 weeks gestation. The reduction in lower oesophageal sphincter pressure was accompanied by heartburn, with subsequent return of normal lower oesophageal sphincter pressure post partum. In contrast, Fisher et al.,[11] found no significant difference in lower oesophageal sphincter pressures before and after therapeutic abortion during the first 20 weeks of gestation, but did notice that the 'normal' adaptive sphincter responses to hormonal and pharmacological agents were blunted.[12] This suggests that subtle physiological alterations are seen early in pregnancy followed later by absolute decreases in lower oesophageal sphincter pressure.

Animal and human studies have confirmed that female sex hormones alter lower oesophageal sphincter function. Schulze and Christensen,[13] using an animal model (female opossums), confirmed that lower oesophageal sphincter pressure can be lowered by the sequential administration of female hormones inducing a pseudopregnancy state. Fisher et al.[12] found that 17-β estradiol, progesterone or a combination of the 2, significantly decreased the maximal lower oesophageal sphincter response in opossums to gastrin, norepinephrine (noradrenaline) and acetylcholine. However, the greatest inhibitory effect was seen with the combination of estrogen and progesterone. Van Thiel et al.[14] measured lower oesophageal sphincter pressures sequentially in female volunteers using oral contraceptives, finding that lower oesophageal sphincter pressures were unchanged when taking ethinylestradiol; however, when progesterone (dimethisterone) was taken in addition, the lower oesophageal sphincter pressure significantly decreased. Finally, Fillipone et al.,[15] in a study of male transsexuals, found that lower oesophageal sphincter pressure decreased with a combination of estrogen plus progestin but not with either estrogen or progestin alone. Thus, the overall data suggest that the combination of estrogen with progesterone is required to decrease lower oesophageal sphincter pressure. While progesterone is the mediator of lower oesophageal sphincter smooth muscle relaxation, estrogen may serve as a 'primer' for this action to occur.

Delayed gastric emptying due to hormonal and/or mechanical factors is also postulated to play a role in gastro-oesophageal reflux of pregnancy. However, several studies,[16-19] using indirect measurements of gastric emptying in pregnancy, were not able to verify significant delays in gastric emptying when measured during all 3 trimesters. Of interest, 1 study[17] found gastric emptying significantly delayed in mothers during labour up to the first 2 hours after delivery; this returned to normal by the second post partum day. This delay was due to the administration of opioid analgesia during labour, thus confirming the importance of aspiration precautions in recently delivered mothers or those requiring anaesthesia.

Another hypothesis is that the enlarging gravid uterus causes increased intra-abdominal pressure, thus compressing the stomach and provoking reflux symptoms during pregnancy.[20] However, Van Thiel and Wald[21] disproved this commonly held theory by evaluating cirrhotic men with tense ascites as a pseudopregnancy state while measuring lower oesophageal sphincter pressures before and after aggressive diuresis. Surprisingly, prior to diuresis lower oesophageal sphincter pressures were elevated in parallel with the associated increased intra-abdominal pressures, thereby preventing gastro-oesophageal reflux. After diuresis, intra-abdominal and lower oesophageal sphincter pressures decreased returning to normal values. Thus, an increase in intra-abdominal pressure alone cannot account for the heartburn of pregnancy.

2. Evaluating Gastro-Oesophageal Reflux in the Pregnant Patient

In the pregnant patient, the initial diagnosis and treatment of gastro-oesophageal reflux is based on symptoms alone. Invasive studies such as manometry and pH probes are rarely needed, although these can be safely performed during pregnancy (unpublished observations).[1] Some patients may need to undergo an endoscopy because of intractable symptoms or complications, such as bleeding. This can be safely performed without harm to the mother or fetus by careful monitoring of blood pressure and oxygenation, as well as the judicious use of conscious sedation. Fetal monitoring may increase the safety of upper endoscopy during late pregnancy.[22]

