

The spectrum and treatment of gastrointestinal disorders during pregnancy

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SUMMARY

Gastrointestinal symptoms are extremely common during pregnancy. Increased levels of female sex hormones cause or contribute to symptoms such as heartburn, nausea, vomiting and constipation. If these symptoms do not respond adequately to lifestyle and dietary changes, drug therapy is often warranted to improve quality of life and to prevent complications. Physicians, therefore, need to be familiar with the low-risk treatment options available. Treatment of chronic conditions such as IBD or chronic liver disease during pregnancy can be demanding. In women with IBD, maintenance of adequate disease control during pregnancy is crucial. Most IBD drugs can be used during pregnancy, but the benefits and risks of specific drugs should be discussed with the patient. Liver diseases can be coincidental or pregnancy-specific. Pregnancy-specific liver diseases include not only benign disorders such as intrahepatic cholestasis of pregnancy, but also pre-eclampsia, eclampsia and HELLP syndrome (hemolytic anemia, elevated liver enzymes and low platelet count). Accordingly, the spectrum of therapeutic measures ranges from expectant management to urgent induction of delivery. During pregnancy, lamivudine therapy for chronic hepatitis B can be continued; however, interferon and ribavirin therapy for chronic hepatitis C is contraindicated. This Review provides an overview of the spectrum and therapy of motility disturbances that occur during pregnancy, and discusses pregnancy-specific aspects of IBD and liver diseases.

KEYWORDS constipation, gastroesophageal reflux disease, hepatitis, inflammatory bowel disease, nausea

REVIEW CRITERIA

PubMed was searched in December 2007 and January 2008 for articles published between January 1970 and January 2008 containing the term "pregnancy" in combination with the terms "heartburn", "gastroesophageal reflux", "motility", "nausea", "vomiting", "constipation", "inflammatory bowel disease" or "liver disease". Moreover, reference lists of review articles were searched for pertinent publications within the same time frame. The reference list was updated in May 2008.

CME

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Describe the most appropriate dietary advice for pregnant women with nausea or heartburn.
- 2 List therapeutic approaches associated with reduction of nausea and vomiting in pregnancy.
- 3 Identify treatments contraindicated for the treatment of constipation in pregnancy.
- 4 Identify factors that predict the course of inflammatory bowel disease during pregnancy.
- 5 Describe clinical features of intrahepatic cholestasis of pregnancy.

Competing interests

The authors, the Journal Editor N Wood and the CME questions author D Lie declared no competing interests.

INTRODUCTION

Most pregnant women experience gastrointestinal symptoms such as nausea, vomiting, heartburn or constipation. Motility disturbances, caused by altered hormone levels, probably explain most of these symptoms, but several other factors can contribute. While new-onset gastrointestinal symptoms are usually mild to moderate and respond to simple therapeutic measures such as lifestyle and dietary changes, some women suffer severe symptoms and need medical therapy. Moreover, chronic gastrointestinal diseases that affect young women, such as IBD or chronic liver disease, can deteriorate and/or need altered diagnostic and therapeutic approaches during pregnancy. The treatment of gastrointestinal disorders during pregnancy requires special attention

because the safety of both mother and child is of pivotal importance. This Review provides an overview of the spectrum and therapy of motility disturbances during pregnancy, and discusses specific aspects of IBD and liver disease in pregnant women. To facilitate understanding of the different levels of risk posed by various gastrointestinal drugs, US FDA pregnancy categories are listed where appropriate (categories A–D and X: category A drugs do not increase the risk of fetal abnormalities, as shown by adequate, well-controlled studies in pregnant women; category D drugs are contraindicated in pregnancy but known benefits may warrant their use despite potential risks; category X drugs are absolutely contraindicated in pregnancy); detailed information on the FDA categories for drugs used during pregnancy can be found elsewhere.^{1,2}

MOTILITY DISTURBANCES

Esophagus: GERD

Heartburn is experienced by approximately 40–80% of women at some time during pregnancy and is associated with decreased quality of life.^{3–5} Whether symptoms become worse and/or occur more frequently during the late stages of pregnancy is debated. A longitudinal survey published in 2007 suggests that although the prevalence of heartburn increases with gestational age, the incidence remains the same in all three trimesters.³

Functional and structural alterations of the gastroesophageal junction that occur during pregnancy explain the high prevalence of reflux symptoms. Mechanical factors attributable to cumulative weight gain might contribute to reflux during the third trimester but are of minor importance.³ Instead, a decrease in lower esophageal sphincter (LES) pressure is the predominant etiological factor; this decrease is caused by increased levels of female sex hormones, particularly progesterone.⁵ Van Thiel *et al.* showed that (in four pregnant women) the LES pressure returned to normal in the postpartum period.⁶ Data now suggest, however, that pregnancy alone³ and particularly the occurrence of reflux symptoms during pregnancy⁷ both considerably increase the risk of going on to develop GERD (the prevalence of GERD is 36.1% in women with a history of heartburn during more than two pregnancies), independently of obesity and age.⁷ Some of the functional and/or structural alterations of the LES that are induced by pregnancy might, therefore, persist.

