

# Gallstones in pregnancy

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## Abstract

Gallstone disease is the most common gastrointestinal disease in developed countries and is present in up to 15% of the population. Owing to the increased risk factors for gallstones in pregnancy, it is the second most common non-obstetric emergency, affecting up to 12% of pregnant women with a risk of recurrence. Up to 3% of pregnant women in America require a cholecystectomy in the first year after delivery. Gallstone disease has a high risk of developing associated complications, and maternal mortality can be up to 37% if the patient develops gallstone pancreatitis.

Endoscopic retrograde cholangiopancreatography and cholecystectomy can be performed safely in the second trimester when benefits outweigh the risks. However, if the patient is able to be managed conservatively, then a cholecystectomy should be performed in the postnatal period to avoid further recurrences and complications. Despite this, there is currently no national UK guidance on how to manage gallstones and related diseases during pregnancy.

**Key words:** Abdominal pain, Cholecystectomy, Cholelithiasis, Gallbladder, Pregnancy

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## Introduction

Gallstone disease is a major global medical problem (Njeze, 2013). It is the most common gastrointestinal disease in developed countries that requires hospitalisation and is present in around 10–15% of the population (Ansaloni et al, 2016).

Gallstones, otherwise known as cholelithiasis, is defined as ‘the presence of solid concretions in the gallbladder’ (BMJ Best Practice, 2020a). Over 90% of gallstones are formed from cholesterol, but they can be made of other substances, such as bilirubin or calcium bilirubinate. When these constituents are present in higher concentrations than are soluble, gallstones can form. When concentrated in the gallbladder, these substances can become saturated and form microscopic crystals in bile. Over time, the crystals within the sludge grow and aggregate to form gallstones (Heuman, 2019). When a gallstone or sludge forms in the gallbladder, it can become symptomatic, either as a result of obstruction or of developing inflammation or infection.

## Complications of gallstone disease

Although the incidence of gallstones within the population is significant (19% of women and 10% of men), they do not always cause symptoms or complications (Ansaloni et al, 2016). Biliary colic, which is defined as a symptomatic cholelithiasis, occurs in around 1–4% patients annually (BMJ Best Practice, 2020a). Acute calculus cholecystitis arises when the gallbladder becomes inflamed as a consequence of gallstones. Acute calculus cholecystitis occurs in 10–20% of untreated patients and, without surgical intervention, has a high recurrence rate of 29% within the first year (Ansaloni et al, 2016).

Choledocholithiasis describes the migration of gallstones to the common bile duct. An associated complication is ascending cholangitis, which is when the bile duct becomes obstructed and inflamed. This occurs in 9% of patients with gallstones who are admitted to hospital and carries a 5% mortality rate (Anonymous, 2005). Most critically, gallstones can also cause acute pancreatitis (Abraham et al, 2014). Acute pancreatitis is thought to affect 0.05–0.2% of patients with gallstones annually (Banks et al, 2010) and, in severe cases, has a mortality rate of up to 30% (Stoppacher, 2018). Gallstones represent a longer-term risk of developing gallbladder cancer. In fact, 85% of patients with gallbladder cancer have

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been found to have gallstones present, with a strong correlation between the increasing stone size and gallbladder cancer. Although gallbladder cancer generally develops slowly (over 5–10 years), it is often diagnosed late and has a poor prognosis, with a mean survival of 6 months (Hundal and Shaffer, 2014).

## Risk factors for gallstones

There are several known risk factors for developing gallstones. For medical professionals these are often presented as the mnemonic ‘the five Fs’ (fair, fat, female, fertile and forty’) (Bass et al, 2013). Additional risk factors include a genetic predisposition, diabetes and medications (oral contraceptives, nitric oxide donors and calcium-channel antagonists) (Banks et al, 2010). The five Fs were validated in a retrospective study performed in 2009–10 at a hospital in Dublin, which looked at 400 patients admitted with upper abdominal pain. They found that, of the patients they studied, 75% were women, 62% were fair in complexion and 68% were in the fertile age group (Bass et al, 2013).