In the largest endoscopic experience in pregnant women, Cappell et al.[22] in a case-controlled study assessed 83 consecutive pregnant patients undergoing upper endoscopy between 1980 to 1995. The mean gestational age was 19.8 weeks. Oesophagitis was identified in 62% of patients. The effects of endoscopy with sedation on vital signs and oxygen saturation were clinically and statistically insignificant. There were no labour induction or significant endoscopic complications. Of the 83 patients, 95% delivered healthy babies. Four poor outcomes (3 stillbirths and 1 involuntary abortion) occurred in high risk pregnancies but were unrelated to endoscopy temporally or aetiologically. Although fetal cardiac monitoring was used in only 3 cases, endoscopy did not induce abnormal fetal heart rates. The results of this study support the judicious use of upper endoscopy when indicated in pregnant women.

3. Treatment for Gastro-Oesophageal Reflux in Pregnancy

The challenge in treating gastro-oesophageal reflux during pregnancy is the potential for commonly used antireflux medications to have teratogenic effects on the fetus. In pregnant women with only mild symptoms, conservative lifestyle and dietary modifications may be all that is required. This includes avoiding eating late at night or before retiring to bed, raising the head of the bed by 10 to 15cm and avoiding certain foods (fats, spices, carbonated beverages, coffee) and medications that may cause heartburn. Abstaining from alcohol and tobacco is strongly encouraged as it will not only reduce reflux symptoms but also avoid fetal exposure to these harmful substances.

In pregnant women with moderate to severe reflux symptoms, the physician must discuss with the patient the benefits versus the risks of using drug therapy. Informed consent is appropriate in this setting. Medications used for treating gastro-oesophageal reflux are not routinely or rigorously tested in randomised controlled trials in pregnant women due to the ethical and medico-legal ramifications. Most recommendations arise from case reports and cohort studies as offered by physicians, pharmaceutical companies and the US Food and Drug Administration (FDA). However, major problems with reliance upon voluntary reports offered by the manufacturer include the inability to assess the quality of these reports, unknown duration of follow-up, absence of appropriate controls and the possibility of reporting bias (i.e. an unknown number of exposures not reported).

The commonly used medications for treating gastro-oesophageal reflux includes antacids, mucosal protectants, histamine H_2 receptor antago-

Table I. Definitions of US Food and Drug Administration (FDA) classifications

FDA classification	Definition
Category A	Well controlled studies in humans show no fetal risk
Category B	Animal studies show no risk, 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

nists, promotility drugs and proton pump inhibitors. The overall incidence of major fetal malformations in the general population ranges between 1 to 3%.[23-26] The safety of drugs in pregnancy is commonly divided into 5 categories by the US FDA (A, B, C, D, X) indicating the potential for systemic absorption, and animal and human reports of birth defects (see table I).[23]

The typical teratogenic period ranges from day 31 (in a 28 day cycle) to day 71 from the last menstrual period,[24] essentially the first 10 weeks of gestation. This is the critical period of organogenesis. Before this period, exposure to a teratogen usually causes an all-or-nothing effect (i.e. the conceptus either does not survive or survives without anomalies).[24] The cells are totipotential at this time with respect to organogenesis; therefore, if a few cells die off the remaining cells can take over as they have not differentiated for organogenesis. Thus, if drugs are not required urgently, they should be withheld until this time period has elapsed, although drugs can still affect the fetus in later gestation.

4. Medications

Drugs used for gastro-oesophageal reflux in pregnancy, and their US FDA categories are summarised in table II.

4.1 Antacids

Antacids are used by 30 to 50% of women for the relief of heartburn and other acid reflux symptoms during pregnancy. However, there are only limited data concerning the effect of antacids on the fetus and no controlled trials of efficacy included in many of the larger prospective drug surveillance studies. Teratogenic effects of magnesium, aluminum or calcium containing antacids are not observed in animal studies[27,28] although 15 to 30% of magnesium and a smaller percentage of aluminum preparations are available for absorption after they react with hydrochloric acid.

