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Gastrointestinal and Liver Disease in Pregnancy

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liver transplantation

This chapter on the gastrointestinal and hepatic systems in pregnancy focusses on those conditions that are frequent and troublesome (gastro-oesophageal reflux and constipation), distressing (hyperemesis gravidarum) or potentially fatal (obstetric cholestasis, acute fatty liver of pregnancy and HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome). It also highlights the clinical challenge obstetricians may face in managing rare conditions such as the Budd–Chiari syndrome, liver transplantation, primary biliary cirrhosis and Wilson disease.

The clinical presentation of liver and gastrointestinal dysfunction in pregnancy is not specific, and certain 'abnormalities' may represent physiological changes of pregnancy. Diagnosis and management are often difficult because of atypical symptoms, a reluctance to use invasive investigations and concerns about the teratogenicity of the medications. The best available evidence to manage these conditions is discussed in the chapter.

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Gastrointestinal disease

Hyperemesis gravidarum

Nausea and vomiting are common in the first trimester of pregnancy and are usually self-limiting. It is estimated that 70–90% of pregnant women experience nausea and 50% have at least one episode of vomiting or retching. Most doctors and pregnant women are excessively cautious with anti-emetics during pregnancy especially in the first trimester and they are generally avoided, unless vomiting is very severe, due to the fear of teratogenicity.

Clinical features

Hyperemesis gravidarum (HG) occurs in around 0.1% of pregnancies and presents with severe and persistent nausea and vomiting leading to dehydration. Onset is usually in the first trimester (6–8 weeks' gestation) of pregnancy. In addition to nausea and vomiting, there may be ptyalism (inability to swallow saliva) and spitting. The persistent vomiting may also lead to postural hypotension, tachycardia, electrolyte disturbances, ketosis, muscle wasting and weight loss.

Pathogenesis

The pathophysiology of hyperemesis is poorly understood. It appears to have a complex metabolic background and a number of hormonal, mechanical and psychological factors have been implicated. Hormones such as human chorionic gonadotropin (HCG), low levels of prolactin and high levels of oestradiol have been implicated [1–3]. Recent reports have suggested an association between HG and *Helicobacter pylori* infection [4]. Some studies have shown increased concentrations of cell-free foetal deoxyribonucleic acid (DNA) and activation of natural killer and cytotoxic T-cells in women with hyperemesis [5,6]. A recent pilot study has shown a possible role of leptin and nesfatin-1 in the pathology of hyperemesis [7].

Diagnosis

HG is a diagnosis of exclusion with no single confirmatory test. Therefore, other causes of nausea and vomiting such as systemic infection, peptic ulceration, pancreatitis and, rarely, Addison's disease must be considered. Hyperemesis usually recurs (women with a history of HG, 15.2%, vs. without a history of HG, 0.7%) in subsequent pregnancies; hence, a previous history makes the diagnosis more likely [8].

Investigations

Laboratory investigations may reveal hyponatraemia, hypokalaemia, low urea, ketosis and a metabolic hypochloraemic alkalosis. Two-thirds of patients with HG may have abnormal thyroid function tests, which are more common in Asians than in Europeans [9,10]. These patients have raised free thyroxine (T4) and/or a suppressed thyroid-stimulating hormone (TSH) but are clinically euthyroid and do not require treatment.

Effect of HG on pregnancy

Maternal

Serious morbidity can result from inadequate or inappropriate treatment [11]. Death can result from aspiration of vomit or Wernicke's encephalopathy. The latter is due to vitamin B_1 (thiamine) deficiency and it has been reported in as many as 60% of HG patients [12].

Wernicke's encephalopathy is characterised by diplopia, abnormal ocular movements, ataxia and confusion. It may be precipitated by dextrose-containing fluids and total parenteral nutrition (TPN). The diagnosis may be confirmed by the finding of a low red-cell transketolase activity or a raised thiamine pyrophosphate effect. Magnetic resonance imaging (MRI) of the brain in acute Wernicke's encephalopathy may reveal symmetrical lesions around the aqueduct and the fourth ventricle. The recovery rate is only about 50%, if Korsakoff's psychosis has ensued.

Severe hyponatraemia and rapid correction with hypertonic saline can precipitate central pontine myelinolysis [11]. This is associated with the symmetrical destruction of myelin at the centre of the basal pons and it causes pyramidal tract signs, spastic quadriparaesis, psuedo-bulbar palsy and impaired consciousness. Other complications of hyperemesis include Mallory–Weiss oesophageal tears, protein and calorie malnutrition and other deficiencies of vitamins such as cyanocobalamin (vitamin B_{12}) and pyridoxine (vitamin B_6).

Foetal

Wernicke's encephalopathy is associated with a 40% incidence of foetal deaths. Infants of mothers with severe hyperemesis have significantly lower birth weight than infants of mothers with mild hyperemesis and those of the general population.

Management

The treatment of HG includes prompt rehydration with normal saline and the earliest administration of high-dose thiamine (150 mg daily orally or 100 mg weekly intravenously) to prevent Wernicke's encephalopathy [12]. Attention to nutrition is vital and occasionally TPN is required. Restoration of adequate nutrition usually improves liver biochemical abnormalities. Anti-emetics may play a part in the management of patients who do not respond to fluid and electrolyte replacement.

Dopamine agonists (metoclopramide and domperidone), phenothiazines (chlorpromazine and prochlorperazine) and antihistamines (cyclizine and promethazine) have all been shown to be safe [13]. H2 receptor antagonists have been used occasionally with some benefit. The use of the 5-hydroxytryptamine (5-HT_3) receptor blocker, ondansetron, has been reported to be safe in intractable hyperemesis. Continuous subcutaneous metoclopramide and ondansetron to treat nausea and vomiting during pregnancy therapy should remain experimental and its use restricted to intractable HG as more randomised controlled trials (RCTs) are needed and also due to cost implications [14].

Recent uncontrolled studies showed the successful use of oral prednisolone (40–60 mg daily) or intravenous hydrocortisone (100 mg twice daily) in HG [15,16]. Randomised controlled studies did not show a reduction in the need for rehospitalisation later in pregnancy [17,18]. In few case series, feeding via jejunostomy was found to be a potentially safe, effective and well-tolerated mode of nutrition support therapy in intractable HG [19].

