Gastroparesis in pregnancy

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Gastroparesis is a functional gastrointestinal disorder that more commonly affects women, with most cases being diagnosed during childbearing age. However, there is a paucity of data and guidelines to specifically highlight the epidemiology, disease course, maternal and fetal impact, and the management of existing gastroparesis during pregnancy. Apart from metoclopramide, there is no approved therapy specifically indicated for gastroparesis. More importantly, pregnant and breastfeeding women are excluded from clinical trials evaluating pharmacologic agents in the management of gastroparesis. This poses a real challenge to healthcare providers in counseling and managing patients with gastroparesis. In this systematic review, we summarize the current available literature and the knowledge gaps in the impact of pregnancy on gastroparesis and vice versa. We also highlight the efficacy and safety profiles of available pharmacologic and nonpharmacologic therapies in the management of patients with gastroparesis, with emphasis on judicious use of dietary approaches that are deemed relatively safe during pregnancy.

Key words: gastroparesis, pregnancy

Introduction

Gastroparesis is a sensorimotor disorder of the stomach, defined as the presence of symptoms associated with delayed gastric emptying without a mechanical obstruction. Nausea and vomiting are considered the cardinal features, but often dyspeptic symptoms, epigastric pain, upper abdominal bloating, and fullness coexist.[1]

Data remain sparse on the exact prevalence of gastroparesis. The estimated age-adjusted prevalence of definite gastroparesis based on symptoms and measured delayed gastric emptying on scintigraphy, is 37.8 (per 100,000 persons) in women, and 9.6 for men. The mean age±standard deviation at diagnosis of definite gastroparesis is 44 (±21) years.[2] Therefore, patients with gastroparesis can potentially suffer from their disease manifestation during their fertile years.

The literature on gastroparesis in pregnancy remains limited, which poses substantial challenges to healthcare providers in counseling and treating these patients. The pharmacotherapy for gastroparesis is limited; apart from metoclopramide, there is no other US Food and Drug Administration (FDA)—approved therapy for gastroparesis in nonpregnant women. Hereby, we systematically review (supplementary material, literature search) and summarize the available literature on pathophysiology, diagnosis, and management of gastroparesis in pregnancy. We highlight the knowledge gaps in the effect of gastroparesis on pregnancy, and vice versa. We outline the safety and efficacy profiles of commonly used nonpharmacologic and pharmacologic therapies for gastroparesis in pregnancy.

Effect of gastroparesis on pregnancy

Very little is known about the impact of preexisting gastroparesis on pregnancy, with low-quality data currently available in the literature. Gastric dysrhythmias demonstrated in pregnant patients with diabetes mellitus or idiopathic gastroparesis can correlate with nausea during the first trimester.[3,4] Diabetes mellitus remains the most frequently recognized systemic disease associated with gastroparesis[5]; it is associated with poor perinatal and pregnancy outcome (odds ratio [OR], 2.6; 95% confidence interval [CI], 1.3—4.9).[6,7,8] Gastroparesis can lead to the development of diabetic ketoacidosis (DKA), with vomiting precipitating 50% of episodes of DKA in pregnancy.[9] DKA has been reported to have fetal mortality ranging from 30% to 90%, although this has decreased to 10% in recent years.[10,11] In a vicious cycle, delayed gastric emptying has a major impact on glucose control, whereas hyperglycemia exacerbates delayed gastric emptying.[12] Compared with pregnant people without gastroparesis, those with gastroparesis have higher risk of preeclampsia (7.9% vs 4.8%; OR, 1.7; 95% CI, 1.3—2.2), malnutrition (2.2% vs 0.6%; OR, 2.2; 95% CI, 1.2—4.4), and 30-day readmission (22.8 % vs 10.7%; OR, 2.5; 95% CI, 2.00—3.02).[13] In summary, gastroparesis poses a risk to maternofetal health. Therefore, multidisciplinary preconception counseling for women with preexisting gastroparesis is advisable.

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Effects of pregnancy on gastric emptying/gastroparesis

The precise effect of pregnancy on gastroparesis is not clear, with conflicting data in the literature. Few human studies are available evaluating gastric motor function during pregnancy because of potential adverse fetal effects.

Compared with the prepregnancy state, an enlarging uterus increases end-expiratory intragastric pressure.[14] However, when using ultrasound to evaluate the antral cross-sectional area and volume of the stomach, the gravid uterus does not seem to affect the gastric volume.[15]

Various hormones could potentially affect gastric emptying, although the exact effect remains unclear because of mixed literature. Exogenous estrogen and progesterone have shown to delay gastric emptying.[16] Day-to-day hormonal variation during the menstrual cycle could affect severity of gastroparetic symptoms.[17] Using the rate of paracetamol absorption, pregnancy was shown to delay liquid gastric emptying.[18] In an animal study, high progesterone level and low estradiol during pregnancy can be associated with decreased gastric contraction frequency and delayed emptying.[19] Conversely, administration of estradiol and progesterone in combination or estradiol alone to ovariectomized rats was shown to slow gastric emptying, whereas progesterone alone enhanced it.[20] These findings support the hypothesis that sex hormones likely have variable inhibitory effects on gastric emptying of mixed meals.[16] In addition, increased nitrergic activity of nonadrenergic, noncholinergic nerves in pregnancy may prolong gastric emptying.[21] Pregnancy decreases the levels of motilin, which is involved in gastric motility.[22–24]

