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Journal

Abdominal Radiology, 48(6)

ISSN

2366-004X

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Publication Date

2023-06-01

DOI

10.1007/s00261-023-03832-1

Abdominal Radiology
https://doi.org/10.1007/s00261-023-03832-1

SPECIAL SECTION: BENIGN BILIARY DISEASE

Imaging of benign gallbladder and biliary pathologies in pregnancy

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Received: 3 December 2022 / Revised: 23 January 2023 / Accepted: 23 January 2023

Abstract

The rising incidence combined with pregnancy-related physiological changes make gallbladder and biliary pathology high on the differential for pregnant patients presenting with right upper abdominal pain. Imaging plays a crucial role in determining surgical versus non-surgical management in pregnant patients with biliary or gallbladder pathology. Ultrasound (first-line) and magnetic resonance with magnetic resonance cholangiopancreatography (second-line) are the imaging techniques of choice in pregnant patients with suspected biliary pathology due to their lack of ionizing radiation. MRI/MRCP offers an excellent non-invasive imaging option, providing detailed anatomical detail without known harmful fetal side effects. This article reviews physiological changes in pregnancy that lead to gallstone and biliary pathology, key imaging findings on US and MRI/MRCP, and management pathways.

Graphical abstract

Keywords Pregnancy · MRI/MRCP · Biliary · Ultrasound · Gallbladder

Abbreviations

CBD	Common bile duct
ERCP	Endoscopic retrograde cholangiopancreatography
GBCA	Gadolinium-based contrast agents
ICP	Intrahepatic cholestasis of pregnancy
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
PTBD	Percutaneous transhepatic biliary drainage
RUQ	Right upper quadrant
SAR	Specific absorption rate
US	Ultrasound

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Introduction

Benign biliary and gallbladder pathologies are common during pregnancy and the immediate post-partum period. For example, acute cholecystitis, the second most common

Published online: 15 February 2023

non-obstetric indication for surgery during pregnancy, occurs in approximately 1 in 1600–10,000 pregnancies [1]. More recent epidemiological studies indicate that the incidence of gallbladder and biliary pathologies is increasing over time resulting in rising health care costs [2]. Over the past three decades, several investigations including large population retrospective studies have revealed changes in treatment approaches. Surgical intervention and definitive management such as ERCP during pregnancy are favored over expectant management [3–7]. Pathologies of the gallbladder also represent the most common non-obstetric cause of hospitalization in the first-year post-partum [8]. Additionally, 76% of hospitalized women underwent cholecystectomy, while 5% underwent endoscopic retrograde cholangiopancreatography (ERCP). Hence, in pregnant and post-partum patients presenting with biliary colic and elevated bilirubin, biliary and gallstone pathology is a highly likely etiology.

In this review, we describe the physiological changes in pregnancy that can lead to an increase in gallbladder and biliary pathologies. We demonstrate how ultrasound (US) and magnetic resonance imaging (MRI) combined with magnetic resonance cholangiopancreatography (MRCP) can play a crucial role in deciding between surgical vs. non-surgical management. We focus on the role of MRI/MRCP in providing excellent non-invasive imaging options without harmful fetal side effects. We also discuss current surgical and non-surgical guidelines for management.

Physiology of bile and gallstones

The bile that is produced in the normal physiological state is approximately 95% water, with a small percentage of bile salts, phospholipids such as phosphatidylcholine, cholesterol, and numerous other trace substances excreted by hepatocytes [9]. Since cholesterol is not water soluble, hydrophilic bile salts are needed to keep it in solution. When there is an imbalance in the relative quantities of bile salts and cholesterol in the bile, a complex process called "nucleation" occurs, in which cholesterol forms submicroscopic nuclei. These nuclei then crystallize, grow, and eventually form the gallstones visualized on imaging [10]. Because of nucleation, conditions that cause stasis, such as prolonged fasting states or situations of parenteral nutrition, can lead to stone formation.

The secretion of bile from hepatocytes into the canalicular system, subsequent storage, and transport into the bowel are important for proper digestion and for excretion of wastes and toxins. An "enterohepatic circulation" is also present in which the bile salts excreted into the bowel are reabsorbed (primarily in the distal ileum) and then transported back to the liver via the portal circulation (Fig. 1a).

Physiological changes during pregnancy

Major risk factors for gallstones are pre-pregnancy obesity and non-parity [11]. However, the hormonal changes in pregnancy can create an imbalance within the biliary system, cause cholestasis, and precipitate gallstone formation. For example, elevated progesterone levels act as a smooth muscle relaxant leading to a larger gallbladder volume, impaired gallbladder emptying, and slowed intestinal transit [12] (Fig. 1). Elevated estrogen levels have also been associated with an increased risk of gallstone formation [13], although the role is not completely understood.

Pregnancy alters bile composition. The amount of cholesterol relative to bile salts and phospholipids increases in the second and third trimesters, which results in

