Hyperemesis, gastrointestinal and liver disorders in pregnancy

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Kylie Gilmore

Abstract
Pregnant women may be affected by diseases of the gastrointestinal tract or liver. These disorders can be related or unrelated to pregnancy. Conditions unrelated to pregnancy can be pre-existing or co-incident. These diseases have varying effects on obstetric outcome. Severe liver disease in pregnancy is rare. We present some common gastrointestinal and liver disorders focussing on the diagnosis, management and effects on pregnancy outcomes.

Keywords AFLP; appendicitis; Crohn’s disease; HELLP; hepatitis; hyperemesis gravidarum; obstetric cholestasis; pancreatitis; pregnancy; ulcerative colitis

Overview
There are a number of normal physiological and biochemical changes associated with the liver and gastrointestinal tract in pregnancy.

Liver – pregnancy is associated with an increase in liver metabolism. Blood changes include a raised alkaline phosphatase due to placental production, albumin is reduced (although some of this is dilution due to increased blood volume in pregnancy), fibrinogen is increased. Other liver enzymes are within normal prepregnancy ranges.

Gastrointestinal – relaxation of smooth muscle in pregnancy results in decreased gut motility and consequent increased bowel transit times and constipation. There is also relaxation of the gastro-oesophageal sphincter which can result in gastric reflux, nausea and vomiting.

Pregnancy related gastrointestinal diseases

Hyperemesis
Nausea and vomiting affects up to 50% of pregnancies, however, hyperemesis only affects 0.5–1% of pregnancies. Hyperemesis is defined as severe protracted nausea and vomiting, which results in dehydration, ketosis and weight loss. It commonly starts between 6 and 12 weeks gestation and corresponds with the human chorionic gonadotrophin (HCG) rise. HCG shares a common subunit with thyroid stimulating hormone (TSH), thus causing an increase in levels of thyroxine and a drop in TSH (i.e. a biochemical hyperthyroidism). It has been suggested that this may be causative for the nausea and vomiting. Severe vomiting occurring for the first time after 12 weeks should have other potential causes investigated (such as urinary tract infection, Addison’s disease, pancreatitis).

Investigations: initial investigations are listed in Table 1. Fifty per cent of cases will have abnormal LFTs (rise in transaminases and bilirubin—although no clinical jaundice) and 66% a rise in TFTs. Both should resolve with treatment. If there are concerns about true thyrotoxicosis, a history of symptoms pre-pregnancy, presence of thyroid stimulating antibodies and presence of thyroid eye disease, make this a more likely diagnosis.

Hyperemesis conveys a number of risks to the mother and fetus (Table 2).

Management: this revolves around intravenous fluid resuscitation and electrolyte balance. Care must be taken to not correct hyponatraemia too quickly as this will precipitate central pontine myelinolysis (consequently 0.9% normal saline is recommended and not double strength normal saline). It is also best to avoid dextrose containing fluids initially as these may precipitate Wernicke’s encephalopathy.

Vitamin B1 (thiamine) should be supplemented to prevent Wernicke’s encephalopathy. Thrombosis prophylaxis also needs to be instituted. Regular antiemetics, such as dopamine antagonists (metoclopramide), Phenothiazines (prochlorperazine), antihistamines (cyclizine) or selective 5HT3 antagonist (ondansetron) should be charted. If dyspeptic symptoms are an issue, the use of histamine receptor blockers (ranitidine) or protein pump inhibitors (omeprazole) is warranted.

Refactory cases may respond to corticosteroids. If malnutrition is an issue then use of enteral feeding or total parental nutrition may also be required. Dietician involvement should be sought early.

The normal course of hyperemesis is improvement with gestation, with the majority having resolved by midgestation. Due to the nature of hyperemesis presenting in the first trimester it is also important to ensure usual antenatal cares and early education is given. (For example, ensuring appropriate folic acid supplementation and access to chromosomal screening tests.)