Davison showed delayed gastric emptying during labor, but not in the third trimester of pregnancy, when compared with nonpregnant, healthy patients, using serial aspiration of gastric content after ingesting a liquid test meal.[25] Although data are conflicting, the degree of gastric emptying delay seems to be variable during pregnancy. Using the indirect method of acetaminophen absorption, gastric emptying in 20 pregnant patients at 8 to 12 weeks of gestation was shown to be considerably prolonged relative to that of 20 nonpregnant controls.[26] The half-emptying time and the final gastric emptying time did not differ in the first and third trimesters according to ultrasound examination of gastric emptying. Orocecal transit time did not differ considerably in the first trimester, whereas it was prolonged during the third trimester.[22] Relative to nonpregnant controls, gastric emptying did not differ across trimesters of pregnancy when using an indirect paracetamol absorption technique.[27] Given the mixed findings in the literature, further studies are required to assess the impact of pregnancy on gastroparesis (Figure 1).

Diagnosis and workup of nausea and vomiting in pregnancy: when and how?

Nausea and vomiting in pregnancy are quite common, possibly because of hormonal changes or even transient abnormal gastrointestinal (GI) motility.[28,29] Other etiologies include medications, infection, endocrinopathies, metabolic disturbances, central nervous system pathologies, mechanical bowel obstruction, and GI motility disorders, including gastroparesis.[30] Most pregnant patients with nausea and vomiting respond to conservative therapies, with complete symptom resolution postdelivery, whereas formal workup of gastroparesis is generally postponed to the postpartum period, if symptoms persist.

In pregnant patients with severe or refractory nausea, vomiting, or abdominal pain, mechanical obstruction should be ruled out.

Documenting delayed gastric emptying is often required for diagnosing gastroparesis. The conventional test is the solid-phase meal gastric emptying scintigraphy for 4 hours. Most centers use a 99mTc sulfur colloid-labeled Egg Beater sandwich with jam, toast, and water as the test meal, with imaging at 0, 1, 2, and 4 hours.[31–33] There are no data in the literature evaluating the safety and validity of gastric scintigraphy during pregnancy.[34] Thus, gastric emptying study should be deferred until after pregnancy.

Breath testing with 13C-octanoate or spirulina provides reproducible results that correlate well with results on gastric emptying scintigraphy.[35–37] 13C is not radioactive and is thus considered safe. Other nonradiation techniques, such as wireless motility capsule, cross-sectional antral area measurement on ultrasonography,[38,39] and epigastric impedance technique[40] have been used in limited studies to evaluate gastric emptying (Figure 2). The latter has not been further validated and is not widely used. Overall,

FIGURE 1

Factors affecting gastroparesis during pregnancy and areas with substantial knowledge gaps in pathophysiology and management in pregnancy