In the recent years, there has been increased interest in alternative therapies, such as acupuncture and hypnosis [20,21]. With appropriate management, the outcome of pregnancy in HG is comparable to the general population. Termination of pregnancy is recommended only in extreme cases and, in our experience, we never had to resolve for this option. It is extremely important to assess these patients and prescribe venous thrombo-embolism (VTE) prophylaxis as there is increased risk of thrombo-embolic disease [22].

Reflux oesophagitis

Up to 80% of pregnant women may experience dyspepsia and heartburn at some stage during their pregnancy, mostly in the third trimester. Reflux is due to a combination of factors that may be worsened in late pregnancy by the enlarging uterus, including an increase in gastric pressure, reduction in lower oesophageal sphincter (LOS) tone, decrease in gastric peristalsis, delayed gastric emptying and a reduction in pyloric sphincter competence. Both oestrogen and progesterone may relax the LOS, which is also under the control of a variety of humoral agents including motilin, acetylcholine, noradrenaline, histamine, 5-HT and prostaglandins [23].

Antacids which are safe in pregnancy are the mainstay of treatment and may be used liberally. Most women will find that antacids taken before meals and at bedtime, together with avoidance of eating late at night and sometimes raising the head of the bed, will adequately control reflux symptoms. Acid-suppressing drugs are safe in pregnancy, including both H_2-receptor antagonists and omeprazole. Ranitidine is preferable to cimetidine as it does not interact with androgen receptors. Omeprazole may be even better at suppressing gastric acid, and a study of nearly 1000 infants with (mostly first-trimester) exposure to omeprazole *in utero* found no difference in the rate of congenital

malformations, perinatal survival, birth weight or Apgar score [24]. Metoclopramide and sucralfate are both useful and safe in pregnancy for reflux oesophagitis [25].

Peptic ulcer disease

Peptic ulcer disease is probably less common in pregnant women and the complications of bleeding and perforation are very rare. Ulcers which remain quiescent during pregnancy may cause recurrence of symptoms in the puerperium. Treatment includes advice on smoking cessation, H_2-receptor antagonists and proton pump inhibitors. Upper-gastrointestinal endoscopy is safe in pregnancy, if indicated [26]. Eradication therapy for *H. pylori* could be used if essential but can generally be postponed until after pregnancy. Misoprostol is contraindicated because of the risk of uterine contractions and spontaneous abortion [27].

Constipation

Constipation is a common symptom experienced by 40% of pregnant women, especially in early pregnancy. A recent prospective study showed that constipation measured using the Rome II criteria affects up to one-fourth of women throughout pregnancy and at 3 months post-partum [28]. The factors contributing to this are decreased colonic motility, poor fluid intake as a consequence of nausea and pressure on the rectosigmoid colon by the gravid uterus in the third trimester. Iron supplements may cause constipation but this is not dose-related and can usually be alleviated with simple medication. Oral iron should not be discontinued because of constipation. Management usually involves reassurance and advice about increasing fluid and fibre intake. Laxatives are rarely required but osmotic laxatives and bulking agents are safe and may be helpful in some women; it is recommended that they should be used only in the short term or used occasionally to avoid dehydration or electrolyte imbalances in pregnant women [29]. Few pilot studies have shown use of probiotic mixtures for treatment of constipation in pregnancy; further larger trials are necessary to recommend them in clinical practice [30].

Diarrhoea

Enteric infection

The incidence of gastrointestinal infections in pregnancy is not increased compared to that in non-pregnant individuals. There is very little literature on the severity or persistence of enteric infection in pregnancy and, in general, investigation and management are unchanged. *Salmonella enteritidis* and *Campylobacter jejuni* infections have been associated with foetal mortality due to transplacental passage of organisms and maternal mortality has also been reported [31,32]. There are currently no treatment recommendations for these infections in pregnancy, but reports of severe, sometimes fatal, infection might suggest that early use of antibiotic therapy might be appropriate.

Infection with *Listeria monocytogenes* is a well-recognised cause of intrauterine infection and perinatal death. The infection is acquired through eating foods contaminated with the organism and appropriate dietary advice should be given to all pregnant women about the avoidance of foods such as pâtés and soft and blue-veined cheeses. Clinicians must maintain a high index of suspicion for this infection, which can present with 'flu-like' symptoms and premature labour which is not infrequently associated with meconium-stained liquor. Once suspected, appropriate stool specimens for *Listeria* culture should be sent and empirical therapy with amoxicillin instituted [33,34].

Inflammatory bowel disease

Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC). Pregnancy has little effect on IBD. UC exacerbations are not frequent, occur early in pregnancy and are milder. CD may be associated with post-partum flare. Active disease is associated with increase in miscarriage, prematurity and low birth weight [35].

Management

Sulphasalazines, dihydrofolate-reductase inhibitors, are found to be safe for pregnancy and breast feeding, but folic acid 5 mg day^{-1} should be given periconceptionally and during pregnancy [36]. Prospective studies have revealed oral steroids such as prednisolone to be safe and effective [37]. The use of second-line immunosuppressive agents such as azathioprine and 6-mercaptopurine is relatively safe. There is extensive experience of the use of azathioprine in pregnancy in renal transplant recipients and patients with systemic lupus erythematosus and some data exist about its use in patients with severe IBD. There is no increase in congenital abnormalities or subsequent problems such as childhood malignancy in children followed up for up to 20 years [27]. Patients with complicated IBD, who require azathioprine to remain in remission, may elect to stay on the drug and it is safe as the foetus lacks the necessary liver enzyme to convert it to its active form. However, it is not recommended to start azathioprine or 6-mercaptopurine as a first-line approach during pregnancy. Retrospective studies and case reports have shown intravenous cyclosporine to be effective and safe in steroid-resistant UC and in some cases avoiding termination of pregnancy and colectomy [38,39]. Meta-analysis and prospective studies have shown benefit of using metronidazole peri-anal CD without evidence of teratogenesis. Experience with infliximab during pregnancy is limited; few retrospective studies have shown it be safe for mother and foetus [40]. Methotrexate is contraindicated in pregnancy. Patients with IBD are at an increased risk of recurrent VTE compared to patients without IBD. This disease was an independent risk factor for VTE recurrence (hazard ratio = 2.5; 95% confidence interval (CI): 1.4–4.2; $P = 0.001$) [41].