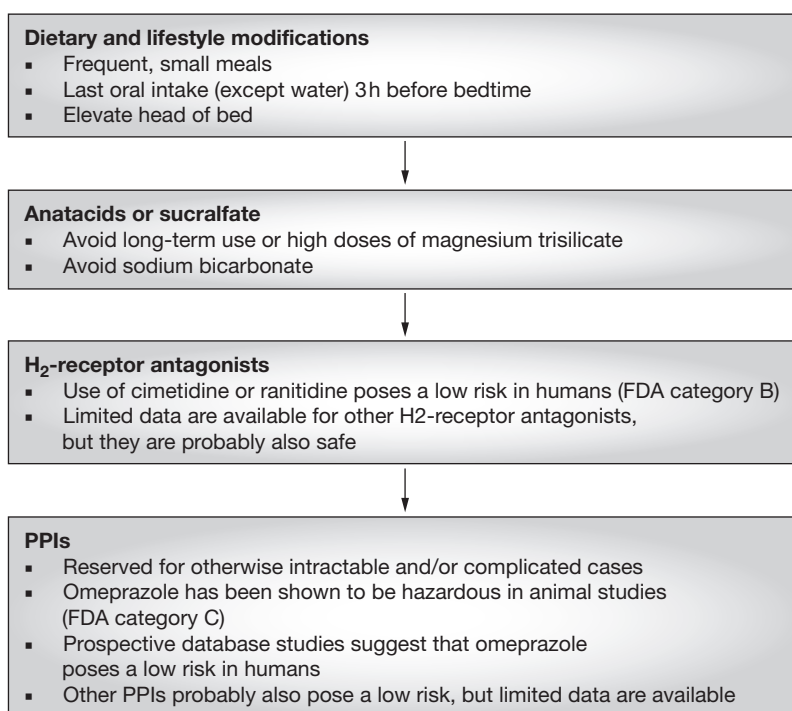


Figure 1 Therapeutic options for the treatment of reflux symptoms during pregnancy. Treatment should start with simple dietary and lifestyle modifications and be stepped up to medical therapy if appropriate. The FDA pregnancy drug categories are defined elsewhere.²

The clinical features of GERD in pregnant women are similar to those found in the general population—heartburn and regurgitation are the predominant complaints, with aggravation of symptoms after meals and when lying in a recumbent position.^{8,9} Serious complications of GERD are rare during pregnancy, so esophago-gastroduodenoscopy and other diagnostic tests are rarely needed.⁵

Reflux symptoms during pregnancy should be treated according to a step-up algorithm that begins with lifestyle modifications and dietary changes (Figure 1). Patients should be instructed to elevate the head of their bed and to avoid assuming positions that worsen their symptoms. Moreover, frequent small meals should be ingested, and oral intake (other than water) stopped 3 h before bedtime. If symptoms persist, antacids or sucralfate can be prescribed. Antacids have been shown to reduce GERD symptoms effectively, and cause no teratogenic effects in animal studies.^{1,10} However, they can interfere with iron absorption,¹ and experiments now suggest that antacid treatment during pregnancy might predispose pregnant mice and their

offspring to the development of food allergies.¹¹ Specifically, sodium bicarbonate should be avoided because ingestion of large amounts can induce metabolic alkalosis and fluid overload.¹ Magnesium trisilicate should not be used in high doses for long periods of time because this treatment can result in fetal nephrolithiasis, hypotonia and respiratory distress.¹ Sucralfate is not absorbed and seems to be safe (FDA category B). Human data on sucralfate administration during pregnancy are scarce, but sucralfate has been shown to reduce GERD symptoms significantly in pregnant women when this treatment was compared with lifestyle modifications alone.⁸

If symptoms do not respond adequately to antacids or sucralfate, H₂-receptor antagonists should be used. Data from large databases show that cimetidine and ranitidine (both FDA category B) have no unfavorable effects on pregnancy outcome, although one study revealed an increased incidence of premature deliveries in women exposed to H₂-receptor antagonists.¹² Other H₂-receptor antagonists are probably also safe to use during pregnancy, but limited safety data are available from animal and human studies.¹

PPIs should be reserved for women who have otherwise intractable symptoms or complicated reflux disease. Animal experiments have shown that therapeutic doses of omeprazole (FDA category C) increase embryonic and fetal mortality and that excessive doses have teratogenic effects.^{1,8} However, several analyses of prospectively collected databases have demonstrated the safety of omeprazole in humans even if therapy is started during the first trimester.^{13–15} Other PPIs such as esomeprazole and lansoprazole (both FDA category B) have shown a low risk of fetal toxicity in animal studies, but the paucity of human data does not allow definite conclusions to be drawn on their safety during pregnancy.¹

Stomach: nausea and vomiting

Nausea affects 80–90% of women at some time during pregnancy, is accompanied by vomiting in about 50% of cases, is more frequent during the first trimester than during the later stages of pregnancy and varies in severity from mild to severe or even unremitting (hyperemesis gravidarum).^{8,16,17} Severe nausea and vomiting can result in weight loss and dehydration. Disturbances in gastric motility have a role in the pathophysiology of nausea and vomiting during pregnancy, but there are several other factors

that can cause or contribute to these symptoms, including pregnancy-associated alterations to the vestibular system, taste and olfaction, and behavioral and/or psychological aspects.

When limited to the gastrointestinal tract, gastric dysrhythmias—acute loss of the normal gastric slow wave frequency of 3 cycles per minute—are related to stomach dysfunction and nausea in pregnancy.¹⁶ Gastric dysrhythmias are probably caused by increased levels of female sex hormones, but raised levels of vasopressin might also have a role.^{16,17} Moreover, increased release of nitric oxide and downregulation of stimulatory G-protein expression (which stimulate muscle contraction) and upregulation of inhibitory G-protein expression have been detected in gastric and intestinal muscle preparations from pregnant animals.^{18–20} These changes could explain how gastric contractility is reduced and consequently how gastric emptying is impaired. Recurrent abdominal pain can be caused by gastrointestinal dysmotility and can occur in patients with nausea and vomiting of pregnancy; however, such pain can also be a symptom of other gastrointestinal diseases (e.g. GERD, ulcers, cholecystitis, pancreatitis) that need to be excluded as appropriate, depending on the individual patient's presenting symptoms and signs.¹⁶

Reassurance and the avoidance of precipitating factors are the first therapeutic steps to be recommended in patients with mild symptoms (Figure 2). The diet should consist of frequent, small meals that are high in carbohydrate and low in fat. Moreover, stimulation of the P6 acupuncture point, applied by finger pressure, a wristband, or electrically, has been shown to reduce nausea and vomiting.²¹ Evidence also suggests that ginger (*Zingiber officinale*) might be an effective treatment for relieving the severity of nausea and decreasing the number of vomiting episodes in pregnancy.^{22,23}

For patients with a protracted course of nausea and vomiting or underlying conditions that can predispose to nausea and vomiting, medical therapy is warranted to prevent complications.¹ Various drugs can be used to treat nausea and vomiting during pregnancy and their use, dosage and safety have been discussed in detail elsewhere;^{1,24} the availability and use of these drugs varies among countries.^{25,26} Women who are unable to tolerate oral fluids require admission to hospital to correct dehydration and electrolyte imbalance. Patients with severe

and prolonged nausea and vomiting might also benefit from thiamine supplementation and enteral or parenteral nutrition.