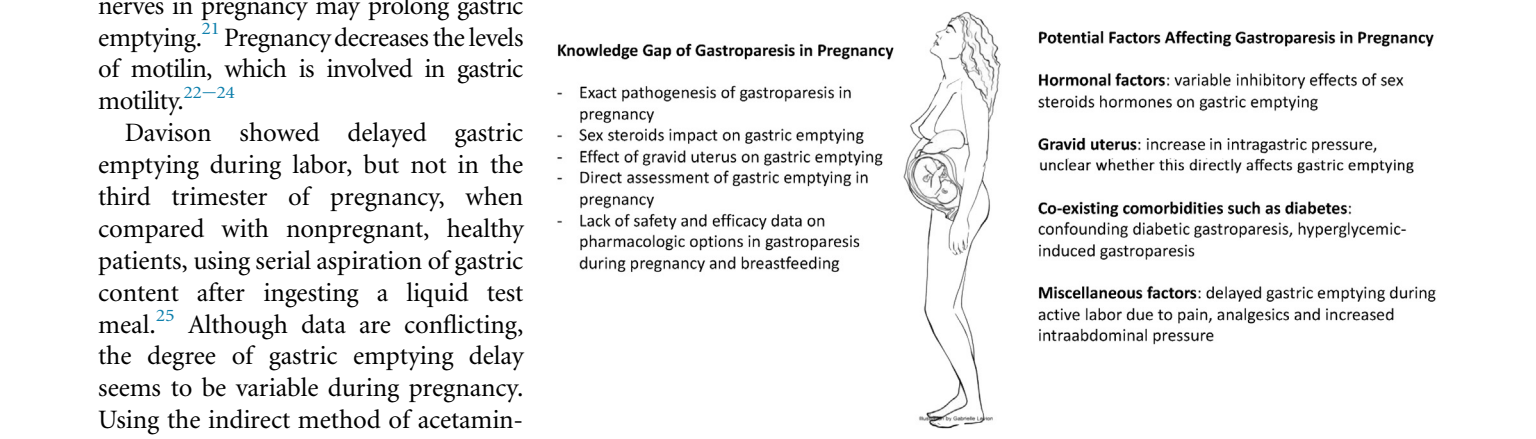

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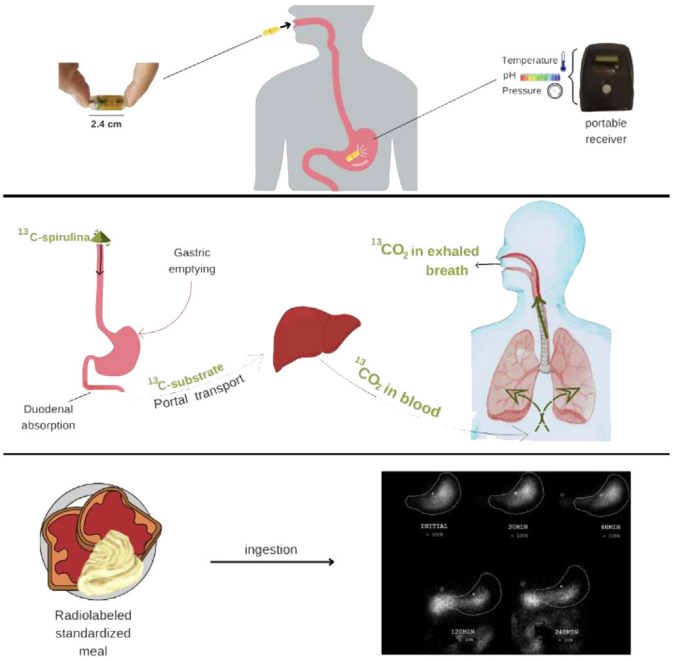
FIGURE 2
Schematic presentation of various diagnostic modalities in workup of suspected gastroparesis



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there are no normative values for any of these investigations in pregnancy. Further research is required to evaluate the validity and reproducibility of these nonradiation techniques in comparison with nuclear medicine gastric emptying study, particularly during pregnancy.

Therefore, formal assessment should be deferred to the postpartum period with gastric emptying scintigraphy for patients without previous evaluation or risk factors for gastroparesis, but with persistent symptoms.

Management of preexisting gastroparesis during pregnancy

The principles of management of preexisting gastroparesis in pregnancy have historically relied on conservative management, including adequate hydration and nutritional support. This requires a multidisciplinary approach, including input from an obstetrician, maternal–fetal medicine specialist, registered dietitian, and gastroenterologist, to ensure the safety of both the fetus and mother.

The optimal management of diabetes mellitus during the course of pregnancy is not only important for maternal and fetal outcomes, but also essential in symptomatic control of diabetic gastroparesis. Uncontrolled hyperglycemia reduces gastric contraction and can exacerbate gastroparesis.[41] Therefore, pregnant women with diabetes mellitus should be closely monitored by their obstetrician and endocrinologist to ensure optimal glycemic control.

Several medications have been shown to delay gastric emptying, including but not limited to opioids,[42] anticholinergic agents, tricyclic antidepressants, calcium channel blockers,[43] and antidiabetic medications, including short-acting glucagon-like peptide-1 receptor agonists and pramlintide.[44] Therefore, taking a thorough medication history, reviewing each medication for its potential side-effect on GI motility, and discontinuing it if appropriate, are pertinent steps in the management of gastroparesis in pregnancy.

Hereby, we review the nonpharmacologic options in the management of nausea and vomiting during pregnancy, which are also applicable to pregnant patients with preexisting, yet mild gastroparesis. In those with more severe disease, prokinetic agents and potentially alternative routes of feeding support may be required.

Overall dietary consideration

Severe nausea and vomiting can lead to poor oral intake and thus macro- and micronutrient deficiencies in vitamins and minerals. Parkman et al[45] demonstrated that the average caloric intake in patients with gastroparesis amounts to 58%±39% of daily total energy requirements (1168±801 kcal/d), which is much lower than the caloric requirement for normal-weight pregnant women, averaging approximately 1800 kcal/d during the first trimester, 2200 kcal/d during the second trimester, and approximately 2400 kcal/d during the third trimester.[46] The recommended amount of weight gain during pregnancy is 11.5 to 16 kg, inversely proportional to maternal body mass index at conception.[47,48] Suboptimal maternal caloric intake and inadequate weight gain during pregnancy can have negative impact on fetal development, including intrauterine growth restriction, with a relative

risk of 1.7 (1.3−2.3).[49] In addition, patients with gastroparesis are more likely to have diets with estimated deficiencies in vitamins A, thiamine, niacin, B6, B12, C, and K, iron, potassium, magnesium, phosphorus, zinc, and folate, with lower likelihood of voluntary supplementation and diminished intake of protein, iron, potassium, and niacin.[45,50] This in turn can have substantial negative impact on the well-being of both mother and the development of the fetus.

Initial management of preexisting gastroparesis, manifesting with nausea and vomiting in pregnancy, focuses on the correction of electrolyte imbalance, ensuring adequate vitamin and other micronutrient intake, and rehydration. There are no randomized controlled studies evaluating the role of dietary interventions in gastroparesis, and more specifically in pregnant women with gastroparesis. Generally, consuming small and frequent meals that are low in fat and fiber content is recommended because they both may delay gastric emptying. Given that gastric emptying of liquids is often preserved in gastroparesis, blenderized solids or nutrient liquids may be better tolerated, although this approach is not validated by controlled studies.[51−53] Carbonated beverages may release carbon dioxide, causing gastric distention, which may not be well-tolerated in this patient population[54]; therefore, their use should be minimized. Alcohol and tobacco smoking should be avoided, not only because of their negative impact on the fetal health and development, but also because they delay gastric emptying.[43]