In women with IBD, pregnancy outcome is usually normal. Active disease is a definite adverse factor and a more serious concern than any risk of drug therapy. It is advisable for patients to aim for conception during remissions, as the outcome is good for both the mother and the baby. Women with IBD tend to deliver earlier than healthy women but can have a vaginal delivery in most cases. Caesarean sections are generally recommended for women with active peri-anal disease or after ileo-anal pouch surgery [42].

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is common and most patients who are pregnant will already be aware of their diagnosis. There are no abnormal findings on examination. Symptoms of IBS may be exacerbated by pregnancy, especially if constipation is the prominent feature. A high-fibre diet and stool-bulking agents may help some women. Antispasmodic agents such as hyoscine (Buscopan), dicyclomine (Merbentyl) and mebeverine (Colofac), which are widely used in the management of IBS, should be avoided in pregnancy. Few studies have suggested that preconceptional counselling is important as IBS increases the risk of miscarriage and ectopic pregnancy [43].

Abdominal pain

Abdominal pain is a common symptom in pregnancy. Acute abdominal conditions both related and unrelated to pregnancy can prove life-threatening for both mother and foetus. Delay in diagnosis of abdominal pain in the pregnant woman may result from mimicry of symptoms and signs of pregnancy-related conditions, a change in the usual presentation of abdominal disease and a reluctance to use radiological and endoscopic investigations during pregnancy. Ectopic pregnancy/miscarriage, constipation, cystitis and labour pains are the most common causes of abdominal pain but do not usually present diagnostic difficulty. Other conditions that can cause abdominal pain are listed in Table 1. There are concerns about the effect of anaesthetics and surgery on pregnancy and there is some evidence for an increase in spontaneous abortion (up to 25%) if surgery is performed in the first few weeks of pregnancy [44].

Appendicitis

Appendicitis is the most common non-obstetric indication for laparotomy in pregnancy. It usually occurs in the first two trimesters with an incidence of 1:2500–3500. Acute appendicitis during pregnancy often shows an aggressive progression with abdominal complications such as perforation,

Table 1
Causes of Abdominal pain in Pregnancy.

Obstetric Causes	Non Obstetric causes
Ectopic pregnancy/miscarriage	Ovarian cyst
Labour	Constipation
Placental abruption	Pyelonephritis, Cholecystitis, Pneumonia
Uterine fibroids	Appendicitis, Pancreatitis, Peptic ulcer
Ligamentous pain	Renal Colic
HELLP Syndrome/Acute fatty liver of pregnancy	Diabetic Ketoacidosis/Hypercalcaemia

wall abscess and paralytic ileus. Perinatal mortality occurs in about a fifth of cases with perforation. Increased risks were observed for having low birth weight, pre-term infants, small-for-gestational-age babies and congenital anomalies among women with acute appendicitis during the first and second trimesters of pregnancy [44].

Clinical features and investigations

Women commonly present with abdominal pain accompanied by rebound tenderness, nausea and vomiting. A raised white cell count ($>15 \times 10^6$) and granulocytes >87% are risk factors for perforation. High-resolution ultrasonography has improved the diagnostic accuracy and reduced the negative laparotomy rate in suspected appendicitis [45]. The inflamed appendix is characterised by an outer diameter of >6 mm, non-compressibility and lack of peristalsis or the presence of a periappendiceal fluid collection. These criteria are 82% sensitive and 100% specific. According to the American College of Radiology appropriateness criteria, ultrasound of the right lower quadrant with graded compression is the most appropriate initial imaging test in suspected appendicitis in a pregnant patient, especially during the first and early second trimester. If ultrasound is non-diagnostic, MRI (if available), which lacks ionisation radiation, is more appropriate than computed tomography (CT) for abdominal pain. The additional advantage of MRI is its usefulness in identifying conditions that may mimic acute appendicitis in pregnant patients, such as obstructing urinary tract calculi, pyelonephritis, adnexal and ovarian pathology, gallbladder disease, small-bowel obstruction and other gastrointestinal conditions [46]. Studies have shown that early diagnosis and early intervention can avoid the morbidity associated with delayed diagnosis [47].

Management

If diagnosis is confirmed, surgical treatment is the best option. In RCTs, there were no significant differences between the laparotomy and laparoscopy groups in terms of clinical characteristics, hospital stay, haemoglobin change, return of bowel activity, complication rates, gestational age at delivery and birth weight. However, there were significantly shorter operating time and less use of postoperative analgesics in laparoscopy groups [48]. Case reports with single-port laparoscopic appendectomy (SP-LA) using Gelport access for the treatment of acute appendicitis in pregnant women have been documented [49].

Gallbladder disease

Asymptomatic gallstones are present in 2.5–11% of pregnant women and cholecystitis occurs in about 0.1% of pregnancies. Multiparity, overweight and increasing age are considered risk factors for gallstone development. Biliary sludge has been detected in studies on ultrasound in up to a third of pregnant women but does not usually cause symptoms.

Pathogenesis

Pregnancy increases cholesterol saturation of bile, the ratio of cholic acid to chenoxycholic acid and the rate of secretion of cholesterol. It also decreases gallbladder motility with the net result of increased bile lithogenicity. Both gallbladder stasis and stone/sludge formation may disappear after pregnancy.

Clinical features

The clinical features of gallbladder disease in pregnancy are similar to those in non-pregnant individuals. They include pain in the right-upper quadrant or epigastrium, nausea and vomiting and in acute cholecystitis, tenderness and guarding in the right hypochondrium, fever and shock depending on the degree of sepsis. Pancreatitis and jaundice secondary to oedema or stones in the common bile duct may also occur.