Small and large bowel: abdominal bloating and constipation

Pregnant women frequently report abdominal bloating and constipation, and the prevalence of these conditions ranges from 25% to 40% in Western countries.^{8,27–29} Many women who are affected by constipation when they are not pregnant experience a worsening of this symptom during pregnancy. Reasons for the increased prevalence of constipation and bloating during pregnancy include changes in water absorption, mechanical factors, dietary factors, reduced physical activity and, particularly, hormonal effects on gastrointestinal motility.²⁷ Gastrointestinal transit time is prolonged during the second and third trimester, but normalizes during the postpartum period.²⁷ This prolongation of gastrointestinal transit time is probably explained by hypomotility of the small and large bowel, which is mainly caused by increased progesterone levels.²⁷ Some evidence indicates that intestinal hypomotility is mediated by an increased release of nitric oxide, downregulation of stimulatory G-protein expression and upregulation of inhibitory G-protein expression.^{18–20,30} Whether iron supplementation contributes to constipation in pregnant women remains a matter of debate.^{1,28,31}

In most pregnant women, constipation has no sinister cause; however, a few women have an underlying disease that needs to be treated. Only a detailed evaluation of the patient will allow its identification. Appropriate investigations include taking the patient's history (in relation to their specific symptom pattern, frequency of stool passage, prolonged straining, urge to defecate, laxative use, intake of other medications, alarm symptoms), clinical examination (including digital rectal examination) and laboratory investigations (full blood count, thyroid-stimulating hormone levels, serum calcium level and glucose level). Endoscopy is not indicated unless compelling evidence suggests the presence of serious disease.

Constipated patients are commonly recommended to ensure that their water intake is adequate and to ingest a high-fiber diet. Fiber supplements have been shown to increase the frequency of defecation and to soften stools in pregnant women;³² however, certain fibers such

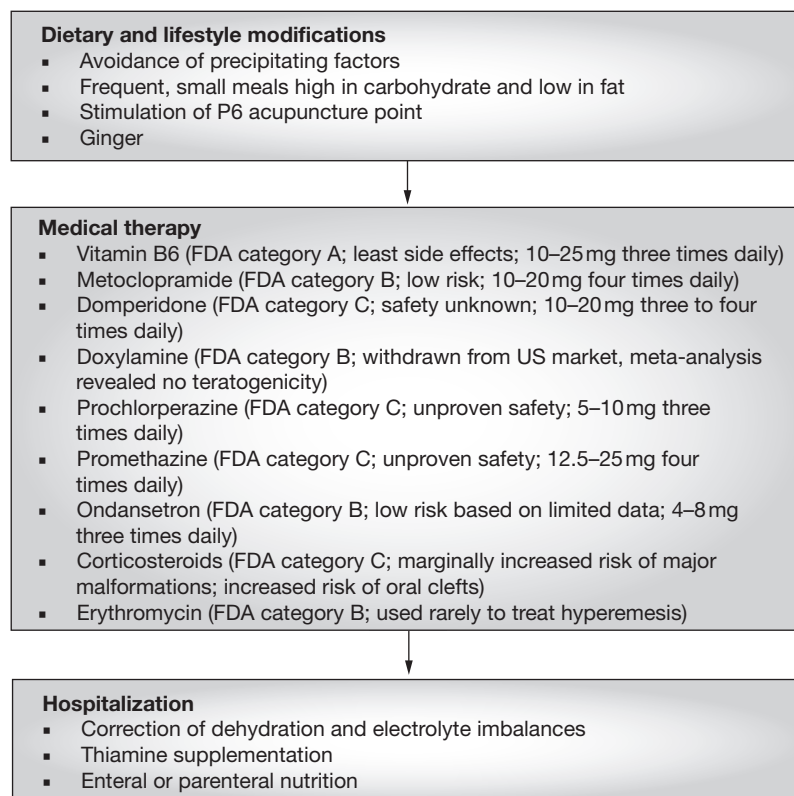


Figure 2 Therapeutic options for the treatment of nausea and vomiting during pregnancy. The FDA pregnancy drug categories are defined elsewhere.²

as bran can actually worsen other symptoms, particularly bloating and abdominal pain,³³ such that soluble fibers might be preferred. Moreover, patients should be advised (within reason) to undertake light physical exercise to improve gastrointestinal transit.