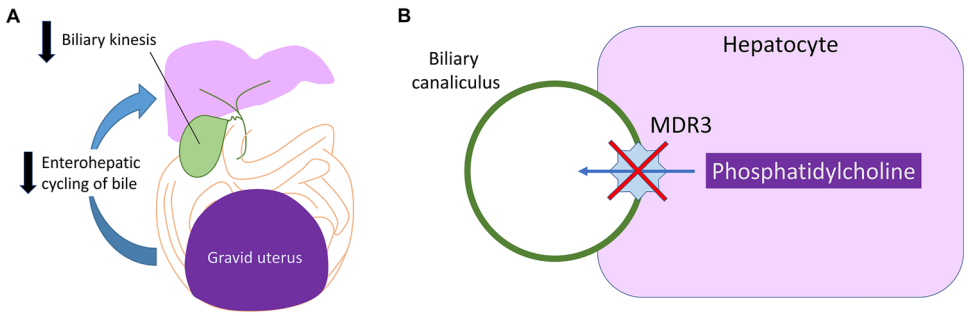

Fig. 1 Physiological changes during pregnancy. Biliary secretion, storage, transport, and cycling are complex processes and hormonal changes during pregnancy can affect the balance. **a** In particular, decreased gallbladder motility and biliary kinesis promotes gallstone formation of cholesterol-saturated bile and decreased enterohepatic cycling creates a positive feedback loop, promoting increased bile synthesis. **b** Heterozygous mutations in the multidrug resistance protein 3 bile salt export transporter have been identified in the development of cholestasis of pregnancy. Estrogens and progesterones are thought to inhibit the transporter in genetically susceptible individuals. Phosphatidylcholine is the predominant phospholipid in bile and is important for proper transport of cholesterol in bile. A lack of phosphatidylcholine can result in phospholipid-associated cholelithiasis, a form of cholesterol gallstone disease, and also diminishes the shielding of hydrophilic bile salts, which has toxic effects on the cholangiocyte membrane

cholesterol supersaturation in the bile and nucleation [12, 14]. Decreased enterohepatic cycling during pregnancy leads to an alteration in bile acid synthesis and increased cholesterol secretion relative to bile acid and phospholipid secretion [12]. These changes have a practical impact. A prospective study of over 3200 pregnant patients examined by US demonstrated that the incidence of new sludge, new stones, or progression of sludge to stones was 7.9% in the third trimester and 10.2% at 4- to 6-weeks post-partum [11]. As biliary motility is restored in the post-partum period, sludge and stones resolved in 61% and 28% of women, respectively [15] (Fig. 2).

Estradiol and progesterone metabolites are thought to contribute to intrahepatic cholestasis of pregnancy (ICP) in some patients with a genetic predisposition [16–18]. ICP is a liver disorder that occurs in the third trimester. It can result in elevated serum bile acids and maternal symptoms, such as pruritis or jaundice. Importantly, ICP has also been linked to poor fetal outcomes (e.g., prematurity, perinatal death, fetal distress, and stillbirth) through chronic placental insufficiency [19, 20]. Cholestasis is thought to be due to inhibition of a bile salt export pump, although the mechanism has not been fully elucidated [16–18] (Fig. 1b).

Imaging considerations

Patients with underlying gallbladder and biliary pathology often present with RUQ or epigastric pain. Given the wide availability, lack of ionizing radiation, and relatively low cost, US represents the first-line imaging modality for evaluating the biliary system, pancreatic head, and right kidney in both pregnant and non-pregnant patients presenting with right upper quadrant (RUQ) pain. Second-line imaging with MRI/MRCP is considered when there is concern for distal obstruction and can be helpful clarifying equivocal or inconclusive biliary findings on US.

Ultrasound

Ultrasound is advantageous over other imaging modalities given the ease of repeat imaging and monitoring in the cases of conservative management (Fig. 2). The limitations of US are primarily related to operator dependence and difficulty with US beam penetration, commonly associated with patient body habitus or the presence of bowel gas in the abdomen. Pregnant patients in their second and third trimesters can be a challenge to image with this modality

