Clinical Medicine 2013, Vol 13, No 3: 269–74

Gastrointestinal and liver disease in pregnancy

Charlotte J Frise and Catherine Williamson

ABSTRACT – Gastrointestinal (GI) conditions are common in women of childbearing age. They often present before pregnancy but can arise *de novo* during pregnancy. The physiological changes that occur during pregnancy can influence the differential diagnosis of common GI presentations, affect the interpretation of diagnostic tests and restrict the use of diagnostic or therapeutic procedures. In this article, we summarise the clinical features, investigation and management of common GI and liver conditions that are incidental to pregnancy, and describe the specific features of pregnancy-related disorders that are less frequently encountered by general physicians. Newer developments in areas that are increasingly encountered in obstetric medical practice, including pregnancy after bariatric procedures, are also described.

KEY WORDS: Pregnancy, liver disease, HELLP syndrome, hypertensive disorders of pregnancy, obstetric cholestasis, hyperemesis gravidarum

Introduction

There are many gastrointestinal (GI) and liver conditions in the non-pregnant population that take a benign course and are unaffected when an individual becomes pregnant. Others can occur during pregnancy for the first time, but the pregnant state does not alter the time course of the condition or the management options. However, there are some disorders that, for reasons that are still unclear, can have a relatively benign course outside pregnancy but become life threatening during pregnancy, such as hepatitis E. There are several pregnancy-specific conditions that are described in this article that can be challenging not only for the general physician who only infrequently encounters this in day-to-day practice, but also for the obstetrician who rarely encounters the non-pregnancy-related medical conditions that can have similar presenting features to gestational disorders.

Gastrointestinal conditions

Diseases incidental to pregnancy

GI diseases that are incidental to pregnancy and the pregnancy-specific considerations relevant to these conditions are summarised in Table 1. The reader is referred to more detailed texts for more comprehensive descriptions of these disorders.[1,2]

Charlotte J Frise,[1] specialist registrar in acute and general medicine and obstetric medicine; **Catherine Williamson,**[2] professor in obstetric medicine

[1]Oxford University Hospitals NHS Trust, Oxford, UK; [2]Queen Charlotte's and Chelsea Hospital, London, UK

Pregnancy-specific conditions

Hyperemesis gravidarum. Although transient nausea and vomiting affect up to 50% of pregnant women, the development of severe nausea and vomiting sufficient to cause dehydration, biochemical derangement and nutritional deficiencies occurs in less than 1%. It is important to consider alternative diagnoses at the time of initial presentation because many other underlying pathologies can cause vomiting during pregnancy, including intracranial space-occupying lesions, peptic ulcer disease and hyperthyroidism. In each triennium reported in the Confidential Enquiry into maternal deaths, there are deaths associated with hyperemesis gravidarum.[3]

Admission to hospital might be required for rehydration and anti-emetic administration. Drugs commonly used include cyclizine, metoclopramide, promethazine and prochlorperazine. There are good safety data for these drugs in pregnancy. If these drugs are not successful alone or in combination, ondansetron and parenteral hydrocortisone, followed by prednisolone, are second-line treatment options. Thiamine supplementation should also be given to prevent Wernicke's encephalopathy. Fetal scanning is required on presentation because the incidence of hyperemesis is increased in multiple or molar pregnancies. Care should be taken to identify and correct hyponatraemia and hypokalaemia. Blood tests can also reveal biochemical hyperthyroidism, but this is usually a transient phenomenon and resolves with treatment of the hyperemesis.

Special situations

Bariatric surgery

As the mean body mass index of the pregnant population is increasing, so too is the number of pregnant patients who have previously had some form of bariatric procedure, including gastric banding or Roux en Y surgery. These patients are usually advised to avoid conception during the year following the procedure owing to theoretical concerns about nutrition and conception during a period of significant weight loss; however, studies have not shown that adverse fetal outcomes are reduced if conception is delayed in this way.[4]

There is a risk of malabsorption and nutritional deficiencies, including fat soluble vitamins, particularly if biliopancreatic diversion has been performed. Therefore, this requires monitoring and appropriate replacement during pregnancy.