Drug therapy for constipation during pregnancy is reserved for patients with otherwise intractable symptoms. If needed, such therapy should be effective, nonteratogenic, and well tolerated. Some laxatives such as anthraquinones are associated with congenital malformations and are clearly contraindicated during pregnancy.¹ Castor oil must also be avoided as it has been associated with uterine contraction and, in women with prior Cesarean sections or other uterine surgery, even rupture.¹ Lactulose is regarded as a low-risk treatment (FDA category B), but no human studies are available¹ and it can exacerbate bloating. The American Gastroenterological Association guidelines recommend a stool softener (such as sodium docusate, an FDA category C drug) for symptomatic relief, and, if this approach proves

insufficient, an osmotic laxative, particularly a polyethylene glycol (PEG) solution.¹ Although PEG solutions are classified as FDA category C (because of the lack of data on their safety), a European consensus conference decided that these solutions meet the criteria for an ideal laxative during pregnancy.³⁴ In addition, high-dose PEG therapy has been effective in very severe cases of constipation.³⁵ Saline osmotic laxatives are probably also safe, but are intended for short-term relief only.¹

INFLAMMATORY BOWEL DISEASE

Crohn's disease and ulcerative colitis are chronic diseases with, typically, first onset during women's peak reproductive years. An estimated one-quarter of female patients with Crohn's disease conceive after their diagnosis.³⁶ The influence of pregnancy on the course of the disease, the influence of the disease on pregnancy outcome, and optimal diagnostic and treatment regimens during pregnancy are, therefore, of importance for many patients with IBD and their physicians.

Influence of pregnancy on the course of inflammatory bowel disease

The course of IBD during pregnancy generally depends on whether the patient becomes pregnant during remission or during an acute phase. In about two-thirds of cases, women who become pregnant during remission of IBD can expect to have stable disease during their pregnancy.^{36–38} On the other hand, if pregnancy commences when the disease is active, inflammatory activity will remain the same or worsen during pregnancy in about two-thirds of cases.^{36–38}

Influence of inflammatory bowel disease on pregnancy outcome

A meta-analysis that compared pregnancy outcomes in nearly 4,000 women with IBD and more than 320,000 controls showed that the incidence of premature delivery, low birth weight and congenital abnormalities was approximately doubled for offspring of women with IBD.³⁶ Women with IBD are also 1.5-fold more likely than controls to undergo Cesarean section.³⁶ However, the increased risk of congenital malformations was found in a single study conducted in patients with ulcerative colitis, and included all types of malformations; furthermore, this study did not take disease activity or medication use into consideration.³⁹ When analyses were limited

to data from high-quality studies, there was no greater risk of congenital abnormalities in the offspring of women with IBD than there was in the offspring of women without IBD.³⁶

Generally, the risk of unfavorable pregnancy outcomes is increased if conception occurs during active disease.^{36–38} Conception should, therefore, preferably be attempted at a time when disease is in remission; for most patients, such planning requires their medications to be continued.^{1,38}

Diagnostic procedures

Most diagnostic procedures necessary for the characterization of disease activity in patients with IBD can be performed during pregnancy. However, for some laboratory investigations, pregnancy-specific normal values need to be considered (e.g. physiologically decreased hemoglobin and serum albumin levels and increased erythrocyte sedimentation rate). Some examinations might be difficult to perform (e.g. abdominal ultrasound during late pregnancy). Pregnant women with IBD who have worsening symptoms despite appropriate medical therapy might benefit from sigmoidoscopy, as this technique has a lower risk than total colonoscopy and often provides adequate information. Colonoscopy is, therefore, indicated less often.⁴⁰ Box 1 lists the principles that should guide endoscopy in all pregnant women, including those with IBD (other indications for endoscopy during pregnancy include gastrointestinal bleeding and ulcer disease).⁴¹

Treatment

The maintenance of adequate disease control during pregnancy is crucial for the health of the mother and the fetus. To achieve this goal, a multidisciplinary approach that involves gastroenterologists and obstetricians should be adopted.³⁸ Most drugs used for the therapy of IBD—except the teratogenic drugs methotrexate and thalidomide (both FDA category X)—are considered low-risk IBD treatments during pregnancy (assessments of the risk posed by IBD treatments include consideration of the beneficial effects of reduced disease activity on pregnancy outcome; consequently, several class C drugs have been assessed as low risk when used to treat IBD during pregnancy).¹

Treatment of mothers-to-be

For the treatment of mothers-to-be with IBD, aminosalicylates (including sulfasalazine, but not

olzalazine) are regarded as low-risk drugs (FDA category B). If sulfasalazine is to be used, women are recommended to take 1 mg of folic acid twice daily throughout their pregnancy because of concerns about the potential antifolate effects of sulfasalazine.¹ Mesalamine confers no teratogenic risk, but it does confer an increased incidence of premature birth, low birth weight and stillbirth;¹ however, these unfavorable pregnancy outcomes are probably attributable to the maternal disease itself and not to drug exposure.⁴²

Corticosteroids (FDA category C), particularly if used during the first trimester, are associated with a small risk to the developing fetus: one meta-analysis demonstrated that the use of corticosteroids during pregnancy only marginally worsens the risk of major congenital malformations, but increases the risk of oral clefts by more than threefold.⁴³ Mothers-to-be should, therefore, be informed of both the benefits and the risks of corticosteroid therapy.¹ Short-acting corticosteroids such as prednisone, prednisolone and methylprednisolone are preferable to long-acting substances, because the short-acting agents are metabolized by placental enzymes so that the fetus is exposed to only about 10% of the maternal dose.²⁴ No data have been published on the safety of oral budesonide in pregnancy, but large clinical series have shown that inhaled budesonide is not associated with adverse fetal outcomes.^{44,45}

The immunomodulators azathioprine and 6-mercaptopurine are classified as FDA category D drugs. Animal studies have demonstrated that these drugs have teratogenic effects,⁴⁶ but several case series in patients with IBD and in transplant recipients have not noted an increase in congenital abnormalities.^{47,48} According to a nationwide Danish survey published in 2007, congenital abnormalities are more prevalent in the offspring of women with Crohn's disease who are exposed to azathioprine or 6-mercaptopurine than in the offspring of women with Crohn's disease who are not exposed to these medications (15.4% versus 5.7%).⁴⁹ However, only 26 women were actually exposed to these drugs, congenital malformations included severe as well as minor and unspecified abnormalities, and the differences between the patient groups failed to reach statistical significance (confidence interval 0.9–8.9).⁴⁹ Accordingly, these drugs are often continued during pregnancy to prevent a flare of the disease, which could be more deleterious to pregnancy outcome than any potential

Box 1 Endoscopy in pregnant patients.