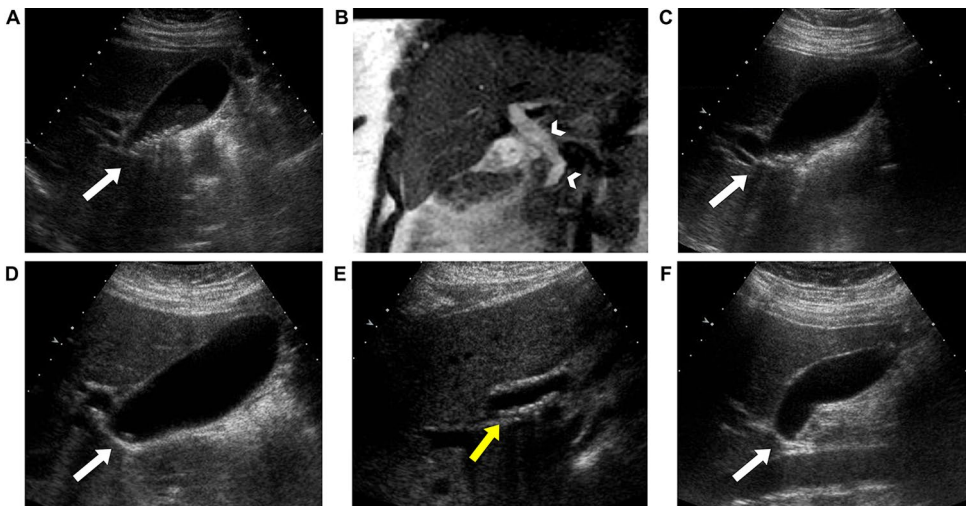

Fig. 2 Improvement of stone burden after ERCP and delivery. A 20-year-old pregnant female (29 weeks, 5 days) presented with mild pre-eclampsia, abnormal liver function tests, and right upper quadrant pain. The patient was afebrile with a normal white blood cell count. **a** A RUQ US demonstrated echogenic foci consistent with cholelithiasis, without evidence of cholecystitis (white arrow). Mild intrahepatic and extrahepatic ductal dilatation was observed (not shown). **b** Subsequent MRI/MRCP demonstrated a dilated extrahepatic duct of 1.6 cm that smoothly tapered to the ampulla where it measured 0.4 cm and without obstructing stone (white arrowheads). The patient was conservatively managed. Due to worsening bilirubin and AST/ALT levels, patient underwent repeat RUQ US, which continued to demonstrate cholelithiasis without cholecystitis. The patient subsequently underwent ERCP, sphincterotomy, and distal CBD stone removal. Her symptoms improved and her liver function tests began to normalize. **c** Subsequent RUQ US performed for abdominal pain 2 weeks after the procedure continued to demonstrated cholelithiasis without cholecystitis (white arrow). The patient was conservatively managed. She delivered a term infant approximately 8 weeks later without complication. **d**, **e** A RUQ US performed 2 days post-partum demonstrated improved stone burden in the gallbladder (white arrow) and migration of stones to the proximal CBD, which remained dilated to 1.4 cm (yellow arrow). **f** A RUQ US approximately 3 years after delivery demonstrated no gallstones in the gallbladder (white arrow) and a CBD that measured 1.2 cm (not shown)

due to the shifting of intra-abdominal organs that results from progressive enlargement of the uterus. This can make it more difficult to visualize the gallbladder and biliary tract. Specific techniques may be utilized to optimize visualization, including alterations in patient positioning (e.g., left lateral decubitus or standing positions) or use of patient breath-holding.

Off-label use of contrast-enhanced US with microbubbles has been explored on a limited basis for the evaluation of various conditions in obstetric patients. Data on a small subset of patients have demonstrated safety and efficacy [21]. Larger-scale studies have not been performed and societal guidelines do not exist on the use of contrast-enhanced US.

Computed tomography

CT of the abdomen and pelvis carries a higher risk of radiation exposure to the fetus compared to other anatomical locations. However, there are no reports of fetal anomalies, growth restriction, or abortion associated with radiation exposure of less than 50 mGy, which is above the range of exposure for typical diagnostic procedures [22] (Table 1). Calculators that attempt to accurately estimate fetal dose based on gestational age, volume CT dose index, tube voltage, and scan region are available [23]. Newer technologies such as photon counting detector CT could enable further reduction of the radiation dose while preserving image quality [24].

Table 1 Estimated fetal absorbed radiation doses associated with common radiologic examinations. Adapted from reference [70]

Type of examination	Typical fetal dose* (mGy)
No radiation	
Ultrasound	N/A
MRI/MRCP	N/A
Very low-dose examinations (< 0.1 mGy)	
Radiography of any extremity	< 0.001
Chest radiography (two views)	0.002
Low-to moderate-dose examinations (0.1–10 mGy)	
CT chest (routine or PE protocol)	0.2
Abdominal radiograph	3
Hepatobiliary nuclear medicine scan (Technetium 99 m)	< 5
Double-contrast barium enema	7
CT abdomen and pelvis (renal stone protocol)	10
Higher-dose examinations (10–50 mGy)	
Endoscopic Retrograde Cholangiopancreatography	< 12
CT abdomen (routine)	4
CT abdomen and pelvis (routine)	25
CT angiography (chest, abdomen, and pelvis)	34

*Fetal exposure can vary with gestational age, maternal body habitus, and acquisition parameters

CT computed tomography; *MRI* magnetic resonance imaging; *MRCP* magnetic resonance cholangiopancreatography

No harmful side effects have been associated with the use of oral contrast (iodine or barium) agents. Although intravenous iodinated contrast can cross the placenta, animal studies have not demonstrated any mutagenic or teratogenic effects [22]. Regardless, iodinated contrast is only recommended in cases where the diagnostic benefits to the fetus or mother outweigh the potential harms [22].

Magnetic resonance imaging/magnetic resonance cholangiopancreatography

MRI provides superior soft-tissue contrast and improved spatial resolution compared to US while also providing multi-planar capabilities for detailed anatomical evaluation of the biliary tree. The use of heavily T2-weighted sequences for MRCP allows for visualization of bright bile in the biliary tree and pancreatic fluid in the pancreatic ducts. Current protocols for MRI/MRCP are similar for pregnant and non-pregnant patients. However, 1.5 T is sometimes preferred over 3.0 T and gadolinium-based contrast agent (GBCA) use is avoided [25]. Some institutions are exploring the use of an abbreviated MRCP protocol to evaluate for choledocholithiasis. The abbreviated protocol could reduce the imaging time thereby reducing patient discomfort and decrease motion-related artifacts compared to conventional MRCP, while maintaining diagnostic accuracy [26]. However, these protocols have not been explored in pregnant patients.

Primary concerns for MRI relate to tissue heating caused by energy deposited by radiofrequency pulses and acoustic noise. The specific absorption rate (SAR) refers to the rate of absorption of thermal energy. MRI with dedicated MRCP protocols is often done at 1.5 T due to SAR considerations (doubling of field strength leads to quadrupling SAR if all parameters are left equal). No adverse effects on fetal growth in any trimester were reported when imaging was performed at 3.0 T [27]. Regarding noise, approximately 80–120 dB of acoustic noise is created from fast gradient switching. A recent study examined the safety of 1.5-T MR imaging on fetuses and found no evidence of adverse effects on hearing or birthweight in babies [28]. Lastly, shorter wavelengths of radiofrequency waves can promote unwanted wave interference in central portions of the abdomen. This may be a problem in patients with large amounts of free water in the abdomen where dielectric effects can degrade the imaging quality at 3.0 T.