One retrospective case-controlled study in the 1960s[26] found a significant increase in major and minor congenital abnormalities in infants exposed to antacids during the first trimester of pregnancy. However, analysis of individual antacids (aluminum hydroxide, sodium bicarbonate, magnesium trisilicate and calcium carbonate) found no association with increased congenital anomalies. At present, the use of most aluminum-, magnesium- and calcium-containing antacids in therapeutic doses is considered is acceptable for use during pregnancy.[23]

Sodium bicarbonate should not be used as it may cause metabolic alkalosis and fluid overload in both the mother and fetus. Compounds containing magnesium trisilicate (e.g. 'Gaviscon'), when used long term and in high doses, can lead to nephrolithiasis, hypotonia, respiratory distress and cardiovascular impairment in the fetus.[23] Neither aluminum nor magnesium hydroxide enter breastmilk in substantial amounts and no problems have

Table II. US food and Drug Administration (FDA) classification of drugs used for gastro-oesophageal reflux in pregnancy

Drug	FDA class	Comments
Antacids	None	The majority are acceptable for use in pregnancy and for aspiration prophylaxis during labour
Sucralfate	B	No teratogenicity in animals, suggested as acceptable for use in humans due to minimal systemic absorption
Cimetidine Ranitidine Famotidine Nizatidine	B B B B	Prospective controlled study suggests acceptable for use and efficacious in pregnancy with the exception of nizatidine[a]
Cisapride	C[b]	Embryotoxic and fetotoxic in animals, however a recent prospective controlled study in humans suggests acceptable for use[b]
Metoclopramide	B	No teratogenic effects in animals or humans reported
Omeprazole	C	Embryotoxic and fetotoxic in animals. Case reports in humans suggest similar concerns. Acceptable for use for aspiration prophylaxis in labour
Lansoprazole	B	No teratogenicity in animals, human studies not available. Acceptable for use for aspiration prophylaxis in labour

a See section 4.3.4.
b See section 4.4.2.

been reported in nursing mothers. No information is available regarding the use of magaldrate (hydrated magnesium aluminate, 'Riopan') or alginic acid ('Gaviscon') in pregnancy; however, both are not absorbed and probably acceptable for use. As normal gastric secretion and organic acids enhance absorption of iron, use of antacids should be followed carefully in pregnant patients with significant iron deficiency anaemia.

4.2 Mucosal Protectants

4.2.1 Sucralfate

Mucosal protectants (e.g. sucralfate) are not systemically absorbed and have few adverse effects; therefore, they are commonly used during pregnancy. Studies performed in rats, mice and rabbits, revealed no teratogenicity or impaired reproductive effects with doses up to 50 times the recommended human dose.[29] In a randomised study of 66 patients, Ranchet et al.,[30] compared sucralfate 1g 3 times daily with lifestyle modifications (controls) for the treatment of heartburn of pregnancy. They found that the sucralfate group had a greater number of patients with complete remission of symptoms (heartburn and regurgitation) when compared to controls (90 *vs* 43% and 83 *vs* 27%, respectively). No data are available on the transfer of sucralfate into breastmilk. However, given that little if any is absorbed, transfer would be expected to be minimal.

4.3 Histamine H_2 Receptor Antagonists

4.3.1 Cimetidine

Cimetidine, the first approved H_2 receptor antagonist, has been in available in the US since 1975. The results of reproductive studies in animals involving cimetidine are conflicting. The manufacturer reports that dosages as high as 950 mg/kg/day in pregnant rats and rabbits produced no adverse effects on litters or on the early development of the pups, despite plasma cimetidine concentrations in the offspring approximately 300-fold higher than those concentrations needed to produce a 50% inhibition of basal acid secretion.[23] In contrast, others report that the sexual development and behaviour of male rat pups was impaired after exposure of the pregnant dams to dosages of cimetidine as low as 17.1 mg/kg/day, equivalent to a 70kg human taking 1200 mg/day. The observed effects were still present 35 days after drug discontinuation suggesting that both central and end organ androgen receptor activity or responsiveness may be modified.[31,32] However, there are no reports of human sexual defects in infants exposed to cimetidine.