Enteral−parenteral nutrition

In severe cases with persistent nausea and vomiting unresponsive to pharmacotherapies (outlined below) and intolerance to oral intake to meet nutritional requirements, enteral feeding support may be required. The patient is often admitted for a trial of nasojejunal (NJ) tube feeding, before placement of a percutaneous NJ tube.[51] Literature is very limited on enteral nutritional support in pregnant women with severe gastroparesis. Placement of NJ tube in pregnancy, whether done endoscopically or through interventional radiology, is associated with risk of sedation, radiation exposure, uterine damage, fetal injury, premature labor, and infection. In addition, there is often the risk of NJ tube dislodgment or migration, limiting its long-term utility in these complex patients. However, in a case series of 11 patients, percutaneous endoscopic gastrostomy tube placement was feasible even in the third trimester.[55] A case series of 5 women with severe hyperemesis gravidarum reported successful surgical placement of jejunostomy feeding tube under general anesthesia during the second trimester. All pregnancies ended with term deliveries. Tube-related complications were limited to dislodgment in 2 patients in the third trimester, with no cases of infection, bleeding, or preterm labor.[56]

Enteral polymeric formula (ie, intact macronutrients) without fiber is generally recommended for patients with gastroparesis. Diabetic formulas are often used to assist with management of glycemic levels in patients with hyperglycemia or diabetic gastroparesis, although the efficacy of the latter in gastroparesis has not been shown. In addition, diabetic formulas generally contain fructo-oligosaccharides as a source of fiber, which are not as well tolerated by some patients.[57]

Generally, enteral feeding is preferred over parenteral nutrition (PN) for several practical reasons, such as costs, ease of delivery, and potential for complications.[43] However, for those who cannot tolerate oral or enteral feeding trial to meet calorie requirement or for those with refractory symptoms, PN may be required. A thorough discussion with the patient about the indications, risks, benefits, and implications of PN is required. These complex patients should be closely monitored by a multidisciplinary team of experts to minimize the risk of refeeding syndrome and electrolyte disturbances, and to ensure maternal and fetal health and safety during pregnancy and postpartum.[57]

Pharmacotherapy (prokinetics and antiemetics)

Several prokinetic agents have been used in the management of gastroparesis to promote gastric motility. When symptoms of nausea, vomiting, and dyspepsia persist, antiemetics may be required. The available literature is summarized below and in the Table.

Dopamine-2 antagonists

Metoclopramide stimulates gut motility through principally dopamine D2 antagonism, but also agonism at serotonin 5-hydroxytryptamine (5-HT) 4 receptors, and a weak inhibition of 5-HT3 receptors.[62] It leads to increased gastric emptying by enhancing antral contraction and decreasing postprandial fundic relaxation.[63] Metoclopramide is the only drug currently approved by the FDA for treatment of gastroparesis, for no longer than 12 weeks.[64] Its short-term efficacy has been shown in several studies[65,66]; however, the data are lacking on the long-term efficacy beyond 1 month.[67] Gastric emptying has been demonstrated to improve with short-term use of metoclopramide, but return to baseline with use after 1 month.[68] However, some patients report continued symptomatic relief without persistent improvement of gastric emptying rate.[67] Symptomatic improvement from metoclopramide may not be limited to promoting gastric emptying, but may also be secondary to its antiemetic effect and normalization of gastric slow-wave dysrhythmias.[69] Metoclopramide carries a black-box warning because it may not be well-tolerated given the increased risk of extrapyramidal side-effects with chronic use beyond 12 weeks and potentially irreversible tardive dyskinesia in a small percentage of cases (0.14 per 100,000 patient-years).[62,70,71]

Nasal formulation of metoclopramide was approved by the FDA in 2020, which allows bypassing a poorly emptying stomach. In addition, intramuscular injection of metoclopramide[72] and intravenous (IV) administration during labor have been shown to increase gastric emptying.[73] However, its efficacy on promoting gastric motility may be lower

TABLE
Summary of pharmacotherapies in the management of gastroparesis and their safety concerns with use in pregnancy

Class	Agent	Summary of studies in pregnancy	Safety with pregnancy	Safety with breastfeeding
Dopamine-2 antagonist	Metoclopramide	No increased risk of stillbirth, preterm birth, low birthweight, or small-for-gestational-age neonates	No risk in pregnancy	Excreted in variable amounts in breast milk. Limited safety data, but no adverse effects in breastfed infants
	Domperidone	Increased risk of cardiovascular adverse effect to both mother and fetus	Use should be limited in pregnancy	No adverse effects have been found in a limited number of published cases of breastfed infants
Acetylcholinesterase inhibitor	Neostigmine	No adequate studies	Use is not recommended unless clearly needed	Limited data, abdominal cramps after breastfeeding have been reported
	Pyridostigmine	Safe in pregnant patients with myasthenia gravis (oral 30—60 mg, every 4—8 h), limited data in pregnancy and gastroparesis	Safe in pregnancy, IV administration is not recommended because of induction of uterine contractions	Low levels of pyridostigmine in breast milk, not expected to cause adverse effects in breastfed infants
Motilin-receptor agonist	Erythromycin	Increased risk of congenital cardiovascular malformation with exposure in early pregnancy in a Swedish population-based study,[58] although no associations with fetal cardiovascular or other malformations with exposure in the first trimester of pregnancy in a Norwegian data registry[59]	If any, low risk in pregnancy	Low levels of erythromycin in breast milk, not expected to cause adverse effects in breastfed infants
	Azithromycin	No evidence of fetal teratogenicity in animal studies, no controlled data in human pregnancy	Use is not recommended unless clearly needed	Low levels of azithromycin in breast milk, not expected to cause adverse effects in breastfed infants
	Clarithromycin	Low incidence of cardiovascular anomalies, variable incidence of cleft palate, delayed fetal growth, spontaneous abortions in animal studies, limited controlled data in human pregnancy	Use is not recommended unless clearly needed	Low levels of azithromycin in breast milk, not expected to cause adverse effects in breastfed infants
5-HT4 receptor agonist	Prucalopride	Quite limited data, cases of spontaneous abortion during clinical studies	Avoid in pregnancy	A relatively low amount in breast milk, lack of adequate evidence to make any recommendation
	Cisapride	Embryo- and fetotoxicity observed in animal studies, no controlled data in human pregnancy	Use is not recommended unless clearly needed	Low levels of cisapride in breast milk, not expected to cause adverse effects in breastfed infants
	Tegaserod	No evidence of fetal teratogenicity in animal studies, no controlled data in human pregnancy	Use is not recommended unless clearly needed	No available information in humans, an alternate drug is preferred
Phenothiazine	Prochlorperazine	Spermatocyte and sperm aberrations in animal studies, no controlled data in human pregnancy	Use is not recommended unless clearly needed	No available information