Overall, no deleterious effects of MRI at 1.5 T or 3.0 T have been documented and no special consideration is recommended for any trimester in pregnancy per ACR and ACOG guidelines [22, 29]. MR examinations can be performed if the duration is less than 30 min and based on

local institutional policies, medical needs, and accessibility to 1.5 T versus 3.0 T MR scanners [29]. Other national and international societal guidelines advocate more judicious use of 3.0 T due to the SAR and acoustic noise risk. For example, the Canadian Association of Radiology recommends 1.5 T during the first trimester [30], while the International Society of Ultrasound in Obstetrics and Gynecology does not recommend the use of field strengths greater than 1.5 T for fetal MRI [31].

The use of GBCAs in pregnancy is avoided due to concern regarding the effects on the fetus since gadolinium has been shown to cross into the placenta [32]. Theoretical concerns include (1) teratogenic effects in the first trimester during organogenesis or (2) risk of nephrogenic systemic fibrosis in the second or third trimester where free gadolinium (Gd^{3+}) may be excreted by the fetal kidneys into the amniotic fluid and deposited in tissues [33]. A recent large retrospective study evaluated the long-term safety of exposure to MRI in the first trimester or to GBCA at any time during pregnancy [34]. Broadly, exposure to MRI during the first trimester of pregnancy was not associated with an increased risk of harm to the fetus or young child as compared to non-exposed patients. However, comparing GBCA MRI ($n = 397$) with no MRI ($n = 1{,}418{,}451$), the incidence rate for rare NSF-like outcomes was higher in the gadolinium MRI group (3.3 per 1000 person-years [< 5 events]) than in the non-MRI group [1.8 per 1000 person-years (8705 events)] noting that the confidence intervals for the adjusted HR (1.00, 95% CI, 0.33–3.02) and adjusted risk difference (0.0, 95% CI, −2.2–6.7) were wide. The broad outcome of any rheumatological, inflammatory, or infiltrative skin condition was higher following GBCA-enhanced MRI [125.8 per 1000 person-years (123 events)] than no MRI [93.7 per 1000 person-years (384, 180 events)], with an adjusted HR of 1.36 (95% CI, 1.09–1.69) and an adjusted risk difference of 45.3 (95% CI, 11.3–86.8) [34]. A limitation of the study was the control group included those who did not undergo MRI rather than a group of patients that underwent MRI without GBCAs. A more recent large cohort analysis of 5,991 qualifying pregnancies found a 0.73 adjusted relative risk (95% CI, 0.34–1.55) of fetal or neonatal death in patients receiving GBCA compared to non-GBCA MRI [35]. Regardless, GBCA use should be limited to situations in which the benefits clearly outweigh the possible risks [36].

Given the limited long-term safety data for pregnant patients undergoing MR examinations, some institutions choose to initiate a conversation with the patient prior to scanning regarding the theoretical risks discussed above and consider obtaining written consent prior to proceeding with the study.

Endoscopic ultrasound/endoscopic retrograde cholangiopancreatography

Although ERCP and sphincterotomy for choledocholithiasis uses ionizing radiation, the procedure has been proven safe in various investigations without reported maternal or fetal deaths, stillbirths, congenital malformation, or long-term complications [37, 38]. The radiation dose used for ERCP has a median effective radiation dose between 2 and 12 mGy, which is lower than the doses causing deterministic radiation outcomes to the fetus in pregnant women [22]. In a study including 24 children whose mothers underwent ERCP during pregnancy, there were no developmental delays or malignancies reported after a median of 11-year follow-up [39]. Nonetheless, endoscopists limit fluoroscopy time to reduce radiation exposure and procedures are postponed until the second trimester. An alternative approach using a non-ionizing imaging modality such as US for guidance of ERCP without any radiation exposure is a promising tool [40, 41].

Nuclear medicine imaging

Radiotracers used for hepatobiliary imaging such as iminodiacetic acid (HIDA scan) and mebrofenin (Choletec™) utilize technetium-99 m. Administered doses are < 5 mGy and within the safe range for fetal exposure [42]. Although a low exposure, given alternate modalities with equivalent or better diagnostic value, hepatobiliary scans are generally avoided in pregnancy. In most institutions, use of these radiotracers requires a discussion of risks versus benefits between the patient, provider, and radiology and written consent by the patient.

Common benign biliary conditions

When pregnant patients present with RUQ or epigastric pain, initial investigations are similar to those in a non-pregnant population and include a complete blood cell count, liver function tests (transaminases and total bilirubin), serum amylase, and serum lipase. Additionally, pregnancy-related conditions that cause elevated liver enzymes such as pre-eclampsia, HELLP syndrome, acute fatty liver, and ICP must be excluded. Pelvic conditions that cause referred pain such as appendicitis or uterine-related complications (e.g., placental abruption, uterine rupture, and uterine infection) should also be considered. In general, the presentation and diagnostic work-up of benign biliary pathology in a pregnant patient are similar to non-pregnant females. The presentation of RUQ pain prompts a dedicated RUQ US, which includes imaging of the liver, gallbladder, biliary tract, right kidney, pancreas, and vasculature.

Ductal dilation and choledocholithiasis

Changes in the size of the common hepatic duct during pregnancy have not been reported [43]. However, the caliber of the bile duct may be increased in post-cholecystectomy patients. In pregnant patients with a gallbladder, identification of intrahepatic (3 mm) or extrahepatic ductal dilation (6 mm) on US performed for RUQ should prompt investigation of the underlying cause. MRI/MRCP should be considered when there is concern for distal bile duct obstruction (Fig. 3c).

Cholelithiasis and biliary colic

Asymptomatic gallstones are observed incidentally in 1–3.5% of pregnant women and generally do not require any further follow-up or management. However, gallstones may become symptomatic in 0.05–8% of patients, which requires further investigation and possible treatment [44, 45]. Historically, pregnant women with biliary colic were managed conservatively with close monitoring, expectant management, and elective surgery in the post-partum period.