Obstetric cholestasis
Obstetric cholestasis can affect 0.5–2% of pregnancies. It presents normally in the third trimester with severe pruritus (particularly of the palms and soles of feet), without a rash and with deranged LFTs and bile acids. There appears to be a genetic element with 35% of affected women having a positive family history. The causative effect appears to be an increased sensitivity to the cholestatic effect of the raised levels of oestrogen in pregnancy (progesterone may also play a role).

Investigations (Table 3): these rest around exclusion of other causes of abnormal LFTs and pruritus, as obstetric cholestasis is a diagnosis of exclusion.

In 90% of cases of obstetric cholestasis there are raised liver transaminases and abnormal bile acids. However, symptoms

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may predate biochemical changes so bloods should be repeated weekly if symptoms persist.

Risks associated with obstetric cholestasis are listed in Table 4. Whilst there are significant fetal risks, they do not correspond with severity of maternal symptoms or biochemical derangement. No surveillance method has been able to predict fetal compromise or improve outcome.

Management: this should include weekly maternal bloods for LFTs and bile acids. Prothrombin time should be checked prior to delivery if LFTs are severely deranged. Symptoms of pruritus should be managed, this can be with antihistamines or ursodeoxycholic acid (UDCA). Whilst UDCA has been shown to improve LFTs, it has not improved fetal outcomes. Dexamethasone should be used with caution and discussed with the woman due to the risk for adverse neonatal neurological outcomes.

Vitamin K deficiency is present in obstetric cholestasis due to reduced absorption likely secondary to steatorrhoea. Use of water soluble vitamin K should be considered if the prothrombin time is prolonged. This needs to be discussed carefully with the woman as early studies showed increased risk of neonatal hyperbilirubinaemia, haemolytic anaemia and kernicterus. However, at low dose such as 10 mg these risks are low; benefits include reduced risk of maternal postpartum haemorrhage and neonatal intracranial haemorrhage. Vitamin K should be offered to the newborn as routine.

Careful discussion is required around timing of delivery. As detailed above, fetal surveillance has not altered outcomes or helped predict stillbirth. Induction may be offered from 37 weeks gestation; the mother must be aware that this may result in increased maternal morbidity and increased neonatal morbidity in the form of prematurity. There is some evidence that early induction at this time may be most appropriate in those with more severe abnormalities in liver function tests. During labour continuous monitor should be utilized.

Postnatally, liver function tests should be checked at 10 days and followed until normal. Due to obstetric cholestasis-associated sensitivity to oestrogen, contraceptives containing oestrogen should be avoided. There is a risk or recurrence in subsequent pregnancies of 90%.

Acute fatty liver of pregnancy (AFLP)
The incidence of AFLP ranges between 1 in 7000 and 1 in 12,000 pregnancies. It most commonly presents in the third trimester. Risk factors for its development include primiparity, obesity, pre-eclampsia, a male fetus and multiple pregnancy. It is thought to be associated with heterogeneity for long-chain 3-hydroxy-acyl-coenzyme A dehydrogenase (LCHAD) deficiency which is a disorder of mitochondrial fatty acid oxidation. AFLP can occur in women with this disorder if the fetus is homozygous for fatty acid oxidation disorders.

Diagnosis is difficult as symptoms may be vague or be mistaken for pre-eclampsia or HELLP syndrome. Presentation may include pruritus, headache, nausea and vomiting, epigastric or right upper quadrant pain, diabetes insipidus with polyuria. Severe vomiting and upper abdominal pain tend to be the hallmarks of presentation and should alert the clinician to this possible diagnosis.