There are few published safety reports of cimetidine being taken by pregnant women and no efficacy studies. In 3 anecdotal reports, no adverse fetal effects were noted in 12 infants exposed for periods as long as 27 weeks.[33-35] The manufacturer is also aware of approximately 50 additional cases where pregnant women were exposed to cimetidine for a time period of anywhere from 3 weeks to the entire pregnancy in dosages ranging from 400 to 1000 mg/day without untoward fetal effects.[2] A case of cimetidine-related hepatitis was reported in a newborn exposed to the drug in the last month of gestation.[35] In a surveillance study of Michigan Medicaid recipients involving 229 101 pregnancies between 1985 and 1992, 460 newborns were exposed to cimetidine during the first trimester.[36] A total of 20 (4.3%) major birth defects were observed, similar to the reported prevalence in women taking no medications, thus supporting the lack of association between cimetidine and congenital defects.

Animal studies demonstrate that cimetidine crosses the placenta freely and is excreted into breastmilk, where it can reach concentrations several fold higher than those in maternal serum.[31] One report documents the excretion of cimetidine into breastmilk in a nursing mother.[37] Previously, nursing was not recommended during the time of maternal exposure to cimetidine. However, the American Academy of Paediatrics has reclassified the drug as compatible with breastfeeding in the absence of adverse reports.[36]

Despite the fact that H_2 receptors are present in the myometrium, no adverse effects on uterine contractions are observed in animals.[38,39] In addition,

no changes in the pattern of contractions, fetal heart rate or the course of labour are reported in women during active labour.[40] Apgar scores and infant progress were reported to be unaffected.[40,41] Blood concentrations of cimetidine in the newborn are no longer detectable 19 hours following exposure.[40]

4.3.2 Ranitidine

Ranitidine has a similar safety profile to cimetidine in pregnancy and labour. Animal studies, using doses equivalent to 160 times the maximum recommended human dose, resulted in no fetal abnormalities,[29] as well as no impairment of sexual development or function in male rat pups in contrast to cimetidine.[32] In anecdotal reports of 10 women taking ranitidine while pregnant, there was no evidence of maternal or fetal abnormalities.[42,43] A single case report describes the use of ranitidine throughout pregnancy without any adverse fetal or neonatal outcome.[44] Another report[45] described the outcome of first trimester exposure to ranitidine in 14 women. The total dose exposure was unknown in 13 women and 1 women was exposed to both ranitidine and cimetidine. Follow-up revealed the births of 10 healthy infants, 2 spontaneous abortions, and 1 baby had an eyelid haemangioma. In the previously mentioned surveillance study of 229 101 pregnancies in Michigan Medicaid recipients,[36] 516 newborns were exposed to ranitidine during the first trimester. Of the babies, 23 (4.5%) had major birth defects compared with the expected prevalence of major birth defects of 22 (4.3%).

Ranitidine, like cimetidine, crosses the placenta. However, the plasma concentrations rapidly decline in the neonate and are virtually undetectable 12 hours after birth. However, the metabolised ranitidine is excreted in breastmilk with concentrations greater than in the plasma, but the effect in the nursing infant is unknown.[36]

Ranitidine is the only H_2 receptor antagonist whose efficacy has been studied during pregnancy. In a recently reported double-blind, placebo-controlled, triple crossover study, Larson et al.[46] compared the efficacy of ranitidine taken once or twice daily with placebo in pregnant women with gastro-oesophageal reflux symptoms not responding to lifestyle changes and antacids. A group of 20 women at at least 20 weeks gestation were randomised to receive ranitidine 150mg twice daily, placebo in the morning and ranitidine 150mg in the evening, or placebo twice daily. Symptom diaries were scored, and global assessments and the number of antacid tablets taken were compared. In the 18 patients who completed the study, only twice daily dosages of ranitidine reduced symptoms and antacid usage, when compared with baseline ($p < 0.001$) or placebo ($p < 0.01$). The average reduction of heartburn was 55.6% [95% confidence interval (CI) 34.8 to 76.5%] in patients receiving twice daily ranitidine therapy when compared with baseline and 44.2% (95% CI 15.4 to 72.9%) when compared with placebo. No adverse pregnancy outcomes or drug reactions were noted. Only 1 patient reported continued heartburn after delivery and this responded to antacids or ranitidine therapy.