Gallstones are mainly divided into cholesterol stones (90%) and pigment stones (10%). Pure cholesterol stones contain > 95% cholesterol content by weight, while mixed cholesterol stones contain > 50% cholesterol content by weight. Pigment stones contain excess bilirubin with < 20% cholesterol [46]. All gallstones generally appear as mobile, hyperechoic foci within the gallbladder lumen on US, with posterior acoustic shadowing (Fig. 2a). These features can be useful for differentiating between gallstones and hyperechoic gallbladder sludge, which often lacks associated posterior acoustic shadowing. Additionally, color Doppler imaging of gallstones may demonstrate a "twinkling artifact" that can be useful for diagnostic confirmation, especially for small gallstones. Paradoxically, a gallbladder full of stones may be difficult to visualize due to a large amount posterior acoustic shadowing that can be mistaken for bowel gas. In this scenario, the sonographic wall-echo-shadow sign, the sequential appearance of the hyperechoic gallbladder wall, a thin hypoechoic stripe of bile, and the hyperechoic shadowing gallstones, can help to distinguish cholelithiasis from bowel gas [47].

On MR imaging, gallstones will appear as T2 hypointense filling defects within the gallbladder. Cholesterol stones tend to demonstrate corresponding T1 hypointensity, while pigmented stones more commonly demonstrate T1 hyperintensity (Fig. 3c). Heavily T2-weighted MRCP sequences may show round or oval signal voids within the gallbladder (Fig. 3c), with the bile otherwise appearing T2 hyperintense.

Acute cholecystitis

The diagnosis of acute cholecystitis during pregnancy is similar to non-pregnant patients. A positive Murphy's sign, the arrest of inspiration during palpation of the RUQ due to pain, is pathognomonic of acute cholecystitis. While a hepatobiliary nuclear medicine scan is thought to be the most sensitive imaging modality for the diagnosis of acute cholecystitis, US is the most commonly performed initial diagnostic examination in pregnant patients given accessibility, ease of use, and lack of ionizing radiation. US offers a sensitivity and specificity of 65% and 89%, respectively, while MRI offers a sensitivity and specificity of 88% and 89%, respectively, for diagnosing acute cholecystitis [48].

Classic US features of acute cholecystitis include a distended gallbladder, the presence of hyperechoic shadowing gallstones, gallbladder wall thickening (> 3 mm), and a positive sonographic Murphy's sign (Fig. 3a). MR imaging will demonstrate similar imaging features, including gallbladder wall thickening and pericholecystic fluid or fat stranding, best seen on T2-weighted fat-suppressed sequences. Importantly, the finding of gallbladder wall thickening is not very specific for the diagnosis of acute cholecystitis,

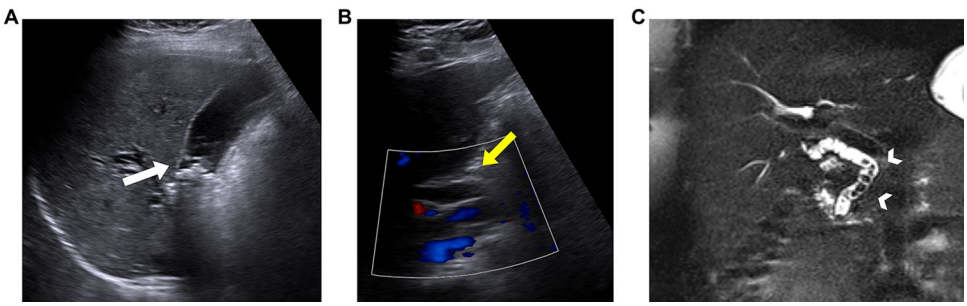

Fig. 3 Biliary colic and choledocholithiasis in a 23-year-old pregnant patient (27 weeks). **a** Patient was evaluated with RUQ ultrasound, which demonstrated cholelithiasis without a positive Murphy's sign or secondary features of cholecystitis (white arrow). **b** The visualized proximal CBD was dilated to 1.0 cm (yellow arrow). **c** The patient underwent MRI and MRCP, which showed choledocholithiasis in the mid and distal CBD (white arrowheads). No imaging features suggested cholecystitis. This patient then underwent ERCP, which confirmed choledocholithiasis. Stone removal was accomplished by biliary sphincterotomy and balloon extraction

as it can also be seen in chronic cholecystitis, malignancy, fluid overload, and various other hepatobiliary pathologies. Fat-suppressed T2-weighted imaging can help distinguish acute from chronic inflammation, which would suggest acute cholecystitis by the presence of patchy T2 hyperintense foci in the thickened gallbladder wall (Fig. 4c) [49].

Choledochal cysts

A choledochal cyst is a rare congenital malformation of the biliary tree that can occur anywhere along the biliary tract. Although commonly diagnosed in childhood, adult cases may be more frequently diagnosed during pregnancy. Pregnant patients become symptomatic due to the mass effect from the enlarging uterus, which results in pain, jaundice, cholestasis, cholangitis, or rupture [50]. Prior biliary surgeries (e.g., choledochojejunostomy and hepaticojejunostomy) can also predispose to ascending infection (Fig. 5a).