### Table 1

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Bloods</td>
<td>Full blood count</td>
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<td></td>
<td>Urea and electrolytes</td>
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<td>Liver function tests (LFTs)</td>
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<td>Thyroid function tests (TFTs)</td>
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<td>Urinalysis for ketones</td>
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<td>Microscopy and culture</td>
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<td>Radiology</td>
<td>Early pregnancy ultrasound scan</td>
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### Table 2

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<thead>
<tr>
<th>Maternal Risk</th>
<th>Fetal Risk</th>
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<tr>
<td>Wernicke's encephalopathy</td>
<td>40% fetal death associated with Wernicke's encephalopathy</td>
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<tr>
<td>Hyponatraemia and pontine demyelination</td>
<td></td>
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<tr>
<td>Mallory–Weis tear</td>
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<tr>
<td>Malnutrition</td>
<td>If &gt;5 kg maternal weight loss or significantly reduced weight gain-lower birth weight</td>
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<td>Psychological problems</td>
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<td>Thrombosis</td>
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### Table 3

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<tr>
<th>Investigation</th>
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<tr>
<td>Blood tests</td>
<td>FBC</td>
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<td>LFTs</td>
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<td>Coagulation profile (prothrombin time)</td>
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<td>Bile acids</td>
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<td>Urea, electrolytes and creatinine</td>
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<td>Glucose</td>
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<td>Serology for hepatitis A, B, C, E</td>
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<td>Serology for viral infections</td>
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<td>Anti-smooth muscle antibodies</td>
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<td>Anti-mitochondrial antibodies</td>
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<td>Urinalysis and culture</td>
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<td>Radiology</td>
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### Table 4

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<th>Fetal Risk</th>
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<tr>
<td>Vitamin K deficiency</td>
<td>Meconium liquor and aspiration</td>
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<tr>
<td>Postpartum haemorrhage</td>
<td>Prematurity</td>
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<tr>
<td></td>
<td>Intrauterine death</td>
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Initial investigations in hyperemesis

Investigations for abnormal LFTs

Hyperemesis risks

Obstetric cholestasis risks
Investigations: these should include bloods for FBC, urea and electrolytes, LFTs, urate, glucose, coagulation screen and a urine protein:creatinine ratio. Hallmarks are markedly raised urate and liver transaminases, coagulopathy (without thrombocytopenia) and severe hypoglycaemia. Radiology such as MRI, CT or USS may be utilized and may show steatosis, but may also be normal. Often in the clinical setting the need for expedient management warrants radiological investigation unnecessary and liver biopsy is often not appropriate given the coagulopathy.

Management: the mainstay of management is expeditious delivery. Each case needs to be managed on an individual basis as to whether this is best achieved by vaginal delivery (which may take longer with risks of post-partum haemorrhage) or caesarean section (with it significant risk of surgical haemorrhage). Management should involve a multidisciplinary team including obstetricians, obstetric physicians, anaesthetics, intensive care unit and liver unit specialists. Aggressive correction of the hypoglycaemia and coagulopathy should occur. Blood glucose should be checked at least 2 hourly and coagulation and LFTs at least 6 hourly. If there is fulminant hepatic failure, a liver transplant may need to be considered, ventilated stay in the intensive care unit may be required if multi-system failure occurs.

The majority of patients will have dramatic improvement and recovery after delivery. There remains a risk of requiring surgery immediately postpartum due to postpartum haemorrhage. If the woman survives through the delivery period, recovery is often complete, with no longstanding liver damage. Data on recurrence is limited; if future pregnancy is embarked on, LFTs should be monitored through out.

Haemolysis, elevated liver enzymes and low platelets (HELLP)
This is a continuum on the pre-eclamptic spectrum. It affects 5 –20% of cases of pre-eclampsia, although only a total of 0.5% pregnancies in the third trimester. Presentation is generally with right upper quadrant or epigastric pain, nausea and vomiting and raised blood pressure. However, HELLP may also be asymptomatic.

Investigations: bloods will show low grade haemolysis, low platelets (with a down ward trend), raised liver transaminases and bilirubin. There will be proteinuria in the majority of cases.

There is still a significant risk of maternal (1%) and perinatal (10–60%) mortality. This can be due to liver rupture, necrosis, subcapsular haematoma or abruption.