Diagnosis

Ultrasound usually provides a safe and accurate method of detecting gallstones. A diagnosis of acute cholecystitis is suggested if ultrasound findings show gallstones, pericholecystic fluid with distension and thickening of the gallbladder wall, in addition to right hypochondrial tenderness, a raised white blood cell count and abnormal liver function tests (LFTs). A twofold raised amylase is also consistent with the diagnosis, although greater rises suggest pancreatitis or common bile duct stones. Abdominal ultrasonography is insensitive for the detection of common bile duct stones. MRI is not associated with known adverse effects and seems to be an excellent diagnostic modality in this context. Paramagnetic contrast agents have been associated with increased spontaneous abortion rates and other abnormalities in animals and should only be used when absolutely necessary. Endoscopic ultrasonography is highly accurate for the detection of common bile duct stones and may be useful before consideration of endoscopic retrograde cholangiopancreatography (ERCP) in select patients [50].

Management

The management is the same as in non-pregnant patients. Conservative management, with withdrawal of oral food and fluids, nasogastric aspiration, intravenous fluids, antibiotics and analgesia, leads to resolution of symptoms in over 75% of women. In those with severe symptoms of cholecystitis who do not settle, laparoscopic cholecystectomy has been reported to be safe for mother and foetus. Delaying cholecystectomy for the hospitalised pregnant patient with gallbladder disease results in increased short- and long-term morbidity. There was a high loss to follow-up among patients who were observed during pregnancy. By contrast, cholecystectomy during pregnancy resulted in a low rate of complications [51].

The second trimester seems to be the safest time to perform surgery, as organogenesis is complete and the incidence of spontaneous miscarriage is lower. ERCP, followed by sphincterotomy and stone extraction, is very effective and can be performed safely during all trimesters of pregnancy with a premature delivery rate $<5\%$. All efforts to minimise radiation exposure should be undertaken. These include lead shielding and avoiding hard-copy radiographs. When possible, category B (such as meperidine) or C drugs only should be used for sedation during pregnancy. Therapeutic ERCP is now the standard of care for treating choledocholithiasis during pregnancy. Endoscopic sphincterotomy for symptomatic patients with normal cholangiograms is controversial. Consideration of ERCP demands a judicious approach, paying careful attention to the risks and benefits of intervention [52].

Pancreatitis

Pancreatitis is an uncommon gastrointestinal disorder seen in pregnancy. The most common cause of pancreatitis is usually biliary pancreatitis, often mild, occurring in the third trimester. Other causes include alcohol and, rarely, hypertriglyceridaemia and primary hyperparathyroidism [53]. The clinical features are similar to those in non-pregnant patients and include epigastric pain, nausea and vomiting and in severe cases cardiac, renal, pulmonary and gastrointestinal complications. Serum amylase (not affected by pregnancy) is invariably raised with levels >1000 U l^{-1}. There is no specific cure for pancreatitis and the management is exactly as in a non-pregnant patient, according to Ranson's criteria (Table 2); severe acute pancreatitis in pregnancy usually occurs in the third trimester, and the affected severe patients are more liable to develop a critical condition that results in a higher risk of intrauterine foetal death [54].

Management should be supportive and usually involves intravenous fluids, analgesia and fasting with nasogastric suction in the presence of intestinal obstruction. Endoscopic removal of stones and stent drainage can, in exceptional circumstances such as the presence of a common bile duct stone, be

Table 2
Ranson criteria for predicting the severity of acute pancreatitis.

At admission:
1. Age in years >55 years
2. White blood cell count >16000 cells/mm^3
3. Blood glucose >10 mmol/L (>200 mg/dL)
4. Serum AST >250 IU/L
5. Serum LDH >350 IU/L

Within 48 hours:
1. Calcium (serum calcium <2.0 mmol/L (<8.0 mg/dL)
2. Hematocrit fall >10%
3. Oxygen (hypoxemia P_{O2} < 60 mmHg)
4. BUN increased by 1.8 or more mmol/L (5 or more mg/dL) after IV fluid hydration
5. Base deficit (negative base excess) >4 mEq/L
6. Sequestration of fluids >6 L

Interpretation
- If the score ≥3, severe pancreatitis likely.
- If the score <3, severe pancreatitis is unlikely

Or
- Score 0 to 2: 2% mortality
- Score 3 to 4: 15% mortality
- Score 5 to 6: 40% mortality
- Score 7 to 8: 100% mortality

performed safely by an experienced operator with minimal or no radiation to the foetus. It is preferable to defer sphincterotomy, which may require considerable screening time, until after delivery [54].

Liver disease

Normal physiological changes

Pregnancy is associated with increased liver metabolism. There is a 20–40% fall in serum albumin with a concomitant fall in total serum protein probably due to the increase in total blood volume as depicted in Table 3. There is a dramatic increase in fibrinogen and alkaline phosphatase concentrations but no significant change in bilirubin concentration. A fall in the upper limit of the normal ranges for alanine transaminase (ALT; serum glutamic pyruvic transaminase, SGPT) and aspartate transaminase (AST; serum glutamic-oxaloacetic transaminase, SGOT) occurs throughout pregnancy (Table 2). The concentrations of other liver enzymes are not significantly altered. Post-partum levels of AST increased by up to 230% on days 2–5, of ALT by up to 280% on day 5 and of gamma glutamyl transferase (GGT) by 150% on days 5–10.

The physiological changes of normal pregnancy result in signs and laboratory results which mimic abnormalities that are usually associated with liver disease in non-pregnant individuals. Up to 60% of pregnant women may exhibit spider naevi or palmar erythema. Serum albumin drops from a mean of

Table 3
Physiologic changes during pregnancy.

Increased
Blood volume and cardiac output rise by 35%–50%
Alkaline phosphatase levels rise threefold or fourfold due to placental production
Clotting factor changes create a hypercoagulable state
Decreased
Gallbladder contractility
Hemoglobin
Uric acid levels
Albumin, total protein, and antithrombin III concentrations
No change
Liver aminotransferase levels (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase)
Bilirubin level, Prothrombin time

42 to 31 g l^{-1} in late pregnancy and serum alkaline phosphatase levels rise to two to four times the normal range after the fifth month of pregnancy. Alkaline phosphatase levels are therefore not useful in the assessment of liver disease in pregnancy. Other liver enzymes remain normal, and in fact transaminases, bilirubin and gamma glutamyl transaminase levels are lower than the expected non-pregnant laboratory ranges in uncomplicated pregnancy [55]. An increase in any of these markers may reflect hepatobiliary pathology.