Choledochal cyst in pregnancy can pose a diagnostic challenge in part because modalities that utilize radiation such as CT or ERCP are often avoided in this population. Additionally, as mentioned above, US may have limited ability to evaluate the biliary anatomy in pregnant patients due to the challenges of a gravid body habitus. By contrast, MRI/MRCP can provide a detailed evaluation of any abnormal cystic dilation of a portion of the intrahepatic

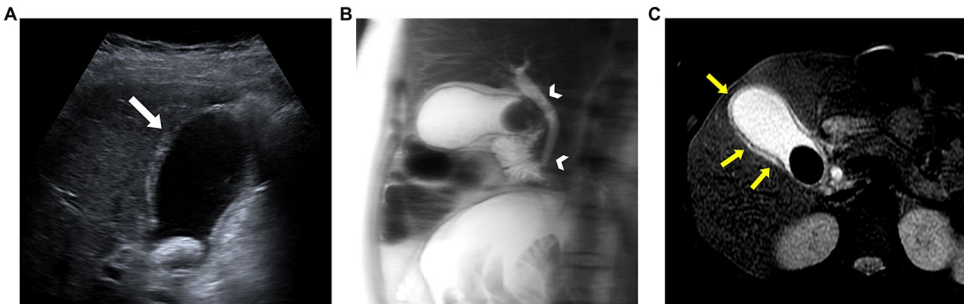

Fig. 4 Acute cholecystitis without choledocholithiasis in a 37-year-old female pregnant female (24 week, 0 days) that presented with epigastric pain for 3 days. **a** RUQ US demonstrates a moderately distended gallbladder with a large echogenic, shadowing gallstone (~ 3.0 cm) in the gallbladder neck, thickened gallbladder wall measuring up to 0.6 cm (white arrow), and a positive Murphy's sign, consistent with acute cholecystitis. The common bile duct (CBD) was mildly dilated to 0.7 cm and the distal CBD obscured (not shown). **b** The patient underwent MRI and MRCP to exclude choledocholithiasis. Coronal thick-slab MRCP image demonstrates the intrauterine gestation, T2 hypointense gallstone at the gallbladder neck, thickened gallbladder wall, and extrahepatic ductal dilation to 0.9 cm without obstructing stones and smooth tapering to the ampulla (white arrowheads). **c** Axial T2-weighted imaging with fat saturation demonstrates patchy foci of T2 hyperintensity in a thickened-appearing gallbladder wall which also suggests cholecystitis (yellow arrows). The patient underwent laparoscopic cholecystectomy. Histologic evaluation was compatible with cholelithiasis with acute on chronic cholecystitis

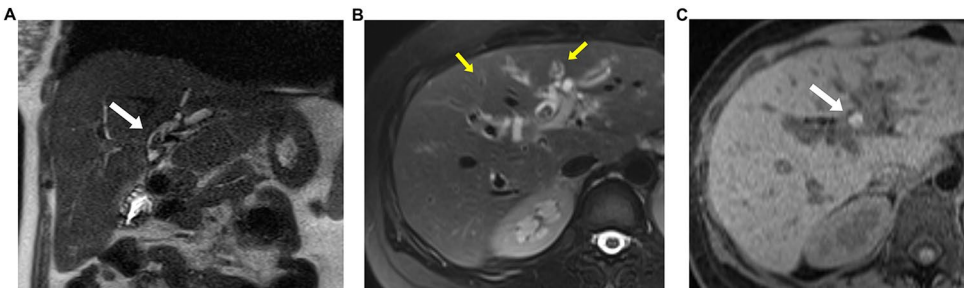

Fig. 5 Ascending cholangitis in a 39-year-old pregnant patient (12 weeks, 1 day) with history of type 1 choledochal cyst status post-choledochojejunostomy prior to pregnancy. The patient presented with severe RUQ pain, fever, jaundice, confusion, and sepsis with hypotension (Reynolds' pentad). **a** Coronal T2-weighted images demonstrated a dominant stone in the left intrahepatic bile duct, left intrahepatic biliary ductal dilation, and ductal wall thickening (white arrow). **b** Axial T2-weighted fat-saturated imaging demonstrated a left intrahepatic stone and intrahepatic ductal dilatation, as well as peri-portal edema (yellow arrow). **c** Axial T1-weighted imaging demonstrated the left hepatic stone is intrinsically T1 hyperintense. The patient underwent percutaneous transhepatic left internal–external biliary drain placement with interventional radiology during admission rather than ERCP due to hemodynamic instability requiring ICU admission. After multiple exchanges, the drain was ultimately removed 6 months after placement

or extrahepatic biliary tree and complications such as cyst rupture [50].

Cholangitis

Ascending cholangitis arises due to obstruction of the common bile duct (CBD), which allows gastrointestinal bacteria to ascend the biliary tract. The typical presentation includes Charcot's triad of fever, RUQ pain, and jaundice. Even without the use of contrast, T2-weighted MR imaging can demonstrate features of cholangitis such biliary wall thickening, peri-portal edema, and hypointense debris within the intrahepatic ducts (Fig. 5). US may be able to demonstrate similar findings, particularly biliary ductal dilation, wall thickening, and debris within the biliary system. However, MRI generally can demonstrate these features more reliably in both pregnant and non-pregnant patients.

The incidence of primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC) in pregnancy is extremely rare. A retrospective case series of 61 pregnant patients with PBC and PSC from 10 centers over 20 years reported higher rates of pre-terms births but no significant adverse maternal outcomes. Although imaging with US and MRI/MRCP is often requested to assess active cholangitis or disease progression, no consensus statements or recommendations exist on the management of pregnant women with cholestasis due to these autoimmune diseases. Use of ursodeoxycholic acid is suggested during pregnancy and patients are cautioned about the risk of preterm birth [51, 52].