Management: initially this is to stabilize the patient. Blood pressure should be stabilized and magnesium sulphate commenced if eclampsia is felt to be imminent. It is important to investigate for and to correct coagulopathy. Platelet transfusion will be required if there is active bleeding or prior to surgery if <50 × 10^9/Litre or prior to regional block if <80 × 10^9/Litre. Once stable, prompt delivery is the mainstay of management. Blood tests will need to be repeated regularly as deterioration can occur rapidly, even in the postpartum period.

Outcomes are generally good, with complete recovery. There is a significant recurrence risk in subsequent pregnancies.

Pregnancy unrelated gastrointestinal diseases

Viral hepatitis
Viral hepatitis is one of the most common causes of deranged liver function tests during pregnancy. Common viruses include Hepatitis A, B, C, D, E and Epstein Barr virus, Herpes Simplex Virus and Cytomegalovirus. Clinical features of hepatitis in pregnancy are the same in the non-pregnant population. Exceptions to this are Herpes Simplex Virus (HSV) and Hepatitis E Virus (HEV) which can be very severe in pregnancy. The symptoms of acute hepatitis range from asymptomatic infection to right upper quadrant pain, vomiting, jaundice, and encephalopathy from liver failure. Viral hepatitis causes deranged transaminases (often >1000 IU) with evidence of hepatic synthetic dysfunction in severe infection (prolonged prothrombin time, low serum glucose, low serum albumin). Hepatitis B, C and D can result in chronic infection (Refer to Table 3 for investigations required).

Hepatitis A: hepatitis A (HAV) usually has a mild self-limiting course. Infection occurs via the faecal oral route and is often associated with travel to areas with poor sanitation. Acute infection is confirmed by serology showing a positive HAV IgM. HAV does not cause chronic infection. The severity of disease is related to advanced maternal age and gestation (third trimester). Severe infection in the third trimester is associated with premature delivery. Vertical transmission is rare, but if HAV is contracted around the time of delivery the neonate should be given immune globulin.

Hepatitis B: most acute Hepatitis B (HBV) infections (>90%) are asymptomatic and self-limiting. HBV is transmitted via blood, saliva, vaginal secretions and semen. The course of acute Hepatitis B is not affected by pregnancy. Treatment of acute infection is mainly supportive. HBV acquired in the third trimester has a higher risk of transmission to the neonate (90%) compared to first or second trimesters.

Chronic HBV infection can lead to cirrhosis and hepatocellular carcinoma (100 fold increased risk compared to non-infected population). Routine maternal serum screening and vaccination have reduced vertical transmission rates. A positive serum surface antigen (HBsAg) confirms the presence of disease. HBsAg positive women should be tested for the presence of e-antigen (HBeAg) which indicates high infectivity. HBsAg positive women should be monitored during pregnancy with regular liver function tests and HBV DNA levels checked 3 monthly.

Infection with HBV is usually trans-placental. The most important risk factors for neonatal transmission are the presence of HBeAg and a high HBV viral load, with infection rates of 80 –90%. This is in contrast to 5 –10% infectivity rates with HBeAg negative mothers. Method of delivery and avoidance of breastfeeding do not affect transmission rates. Hepatitis B transmission to neonates is reduced with HBV immune globulin administered at birth followed by vaccination. Neonatal infection in 90% of cases leads to chronic HBV carriage.

There are two considerations for treatment of chronic HBV during pregnancy, treatment of maternal disease and treatment to reduce vertical transmission. Treatment is recommended if HBV DNA levels are high (>6 log_{10} copies/mL), HBeAg is positive and if liver disease is present. Treatment should be
Hepatitis C: hepatitis C (HCV) is transmitted via blood usually in the context of blood transfusions or intravenous drug use. Infection is confirmed by serum anti-HCV antibodies and HCV RNA viral load. The course of HCV is not altered by pregnancy. 80% of people with acute HCV infection will develop chronic HCV. Chronic HCV can lead to cirrhosis and hepatocellular carcinoma. Hepatitis C has a low vertical transmission rate of less than 5%. Maternal HCV-RNA viral load is an important factor for determining infectivity. Mode of delivery and breastfeeding do not affect the vertical transmission rate. Patients with genotypes 1 or 3 or HIV co-infection have increased vertical transmission rates. Treatment with Ribavirin is contraindicated during pregnancy. Pegylated interferon is not recommended in pregnancy.