- A strong indication is always needed, particularly in high-risk pregnancies
- Whenever possible, endoscopy should be deferred until the second trimester
- The lowest dose of sedative medication should be used (wherever possible FDA category B drugs)
- Procedure time should be minimized
- To avoid vena caval or aortic compression, the patient should be positioned in the left pelvic tilt or left lateral position
- Presence of fetal heart sounds should be confirmed before sedation and after the procedure
- Obstetric support should be available
- No endoscopy should be performed in patients with obstetric complications (placental abruption, imminent delivery, ruptured membranes or pre-eclampsia)

The FDA pregnancy drug categories are defined elsewhere.² Permission obtained from Elsevier Ltd © O'Mahony S (2007) *Best Pract Res Clin Gastroenterol* 21: 893–899.

risk of the medication. Moreover, treatment with immunomodulators might be necessary to improve the health status of severely ill women so as to enable conception. Nonetheless, the benefits and risks of therapy need to be discussed in detail with the mother-to-be—if possible, even before conception is planned.

The biologic agents infliximab and adalimumab are FDA category B drugs. Although little information is available on the use of adalimumab during pregnancy, so far the available evidence suggests that infliximab is a low-risk treatment option. Indeed, in 36 pregnant women with Crohn's disease and prior infliximab exposure, no fetal malformations occurred and the rates of miscarriage and neonatal complications were similar to those seen in pregnant women with Crohn's disease who had never been treated with the drug.⁵⁰ In addition, after direct exposure of 96 pregnant women to infliximab, the observed pregnancy outcomes were no different to those expected of the general population.⁵¹ Nonetheless, evidence shows that infliximab crosses the placenta, and the long-term effect of antibodies to tumor necrosis factor (TNF) on the developing fetal immune system is not

Table 1 Safety of drugs that are not commonly used to treat IBD.^{1,18}

Drug	FDA Pregnancy category ^a	Comments
Fish-oil supplements	N/A	Low risk, and of possible benefit
Metronidazole	B	Use is avoided or limited to second and third trimesters by most clinicians; an alternative antibiotic for treatment of pouchitis is amoxicillin and clavulanic acid
Fluoroquinolones	C	Limited data suggest that these drugs are not teratogenic when used for short periods of time, but best avoided because of potential toxicity to cartilage
Rifaximin	C	New drug known to be an animal teratogen, no human data available, best avoided
Ciclosporin	C	Use justified in patients who have active disease that is refractory to other oral or topical agents, particularly to avoid colectomy in those with severe ulcerative colitis; ciclosporin can cause small-for-gestational-age births
Tacrolimus	C	Very limited data available on use in patients with IBD
Methotrexate	X	Teratogenic and contraindicated; should be stopped in both female and male patients at least 3–6 months before conception
Thalidomide	X	Teratogenic and contraindicated

^aThe FDA pregnancy categories are defined elsewhere.² Abbreviation: N/A, not applicable.

known.^{1,52} Thus, detailed discussion with the patient is necessary to decide whether the potential benefits of these treatments outweigh the risks. In 2006, a European consensus conference recommended that treatment with anti-TNF antibodies should preferably be avoided during the last trimester of pregnancy.³⁸ Currently there is no consensus on whether anti-TNF agents (particularly adalimumab, which received FDA approval in December 2002) should be completely avoided during pregnancy, but anti-TNF antibodies are often given until early in the third trimester and then withheld, if the mother can tolerate their withdrawal without flaring. Information on the safety during pregnancy of drugs less commonly used to treat IBD is summarized in Table 1.

Medical therapy for fathers-to-be with IBD

Medical therapy for men with IBD who want to have children is generally less complicated than it is for women, because the embryo and fetus are not directly exposed to potentially toxic substances. However, some drugs reduce male fertility and/or have teratogenic effects if given to the father within 4 months of conception. This period reflects that of spermatogenesis and sperm storage (up to 120 days).

Sulfasalazine has been clearly associated with infertility as a result of abnormalities in sperm

number, motility, and morphology.⁵⁰ Moreover, an association has been described between sulfasalazine use in the father and congenital malformations in the offspring.⁵⁰ Consequently, men who want children should either discontinue sulfasalazine or switch to mesalamine at least 4 months before conception is attempted.

Methotrexate has been shown to cause reversible oligospermia in men⁵⁰ and, although there are no reports to date of congenital anomalies in the progeny of men on methotrexate, guidelines recommend that men stop taking methotrexate at least 4 months before they attempt conception.

Azathioprine and 6-mercaptopurine clearly impair fertility in animal experiments,⁵³ but further studies are needed to determine the effect of these agents on human male fertility.⁵⁴ In addition, the evidence is conflicting on whether a moderate increase in the incidence of congenital malformations occurs in the offspring of men taking azathioprine or 6-mercaptopurine.^{55,56} Thus, the use of azathioprine or 6-mercaptopurine to treat a man whose partner is trying to conceive remains controversial: whether these therapies should be used at all, and whether they can be stopped in good time before conception is attempted needs to be decided together with the patient, and bearing in mind his clinical situation.

Table 2 Liver diseases unique to pregnancy.¹

Liver disease	Onset	Treatment
Hyperemesis gravidarum	First trimester	Supportive, rehydration
Intrahepatic cholestasis of pregnancy	Third trimester	Ursodeoxycholic acid or cholestyramine; preterm delivery at fetal maturity
Pre-eclampsia and eclampsia	Second to third trimester	Antihypertensive drugs, magnesium sulfate
HELLP syndrome	Second to third trimester, or within a few days of delivery	Induction of delivery
Acute fatty liver of pregnancy	Third trimester	Induction of delivery

Abbreviation: HELLP, a syndrome characterized by hemolysis, elevated liver enzymes and a low platelet count.