There is a strong link between the prevalence of gallstones and diet. Despite being present worldwide, the nutrition in a typical western diet tends to increase the risk of developing gallstones. This is generally understood to be caused by the increased levels of fats and refined carbohydrates, as well as a low fibre intake (Njeze, 2013) (Table 1).

Despite the recognised variances in the overall gallstone prevalence across populations, one constant is that fertile women are twice as likely to develop the disease. This is shown by the narrowing of incidence between genders with increasing age. It is hypothesised that increased levels of oestrogen circulating in the body can increase cholesterol levels in the bile (Njeze, 2013) and high levels of progesterone reduce gallbladder motility.

## Prevalence of gallstone disease in pregnancy

Owing to the increased risk factors, gallstone or gallbladder disease is the second most common non-obstetric abdominal emergency in pregnant women (Date et al, 2008). A systematic review performed in the USA found that an estimated 5–12% of pregnant women had gallstones on ultrasound scan (Mendez-Sanchez et al, 2006). In women

**Table 1. Risk factors and physical mechanisms involved in gallstone disease in pregnancy**

Risk factors	Age
	Dietary fat
	Iron supplements
	Previous pregnancies*
	History of gallstone disease*
	Physical activity prenatally*
	Weight gain
	Serum cholesterol level
	Body mass index*
Pathogenic pathways	Gallbladder hypomotility
	Decreased enterohepatic circulation
	Increased bile acid pool size
	Larger gallbladder volumes
	Sex steroid
	Incomplete postprandial emptying

\* risk factors with the most evidence

who presented to hospital with symptoms relating to gallstones, 50% had recurrence of symptoms before delivery (Mendez-Sanchez et al, 2006). Follow-up imaging 2–4 weeks postpartum demonstrated a 15% reduction in the presence of gallstones with biliary sludge disappearing in 38.7% (Gangwar et al, 2011). In the USA, it is estimated that 1–3% of pregnant women require a postpartum cholecystectomy within the first year after delivery, which is the equivalent of around 40 000 women each year (Bari et al, 2014).

In addition to the stated risk factors found within the population, pregnant women display a positive correlation with increasing parity and prolonged breastfeeding (Gangwar et al, 2011). Fortunately, most gallstone disease in pregnancy is mild and can be managed conservatively. Nonetheless, if left untreated, some cases can develop serious complications. The maternal mortality rate can be as high as 37% if the patient develops untreated gallstone pancreatitis (Mendez-Sanchez et al, 2006).

## Signs and symptoms of gallstones

The most common clinical presentation of gallstone disease is episodes of abdominal right upper quadrant or epigastric pain. This is often severe after a fatty or heavy meal. The pain can radiate to between the shoulder blades, with the addition of nausea and vomiting (Njeze, 2013). If pain continues for several hours at an intense level, this indicates cholecystitis or more serious complications, such as ascending cholangitis. If biliary obstruction occurs, symptoms can be accompanied by jaundice, fever or sepsis, with complications such as cholangitis or pancreatitis. Acute presentations of epigastric pain in pregnancy can make diagnoses difficult, as abdominal organs are displaced during pregnancy (Mendez-Sanchez et al, 2006) (Table 2). HELLP syndrome is usually characterised by haemolysis, elevated liver enzymes and low platelets, with the clinical signs giving the acronym HELLP (BMJ Best Practice, 2020b). It is a severe form of pre-eclampsia that can present with right upper quadrant or epigastric abdominal pain in over 40% of affected patients.

On examination, the most common finding is abdominal tenderness in the right upper quadrant or epigastric area. In acute cholecystitis, a positive Murphy's sign is common, with 97% sensitivity. Murphy's sign is the presence of acute tenderness while palpating the gallbladder fossa during inspiration, which is not present on the contralateral side (BMJ Best Practice, 2020a).