4.3.3 Famotidine

There is little literature available on the use of famotidine during human pregnancy. Studies in rabbits and rats administered oral dosages of 200 and 500 mg/kg/day and intravenous dosages of 200 mg/kg/day revealed no impaired fertility, fetotoxic effects, teratogenicity or changes in postnatal behaviour. In the surveillance study of Michigan Medicaid recipients,[36] 33 fetuses were exposed to famotidine during the first trimester. Of these, 2 (6.1%) developed major birth defects compared with the expected prevalence of major birth defects of 1. However, the number of exposures in this study is too small to draw any conclusions. The antiandrogenic effect of cimetidine given to male rat pups has not been found in male humans treated with famotidine.[47]

Famotidine is concentrated in breastmilk, but to a lesser degree than either cimetidine or ranitidine. Exposure to famotidine in the nursing infant via breastmilk has not been reported. Since famotidine is less concentrated in the milk compared with cimetidine and ranitidine, one author has suggested

that perhaps it may be preferred in nursing women.[48]

4.3.4 Nizatidine

Although safety data is limited, adverse effects of nizatidine during pregnancy are concerning. In animal studies, rabbits treated with the equivalent of 300 times the recommended human dose encountered abortions, low fetal weights and fewer live fetuses. Other adverse outcomes reported in the offspring of animals exposed to nizatidine during pregnancy include coarctation of the aorta, cardiac enlargement and cutaneous oedema.[49] However, other studies of pregnant rats given oral dosages up to 506 mg/kg/day reported no adverse effects on fertility. Unlike the adverse effects on male rats with cimetidine use, there were no antiandrogenic effects seen in male rats treated with nizatidine.[50] Likewise, no teratogenicity was observed in rats and rabbits with dosages up to 1500 mg/kg/day, although some abortions occurred in the rabbits at the higher dosage.[51] In contrast, congenital malformations were observed in 2 fetuses of pregnant rabbits administered intravenous dosages of 20 and 50 mg/kg.[36]

Small amounts (0.1%) of nizatidine are excreted into human breastmilk. Growth depression has been noted in pups reared by lactating rats treated with nizatidine[29] and thus the recommendation is to discontinue either nursing or the drug. Unfortunately, no anecdotal reports of human pregnancy outcome after using nizatidine are available from the manufacturer. Although previously classified as category C by the US FDA, nizatidine was recently upgraded to a category B drug.

4.3.5 General Recommendations

In general, H_2 receptor antagonists seem relatively well tolerated during pregnancy although, until recently, there were no controlled studies to support this belief. In the only prospective, controlled, cohort study in the literature, Magee et al.[52] evaluated 230 women who took H_2 receptor antagonists during pregnancy and compared them with an equal number of control individuals matched for maternal age, tobacco and alcohol use. The majority of women only took the H_2 receptor antagonists in the first trimester (88%); ranitidine was the most commonly used drug (77%). In a follow-up telephone interview, the investigators found no significant difference in major congenital malformations between those infants who were exposed to H_2 receptor antagonists during the first trimester, and control group infants (2.1 *vs* 3.5%, respectively). Pregnancy outcome, neonatal health and achievement of developmental milestones were also similar between the 2 groups. Shortcomings of the trial included the fact no information was available regarding the total amount of drug use, sporadic versus prolonged users were combined and 23% of patients were lost to the follow-up.

Our review of the animal and human data gives us confidence that the H_2 receptor antagonists, possibly with the exception of nizatidine, are well tolerated and efficacious in the treatment of heartburn of pregnancy. Nevertheless, we suggest that the use of these drugs should be limited to treat the pregnant women whose gastro-oesophageal reflux disease does not respond to lifestyle changes, antacids, 'Gaviscon' and sucralfate.