Pancreatitis

Pancreatitis is a rare occurrence in pregnancy, with an estimated incidence between 1 in 1000 and 1 in 12,000 pregnancies [53, 54]. Gallstones remain the leading cause of acute pancreatitis during pregnancy. Less common causes include hypertriglyceridemia and certain medications [53]. Anatomical changes to the female in second and third trimester, such as displacement of bowel or constipation, may hinder evaluation of the pancreas by US and can also limit detection of CBD stones, if present. Hence, MRI offers to the ability to detect cholelithiasis, choledocholithiasis, pancreatitis, and complications (Fig. 6). On MRI, the parenchymal edema in the pancreas often manifests as loss of the normal T1 hyperintensity and increased T2 signal with visible peri-pancreatic fluid (Fig. 6B).

In cases requiring intervention, pregnancy may be a risk factor for post-ERCP pancreatitis [27]. However, no increased for other ERCP related events such as perforation, bleeding, and cholangitis were noted [55]. Recent literature suggests that earlier diagnosis and better treatment options have resulted in decreased maternal and fetal mortality. However, there remains a risk of preterm labor, prematurity, and in utero fetal death [53].

Gallstone Ileus

Gallstone ileus is an uncommon cause of mechanical small bowel obstruction and a rare complication of chronic cholecystitis wherein a gallstone passes through a cholecystoenteric fistula. Clinical symptoms often include chronic recurrent RUQ pain with acute nausea/vomiting whenever a gallstone becomes lodged at the ileocecal valve. Classical imaging features of gallstone ileus are the so-called Rigler's triad, which includes air in the gallbladder or biliary tree, a right lower quadrant gallstone, and a small bowel obstruction.

Other indications

If RUQ pain is due to obstructive hydronephrosis or renal colic, a RUQ US or dedicated retroperitoneal US will accurately demonstrate features of obstruction such dilated renal pelvis and calyces, renal enlargement, perinephric stranding, and ureter caliber change [56]. Similar to gallstones, large renal stones will appear as hyperechoic foci

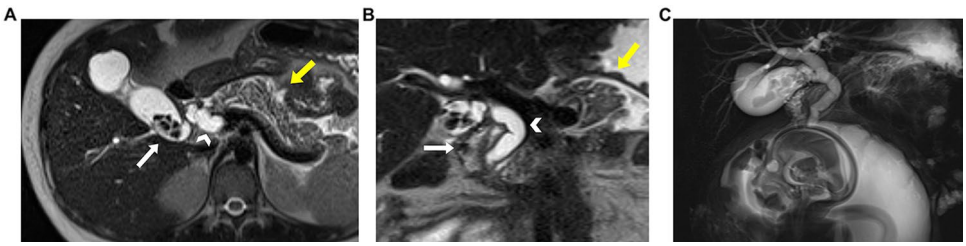

Fig. 6 Presumed gallstone pancreatitis in a 23-year-old pregnant patient (26 weeks, 0 days) who presented with severe abdominal pain radiating to the back after eating a fatty meal. **a** Axial T2-weighted images demonstrate cholelithiasis (white arrow), dilatation of the CBD (arrowhead), and peri-pancreatic fluid and edema (yellow arrow). **b** Coronal T2-weighted imaging demonstrated a passed gallstone in the duodenum (white arrow), dilatation of the CBD (arrowhead), and peri-pancreatic fluid and edema (yellow arrow). **c** MRCP image demonstrates cholelithiasis, peri-pancreatic fluid, normal caliber pancreatic duct, and fetus. ERCP was deferred due to absence of an obstructing CBD stone. The patient was treated with laparoscopic cholecystectomy during hospital admission without complication to the fetus

with associated posterior acoustic shadowing and possible associated "twinkling artifact" on US. In cases with clinical concern for an ascending urinary tract infection, the changes associated with pyelonephritis on US are observed approximately 25% of the time. Imaging features include segmental hypoechoic areas due to edema with decreased vascularity on power Doppler in acute cases, hyperechoic areas in cases complicated by hemorrhage, and shadowing foci of gas in cases of emphysematous pyelonephritis [57]. Appendicitis, the most common cause of hospitalization in pregnant patients, can present with referred RUQ pain which often prompts a right lower quadrant US to look for a blind-ending tubular structure with a thickened wall, large diameter, hyperemia, and fat stranding or for complications, such as free fluid or fluid collection. In ambiguous cases with continued high clinical suspicion, an MRI is often requested for evaluation rather than CT, given the higher specificity for appendicitis (100% vs. 94%, respectively) and lack of ionizing radiation [58].

Imaging abnormalities are rarely present in HELLP syndrome. A retrospective review found that only 3 of 586 patients with perinatal HELLP syndrome/pre-eclampsia had any positive imaging findings [59]. The most frequent abnormal imaging findings of HELLP are hepatic subcapsular and/or intraparenchymal hematoma and rupture. No specific imaging findings for intrahepatic cholestasis of pregnancy (ICP) have been described. However, MRCP may be useful for differentiating choledocholithiasis from ICP due to overlap of the clinical and biochemical presentation [60]. Similarly, cases of acute fatty liver can be diagnosed on clinical and biochemical presentation. Although US may demonstrate diffusely increased echogenicity of the liver parenchyma with US beam attenuation and dual echo MRI may demonstrate intracytoplasmic lipid, these findings are non-specific.

Further management considerations

Conservative management

Patients who are admitted to the hospital are commonly offered conservative management with a surgical consultation (Fig. 7). Conservative watchful management of biliary colic due to uncomplicated gallstone disease includes bowel rest, intravenous hydration, and pain control (opioids). If biliary colic persists despite conservative management, then laparoscopic cholecystectomy should be considered. A high frequency of recurrent symptoms and hospital readmissions (38–72%) is observed in patients who do not respond to conservative management. With recurrent acute episodes of biliary colic, the chances of gallstone disease-induced complications such as acute cholecystitis, obstructive biliopathy, and gallstone-induced pancreatitis are increased (up to 27%) [61].