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TABLE
Summary of pharmacotherapies in the management of gastroparesis and their safety concerns with use in pregnancy *(continued)*

Class	Agent	Summary of studies in pregnancy	Safety with pregnancy	Safety with breastfeeding
Antihistamine	Promethazine	Crosses placenta, platelet aggregation may be inhibited in newborns, no congenital anomaly or serious maternal or fetal outcomes	Low risk in pregnancy	Little risk to the breastfed infant
	Doxylamine succinate	No association between doxylamine–pyridoxine use and birth defects	Seems safe in pregnancy	Larger doses or prolonged use may cause drowsiness and other effects in infants, avoid in breastfeeding
Butyrophenone	Haloperidol	Possible association with limb malformation from first-trimester exposure, risk of extrapyramidal symptoms in the newborn from third-trimester exposure	Avoid in pregnancy	Cases of extrapyramidal side-effects in breastfed infants, an alternate drug is preferred
5-HT3 receptor antagonist	Ondansetron	Conflicting safety data, a slightly increased risk of cardiac defects in 2 studies[60,61]	Limit use to only refractory cases	No adverse infant effects have been reported
Neurokinin receptor-1 antagonist	Aprepitant	No effect on fetal development in animal studies	Lack of adequate evidence to make any recommendation	No available information in humans, an alternate drug is preferred
Tricyclic antidepressant	Amitriptyline, nortriptyline	Reports of developmental delay, fetal limb deformities, and central nervous system side-effects	Avoid in pregnancy	Low levels of drugs in breast milk, usually not expected to cause adverse effects in breastfed infants (especially if the infant is >2 mo), rare sedation has been reported in a neonate
Atypical antidepressant[a]	Mirtazapine	Limited data, no substantial increase in major malformations	May be considered, cautiously in pregnancy	Low levels of drugs in breast milk, usually no adverse effects in breastfed infants, especially if the infant is >2 mo
Antimuscarinic	Scopolamine	Reports of neonatal jaundice and eclamptic seizures after IV and IM administration	Lack of adequate evidence to make any recommendation, avoided in women with severe preeclampsia	No available information in humans, an alternate drug is preferred
Synthetic cannabinoid	Dronabinol	Potential fetal harm with low birthweight, preterm labor, and stillbirth	Avoid in pregnancy	Limited information in humans, an alternate drug is preferred

5-HT, 5-hydroxytryptamine (serotonin); *IM*, intramuscular; *IV*, intravenous.

[a] Pregnant women exposed to antidepressants during pregnancy are highly encouraged to enroll in the National Pregnancy Registry for Antidepressants.

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in the setting of concomitant narcotics administration during labor.[42,74]

Domperidone, a peripherally acting dopamine-2 antagonist (currently not available in the United States), decreases nausea and increases gastric emptying rates. It does not readily cross the blood–brain barrier, making it much less likely to cause extrapyramidal side-effects. A major side-effect of domperidone is hyperprolactinemia, allowing it to be used off-label for the purpose of inducing lactation. It is associated with prolongation of cardiac QTc interval, and subsequently increasing the risk of torsade de pointes. It should be avoided if QTc interval is >450 ms in female patients.[75,76]

In a Danish registry of 1,222,503 pregnant woman, metoclopramide use for management of nausea and vomiting at a median of 40 doses, corresponding to 13 days of treatment, did not increase risk of stillbirth, preterm birth, or low

birthweight.[77] However, exposure to domperidone may be responsible for cardiovascular adverse effects, in both children and adults, as outlined in warnings by the French authorities in 2011 and 2014.[78] Therefore, if clinically indicated in management of moderate to severe gastroparesis during pregnancy, after comprehensive discussion between health allies and patient, consideration could be given to short-term use of metoclopramide, whereas domperidone use should be limited.