The differential diagnosis of acute abdominal pain in pregnancy is wider if the patient has had a previous bariatric procedure, because complications can occur, such as band

Box 1. Diagnostic criteria for acute fatty liver of pregnancy (Swansea criteria).[5]

The presence of six or more of the following features, in the absence of another cause, may indicate acute fatty liver of pregnancy.

- Vomiting
- Abdominal pain
- Polydipsia and/or polyuria
- Encephalopathy
- Elevated bilirubin
- Hypoglycaemia
- Elevated urate
- Leucocytosis
- Elevated transaminases
- Elevated ammonia
- Renal impairment
- Coagulopathy
- Ascites or bright liver on ultrasound scan
- Microvesicular steatosis on liver biopsy

Table 1. Gastrointestinal disease incidental to pregnancy.

Condition	Course in pregnancy and specific considerations	Management
Infective		
Gastroenteritis	• Unchanged	• Supportive
Appendicitis	• Can be harder to identify owing to wider differential diagnosis of acute abdominal pain in pregnancy and the alteration in appendix location that can occur later during pregnancy	• Surgical management as in non-pregnant patient
Inflammatory		
Crohn's disease and ulcerative colitis	• Active disease at conception is associated with adverse fetal outcomes, including miscarriage and preterm birth[17] • Pregnancy does not alter relapse rate • Ileoanal pouch is not an absolute indication for Caesarean section[18] and decisions about mode of delivery should be made on a case-by-case basis with multidisciplinary team input	• Continue medical treatment, including azathioprine, sulfasalazine, steroids and 5-aminosalicylates • Mycophenolate mofetil and methotrexate should not be used • Nutritional support • Indications for surgery are the same as for non-pregnant patients • Anti-tumour necrosis factor agents, including infliximab, can be used during first and second trimester, but should usually be avoided during the third trimester to reduce fetal exposure • Babies born to mothers who were treated with infliximab should not receive live vaccines for first 6 months
Pancreatitis	• Incidence of acute pancreatitis not changed by pregnancy	• Supportive • Patients with chronic pancreatitis need to be monitored for malabsorption and gestational diabetes mellitus during pregnancy
Coeliac disease	• Uncontrolled disease associated with miscarriage, infertility, low birth weight and intrauterine growth retardation[19] • Diagnostic serological testing and endoscopy can be performed as normal	• Strict compliance with gluten-free diet during pregnancy • Regular assessment for fetal growth • Monitor for malabsorption
Other		
Gastro-oesophageal reflux	• Common in pregnancy owing to progesterone-mediated relaxation of lower oesophageal sphincter	• Both histamine 2 receptor antagonists and proton pump inhibitors can be used during pregnancy with no reported increase in adverse outcomes
Peptic ulcer disease	• Incidence can be lower during pregnancy, perhaps reflecting a healthier diet, but under-reporting and reduced use of endoscopy might affect the reported incidence	• *Helicobacter pylori* eradication if non-invasive testing is positive • Upper gastrointestinal endoscopy can be performed if indicated[20]
Bowel obstruction	• Can cause abdominal pain in pregnancy owing to adhesions, pelvic inflammatory disease or volvulus	• Supportive initial treatment, with surgery if required

Table 2. Liver disease incidental to pregnancy.