Liver disease in pregnancy is extremely important and the liver diseases specifically associated with pregnancy may be life threatening for mother and foetus and subsequently the surviving child. Some liver diseases such as viral hepatitis may be more severe in pregnancy and although pregnancy is rare in patients with pre-existing severe chronic liver disease, it is increasingly common in post-transplant patients. The pattern of liver biochemistry abnormalities may be helpful in the diagnosis, as in a non-pregnant patient, provided the physiological changes produced by pregnancy are appreciated [56].

Conditions causing jaundice and abnormal liver biochemistry in pregnancy

HG presents in the first trimester and rarely may persist throughout gestation. Abnormal liver biochemistry is found in up to 50% of women hospitalised with hyperemesis.[57] The bilirubin is mildly elevated ($<$70 μmol l^{-1}) but obvious jaundice is rare. The liver biochemistry abnormalities are thought to be due to malnutrition and impaired excretion of bilirubin but improve dramatically when adequate nutrition is restored. Liver biopsy is not required for diagnosis in this condition, but when performed, it has been reported to be normal or may show fatty change.

Acute fatty liver of pregnancy

Acute fatty liver of pregnancy (AFLP) is a condition of the third trimester, presenting after 30 weeks gestation (mean 36 weeks) and has never been reported in the first trimester of pregnancy. It is rare (1:9000–13,000 pregnancies), but essential to recognise as it is potentially fatal for both mother (20–30% mortality) and foetus (20–50% mortality), especially if diagnosis is delayed [58]. AFLP is most common in first pregnancies and in multiple pregnancies, like pre-eclampsia. It is also more common in mothers carrying male foetuses. Early recognition and appropriate management are crucial in giving both mother and baby any chance of survival. The initial symptoms are vague comprising nausea, anorexia and malaise. More severe vomiting (in 70%) and upper abdominal discomfort or pain (50–80%) may develop. There are often mild co-existing features of pre-eclampsia. These symptoms should alert clinicians to the possibility of AFLP [59]. Jaundice appears 1–2 weeks after the onset of these symptoms and is usually associated with a three- to 10-fold elevation in transaminases. Fulminant hepatic failure with all its sequelae may develop rapidly. (Table 4)

In at least some women, AFLP is a metabolic disorder, and there is a recognised association between AFLP and long-chain 3-hydroxyacyl coenzyme A dehydrogenase (LCHAD) deficiency, a disorder of mitochondrial fatty acid oxidation [60]. A woman who is heterozygous for LCHAD deficiency may develop AFLP if carrying a foetus homozygous for the defect [61]. The mechanism of hepatocellular damage is still unclear but possibly involves the affected foetus producing abnormal fatty acid metabolites. These enter the mother's circulation and overwhelm the mitochondrial oxidation machinery in the heterozygous mother, who is already stressed by the increased demand for fatty acid oxidation in late pregnancy. This results in microvesicular steatosis and liver failure [62]. AFLP appears to occur only

Table 4
Reference range for LFT in pregnancy.

Tests	Non preg	1st trim	2nd trim	3rd trim
AST u/l	7–40	10–28	11–29	11–30
ALT u/l	0–40	6–32	6–32	6–32
Bili umol/l	0–17	4–16	3–13	3–14
GGT u/l	11–50	5–37	5–43	5–41
Alkphos u/l	30–130	32–100	43–135	130–418

in association with certain mutant LCHAD alleles. In affected individuals, the risk of recurrent AFLP is 25% or greater. The baby born from a pregnancy complicated by AFLP should undergo urgent metabolic screening for LCHAD deficiency as this can result in sudden death, cardiomyopathy, skeletal myopathy or fulminant hepatic failure in infancy.

The diagnosis of AFLP is a clinical one. Hypoglycaemia and hyperuricaemia may be prominent features. The liver is not enlarged. There is characteristically a raised white cell count ($>15 \times 10^9\ l^{-1}$), a low albumin and evidence of disseminated intravascular coagulation. Hepatic steatosis can sometimes be visualised by ultrasound and possibly also CT or MRI [63]. The 'gold' standard for diagnosis is liver biopsy with staining for microvesicular fatty change, but this is rarely performed. The management of AFLP involves expeditious delivery, which usually results in dramatic recovery of the mother. Hypoglycaemia and coagulopathy need to be treated aggressively prior to delivery, and the sick patient needs to be managed in an intensive care setting. It is crucial in particular to pay attention to the hypoglycaemia as it is the major cause of maternal death. It is important to note that the critical state continues for days after delivery, requiring intense and close monitoring. The development of hepatic failure requires transfer to a liver unit for assessment for transplantation [64,65].

HELLP syndrome

The HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) is one of several crises which can develop as a variant of severe pre-eclampsia. It is associated with endothelial cell injury and microangiopathic platelet activation and consumption. HELLP syndrome occurs in 4–20% of pre-eclamptic pregnancies, although up to 50% of women with pre-eclampsia have mildly abnormal liver biochemistry without the full-blown HELLP syndrome. There is increased maternal (1%) and perinatal mortality (approximately 35%) [66].

There is significant maternal morbidity from placental abruption (16%), subcapsular liver haematoma, acute renal failure, massive hepatic necrosis and liver rupture. Clinical features include right-upper-quadrant pain (65%) with nausea and vomiting (35%). The liver may be enlarged and tender. There may be features of pre-eclampsia although the HELLP syndrome may be the first manifestation of pre-eclampsia. By our experience, we recommend following the Mississippi Criteria for classification of the HELLP syndrome for ease of management (Table 5) [67]. There is a low-grade haemolysis, rarely with severe anaemia and a low platelet count (usually $<100 \times 10^9\ l^{-1}$). Serum bilirubin and transaminases are mildly elevated (mean 150 U l^{-1}); higher levels are suspicious of hepatic infarction or subcapsular haematoma. Serum lactate dehydrogenase is also raised. In some patients, the platelet count falls below $30 \times 10^9\ l^{-1}$ and disseminated intravascular coagulation develops. The differential diagnosis of the HELLP syndrome includes AFLP, haemolytic uraemic syndrome and thrombotic thrombocytopaenic purpura [67].