Acetylcholinesterase inhibitors

Inhibitors of acetylcholinesterase enzyme have prokinetic effects. Neostigmine, a short-acting agent, has been shown to accelerate gastric emptying of liquids in critically ill patients with delayed gastric emptying through induction of an irregular increase in gastric and duodenal contractility.[79,80] However, use is limited by its parenteral route of administration, short duration of action, and potential risk of vagotonia and bradycardia, requiring close cardiac monitoring during its administration.[81]

Pyridostigmine has a longer half-life, and is available in liquid or tablet formulation; it is the main oral therapy for myasthenia gravis during pregnancy. However, it is not approved for treatment of gastroparesis; therefore, the available data on use of this therapy in isolated gastroparesis in the absence of diffuse GI dysmotility are very limited. In a single case report in an adult patient,[82] and a pediatric case series of children with GI dysmotility, including chronic intestinal pseudo-obstruction, gastroparesis, and chronic constipation, pyridostigmine was showed to be effective and safe in all cases.[83] However, no clinical study to date has been published to confirm its efficacy in gastroparesis. Efficacy data are limited to a case report highlighting its use at escalating doses up to 30 mg, 3 times per day (TID), in a patient with chronic isolated gastroparesis secondary to autoimmune GI dysmotility.[82]

Several studies in pregnant patients with myasthenia gravis have shown that oral pyridostigmine is safe during pregnancy in recommended doses (30−60 mg, every 4−8 hours). Therefore, off-label use of this medication for management of gastroparesis in pregnancy should be discussed with the patient before its use. This drug crosses the placenta freely and achieves good concentration in amniotic fluid.[84] However, extrapolating from data on management of myasthenia gravis during pregnancy, IV administration of cholinesterase inhibitors is not recommended because of induction of uterine contraction.[85]

Motilin receptor agonists

In severe gastroparesis requiring hospitalization, erythromycin at 1.5 to 3 mg/kg infused intravenously over 45 to 60 minutes (to avoid sclerosing veins) every 8 hours was shown to improve gastric emptying, increase fundic and antral contractions, while decreasing pyloric contractions.[51,86] When given orally, erythromycin (40−200 mg, TID) can improve gastric emptying. However, its long-term effectiveness is limited by tachyphylaxis within a few days or weeks, owing to down-regulation of motilin receptors.[87] In addition, there are several drug interactions with erythromycin, especially with dose drugs that are metabolized by cytochrome P450 3A4 (CYP3A4).[88] Like dopamine antagonists, erythromycin is also associated with increased risk of QTc prolongation.[58]

Erythromycin crosses the placenta. In a population-based Swedish study, an increased risk of congenital cardiovascular malformations was found with erythromycin exposure in early pregnancy.[59] However, a subsequent analysis of a Norwegian data registry of 180,120 pregnant women did not find fetal cardiovascular or other malformations with first-trimester exposure to erythromycin. Therefore, the risks associated with the use of erythromycin or other macrolides during early pregnancy, if any, are low.[89,90]

Azithromycin and clarithromycin are other macrolides used in the treatment of chronic gastroparesis with similar concerns about potential for tachyphylaxis.[87] There have been no controlled studies, although observational studies have supported their use in gastroparesis.[91,92] In a crossover randomized controlled trial (RCT), no considerable difference between azithromycin and erythromycin was found in gastric emptying and symptom scores of patients with gastroparesis.[93] Azithromycin has fewer drug interactions,[94,95] less incidence of QTc interval prolongation, a longer half-life, and fewer GI adverse effects, although a recent retrospective study showed a small, but statistically significant risk of cardiac death in azithromycin users.[91,96]

In summary, considering the risk of QTc and drug interactions, macrolide use in the management of moderate to severe gastroparesis in pregnancy should be cautioned.

5-hydroxytryptamine 4 receptor agonists

Agonists of 5-HT4 have been used in the treatment of several motility disorders.[97,98] Prucalopride, a highly selective 5-HT4 agonist, has been approved for management of chronic constipation. It has been shown to enhance gastric emptying, small-bowel transit, and colonic transit in patients with chronic constipation.[99] In a recent placebo-controlled, crossover trial of 34 patients with idiopathic and diabetic gastroparesis, prucalopride was shown to improve gastroparesis and reflux. It was also associated with improved solid gastric emptying rate compared with placebo and baseline. However, there was no correlation between the symptomatic improvement and the enhancement of gastric emptying rate. One serious adverse event occurred (small-bowel volvulus in the prucalopride group), and 3 patients dropped out because of adverse events of nausea and headache.[100]

Safety data with prucalopride in pregnancy are quite limited, with cases of spontaneous abortion, possibly related to increased levels of prolactin reported during clinical studies. Animal studies do not indicate harmful events during pregnancy. However, given the limited data, prucalopride is not recommended during pregnancy, and women of childbearing age are

recommended to use effective contraception during the treatment course with prucalopride.[101−104]

Cisapride, another 5-HT4 agonist, was historically used as a promotilic agent. In a double-blind, crossover study, cisapride was considerably more effective than placebo in shortening the half-life of gastric emptying, but no substantial difference was noted in symptoms.[105] Cisapride is removed from the US market because of cardiac side-effects but is still available in certain countries.[106] The mechanistically similar tegaserod accelerates gastric emptying[107]; however, controlled studies showing substantial effects in patients with gastroparesis are still lacking.[106] It is not currently available in the United States.

There are also investigational drugs in this class, currently under further investigation as a prokinetic agent in management of GI motility disorders.[108,109] However, pregnant and lactating women are excluded from these clinical studies.