Condition	Course in pregnancy and specific considerations	Management
Infective		
Hepatitis A	• Course unchanged	• Supportive
Hepatitis B	• Surface antigen routinely screened for at booking • Course unchanged, but it is important to identify affected individuals to reduce mother to child transmission	• Vaccination and immunoglobulin to infant after delivery • Antivirals after delivery, but are occassionally used in pregnancy if very high viral load
Hepatitis C	• Antibodies measured in women identified at risk • Course unchanged • Increased rates of obstetric cholestasis	• Mode of delivery does not alter mother to child transmission with the exception of cases with high maternal viral load • In these cases, avoid invasive fetal monitoring and prolonged rupture of membranes
Hepatitis E	• Increased susceptibility to severe infection and fulminant liver failure • Increased maternal morbidity and mortality compared with non-pregnant women[21] • Increased perinatal mortality rate	• Supportive
Herpes simplex virus	• Can present without vesicles • Infection during third trimester is associated with increased rates of maternal and perinatal mortality[22]	• Aciclovir
Epstein–Barr virus	• Course unchanged	• Supportive
Cytomegalovirus	• Course of infection unchanged • Maternal infection associated with congenital infection, increased rates of fetal mortality and long-term morbidity (particularly neurological)	• Supportive • No evidence that maternal antivirals reduce perinatal transmission
Inflammatory		
Autoimmune hepatitis	• Uncontrolled inflammation associated with fetal morbidity and mortality • As with other autoimmune conditions, can show improvement during pregnancy, but risk of worsening postpartum	• Need to continue immunosuppression • Azathioprine not associated with adverse outcomes during pregnancy or with breastfeeding • Assess for varices • Assess for anti-Ro and La antibodies
Primary biliary cirrhosis	• Exacerbation of cholestasis typically occurs during pregnancy	• Ursodeoxycholic acid treatment should be continued if ongoing raised serum bile acids (consider continuing treatment after delivery) • Continue immunosuppressive therapy • Assess for anti-Ro and La antibodies
Vascular		
Budd–Chiari syndrome	• Increased incidence during pregnancy • Pre-existing disease associated with preterm birth[23]	• Assess for thrombophilia • Anticoagulation with low-molecular-weight heparin
Other		
Liver transplantation	• Increased incidence of preterm labour, hypertensive disorders and low birth-weight babies[24] • No effect of pregnancy on graft survival or outcome	• Risk of adverse fetal outcomes reduced if conception delayed for 1 year post transplant
Hepatic adenomas	• More prone to bleeding during pregnancy, particularly if >5cm	• Laparoscopic resection and liver transplantation for bleeding during pregnancy have been reported[25,26]

slippage, small bowel obstruction owing to herniation and intussusception.

Nutrition

The precise nutritional requirements during pregnancy are unknown, but malabsorptive conditions are associated with intrauterine growth restriction and therefore it is advisable to perform additional fetal monitoring in any patient with a history of malabsorption. Consideration should be given to assessment of fat-soluble vitamins, calcium and vitamin D and iron, particularly in patients receiving parenteral or enteral feeding.

Liver disease

Mildly deranged liver function tests are common during pregnancy, with one study identifying abnormalities in 3% of all deliveries.[5] However, fulminant liver failure is rare, with a major tertiary centre identifying only 54 cases of pregnancy-related liver failure over an 11-year period.[6] Many features of common liver conditions overlap with pregnancy-specific liver disorders; therefore, a careful history and physical examination are key tools in identifying the underlying disorder. It is important to exclude non-gestational causes of liver dysfunction, including drug-induced hepatic impairment and biliary disease, before assuming that liver dysfunction is secondary to pregnancy.

Disorders incidental to pregnancy

Liver disease incidental to pregnancy and the pregnancy-specific considerations are summarised in Table 2. The reader is referred to more detailed texts for more comprehensive descriptions of these disorders.[1,7]

Pregnancy-specific conditions

Hypertensive disease of pregnancy. Liver function tests are often deranged in the setting of disorders that fall within the spectrum of disease that includes pre-eclampsia, eclampsia and the haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome; significant liver impairment is most commonly associated with the latter. Women can be asymptomatic at the time of onset of hepatic impairment, but headache, right upper quadrant pain and visual disturbance more commonly occur. There can be hypertension and proteinuria on examination, but in HELLP syndrome the haematological and biochemical features can precede the development of these abnormalities, making the diagnosis more challenging.[8] The condition can be unheralded, which adds to the difficulty in identifying affected individuals. There is no consensus on the level at which raised liver transaminases make HELLP syndrome more likely.

There is significant morbidity and mortality associated with HELLP syndrome, including formation of subcapsular hepatic haematoma, capsular rupture and non-hepatic complications of severe pre-eclampsia, such as intracerebral haemorrhage. These cause a few maternal deaths in the UK every year, as described in the Confidential Enquiry into maternal deaths.[3] The only curative treatment is delivery, but given the potential severity of the condition, resuscitation and stabilisation of the patient are required before this. Blood products, including platelets, can be required, but their use depends on the clinical condition of the affected woman.