Ultrasound may be useful in excluding other diagnoses such as hepatic haematoma or biliary disease. Liver biopsy has rarely been performed in this syndrome, because of the coagulopathy. Liver histology is similar to that in pre-eclampsia with periportal and sinusoidal fibrin deposition

Table 5
Main diagnostic criteria of the HELLP syndrome.

Class	Mississippi classification
1	Platelets $\leq 50\ 10^9$/L AST or ALT ≥ 70 IU/L LDH ≥ 600 IU/L
2	Platelets $\leq 100\ 10^9$/L $\geq 50\ 10^9$/L AST or ALT ≥ 70 IU/L LDH ≥ 600 IU/L
3	Platelets $\leq 150\ 10^9$/L $\geq 100\ 10^9$/L AST or ALT ≥ 40 IU/L LDH ≥ 600 IU/L

and haemorrhage. Hepatic necrosis and subcapsular haemorrhage may occur. Prompt delivery is indicated especially if there is severe right-upper-quadrant pain and tenderness suggesting liver capsule distension and risk of liver rupture. Aggressive correction of the coagulopathy in woman with frank evidence of disseminated intravascular coagulation (about 20%) and attention to the blood pressure are important prior to delivery. Use of steroids has been controversial [68]. To date, there is insufficient evidence of benefits in terms of substantive clinical outcomes to support the routine use of steroids for the management of HELLP. The use of corticosteroids may be justified in clinical situations in which increased rate of recovery in platelet count is considered clinically worthwhile [68]. Patients may initially deteriorate in the 48 h after delivery before improvement is observed post-partum and 30% of cases of the HELLP syndrome present post-partum [69]. These women are at particular risk of pulmonary oedema and renal failure. Recovery is usually rapid and complete but there is a significant risk (up to 25%) of pre-eclampsia and its sequelae in future pregnancies. Risk of recurrent HELLP syndrome is low [70]. For women with existing essential hypertension that predates the pregnancy complicated by the HELLP syndrome, the risk of pre-eclampsia in subsequent pregnancies is about 75% and hence preconceptional counselling is important [71].

Obstetric cholestasis

Obstetric cholestasis (OC), previously known as intrahepatic cholestasis of pregnancy, usually presents in the third trimester (mean gestational age 30 weeks). The pathogenesis is unknown but the disease runs in families, possibly with an autosomal dominant inheritance. A positive family history may be found in about 30% of patients; carriership of LCHAD deficiency has been reported to be associated with an increased risk of OC and the gene is located in the p23 region of chromosome 2 [72].

These individuals may also have a history of cyclical itching during the menstrual cycle and cholestasis with the oral contraceptive pill; hence, a disorder of handling of oestrogens is hypothesised. This is possibly due to a decrease in the sulphation of bile acids in the presence of excess oestrogen and/or a decrease in hepatocyte membrane fluidity, possibly correlated with a defect in the methylation of membrane phospholipid and a modification in the cholesterol:phospholipid ratio. There is also some evidence that hepatitis C and G infections may predispose women to OC.

Effect on mother and foetus

Malabsorption of fat-soluble vitamins may lead to vitamin K deficiency and coagulopathy and there is an increased risk of post-partum haemorrhage. OC is associated with an increased risk of premature labour (12–44%) and stillbirth, as well as foetal distress, foetal passage of meconium and foetal intracranial haemorrhage [73]. The rates of foetal growth restriction, post-partum haemorrhage and pre-eclampsia in OC are almost the same as those of the normal pregnancy. Routine foetal heart-rate-monitoring methods cannot predict foetal death. The important measures to decrease the perinatal mortality include paying attention to foetal monitoring when threatened premature labour, occasional uterine contractions and prenatal meconium occur, and at the early stage of labour, and management of threatened premature labour and timely intervention of pregnancy (at the gestation period of 34–37 weeks) [27].

Foetal mortality is reported as around 2–4% [27]. The risk of adverse events to the foetus is possibly related to the maternal serum bile acid (SBA) concentration and high levels of bile acids have been found in amniotic fluid and the foetal circulation. Foetal asphyxia due to the vasoconstrictive effects of bile acids has been postulated [74]. It is however, very difficult to predict foetal compromise and extremely close surveillance of mother and foetus is required once the diagnosis has been made. Meconium staining of the amniotic fluid obtained at amniocentesis is an important indicator of risk to the foetus. The data indicate that the foetal stress-responsive system is stimulated in mild OC, but it is suppressed in severe OC, which might contribute to the occurrence of unpredictable sudden foetal death. Further studies are warranted to explore the role of impaired foetal adrenal function in the pathogenesis of OC and the clinical implications [75].

Clinical features

The major symptom of OC is severe pruritus affecting the limbs and trunk and particularly the palms and soles. Insomnia due to nocturnal pruritus and malaise may be associated, but there is no rash. There may be other features of cholestasis with dark urine, pale stools and anorexia. Jaundice develops in a small percentage of women, 1–4 weeks after the onset of pruritus. The symptoms persist until delivery and resolve quickly afterwards.

Investigations

Liver biochemistry is abnormal. Serum bilirubin levels may be elevated ($<$100 μmol l^{-1}), alkaline phosphatase is higher than that expected in pregnancy (around four times of normal) and ALT levels, which are the most sensitive of the conventional markers, are 2–10 times of normal. An elevated GGT occurs in less than one-third of patients with OC in the UK and, when present, is associated with greater impairment of LFT but no difference in gestational age at onset. Treatment with ursodeoxycholic acid (UDCA) appears to be safe and significantly improves LFT in patients with OC, with the exception of bile acids in the high GGT group. If measured, total SBAs are increased 10–100 times and maybe the first or only biochemical abnormality detected [76,77]. This test is of limited availability but may occasionally be useful to confirm the diagnosis. Mild OC is defined as SBA levels of 10–39 μmol l^{-1} and severe OC is 40 μmol l^{-1}. Liver biopsy is rarely performed but shows cholestasis with minimal or no inflammatory changes. An ultrasound should be performed to exclude common bile duct stones as a cause of the cholestasis.