Antiemetics (symptomatic treatment of nausea, vomiting, and abdominal pain associated with gastroparesis syndrome)

In patients who continue to have GI symptoms despite a trial of prokinetics, off-label use of medications may be necessary. Antiemetic agents such as phenothiazines (including prochlorperazine) or antihistamines (including promethazine) have been considered, although there are concerns about sedation and possible cardiac toxicity, including QTc prolongation.[51,110] Phenothiazines are safe and effective as an adjunctive therapy for severe nausea and vomiting of pregnancy.[111]

Doxylamine succinate is the only FDA pregnancy category A medication approved for nausea and vomiting of pregnancy.[112,113] Promethazine, a first-generation antihistamine, is known to cross the placenta; platelet aggregation may be inhibited in newborns following maternal use of promethazine within 2 weeks of delivery.[114] Promethazine may be used as an adjunctive therapy in the management of nausea and vomiting of pregnancy when preferred agents do not provide initial symptom improvement or when symptoms persist despite other therapies.[115] Sedation and extrapyramidal side-effects can limit promethazine's use for nausea and vomiting. However, there have been no congenital anomalies or serious maternal or fetal outcomes reported with antihistamines.[116] Subcutaneous injection of promethazine can cause tissue injury, including tissue necrosis, gangrene, venous thrombosis, and amputation. Therefore, the preferred route of administration is intramuscular and never subcutaneous.[117]

In a retrospective study, administration of haloperidol reduced the rate of admission of patients with diabetic gastroparesis and lowered the requirement for morphine-equivalent doses of analgesia, without any substantial complications.[118] Haloperidol crosses the placenta in humans.[119] Association with limb malformation following first-trimester exposure in humans cannot be ruled out, although it has not been found to be a major human teratogen. Its use during the third trimester increases the risk of extrapyramidal symptoms, agitation, feeding disorders, hyper- or hypotonia, respiratory distress, somnolence, and tremor in the newborn.[120]

5-HT3 receptor antagonists such as ondansetron are also reasonable options for symptomatic treatment of nausea and vomiting, although there is no evidence that it is superior to metoclopramide or promethazine in decreasing nausea in adults attending the emergency department.[121] Ondansetron crosses the placenta.[60] A systematic review found conflicting data on safety of ondansetron in pregnancy. Although 3 studies showed no increased risk of birth defects as a whole, 2 studies demonstrated a slightly increased risk of cardiac defects specifically (OR, 2.0 [95% CI, 1.3−3.1] and 1.62 [95% CI, 1.04−2.14], respectively), but this was not replicated in other studies. The association, if any, seems to be a small increase in the incidence of cardiac septal defects. Therefore, ondansetron use during pregnancy should be limited to patients with refractory symptoms who do not respond to other options.[61,111,115,122]

Another class of medication for management of severe nausea and vomiting are neurokinin receptor-1 antagonists (NK-1), such as aprepitant. The signaling pathways involved in nausea and vomiting are conveyed by the vagus nerve, and NK-1 activity is prominent in both sensory and motor vagal nuclei in the brainstem.[123] It is currently approved for chemotherapy-related nausea. Aprepitant was effective in the treatment of severe vomiting and repeated episodes of ketoacidosis in a patient with diabetes mellitus.[124] However, in an RCT of patients with chronic nausea and vomiting owing to gastroparesis, aprepitant did not reduce symptoms of nausea on the primary outcome measures, but it reduced symptom severity of nausea, vomiting, and overall symptoms. Adverse event rates were low.[125] Animal studies did not show any effect on fetal development. However, there have been no well-controlled studies in pregnant women; therefore, aprepitant is not recommended for use during pregnancy unless clearly necessary.[126]

Tricyclic antidepressants (TCAs) have been considered for refractory nausea and vomiting in gastroparesis. However, given the anticholinergic effect of certain TCAs, such as amitriptyline, their use should be avoided in patients with gastroparesis because of worsening delayed gastric emptying. Nortriptyline has lower incidence of anticholinergic side-effects.[51,127,128] TCAs and their metabolites cross the placenta, and can be detected in the cord blood.[129] Offspring developmental delay, fetal limb deformities, and central nervous system side-effects have been reported, although a causal relationship cannot be established. TCAs may also be associated with irritability, jitteriness, nausea, difficulty with urination, and rarely convulsions in neonates with exposure to TCA in utero.[130,131] Therefore, TCAs should not be used in the management of nausea and vomiting in pregnancy.

Mirtazapine is an antidepressant with a multifactorial mechanism of action, involving antagonism of central and peripheral presynaptic alpha-2 adrenergic receptors, and actions on several

subtypes of 5-HT receptors and H1 receptors. In a case series of patients with refractory symptoms of gastroparesis, a 4-week course of mirtazapine was associated with a considerable improvement in nausea, vomiting, retching, and perceived loss of appetite at 2 and 4 weeks, compared with pretreatment.[132] It may also improve symptoms of functional dyspepsia, which may coexist with gastroparesis.[133] The safety data on mirtazapine during pregnancy are limited; in a prospective study, mirtazapine did not seem to increase the baseline rate of major malformations of 1% to 3%.[134,135] Mirtazapine may be used cautiously in the management of nausea in pregnancy.