The recurrence rate for HELLP syndrome is low, although the risk of subsequent early-onset pre-eclampsia in these individuals is high.[8]

Acute fatty liver of pregnancy. The symptoms and signs of acute fatty liver of pregnancy (AFLP) can be non-specific, and there are often prodromal symptoms over a few days before presentation, including vomiting, reduced appetite, abdominal pain, polyuria and polydipsia. Hyperlactataemia and hypoglycaemia can also occur. A study performed in Wales assessed the clinical features of patients with a probable diagnosis of AFLP and identified several criteria (referred to as the 'Swansea criteria', listed in Box 1) that can aid diagnosis when other causes of these abnormalities have been excluded.[5]

In contrast to the macrovesicular steatosis seen in non-alcoholic fatty liver disease and the more chronic course that is seen in this condition, the main abnormality in AFLP is microvesicular steatosis, as is seen in Reye's syndrome. Both are associated with acute, severe disease that can be life threatening.

The treatment for AFLP is delivery, but the hepatic insult is so severe in some cases that liver transplantation is required. *N*-acetylcysteine is used in many centres for acute liver failure related to AFLP, but there are no studies to show that this improves outcomes.

Several studies have identified an association between AFLP and fetal homozygosity for disorders of β-fatty acid oxidation, such as long chain 3 hydroxyl-acyl-coenzyme A dehydrogenase (LCHAD) deficiency. This is thought to be explained by inadequate clearance of hepatotoxic metabolites by the liver of the mother who will be an obligate heterozygote for the same mutation as the fetus.[9]

There are limited data relating to the recurrence of AFLP in subsequent pregnancies. If a woman has a confirmed β-fatty acid oxidation disorder, she is likely to have a 25% chance of recurrence. For other cases, it is difficult to advise about recurrence. However, many women do not go on to have a further pregnancy owing to anxiety related to the severity of the AFLP during the previous affected pregnancy.

Obstetric cholestasis. Obstetric cholestasis (OC) is also called intrahepatic cholestasis of pregnancy, and is the most common liver condition specific to pregnancy. The main feature of this condition is pruritus, most commonly affecting the palms and soles, without associated skin changes, in combination with an elevated serum bile acid concentration. Jaundice can occur but is uncommon (affecting $<5\%$). Pale stools and dark urine might also be described. Approximately 15% of affected

women have a history of similar symptoms when taking the combined oral contraceptive pill, and there is often a family history of gallstones or OC in female relatives. Examination is likely to be normal.

It is important to consider other diagnoses; therefore, it is advised to perform liver autoantibodies, hepatitis serology (OC occurs more commonly in women that are seropositive for hepatitis C virus) and an ultrasound scan of liver in all women presenting with these symptoms for the first time during pregnancy. Measurement of serum bile acids helps to confirm the diagnosis, but an elevated result is not specific for this condition. Transaminases can be normal, but require frequent monitoring because these often become deranged as pregnancy progresses.

OC is associated with an increased risk of adverse pregnancy outcomes, including meconium-stained amniotic fluid, spontaneous preterm labour, fetal distress and fetal death. Some studies have suggested that these are more likely with higher bile acid levels.[10] The latter is postulated to be the result of cardiac arrhythmias, because bile acids have been shown to be arrhythmogenic in rat cardiac myocytes.[11] Given that fetal deaths tend to occur during later gestational weeks, the development of OC would prompt induction of labour from 37 weeks' gestation onwards in many centres, but this is not universal practice.[12] Therefore, initial management is usually pharmacological with ursodeoxycholic acid (UDCA), a hydrophilic bile acid that stimulates bile acid release from the hepatocyte. This can reduce maternal symptoms and be associated with an improvement in maternal biochemistry.[13] Several studies have indicated that UDCA treatment can improve pregnancy outcome, but this needs to be evaluated by an adequately powered clinical trial.[14,15]

Table 3. Commonly used investigations in gastrointestinal problems in during pregnancy.