Treatment with anti-TNF antibodies has been associated with decreased sperm motility and abnormal morphology.⁵⁷ Whether or not these findings translate into reduced male fertility has not been formally examined. At present, therefore, men who are considering fatherhood are not generally recommended to stop therapy with anti-TNF antibodies.⁵⁰

LIVER DISEASE

Liver disease during pregnancy can be divided into disorders that are pre-existing, coincidental or unique to pregnancy.⁵⁸ Specific diseases occur more often in certain trimesters, so consideration of the gestational age facilitates diagnosis (Table 2). Moreover, an awareness of the physiological alterations of hepatobiliary function that occur during pregnancy is vital.⁵⁹

Physiological alterations

Increased serum levels of female sex hormones in pregnant women affect liver function and hemodynamics physiologically. Alterations include decreased gammaglutamyl transpeptidase (GGT) secretion and activity, increased serum alkaline phosphatase activity (because of placental isoenzyme production) and hypoalbuminemia caused by increased plasma volume, particularly during the third trimester.⁵⁹ By contrast, serum alanine transaminase (ALT) and serum aspartate transaminase (AST) levels remain within normal ranges.^{59,60} Increased serum activities of ALT, AST, GGT and raised serum bilirubin concentrations during pregnancy should, therefore, prompt further investigations.⁶¹ Telangiectasia and palmar erythema, which can both be signs of liver disease, are observed in up to 60% of normal pregnancies.⁵⁹

Liver diseases unique to pregnancy

Clinically significant abnormalities of liver function test results can be found in 3% of pregnancies.⁵⁹

Hyperemesis gravidarum

Hyperemesis gravidarum is the only pregnancy-related gastrointestinal disorder that occurs during the first trimester. About 67% of patients with hyperemesis gravidarum present with abnormal liver enzyme levels (AST>ALT), which are especially frequent in women with late-onset hyperemesis gravidarum and those with severe ketonuria.⁵⁸ These abnormal liver enzyme levels resolve with rehydration.

Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy (ICP) mainly develops late in gestation (after week 30). This benign cholestatic liver disease is of uncertain etiology and resolves spontaneously postpartum.^{58,62} ICP is most common in Chile, Bolivia, Scandinavia and Poland, and occurs more often during winter than in other seasons.⁶² Women with a history of cholestasis caused by oral contraceptives and a family history of ICP are at risk of developing ICP, as are women who have a multiple pregnancy.⁵⁶

The pathogenesis of ICP is probably multifactorial, and is thought to involve not only genetic hypersensitivity to sex hormones—particularly estrogens—but also alterations of progesterone metabolism. As a consequence of both mechanisms, the expression and functioning of certain transporter proteins is impaired, which, in turn, causes impaired bile-acid excretion.^{56,61} Mutations have been described in the genes that encode hepatobiliary

transporter proteins, especially hepatic phospholipid and aminophospholipid transporters and the bile-salt export pump, but their precise pathophysiological role in the development of ICP is uncertain.⁶³ Increased gastrointestinal permeability might also be involved in the etiology of ICP, because such increased permeability facilitates the absorption of bacterial endotoxins and enhances the enterohepatic circulation of metabolites of bile salts and sex hormones.⁶⁴ In addition, geographic and seasonal variations in environmental factors (e.g. the availability of selenium) might modulate the occurrence of ICP in genetically predisposed women.⁶¹

Elevated concentrations of bile acids cause moderate to severe pruritus and sometimes jaundice. ALT and AST levels are often normal in women with ICP, and GGT levels are normal in nearly 70% of patients with ICP.⁶¹ Maternal outcome is not impaired by ICP; however, up to 44% of women with ICP have a preterm delivery and 11–20% of babies born to women with ICP are affected by morbidity and mortality.^{62,65} Close fetal monitoring is, therefore, required in women with ICP.^{62,66} Ursodeoxycholic acid (UDCA; FDA category B) reduces the maternal symptoms of ICP (i.e. pruritis and jaundice).¹ Cholestyramine (FDA category C) can be used as an alternative to UDCA, but can cause infant coagulopathy.¹ As binding of bile acids may decrease absorption of fat-soluble vitamins, supplementation with vitamins A, D, E and especially vitamin K, should be considered for cholestyramine-treated women.^{58,62}

Pre-eclampsia and eclampsia

Pre-eclampsia causes about half of the cases of elevated liver enzyme levels during pregnancy.⁶⁵ This condition occurs in 2–8% of all pregnancies (usually after week 20),⁵⁸ is characterized by hypertension, proteinuria and sometimes edema, and spontaneously resolves in the postpartum period. The development of seizures or other neurologic symptoms indicates the progression of pre-eclampsia to eclampsia. Atypical features of pre-eclampsia and/or eclampsia are occurrence before week 20 and the absence of hypertension and proteinuria.⁶⁷

Pre-eclampsia is a multisystem maternal syndrome that is triggered by placental pathology. The spectrum of system-wide responses to such pathology includes endothelial dysfunction, vasoconstriction, activation of the coagulation

cascade, increased platelet adhesiveness and enhanced inflammatory responses. Liver injury, caused by hepatic arterial vasospasm and portal and periportal fibrin deposition, results in lobular ischemia and hepatocyte necrosis.^{58,68}

A deficiency of fatty-acid oxidation metabolism in the fetus, similar to that seen in cases of acute fatty liver of pregnancy (AFLP), has been implicated in the pathogenesis of pre-eclampsia.^{58,69} The risk of developing pre-eclampsia is increased in women who have a family history of pre-eclampsia, those with pre-existing hypertension or other medical conditions (such as diabetes, obesity and collagen vascular diseases), those who are pregnant for the first time or are expecting more than one baby.⁵⁶ The risk of pre-eclampsia also rises as maternal age increases.⁵

In pre-eclampsia, liver transaminase levels are elevated by 1.5–5 times normal. Alkaline phosphatase concentrations might be increased slightly (i.e. beyond the normal range in pregnancy), but liver function is not impaired.⁵⁸ Indeed, although women with pre-eclampsia need careful monitoring and treatment (e.g. with antihypertensive drugs such as magnesium sulfate) to prevent complications, liver function usually remains stable and requires no specific therapy.