Other drugs such as transdermal scopolamine patches, which are effective for nausea associated with motion sickness, can be used for nausea and vomiting of gastroparesis, albeit without peer-reviewed studies to support this recommendation.[51] There are no well-controlled studies on safety of scopolamine during pregnancy. Neonatal jaundice has been reported. An embryotoxic effect was observed in animal models at doses producing plasma levels approximately 100 times the levels achieved in humans using transdermal patches. Therefore, scopolamine patches should be used during pregnancy only if the potential benefit justifies the risk to the fetus. Use should be avoided in pregnant women with severe preeclampsia given that eclamptic seizures have been reported after IV and intramuscular administration.[136,137]

Finally, dronabinol, a synthetic cannabinoid, should be avoided during pregnancy because of potential fetal harm with low birthweight, preterm labor, and stillbirth. Some formulations may contain alcohol, and therefore should be avoided. In addition, dronabinol can exacerbate delayed gastric emptying.[51,138]

Nonpharmacologic therapies for nausea and vomiting

Ginger (*Zingiber officinale*) is a spice traditionally used worldwide to treat indigestion, nausea, and vomiting, particularly in pregnancy. It has been shown to substantially increase interdigestive motility on antroduodenal manometry of healthy volunteers in comparison with placebo.[139] Several RCTs showed that ginger was considerably more effective than placebo in reducing the frequency of nausea and vomiting, with mild and infrequent adverse events. However, there are not enough data on the maximum safe dose, duration of therapy, and consequences of overdosage, all of which are important areas for future research.[140,141]

Vitamin B6 (pyridoxine hydrochloride) has been commonly used in the management of nausea and vomiting during pregnancy. In a double-blind, placebo-controlled RCT, vitamin B6 was shown to be more effective than placebo in reducing vomiting after 3 days of therapy.[142] Vitamin B6 was also comparable to ginger and more effective than placebo for the treatment of mild to moderate nausea and vomiting of pregnancy.[143]

Complementary medicine has also gained popularity, particularly among women of childbearing age, with almost 50% reporting use.[144] In a single-blind RCT, all acupuncture techniques showed marked improvement of nausea and dry retching, but not vomiting, during the first trimester, although a time-related placebo effect was found for some women.[145] Wang et al[146] also demonstrated the acupuncture benefit in diabetic gastroparesis. Behavioral therapy techniques such as stimulus control and imagery have been reported to improve symptoms of severe nausea and vomiting.[147] Progressive muscle relaxation also alleviates these symptoms among pregnant patients.[148] However, given the poor methodological quality of the currently available studies on psychological interventions for nausea and vomiting of pregnancy, further studies are needed to assess their effectiveness.[149]

Endoscopic intervention

In patients with severe gastropa resis, endoscopic intervention may offer symptomatic relief. Intrapyloric botulinum toxin injection remains the most commonly used endoscopic therapy for refractory gastroparesis, although it still remains quite controversial, with need for repeated treatments.[150] There is rare potential of gastric and intestinal absorption, leading to peripheral neuromuscular blockade.[151] There are no available data on the utility of botox injections in pregnant women with severe gastroparesis. Therefore, in the absence of safety data, this intervention should ideally be deferred until after delivery. There are no data on the role of gastric per-oral endoscopic myotomy in pregnancy.

Gastric electrical stimulation

Gastric electrical stimulation (GES) was approved by the FDA in 2000 as a humanitarian device exemption in patients with refractory idiopathic or diabetic gastroparesis.[152] It has been shown to have clinical benefit, with marked improvement in symptom severity and gastric emptying time, although high-quality studies are lacking.[153] One case report in the literature highlighted the successful use of GES during pregnancy, which was applied before pregnancy in a patient with severe diabetic gastroparesis.[154] However, there are no data on GES application during pregnancy. Therefore, its use should be deferred to after pregnancy, if indicated.

Conclusions

There is a considerable knowledge gap regarding the pathophysiology of gastroparesis in pregnancy, the effect of pregnancy on gastroparesis, and the safety and efficacy of various, yet limited pharmacologic and dietary options in the management of preexisting gastroparesis during pregnancy. Prospective database registries are required to address the knowledge gap in gastroparesis during pregnancy. Meanwhile, a multidisciplinary approach including gastroenterologists, obstetricians, dietitians, neonatologists, and endocrinologists may be necessary to optimally manage these complex patients while ensuring the safety of the fetus and mother during pregnancy and in the postpartum period.

Literature search

A comprehensive search of MEDLINE, PUBMED, Evidence-Based Medicine Database of English abstracts, reviews of effects, Cochrane Database of Systematic Reviews, clinical answers databases, and abstracts from national conferences, including "American College of Gastroenterology," "Canadian Digestive Diseases Week," and "Digestive Diseases Week" from 1946 to October 2, 2021 was performed to identify studies that described the pathophysiology, maternal and fetal effects, prevalence, and management of gastroparesis in pregnancy. There was no restriction on type of study, types of interventions, or number of subjects or outcomes. Search terms included "gastroparesis" (Medical Subject Headings [MeSH]), "functional gastric diseases" (MeSH), "delayed gastric emptying," "nausea," "spastic colon," "irritable colon," "pregnancy" (MeSH), "pregnan*," "gestation*," "lactation disorders," "lactation" (MeSH), and "breast feeding" (MeSH). All articles were screened for relevance to the study question; 448 references were initially identified for further review. Eligible articles were assessed to identify additional relevant publications. Two investigators (S.M. and M.W.) performed independent assessments of relevant publications. Any disagreement regarding included studies was discussed among S.M. and M.W., and A.R. finalized the decision. ■

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