Investigations	Pregnancy-related changes	Use during pregnancy
Bloods		
Alanine transaminase , aspartate aminotransferase, bilirubin and gamma-glutamyl transferase	• Normal range for pregnancy lower than that in non-pregnant population • Transient increase seen postpartum	• Use of pregnancy-specific reference ranges recommended
Alkaline phosphatase	• Variable in pregnancy owing to placental alkaline phosphatase production • Small proportion of women have very elevated concentration	• Use of pregnancy-specific reference ranges recommended
Amylase	• None	• As normal
Viral serology	• None	• As normal
Liver antibodies	• None	• As normal
Imaging		
Ultrasound scan	• None	• As normal
Upper GI endoscopy	• No increase in adverse fetal outcomes	• Advisable to be performed by experienced practitioner and low-dose sedation with fetal monitoring[16]
Lower GI endoscopy	• No increase in adverse outcomes shown for sigmoidoscopy, and colonoscopy during second trimester • Lack of evidence for colonoscopy during first and third trimester[27]	• Advisable to be performed by experienced practitioner and low-dose sedation with fetal monitoring
CT scan	• None	• Risks of radiation exposure to fetus with abdominal imaging and exposure of breast tissue with chest imaging, but can be performed if indications outweigh risks • Levels of radiation from a single CT scan are not sufficiently high to increase the risk of congenital abnormalities or childhood malignancy
Magnetic resonance imaging	• None	• Theoretical risks during first trimester, but not contra-indicated at any time during pregnancy
Endoscopic retrograde cholangiopancreatography	• One series reported first trimester use associated with preterm birth and low birth weight[28]	• To be performed by experienced endoscopist • Pulsed rather than continuous fluoroscopy • Lead shielding to fetus

CT = computerised tomography; GI = gastrointestinal.

Investigations

Most relevant investigations for GI and liver conditions can be performed as normal during pregnancy. Endoscopy is not contraindicated, although it should only be performed during pregnancy if a woman is sufficiently unwell that it is not appropriate to delay the investigation until the postnatal period and the results would potentially alter management during pregnancy. It is advised that endoscopy should be performed by the most senior operator available, with fetal monitoring and cautious use of sedative agents.[16]

The effect of pregnancy on other investigations is summarised in Table 3.

Conclusions

A careful history and examination are of the utmost importance when assessing a pregnant woman with a GI or liver abnormality. Most drugs can be used safely and appropriately during pregnancy and careful consideration should be given before any medication is stopped in preparation for possible conception. A multidisciplinary team approach is key for the successful management of pregnancies complicated by conditions such as those described here, to optimise the maternal and fetal outcome.