Surgical

Guidelines from the Society of American Gastrointestinal and Endoscopic Surgeons and American College of Obstetricians and Gynecologists recommend laparoscopic cholecystectomy to be performed for acute cholecystitis during any trimester [22, 62]. Recent analysis of United States national data demonstrates that approximately 60% of patients admitted to the hospital with acute cholecystitis were managed nonoperatively. Risk-adjusted analyses

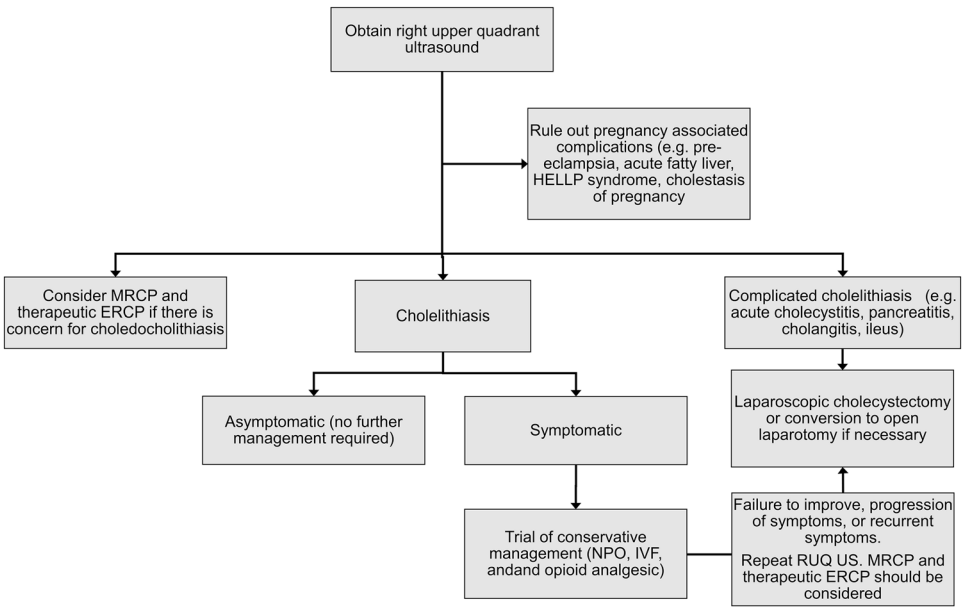

Fig. 7 Management of gallstone pathology during pregnancy adapted from reference [3]. A RUQ ultrasound is requested in the setting of suspicious physical exam findings and laboratory values (e.g., white blood cell counts, liver function tests, serum lipase). *ERCP* endoscopic retrograde cholangiopancreatography, *MRCP* Magnetic resonance cholangiopancreatography, *HELLP* hemolysis, elevated liver enzymes, and low platelets, *IVF* Intravenous fluids

showed that not undergoing cholecystectomy was associated with significantly increased maternal-fetal complications during the index admission [odds ratio 3.0 (95% confidence interval 2.08–4.34), $P < 0.01$] and increased 30-day readmissions [odds ratio 1.61 (confidence interval % CI 1.12–2.32), $P < 0.01$] [63].

Non-surgical

As stated, ERCP in pregnancy is only performed when therapeutic intervention is intended [64]. Sphincterotomy is known to improve gallbladder motility (Fig. 2) [65]. Guidelines for the management of biliary pathology during pregnancy by the American College of Gastroenterology strongly advocate for intervention with ERCP for patients needing management of gallstone pathology related complications (e.g., gallstone pancreatitis and symptomatic choledocholithiasis with or without cholangitis) [36].

Interventional radiology procedures such as percutaneous cholecystostomy and percutaneous transhepatic biliary drainage (PTBD) can be considered in patients who are not candidates for surgery (laparoscopic or open) or ERCP (Fig. 5). Percutaneous cholecystostomy is performed under US guidance using a transhepatic and transperitoneal approach with placement of an external draining catheter within the infected gallbladder in patients with severe acute cholecystitis or gallbladder perforation [66, 67].

PTBD is a suitable alternative which places an external or internal-external bile duct catheter/stents in patients unfit for ERCP. However, no studies have assessed PTBD effectiveness in pregnant patients. Traditionally, combined fluoroscopic and US guidance is used to access the biliary system. Although an attractive alternative, limited investigations exist on the success of US-guided PTBD [68, 69].

Conclusion

Given the rising incidence and increased risk of biliary and gallbladder pathologies during pregnancy, radiologists and referring providers should become familiar with the available imaging modalities and evolving treatment options for pregnant patients presenting with RUQ pain. Non-ionizing radiation techniques such as US and MRI/MRCP provide multiplanar imaging of gallbladder and biliary pathologies during pregnancy. In particular, MRI/MRCP offers excellent soft-tissue contrast and spatial resolution to troubleshoot difficult cases, particularly when anatomical changes during pregnancy can obscure pathology by US. The diagnostic information from imaging provides valuable information on pathologies as providers pursue more definitive and less conservative management of pregnant patients. Future work could focus on investigating robust-abbreviated MRCP protocols, non-GBCAs for MR imaging, and the use of lower radiation techniques, such as photon-counting detector CT.

Author contributions All authors made substantial contributions to the conception or design of the work; drafted the work or revised it critically for important intellectual content; approved the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding No funding or research support for this article.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Conflicts of interest No conflict of interest or competing interests.

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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