HELLP syndrome

HELLP syndrome is characterized by hemolysis, elevated levels of liver enzymes (AST:ALT >1) and low platelet numbers. This syndrome is considered to be a distinct clinical entity, even though 5–10% of women with severe pre-eclampsia develop this condition.⁵⁸ Onset generally occurs during the second or third trimester, but in 20% of cases, HELLP syndrome develops within 2 days of delivery; such late onset of HELLP syndrome is especially common in women who have antepartum pre-eclampsia.⁵⁸

HELLP syndrome is a multisystemic disorder that involves changes in the immunologic fetal-maternal balance, platelet aggregation, activation of complement and coagulation cascades, and endothelial dysfunction.^{58,70} Liver injury is caused by intravascular fibrin deposition, hypovolemia and increased sinusoidal pressure, and is sometimes complicated by subcapsular hematoma or hepatic rupture. Clinical symptoms of HELLP syndrome are headache, visual alterations, epigastric pain and nausea. Disseminated intravascular coagulation or renal failure can

complicate the situation. The only definitive therapy for HELLP syndrome is induction of delivery.^{58,66} In women with early-onset HELLP syndrome (before week 34), corticosteroids have been recommended to stabilize the maternal abnormalities and allow maturation of the fetus.⁷¹ HELLP syndrome is associated with maternal mortality of 1–3.5%.⁵⁸ Fetal outcome is more strongly determined by the gestational age at the time of delivery than by the severity of HELLP syndrome in the mother.⁷¹

Acute fatty liver of pregnancy

AFLP is a rare, but very serious disease of the last trimester of pregnancy (1 case per 10,000–15,000 pregnancies).⁵⁸ Maternal and fetal defects of fatty acid metabolism, particularly deficiency of the enzyme long-chain 3-hydroxyacyl-coenzyme A dehydrogenase, are thought to cause increased accumulation of long-chain fatty acids, first in the fetal liver and then, via the circulation, in the maternal liver, which results in hepatotoxicity.^{58,66} Symptoms vary from nausea and/or vomiting, upper abdominal pain and upper gastrointestinal hemorrhage to acute liver failure with hepatic coagulopathy, encephalopathy, renal failure and multiorgan failure.

NSAID use can increase the risk of developing AFLP, and this disease is more common in patients with pre-eclampsia.^{58,69} If recognized early and treated by induction of delivery, maternal mortality is less than 5%.⁵⁸ Nevertheless, liver transplantation has been performed in women with AFLP, and 23–60% of babies born to women with AFLP die.^{58,66,69} Women at risk of AFLP are those with a history of AFLP and those with children who have a disorder of fatty-acid oxidation or children who died of Reye syndrome. These women should be monitored closely, and must maintain a low-fat, high-carbohydrate diet and avoid fasting.^{58,69}

Liver disease coincidental with pregnancy

The incidence of gallbladder disease during pregnancy is 0.3–0.5%.⁷² Gallbladder disease is the second most frequent indication for nonobstetric surgery.⁷³ Pregnancy itself, a known history of gallbladder disease, obesity and prenatal physical activity⁷⁴ are risk factors for the development of gallstones, just as are iron supplementation, increased age, high serum cholesterol level, prenatal weight gain and a high serum leptin level.^{73,74} The symptoms of gallbladder disease in pregnant women do not differ from those

of nonpregnant patients, and include stabbing pain in the right upper abdomen, nausea and vomiting, intolerance of fatty food, and fever.⁷³

First-line therapy for pregnant women with symptomatic gallbladder disease, especially those in the first trimester, is conservative management including discontinuation of oral food intake, analgesia and antibiotics. In cases of recurrent disease or treatment failure, cholecystectomy should be considered but deferred until the second trimester if possible.⁷³ Published data suggest that conservative management of gallbladder disease increases the risk of relapse before delivery, preterm delivery and biliary pancreatitis, whereas surgical intervention enhances the risk of preterm uterine contractions.^{70,75} Laparoscopic cholecystectomy has become the standard therapy for gallbladder disease during the second trimester,¹ because (compared with open cholecystectomy) the laparoscopic technique results in greatly reduced recovery times and fewer post-operative complications, and also allows facilitated vaginal delivery.⁷⁰ The lack of available data hinders recommendations for the type of gallbladder surgery that should be used in the third trimester of pregnancy; however, use of an open technique might prevent damage to the enlarged uterus.⁷⁶ In patients with choledocholithiasis, endoscopic retrograde cholangiopancreatography is considered to confer little additional risk in pregnant women compared with nonpregnant women.⁷³ The principles listed in Box 1 should be applied, and exposure to ionizing radiation minimized.