Hepatitis D: hepatitis D (HDV) is only found in people co-infected with HBV. Infection is via blood and the course is not altered by pregnancy. Vertical transmission is uncommon. Prevention of HBV infection or vertical transmission also prevents HDV.

Hepatitis E: pregnant women are at increased risk of developing HEV. The disease is transmitted through the faecal-oral route. It is often associated with contaminated water in developing countries. It is usually a self-limiting illness but can be severe in pregnancy. Severity is increased if women contract the virus in the third trimester. HEV can lead to acute liver failure with high fetal and maternal morbidity and mortality rates. Vertical transmission is high with fetal mortality rates of up to 50%. Management is supportive and delivery does not affect maternal outcome.

Herpes simplex virus: acute HSV hepatitis can be severe during pregnancy, particularly in the third trimester. HSV hepatitis can result in liver failure. HSV hepatitis can occur through primary infection or reactivation of HSV-1 or -2. Primary infection with HSV type 2 is more common. Mucocutaneous lesions are present in only 50% of cases.

HSV hepatitis can present with disseminated disease. HSV pneumonitis and/or encephalitis may co-exist. Imaging can be useful in making the diagnosis. Serology showing positive IgM—HSV antibodies is helpful in making the diagnosis. A liver biopsy is required for a definitive diagnosis. Intravenous acyclovir should be administered if this diagnosis is suspected.

Epstein barr virus/cytomegalovirus: EBV and CMV are common infections. EBV is transmitted by saliva and symptoms common symptoms include a sore throat and cervical lymphadenopathy. Perinatal transmission does not occur.

Signs of CMV infection include sore throat, cervical lymphadenopathy, and splenomegaly with a mild febrile illness. Serology may show positive IgM—CMV antibodies. Primary infection may affect the fetus causing congenital abnormalities and growth restriction.

Pepitic ulcer
Pepitic ulcers are uncommon during pregnancy. This is thought to be due to protective effects of oestrogen and prostaglandins on gastric mucosa. Symptoms usually involve epigastric discomfort. Symptoms are similar to reflux disease although pain is a differentiating factor. Pain worsened by food indicates gastric ulceration, whilst pain relieved by food suggests duodenal ulceration. Symptoms such as haematemesis should be investigated with a gastroscopy. Most patients with peptic ulcer disease test positive for *Helicobacter pylori*. Pharmacological treatment including H2 receptor antagonists and proton pump inhibitors are safe in pregnancy.

Gastric reflux
This affects most women (up to 80%) during pregnancy, particularly in the third trimester. Symptoms result from pregnancy changes including increasing gastric pressure from the enlarging uterus, delayed gastric emptying, and failure of the lower oesophageal sphincter pressure to compensate for the increased gastric pressure. This results in reflux of gastric contents into the lower oesophagus and inflammation of the mucosa. Symptoms include epigastric or retrosternal discomfort and dyspepsia. Treatment includes pharmacological and non-pharmacological options. Non-pharmacological options include meal avoidance late at night, eating small meals and sleeping semi-recumbent. Simple aluminium and magnesium containing antacids, proton pump inhibitors and H2 receptor antagonists are safe in pregnancy. Metoclopramide can also be helpful to increase gastric motility.

Inflammatory bowel disease
Inflammatory bowel disease (IBD) usually presents in young adulthood and can affect women in their childbearing years. It can have implications on fertility, pregnancy and breastfeeding. The diagnosis is made endoscopically and is divided into ulcerative colitis and Crohn’s disease. Ulcerative colitis affects the large bowel in contrast to Crohn’s disease which can affect anywhere along the GI tract from mouth to anus. IBD is associated with extra-intestinal manifestations including arthritis, uveitis, scleritis, erythema nodosum and gastrointestinal tract cancers.