Management

Vitamin K 10 mg orally, daily, should be prescribed to pregnant women with OC from 34 weeks as there is vitamin K deficiency leading to post-partum haemorrhage. Active third stage of labour is recommended in these patients [85]. Oral vitamin K should also be given to the neonate at delivery. Antihistamines such as chlorpheniramine, terfenadine or promethazine may be used for pruritus.

Recent data suggest that UDCA is currently the most effective pharmacologic treatment, whereas obstetric management is still debated. Clinical trials are required to identify the most suitable monitoring modalities that can specifically predict poor perinatal outcome [78].

At least one controlled trial has confirmed the efficacy of UDCA, which is a choloretic agent, but UDCA is not licensed for use in pregnancy although there is no evidence of adverse effects in the foetus [79]. Early-term delivery does not seem to be associated with increased incidence of caesarean section and large trials are needed in future to determine foetal benefits or risks of treatment of pregnant women with OC with UDCA. UDCA is more effective than S-adenosyl-L-methionine at improving the concentration of SBAs and other tests of liver function, whereas both therapies are equally effective at improving pruritus [81]. Dexamethasone yielded no alleviation of pruritus or reduction of ALT and was less effective than UDCA at reducing bile acids and bilirubin. In conclusion, 3 weeks of UDCA treatment improved some biochemical markers of OC irrespective of disease severity, whereas significant relief from pruritus and marked reduction of SBAs were only found in patients with severe OC [79,80]. Recent meta-analysis have showed that rifampin is also effective in controlling pruritus in 77% of patients, at least over the short term [82]. Few case reports have reported the use of plasmapheresis in the treatment for severe cholestasis not responding to medical treatment [83]. It is our practice to offer induction of labour at 37 weeks gestation if the bile acid level is $>$40 μmol l^{-1} and after 37 weeks if $<$40 μmol l^{-1}. However, in rare severe cases with very high levels an individual assessment and approach determines the timing of delivery.

OC recurs in subsequent pregnancies in most women (60–70%). Those who have had OC should be advised to avoid oestrogen-containing oral contraceptives but not hormone replacement therapy [84].

Hepatitis

Worldwide, acute viral hepatitis is the most common cause of liver disease in pregnancy. The clinical features of these diseases are similar to those in non-pregnant individuals. There is evidence that hepatitis E, herpes simplex hepatitis and possibly hepatitis A are more severe in pregnancy, especially if acquired in the third trimester and may more commonly lead to fulminant hepatic failure.

Some studies have shown pre-term labour in women with hepatitis A and hepatitis A virus (HAV) serology and maternal vaccination during pre-pregnancy evaluation should be considered in areas of the world in which susceptible adult populations exist [86]. Recent studies in southern Asia have suggested hepatitis E vaccine to prevent maternal deaths due to the hepatitis E virus (HEV) [87]. Pregnant women with jaundice and acute viral hepatitis caused by HEV infection appear to have worse obstetric and foetal outcomes compared to pregnant women with jaundice and acute viral hepatitis due to other causes and a case fatality rate of 20% [87]. Because of this risk, such women should carefully consider the risk of travel to endemic areas. HEV can cause acute hepatitis in the newborn and may be transmitted *in utero* to the foetus [88]. The risk from HEV, which seems to have a predilection for pregnant women, and from the herpes simplex virus, is particularly high probably due to altered T-cell function in pregnancy.

Herpes simplex virus hepatitis is extremely rare and may be diagnosed using serology and histology from liver biopsy, which shows specific changes with extensive focal haemorrhagic necrosis and intranuclear inclusion bodies. Acyclovir is helpful if the disease is recognised at an early stage but the prognosis for mother and foetus is extremely poor if there is systemic hepatitis, which leads to fulminant hepatic failure [89].

Cytomegalovirus, Epstein–Barr virus and adenoviruses can cause hepatitis in association with systemic infection, which are usually self-limited, requiring only supportive care. However, transmission to the foetus can occur.

Auto-immune chronic active hepatitis

This form of chronic active hepatitis is more common in women, particularly in the second and third decades of life, producing the most severe forms of the disease, but it can also be mild. The onset is usually insidious with fatigue, anorexia and jaundice but can also be acute, resembling viral hepatitis. Pregnancy may be uncomplicated in patients with mild, treated, auto-immune chronic active hepatitis, but there is some evidence that this group of patients has an increased risk of pre-eclampsia, prematurity and foetal wastage [90]. Immunosuppressive therapy with steroids alone or in combination with azathioprine results in remission of the disease and therapy should be continued throughout gestation to prevent relapse.

Primary biliary cirrhosis

This disease affects predominantly women, usually in middle age. The cause is unknown but immune reactions causing liver damage are suspected. Primary biliary cirrhosis (PBC) may be diagnosed outside pregnancy on routine testing of liver function with elevated levels of alkaline phosphatase (liver isoenzyme) and gamma glutamyl transpeptidase. Diagnosis is usually confirmed by detection of mitochondrial antibodies. Maternal and foetal outcomes are variable, but the prognosis is good for well-compensated disease. Drug therapy is nonspecific and aimed at relieving symptoms such as pruritus. UDCA (Food and Drug Administration (FDA) category B) at doses of 10–13 mg kg^{-1} is the treatment of choice for PBC and may be continued during pregnancy and breast feeding. Extracorporeal albumin dialysis has been suggested in some studies for prolonged relief of intractable pruritus in-patients with PBC [91].

Wilson's disease (hepato-lenticular degeneration)

This is a rare but important disease in which there is abnormal copper metabolism with an increase in the total body copper and copper deposition and damage in several organs. It is inherited as autosomal recessive. Hepatic disease occurs in childhood and early adolescence, while neurological damage of the basal ganglia occurs in later adolescence. Other manifestations include haemolysis, renal tubular acidosis and osteoporosis.