## Investigations and diagnosis

The preferred imaging for gallstone disease, both during and beyond pregnancy, is ultrasound, which is 95% accurate in diagnosis. It is safe in pregnancy (Mendez-Sanchez et al, 2006), and a cost-effective investigation (Abraham et al, 2014). However, ultrasound has a lower sensitivity for stones in the bile duct, despite improved detection rates compared with

**Table 2. Differential diagnosis of acute epigastric pain in pregnancy**

Viral hepatitis
Pyelonephritis
Duodenal ulcer
Acute pancreatitis
Pulmonary embolism
Acute myocardial infarction
Sepsis
Pre-eclampsia
HELLP syndrome (haemolysis, elevated liver enzymes and low platelets)
Fatty liver disease in pregnancy

other imaging modalities (computed tomography scan) for bile duct dilatation (BMJ Best Practice, 2020a). Where ultrasound has been inconclusive, magnetic resonance cholangiopancreatography can be used for suspected stones in the bile duct. When diagnosing stones in the bile duct, magnetic resonance cholangiopancreatography has a sensitivity of 92%, and a specificity of up to 97%. It is less sensitive (65%) when detecting small biliary stones (BMJ Best Practice, 2020a). An American study examined pregnant patients with symptoms consistent with gallstone disease who had been referred for magnetic resonance cholangiopancreatography. Biliary dilatation had already been detected using ultrasound in 53% of patients, but in 90% of these the cause could not be determined, hence they were referred for magnetic resonance cholangiopancreatography (Oto et al, 2009). Magnetic resonance cholangiopancreatography identified the cause of the biliary dilatation in 50% of patients (Oto et al, 2009). It is also the investigation of choice when scrutinising the pancreas in suspected cases of gallstone pancreatitis. This form of imaging has no known effects on the fetus, and is safe in pregnancy, although it is more expensive (Oto et al, 2009).

Computed tomography scanning can be used for non-pregnant women with high suspicion of gallstones following an inconclusive ultrasound. Computed tomography tends to be avoided, if possible, during pregnancy, because of the slightly increased risk of radiation to the fetus, which is thought to equate to 1 in 1000 greater chance of developing cancer as a child (RadiologyInfo, 2019).

Other investigations can indicate whether the patient has developed any specific complications. A raised white cell count indicates inflammation including acute cholecystitis, cholangitis or pancreatitis. With regards to uncomplicated biliary colic, biochemical inflammatory markers would be within the normal range. If the alkaline phosphatase level is raised, this indicates bile or cystic duct obstruction. Acute pancreatitis presents with elevated serum lipase and amylase levels (more than three times the upper limit) (BMJ Best Practice, 2020a).

Endoscopic retrograde cholangiopancreatography is an important investigation for gallstones, with a specificity of 100% and 94% effective for removing the stones (Abraham et al, 2014). There are limited data into the safety of endoscopic retrograde cholangiopancreatography during pregnancy. Over a 5-year period, an American retrospective review studied endoscopic retrograde cholangiopancreatographies in 17 pregnant patients (Daas et al, 2009). All procedures included maternal observations, and fetal heart rate monitoring throughout. All patients were given prophylactic antibiotics. Follow up included fetal heart rate monitoring and possible maternal complications. Fetal radiation exposure was not assessed. No maternal complications were noted immediately following any of the procedures or in eventual follow up. There were no signs of fetal distress noted, and all Apgar scores on delivery were greater than eight, with healthy infants at 30 days old (Daas et al, 2009). Despite this, because of the limited data, endoscopic retrograde cholangiopancreatography should only be performed in pregnancy when the benefits heavily outweigh the risks.

## Management

### General

If gallstone disease is asymptomatic, the best management option is conservative, with changing lifestyle risk factors such as weight loss and a low-fat diet. If gallstone disease becomes symptomatic or complications develop, the first-line treatment is intravenous antibiotics, alongside fluids and analgesia. A positive blood culture is found in up to 54% of patients with acute cholecystitis, hence the importance of antimicrobials (Yoshida et al, 2007). The choice of antibiotics is determined by local policy and microbial guidelines. The first-line surgical treatment is laparoscopic cholecystectomy. Open laparotomy can be considered if laparoscopic surgery is technically difficult because of anatomy or concerns from injury, but there is no difference in mortality or complications between the two procedures. The main benefit of laparoscopic surgery is the reduction in recovery time and length of hospital stay (BMJ Best Practice, 2020a).