References

1 Powrie RO, Greene MF, Camann W (eds). *de Swiet's Medical Disorders in Obstetric Practice*, 5th edn. Chichester: Wiley-Blackwell, 2010.
2 Van der Woude CJ, Kolacek S, Dotan I *et al.* European evidenced-based consensus on reproduction in inflammatory bowel disease. *J Crohns Colitis* 2010;4:493–510.
3. Cantwell R, Clutton-Brock T, Cooper G *et al.* Saving mothers' lives. Reviewing maternal deaths to make motherhood safer: 2006–2008. The eighth report on confidential enquiries into maternal deaths in the United Kingdom. *BJOG* 2011;118(suppl 1):1–203.
4 Dao T, Kuhn J, Ehmer D *et al.* Pregnancy outcomes after gastric-bypass surgery. *Am J Surg* 2006;192:762–6.
5 Ch'ng CL, Morgan M, Hainsworth I, Kingham JG. Prospective study of liver dysfunction in pregnancy in Southwest Wales. *Gut* 2002;51:876–80.
6 Westbrook RH, Yeoman AD, Joshi D *et al.* Outcomes of severe pregnancy-related liver disease: refining the role of transplantation. *Am J Transplant* 2010;10:2520–6.
7 Frise CJ, Williamson C. Liver disease in pregnancy. *Medicine* 2011;39:576–9.
8 Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. *Obstet Gynecol* 2004;103:981–91.
9 Treem W, Rinaldo P, Hale DE *et al.* Acute fatty liver of pregnancy and long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency. *Hepatology* 1994;19:339–45.
10 Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. *World J Gastroenterol* 2009;15:2049–66.
11 Williamson C, Gorelik J, Eaton BM *et al.* The bile acid taurocholate impairs rat cardiomyocyte function: a proposed mechanism for intrauterine fetal death in obstetric cholestasis. *Clin Sci* 2001;100:363–9.
12 Saleh M, Abdo K. Consensus on the management of obstetric cholestasis: National UK survey. *BJOG* 2007;114:99–103.
13 Glantz A, Marschall HU, Lammert F, Mattsson LA. Intrahepatic cholestasis of pregnancy: a randomized controlled trial comparing dexamethasone and ursodeoxycholic acid. *Hepatology* 2005;42:1399–1405.
14 Chappell LC, Gurung V, Seed PT *et al.* Ursodeoxycholic acid versus placebo, and early term delivery versus expectant management, in women with intrahepatic cholestasis of pregnancy: semifactorial randomised clinical trial. *BMJ* 2012;344:e3799.
15 Bacq Y, Sentilhes L, Reyes HB *et al.* Efficacy of ursodeoxycholic acid in treating intrahepatic cholestasis of pregnancy: a meta-analysis. *Gastroenterology* 2012;143:1492–501.
16 Qureshi WA, Rajan E, Adler DG *et al.* ASGE Guideline: guidelines for endoscopy in pregnant and lactating women. *Gastrointest Endosc* 2005;61:357–62.
17 Nørgård B, Hundborg HH, Jacobsen BA *et al.* Disease activity in pregnant women with Crohn's disease and birth outcomes: a regional Danish cohort study. *Am J Gastroenterol* 2007;102:1947–54.
18 Cornish JA, Tan E, Teare J *et al.* The effect of restorative proctocolectomy on sexual function, urinary function, fertility, pregnancy and delivery: a systematic review. *Dis Colon Rectum* 2007;50:1128–38.
19 Khashan AS, Henriksen TB, Mortensen PB *et al.* The impact of maternal celiac disease on birthweight and preterm birth: a Danish population-based cohort study. *Hum Reprod* 2010;25:528–34.
20 Cappell MS, Colon VJ, Sidhom OA. A study of eight medical centers of the safety and clinical efficacy of esophagogastroduodenoscopy in 83 pregnant females with follow-up of fetal outcome with comparison control groups. *Am J Gastroenterol* 1996;91:348–54.
21 Kumar A, Beniwal M, Kar P *et al.* Hepatitis E in pregnancy. *Int J Gynecol Obstet* 2004;85:240–4.
22 Corey L, Wald A. Maternal and neonatal herpes simplex virus infections. *N Engl J Med* 2009;361:1376–85.
23 Rautou PE, Angermayr B, Garcia-Pagan JC *et al.* Pregnancy in women with known and treated Budd–Chiari syndrome: Maternal and fetal outcomes. *J Hepatol* 2009;51:47–54.
24 Christopher V, Al-Chalabi T, Richardson PD *et al.* Pregnancy outcome after liver transplantation: a single-center experience of 71 pregnancies in 45 recipients. *Liver Transpl* 2006;12:1138–43.
25 Wilson CH, Manas DM, French JJ. Laparoscopic liver resection for hepatic adenoma in pregnancy. *J Clin Gastroenterol* 2010;45:828–33.
26 Santambrogio R, Marconi A, Ceretti A *et al.* Liver transplantation for spontaneous intrapartum rupture. *Obstet Gynecol* 2009;113:508–10.
27 Cappell MS. Risks versus benefits of gastrointestinal endoscopy during pregnancy. *Nat Rev Gastroenterol Hepatol* 2011;8:610–34.
28 Tang SJ, Mayo MJ, Rodriguez-Frias E *et al.* Safety and utility of ERCP during pregnancy. *Gastrointest Endosc* 2009;69:453–61.

Address for correspondence: Prof C Williamson, Maternal and Fetal Disease Group, Institute of Reproductive and Developmental Biology, Imperial College London, Du Cane Road, London W12 0NN.
Email: catherine.williamson@imperial.ac.uk