The course of inflammatory bowel disease is generally unaffected by pregnancy. Patients with quiescent disease at conception do not have reduced fertility. Exceptions to this are women with scarring and adnexal adhesions from surgeries. Active disease at conception is associated with reduced fertility, increased risk of miscarriage and ongoing active disease during pregnancy. Active disease during pregnancy is a risk factor for pre-term delivery and low birth weight. Women with IBD should aim to conceive during remission. Women may have flares of IBD in the post-partum period, particularly women with Crohn’s disease.

Colonic features include abdominal pain, diarrhoea often with blood and/or mucous, and urgency of defaecation. Women with IBD should have their nutrition status assessed during pregnancy with vitamin B12, iron and folic acid levels checked in the first trimester. Women with IBD are at high risk of vitamin B12 and iron deficiencies and supplementation should be considered.
During pregnancy, flares are managed in the same way as the non-pregnant population. Azathioprine, steroids, sulphasalazine and 5-aminosalicylate (5-ASA) medications are safe in pregnancy. High dose folic acid (5 mg) is recommended for women taking sulphasalazine as it interferes with folate metabolism. Prednisone is the steroid of choice as >90% is metabolized by the placenta thus lowering the amount reaching the fetus. Oral and rectal steroid preparations are safe. Azathioprine is not recommended during breastfeeding. Methotrexate is contraindicated during pregnancy and breastfeeding. Data regarding anti-TNF drugs during pregnancy is limited. If indicated, infliximab is compatible for use during the first two trimesters. It is suggested that it be withdrawn during the third trimester due to increased drug placental transfer. Infliximab is compatible with breastfeeding.

Most women can deliver vaginally with IBD. Women with active perineal or rectal disease at the time of delivery warrant a caesarean section. Vaginal delivery can be attempted in women with a colostomy or ileostomy.

**Appendicitis**

This complicates 1 in 1000–2000 pregnancies and is most common in the first or second trimester. It is the most common non-obstetric cause for laparotomy in the pregnant population. Diagnosis can be challenging as symptoms such as nausea and vomiting are common in normal pregnancy. Examination is also not typical due to the fact pain may not be at the classical McBurneys’ point due to displacement of the appendix upward by the gravid uterus.

Appendicitis should be considered in pregnant women presenting with right lower quadrant pain and nausea and vomiting. Helpful signs may include guarding and rebound on examination.

**Investigations:** these should include FBC and abdominal ultrasound scan. A rising white cell count on blood investigations will help with diagnosis and high resolution USS with graded compression can visualize an inflamed appendix with 100% sensitivity and 96% specificity.

Risks of appendicitis are increased by delay in diagnosis and management as this increases risk of perforation, peritonitis and septicaemia. This can lead to miscarriage, preterm delivery and increased maternal morbidity and mortality.

**Management:** this should be with appendectomy, which may be performed laparoscopically prior to 20 weeks if the appendix is unperforated. If open surgery is to be performed then location of incision will need to be individualized depending on gestation. Post-operative cares are routine, with no requirement for routine tocolysis.

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**FURTHER READING**


Royal College of Obstetricians and Gynaecologists. Greentop guideline number 43. May 2011.


**Practice points**

- Hyperemesis is a serious condition, that needs careful management of fluid balance, nutrition requirements and control of symptoms.
- Obstetric cholestasis is a diagnosis of exclusion.
- Both HELLP syndrome and acute fatty liver of pregnancy have significant morbidity and mortality risks, prompt management involving senior clinicians is essential.
- Inflammatory bowel disease is managed in the same way as the non-pregnant population.
- Hepatitis E and HSV can be more severe in pregnancy.
- Carriers of Hepatitis B must be identified and neonates given Hepatitis B immune globulin followed by vaccination to reduce transmission rate.