Therapy with copper chelators such as penicillamine and trientene results in remission of hepatic complications of Wilson's disease. Young women should continue the use of these drugs during pregnancy as interruption of treatment during pregnancy has resulted in fulminant liver, haemolytic

anaemia and maternal death. Intrauterine growth restriction (IUGR) and pre-eclampsia have been shown in these patients, hence the need for regular antenatal follow-up. D-Penicillamine and trientene have been used during pregnancy. However, the dosage should be reduced to the minimum necessary dose, which is about 25–50% of the dose. Few studies have shown zinc to be the agent of choice for Wilson's disease during pregnancy because of its safety for the foetus. It should be maintained throughout the pregnancy at 50 mg three times a day [92–94].

Portal hypertension

Cirrhotic chronic liver disease of all aetiologies is generally associated with infertility but if conception occurs, variceal bleeding has been reported to be a common complication in patients with portal hypertension, especially in the second and third trimesters. It is uncertain whether variceal haemorrhage is more common during pregnancy because pregnancy is so rare in cirrhotic women. Due to the substantial maternal and foetal risks, pregnancy should be avoided in women with advanced cirrhosis and portal hypertension. Few case reports of successful pregnancies in these patients have been reported [95,96]. Patients with portal hypertension, who are stabilised on propranolol, should be advised not to stop their medication as there is an increased risk of variceal bleeding on stopping the drug. The risk to mother and foetus from the mortality of variceal bleeding far outweighs the risk of continuing beta-blocker therapy. There may be decompensation of the liver disease, although this has generally been reported to improve after delivery. Treating bleeding oesophageal varices with variceal band ligation and octreotide is safe and effective during pregnancy [96].

Budd–Chiari syndrome

This syndrome is defined as obstruction of the large hepatic veins which produces congestion and necrosis of the centrilobular areas of the liver. The main mechanism for obstruction is thrombosis of hepatic veins or the intrahepatic or suprahepatic portion of the inferior vena cava. The onset of this syndrome is near term or within the 2 months following delivery [97,98]. There is a recognised association with antiphospholipid syndrome, factor V Leiden mutation, and myeloproliferative disorder [99]. It is characterised by abdominal pain, hepatomegaly and ascites. Proper diagnosis and management require imaging studies such as Doppler ultrasonography, CT and liver biopsy [100]. Treatment with anticoagulants, thrombolytics (warfarin is contraindicated in pregnancy), diuretics and portocaval shunting may be required. Liver transplantation is indicated when hepatic decompensation develops [101]. In the literature, the severity of organ damage has been classified as acute, sub-acute and chronic depending on the duration of onset of signs and symptoms.

The UK End-stage Liver Disease (UKMELD) or Model for End-Stage Liver Disease (MELD) score has been used to describe the extent of liver damage [104].

In general, the prognosis for pregnancy is poor. Lower UKMELD scores are associated with better outcome in pregnant women and also less recurrence in the post-partum period. However, individual cases have been reported without maternal complications. Successful pregnancies have been reported following grafting [102,103]. As such, patients who have received medical management alone may have a better outcome for pregnancy than those requiring surgical or radiological intervention. Obstetric care must be carefully planned in conjunction with a specialist liver team. Following delivery, oral contraceptives are contraindicated following grafting because the coagulation disorder remains [104].

Liver transplantation

After liver transplantation, fertility may return to normal. Delaying conception until at least 24 months after transplantation is advised to allow for stabilisation of the immunosuppressive regimen and to assure that the transplanted organ is functioning well [105]. Pregnancy in liver transplant recipients has been reported to be frequently complicated by pre-term delivery, pre-eclampsia and infection and gestational diabetes [106]. Immunosuppressive drugs must be continued throughout

pregnancy in these patients with careful monitoring of drug levels, although there is no evidence of teratogenesis with tacrolimus. These patients and their partners therefore require careful advice about contraception, preconception counselling and monitoring in a specialised unit during their pregnancy [107].

Although pregnancy does not increase the risk of maternal mortality in liver transplant recipients, these women should be aware of their prognosis for long-term survival and ability to care for a child.

Summary and recommendations

Gastrointestinal and liver disease may make a pregnancy a high-risk one. Extreme vigilance is needed to detect early signs and symptoms of liver and gastrointestinal dysfunction and to distinguish these from the anticipated physiological changes that may occur in pregnancy. Prompt management can lead to better outcomes for both mother and baby. Management of these disorders requires a concerted effort between the primary care physician, liver and gastrointestinal specialists, obstetrician and, on rare occasions, a liver transplant team.

Conflict of interest

None.

Practice points

- The main risk in hyperemesis is from Wernicke's encephalopathy, which may result from thiamine deficiency; hence, thiamine supplementation should be given to all women admitted with hyperemesis.
- There were three HG-related deaths in the Confidential Enquiry into Maternal Deaths in the UK (1991–1993), one related to VTE; hence, there is need for risk assessment at admission.
- Adequate and appropriate (normal saline) fluid and electrolyte replacement is the most important component of management.
- The common anti-emetics are not teratogenic.
- Pregnancy does not usually affect the course of IBD and symptoms generally remain stable if present at conception.
- Both Salazopyrin and corticosteroids are safe to use in pregnancy and whilst breast feeding. Newer drugs such as infliximab have found to be safe in larger trials.
- Elective caesarean section is not usually necessary even in women with ileostomies, except for obstetric indications or in women with peri-anal Crohn's disease.
- Elevated liver function tests can signal gallbladder disease; ultrasound is the initial method of choice for diagnosis.
- Surgical and gastrointestinal consultation should be taken at the earliest possible time.
- AFLP is rare, but potentially fatal. Consider the diagnosis especially if there is severe vomiting and abdominal pain.

Research agenda

- Regarding HG, the pathology is still not clear; further molecular studies should guide clinicians in managing HG.
- In HG, newer routes of medications and alternative therapy need further evaluation.
- Outpatient management of HG needs to be encouraged to reduce the cost of treatment.

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