Acute hepatitis

Acute hepatitis is the most common cause of jaundice during pregnancy.⁷⁷ In women with acute hepatitis A, B, C or D, pregnancy does not worsen the course of hepatitis.⁷⁷ Hepatitis E is particularly severe in pregnant women, with an increased likelihood of fulminant disease and maternal mortality as high as 25%.^{77,78} Pregnancy outcome is generally not impaired in women with nonfulminant acute hepatitis, but infections acquired in the last trimester can result in complications such as preterm labor.⁷⁷ In women who are seropositive for hepatitis B e antigen or hepatitis B surface antigen, the risk of perinatal and/or neonatal transmission of the virus is very high (60–90%).⁷⁷ Postexposure administration of inactivated vaccine against either hepatitis A or hepatitis B viruses, and

immunoglobulins against hepatitis B, are considered to be relatively safe methods of preventing maternal infection during pregnancy, and consequently of reducing the risk of vertical transmission.¹ All babies born to mothers who are seropositive for hepatitis B surface antigen should receive hepatitis B vaccine and immunoglobulins within 12 h of birth.⁷⁹

Chronic liver disease

Pregnancies are rare among women who have severe, chronic liver diseases (such as autoimmune hepatitis, primary biliary cirrhosis and chronic viral hepatitis), because these women tend to have hypogonadism, anovulation and amenorrhea. However, pregnancies in these women have become more common with the availability of improved therapies for the treatment of severe chronic liver diseases.

Autoimmune hepatitis

In most (50–73%) women who have autoimmune hepatitis, pregnancy improves liver function from the second trimester onwards, because of immunotolerance.^{80,81} However, worsening liver function has been described in 21–50% of pregnant women with autoimmune hepatitis, and 30–52% of pregnant women with autoimmune hepatitis experience a flare-up of their condition after delivery.⁸⁰ Autoimmune hepatitis is associated with a high rate of adverse pregnancy outcomes (26%), including premature delivery and death.^{81,82} The presence of autoantibodies might be a risk factor and close monitoring of mother and fetus is, therefore, advisable. Therapy with prednisolone and azathioprine seems to be safe (for detailed information on the safety of these drugs during pregnancy please refer to their use to treat IBD, above).^{81,82} Reduced dosages of prednisolone or azathioprine are often possible during pregnancy.^{80,81}

Primary biliary cirrhosis

There have been only a few reports on primary biliary cirrhosis (PBC) in pregnancy.⁸³ PBC is a progressive, cholestatic liver disease that is characterized by destruction of the intrahepatic bile ducts. PBC is presumed to be an autoimmune disease that predominantly affects females, typically middle-aged women (aged between 40 and 60 years), although it can occur in women as young as 20 years. Pregnancy outcomes in women with PBC are generally good. UDCA is the first-line treatment for PBC and seems to be

a low-risk treatment (FDA category B) in the second and third trimester, but the paucity of data available means that UDCA therapy is not recommended in the first trimester of pregnancy unless essential.^{1,84}

Chronic viral hepatitis

In women with chronic viral hepatitis, stable liver function allows a normal pregnancy.⁷⁹ For women with chronic hepatitis B, continued treatment with lamivudine (although FDA category C) is considered low risk, even during the first trimester.¹ Only limited data exist on the use of adefovir dipivoxil or entecavir during pregnancy: both are FDA category C drugs, so their use is not recommended unless their benefits outweigh their risks.¹ The state-of-the-art treatment for chronic hepatitis C is pegylated interferon plus ribavirin.⁸⁵ Both of these drugs are contraindicated during pregnancy. Ribavirin is a known teratogen (FDA category X) and remains detectable in blood samples 4 weeks after discontinuation, so an exposure-free period of at least 6 months is recommended before conception is attempted.¹

CONCLUSIONS

Increased levels of female sex hormones cause alterations of gastrointestinal motility, and this fact explains, at least in part, why gastrointestinal symptoms such as heartburn, nausea, vomiting and constipation are extremely common during pregnancy. Organic causes of these symptoms need to be appropriately excluded in severe cases, and in patients with alarm symptoms. On the other hand, reassurance, avoidance of precipitating factors and dietary changes are the first therapeutic steps to be recommended in patients with mild symptoms. If symptoms do not respond adequately, drug therapy is often warranted to improve quality of life and to prevent complications.

Women with IBD are advised to plan conception for a time when their disease is in remission because the rate of unfavorable pregnancy outcomes is generally increased if conception occurs during active disease. Maintenance of adequate disease control during pregnancy is crucial for the health of the mother and the fetus, and often requires continuation of drug treatment.

Liver disease during pregnancy can be divided into disorders that are pre-existing, coincidental or unique to pregnancy. The latter

include hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, pre-eclampsia and eclampsia, HELLP syndrome and AFLP. The most important hepatobiliary diseases that are pre-existent or coincidental with pregnancy are gallbladder disease, acute viral hepatitis and chronic hepatitis of various etiologies.

Pregnancies are rare among women who have severe chronic liver diseases, such as autoimmune hepatitis or PBC. In women with chronic viral hepatitis, stable liver function allows a normal pregnancy. For women with chronic hepatitis B, continued treatment with lamivudine is low risk, while the use of adefovir dipivoxil or entecavir is not generally recommended because of limited safety data. Pegylated interferon and ribavirin, which together comprise the state-of-the-art treatment for chronic hepatitis C, are both contraindicated during pregnancy.

KEY POINTS

- Gastrointestinal symptoms such as heartburn, nausea and vomiting, and constipation are very common during pregnancy and are mainly attributable to motility disturbances caused by increased female sex hormone levels
- Therapy for these symptoms usually follows a stepwise approach that starts with reassurance, avoidance of precipitating factors, and dietary changes; drug therapy is reserved for women whose symptoms do not respond adequately
- For pregnant women with IBD, maintenance of adequate disease control is crucial for the health of both mother and fetus and often requires continuation of drug treatment
- According to the available evidence, most drugs used to treat IBD—except the teratogenic drugs methotrexate and thalidomide—are low-risk options during pregnancy
- The spectrum of liver diseases during pregnancy is very heterogeneous, and encompasses diseases unique to pregnancy, coincidental conditions, and pre-existing chronic liver diseases
- Although pregnancy is rare in women with severe chronic liver diseases, clinicians need to be aware that nearly 10% of pregnant women may develop a liver disease that is unique to pregnancy, in particular pre-eclampsia, and that adequate monitoring and therapy are needed

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