4.4 Promotility Agents

4.4.1 Metoclopramide

This antidopaminergic agent improves gastro-oesophageal reflux by increasing lower oesophageal sphincter pressure, improving oesophageal acid clearance and promoting gastric emptying.[53] Metoclopramide has not been reported to cause teratogenic effects in animals at doses ranging from 12 to 250 times the recommended human dose.[29] In the Michigan Medicaid surveillance study,[36] 192 newborns were exposed to metoclopramide during the first trimester; 10 (5.2%) major birth defects were observed (8 were expected).

Metoclopramide crosses the placenta rapidly and may reach fetal plasma concentrations 60 to 70% of maternal concentrations. Metoclopramide is also excreted in breastmilk; however, no untoward neonatal effects were observed in mothers taking up to 45 mg/day.[36] In addition, the drug increases prolactin levels in adults, although no

significant increase in fetal prolactin excretion has been observed.[54]

4.4.2 Cisapride

Cisapride promotes the release of acetylcholine from the myenteric plexus, thereby increasing lower oesophageal sphincter pressure, improving acid clearance and promoting gastric emptying. The drug is toxic to the fetuses of rats and rabbits at doses 100 and 12 times the recommended human dose, respectively.[29] Its use resulted in lower birthweights in rat pups and adversely affected survival. Until recently, human experience with cisapride during pregnancy was limited to case reports that were sent to the manufacturer. Most of these reports documented the birth of healthy infants or therapeutic abortions,[55] but there are a few reports of spontaneous abortions after the use of cisapride.[2]

Recently, the first multicentre prospective controlled study assessing the safety of cisapride use during pregnancy was published by Bailey and colleagues.[55] All women who contacted programmes in Canada offering an antenatal counselling service, including Motherisk, were evaluated for the use of cisapride during pregnancy between November 1988 and May 1996. Relevant information was collected pertaining to pregnancy outcome including history of spontaneous or therapeutic abortions, gravidity, parity, tobacco and alcohol consumption, and maternal medical and genetic history. These same patients were later telephoned after their due date for a follow-up interview and questionnaire, filled out by the telephone interviewer, assessing the course and outcome of pregnancy. Cisapride dose, exposure period and indication for drug use were recorded.

A total of 129 women who had been exposed to cisapride during pregnancy were enrolled in this observational cohort study. Of those 88 (68.2%) reported exposure to cisapride during fetal organogenesis (defined as the period between the fourth and sixteenth week of gestation). Each case was paired for age, smoking and alcohol consumption with control individuals exposed to nonteratogens, in addition to disease-paired control individuals. Indications for cisapride use included gastro-oesophageal reflux (22.5%), motility problems (16.3%), gastrointestinal pain (56.6%) and duodenal ulcer (4.6%). The majority of women were on multiple medications at the time of cisapride use (79.8%) including H_2 receptor antagonists, proton pump inhibitors and antacids. The mean daily dosage of cisapride was 25 ± 17 mg/day with a range between 5 and 120 mg/day. The mean length of exposure was 4.6 ± 7.6 weeks ranging between 0.14 to 41 weeks. Most women took cisapride during the first trimester (87.6%); 3.1% of women took it throughout their pregnancy.

The investigators found no differences in rates of major or minor congenital malformations. Therefore, they concluded that cisapride use during pregnancy was not associated with a major increased risk of congenital malformations, spontaneous abortions or with decreased birthweight.

The main limitation of this study was the limited power to detect a minor increase in malformation rate during fetal organogenesis (i.e. only 88 patients evaluated during this critical period whereas 800 patients would have been necessary to detect a 2-fold increase in major malformations with 80% power).

Although cisapride is presently listed as a category C drug by the US FDA for use in pregnancy, this may well change in the light of this recently published study. If nonsystemic drugs and H_2 receptor antagonists fail to control the symptoms of gastro-oesophageal reflux, we believe that cisapride can be used safely during pregnancy.