If gallstones have migrated and caused obstructive complications in the common bile duct, the management option of choice is endoscopic retrograde cholangiopancreatography.

### In pregnancy

There is no national guidance in the UK for management of gallstone disease in pregnancy. Conservative management is generally deemed the safest option, with intravenous fluids, analgesia and antibiotics, as with non-pregnant patients. Simple analgesia, such as paracetamol, is safe in pregnancy and can be used as first line. A short course of stronger opioids, such as codeine and oral morphine, can be used in the antenatal period for severe pain because of the possible effects of respiratory difficulties and depression in the fetus (Best Practice Advocacy Centre, 2014). Antispasmodics (hyoscine butylbromide) can be used to alleviate pain triggered by muscle spasms as a result of obstruction, but, according to the British National Formulary, the manufacturer advises avoiding the use of hyoscine because of the limited evidence and data regarding its safety. Despite this, if benefits outweigh the risks, it can be considered on a case-by-case basis (British National Formulary, 2020).

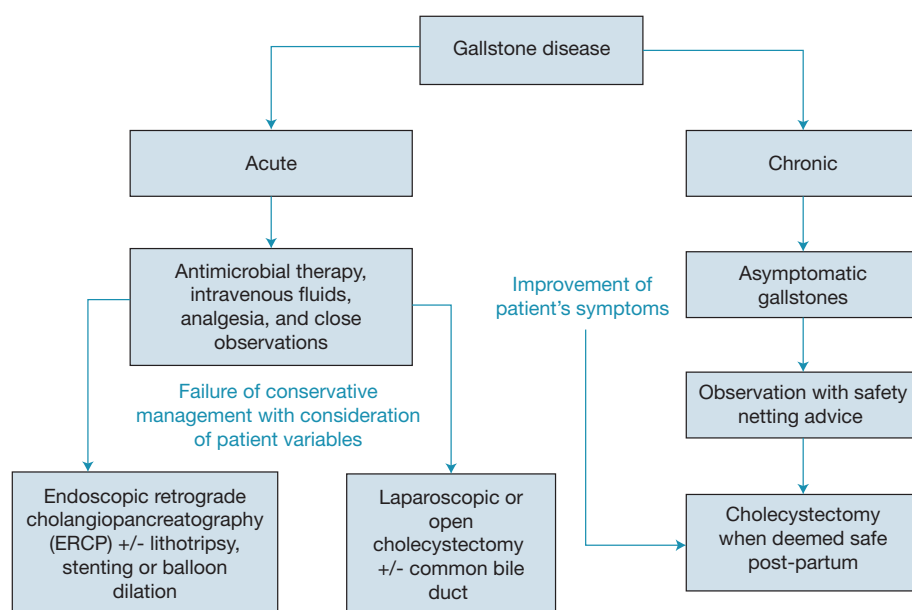
Despite being one of the best analgesic agents for symptomatic gallstones, non-steroidal anti-inflammatory drugs are avoided during pregnancy because of their ability to cross the placenta and cause adverse effects for the fetus and in the neonatal period. Exposure after 30 weeks' gestation has been associated with risk of premature closure of ductus arteriosus and oligohydramnios. In the neonatal period, effects on the brain, kidney, lungs and gastrointestinal tract have been reported (Antonucci et al, 2012). Specifically non-steroidal anti-inflammatory drugs can cause acute renal failure in the neonate as a result of renal vasoactive action and, therefore, reduced glomerular filtration rate (Drukker, 2002), as well as pulmonary hypertension as a result of the decreased volume of amniotic fluid.

If patients remain symptomatic and fail to respond to conservative measures, cholecystectomy should be considered. It is recommended that a cholecystectomy should be performed in the second trimester when there is a reduced risk to the pregnancy. There is a reported 10.5% risk of miscarriage after surgery during the first trimester (Nejdlova and Johnson, 2012). If surgery is undertaken between the third and eighth week of gestation, exposure to teratogenic medications can cause major organ abnormalities (Nejdlova and Johnson, 2012). In the third trimester, there is an increased risk of damage to the gravid uterus and other organs as they are displaced (Best Practice Advocacy Centre, 2014). Preterm delivery of the fetus as a direct result of abdominal surgery is thought to occur in 5% of patients undergoing surgery in the third trimester (Visser et al, 2001). Despite the apparent safety of operating during the second trimester, according to published literature, cholecystectomy only occurs in between 1 in 1600 and 1 in 10 000 pregnancies (Mendez-Sanchez et al, 2006).