4.5 Proton Pump Inhibitors

4.5.1 Omeprazole

Although the proton pump inhibitors (e.g. omeprazole, lansoprazole) are clearly more efficacious in treating gastro-oesophageal reflux than H_2 receptor antagonists, there are limited safety data and they should be used cautiously during pregnancy. In animal studies[29] with rabbits, embryo death, fetal resorption and pregnancy disruption were reported with doses of omeprazole administered at 17 to 172 times the usual human dose. Fetal

toxicity was noted in rats administered 35 to 345 times the usual human dose.

Human data on the safety of omeprazole in pregnancy are limited to a small number of case reports. In 1 report, a woman who unintentionally took omeprazole 40 mg/day during the first month of gestation gave birth to a healthy infant.[56] In another case report, a young woman with Zollinger-Ellison syndrome took high dosages of H_2 receptor antagonists during her first pregnancy and high dosages of omeprazole (120 and 180 mg/day) during 2 other consecutive pregnancies resulting in births of healthy infants.[57] The manufacturer of omeprazole is aware of several additional published case reports of women who received the agent during the first and/or second and third trimesters who later delivered healthy babies.[56-58] There were no adverse fetal or maternal effects noted in these cases.

On the other hand, 2 consecutive pregnancies were recently reported which were terminated due to an anencephalic fetus and severe talipes of the fetus in 1 woman who had taken omeprazole 20 mg/day for severe oesophageal reflux prior to conception.[59] Of note, these pregnancies were conceived by artificial insemination outside the body and then reimplanted: these 'experimental pregnancies' can result in a higher risk of congenital malformations than normal pregnancies.[60]

Since there are no prospective clinical studies or large case series of omeprazole use in pregnant women, no clear conclusions regarding the safety profile of omeprazole in the pregnant female or developing fetus can be made. The manufacturer of omeprazole makes no recommendations regarding the use of omeprazole during pregnancy. No information is available on the excretion of omeprazole into breastmilk.

4.5.2 Lansoprazole

Lansoprazole has, to date, no reports available reports on its safety during pregnancy. However, teratology studies in pregnant rats and rabbits up to 40 and 16 times the recommended human dose respectively have revealed no evidence of impaired fertility or harm to the fetus.[29] It is unknown if this drug is excreted in human breastmilk although, it is excreted in the milk of rats. The manufacturer recommends that lansoprazole be used during pregnancy only if clearly needed and should not be used while nursing.

5. Aspiration Prevention During Delivery

Pregnant women are at higher risk for aspirating gastric contents, especially if they require anaesthesia during delivery. Mendelson's syndrome or aspiration during labour is the most common cause of obstetric morbidity and mortality due to anaesthesia.[61] Pregnant women at term needing general anaesthesia must be protected against the risks of regurgitation and possible aspiration pneumonitis. Vanner and Goodman[62] found that pregnant women at term (even if asymptomatic) have more gastro-oesophageal reflux during provocation tests than do control nonpregnant individuals. The predisposing factors are no different than those promoting gastro-oesophageal reflux during pregnancy. However, they are compounded by the recumbent position and administration of anaesthetics, which decrease lower oesophageal sphincter pressure and slow gastric emptying.[63] The deleterious effects of aspiration during delivery depend on gastric acidity.[64] Therefore, the key to prevention is increasing the pH level of gastric contents to >2.5 during labour and delivery.

Prophylactic ingestion of antacids prior to anaesthesia is recommended but caution should be exercised in the choosing of antacids. Insoluble antacids, such as aluminum and magnesium hydroxides, carbonates and trisilicates, can cause significant lung damage if aspirated because of their particulate composition.[65] Soluble antacids, such as sodium citrate and sodium bicarbonate, produce a less severe and transient pulmonary lesion and are the antacids of choice in this setting.[66] Hodgkinson et al.[67] compared the use of cimetidine versus antacids for elective caesarean section under general anaesthesia. The investigators found the mean gastric pH level at induction of labour was elevated to ≥5.5 when both regimens were used. However, the mean volume of gastric con-