During surgery, certain precautions are required from an anaesthetic and surgical perspective when looking after pregnant women, depending on gestation. Positioning during surgery is important to avoid compression of the main vessels, and it is recommended the patient should be placed in a left lateral position, as this reduces the risk of hypotension to mother and fetus. A head down position is also sometimes needed in later pregnancy when the uterus is enlarged to improve the lower abdominal view. From an anaesthetic perspective, it is more important in pregnancy to monitor the end expiratory carbon dioxide levels and adjust ventilation accordingly, as increased carbon dioxide levels can cause fetal acidosis (Juhasz-Böss et al, 2014). Fetal monitoring should be undertaken after the sixteenth week of pregnancy pre- and postoperatively in order to identify problems early, and ensure fetal health with either sonography or electronic fetal monitoring (Juhasz-Böss et al, 2014). Intraoperative monitoring has not been shown to improve mortality, so is not necessary (Glasgow et al, 1998).

A study by Lu et al (2004), based at two American university hospitals, showed that women who were managed conservatively showed a higher rate of labour induction and preterm delivery (33%). There was also a higher risk of relapsing symptoms (34%). Women who were managed operatively had no increased risk of preterm delivery, labour induction and no cases of relapse. Medical management of gallstones also increases the risk of developing gallstone pancreatitis, which increases the chance of maternal fatality and has a 10–20% risk of fetal loss (Mendez-Sanchez et al, 2006).

A retrospective analysis performed from 2002–12 described patients who had presented during pregnancy with gallstone disease. Just under 20% of patients had safely undergone cholecystectomy in the antenatal period; however, of the remaining patients who responded to the follow-up questionnaire, 59% experienced recurrent postpartum symptoms. For that reason, patients that are stable enough during their pregnancy and can be managed with



**Figure 1.** Suggested management of gallstone disease in pregnant individuals.

conservative measures would be recommended for early postpartum cholecystectomy (Veerappan et al, 2013) (Figure 1).

## Conclusions

There is no current guidance from the National Institute for Health and Care Excellence, Royal College of Obstetricians and Gynaecologists or the Association of Upper Gastrointestinal Surgeons regarding the management of gallstone disease during pregnancy. As gallstone disease affects a significant proportion of expectant mothers, this needs to be addressed. It appears from the research that, if a patient develops symptomatic gallstone disease in pregnancy, there is a high chance that she and her unborn child can develop complications, as well as recurring symptoms, during both the remaining pregnancy and postnatal period.

Ultrasound and magnetic resonance cholangiopancreatography are both safe and highly effective for diagnosis of gallstone disease in pregnancy. For management, this review proposes that, in asymptomatic gallstone disease, the patient should be safety-netted about the associated risks of disease deterioration and should seek healthcare advice if they develop symptoms and become unwell. In cases of acute infection where the patient is stable, conservative management as per local policy guidelines should be first-line management. If further intervention is required, endoscopic retrograde cholangiopancreatography and laparoscopic cholecystectomy have been found to be safe in pregnancy and thus can be performed when the benefits outweigh the risks. The best time to perform any operative management is in the second trimester; however, if the patient is stable and does not go on to develop complications, it would be recommended to wait until after pregnancy to undergo operative management to prevent further recurrence and complications of gallstone disease.

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## Key points

- Gallstone disease is the second most common non-obstetric emergency, affecting up to 12% of pregnant women.
- If left untreated, gallstone disease can develop serious complications such as acute pancreatitis which carries a risk of maternal death.
- Endoscopic retrograde cholangiopancreatography and cholecystectomy is safest performed in the second trimester when benefits outweigh the risks.
- There is currently no UK guidance for the management of gallstone disease and complications in pregnancy.

## Conflicts of interest

The authors declare that they have no conflicts of interests.

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