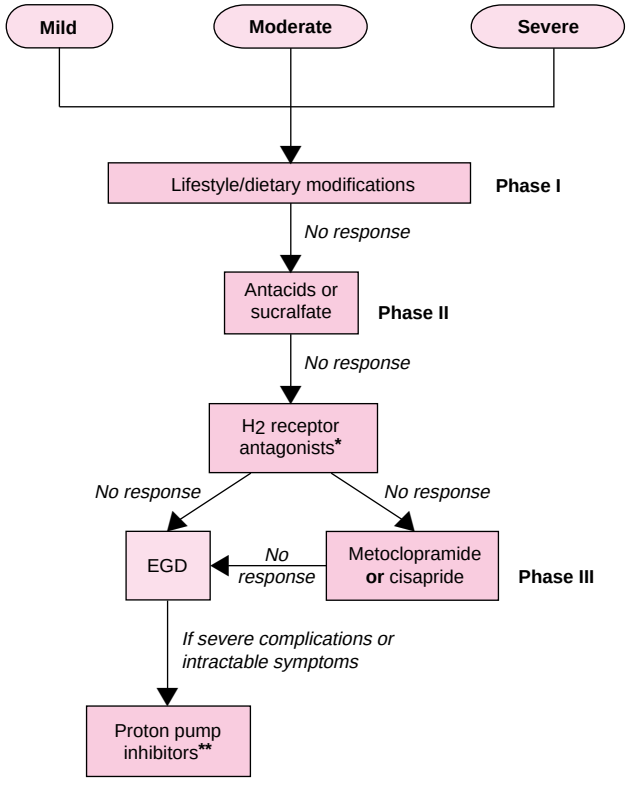

Fig.1. Treatment algorithm for gastro-oesophageal reflux disease in pregnancy. **EGD** = upper gastrointestinal endoscopy; * = avoid nizatidine; ** = lansoprasole may be the best choice.

tents in the cimetidine group was one-third the volume measured in the antacid treated group ($p < 0.01$).

Omeprazole use was also recently evaluated during obstetric anaesthesia. Moore et al.[68] treated women with omeprazole 80mg orally the evening before surgery. They found that the average intragastric pH immediately following endotracheal intubation and prior to extubation was 5.0. In a similar study, the addition of metoclopramide to omeprazole produced a trend toward smaller intragastric volumes but this did not reach statistical significance.[69]

Brocke-Utne et al.[70] evaluated the effect of intravenous metoclopramide 10mg on lower oesophageal sphincter pressure during late pregnancy. They noted that basal lower oesophageal sphincter pressure increased by 15 to 25% compared with baseline and suggested that metoclopramide may be helpful in this setting also by promoting gastric emptying.[61] Nonetheless, antacids and H_2 receptor antagonists remain the cornerstone of therapy for preventing aspiration pneumonitis during labour and delivery. Omeprazole can also be used safely but the role of promotility agents needs further investigation.

6. Conclusion

In conclusion, treatment of pregnant patients with gastro-oesophageal reflux should follow a systematic, step-by-step approach (see fig. 1). Mild cases can be treated by reassuring the patient

that reflux is commonly encountered during a normal pregnancy. Lifestyle and dietary modifications may be all that are required. In more symptomatic cases, nonsystemically absorbed medications, including antacids or sucralfate, may be offered with little if any risk to the unborn fetus.

Systemic therapy with H_2 receptor antagonists or prokinetic drugs should be reserved for patients with more severe symptoms. Proton pump inhibitors are not recommended during pregnancy, except for severe and intractable cases of gastro-oesophageal reflux or possibly prior to anaesthesia during labour and delivery. Use of the least possible amount of drug needed to ameliorate the patient's symptoms is clearly the best choice for therapy. Informed consent should be obtained prior to using any systemic drugs. If symptoms are intractable or atypical, endoscopy can safely be performed with conscious sedation and careful monitoring of the mother and fetus.

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