ERCP in Pregnancy

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Bahar Madani and Paul R. Tarnasky

Introduction

Pregnancy is associated with an increased frequency of gallstones and related disease. Studies worldwide have reported the prevalence of biliary sludge as 5–31 % and cholelithiasis ranging from 2–12 % [1–4]. Physiological changes during pregnancy increase risk of cholesterol stone formation through estrogen-induced bile lithogenicity and progesterone-induced biliary stasis [5].

Most pregnant women with cholelithiasis remain asymptomatic and stones are likely to clear spontaneously during the postpartum period. However, up to one third of pregnant patients with cholelithiasis are at risk of biliary colic [1, 2]. Assuming 3 % prevalence for gallstones of which 5 % become symptomatic, even a conservative estimate is that 1/1000 pregnant women suffer from symptomatic cholelithiasis [6]. More severe complications including acute cholecystitis, cholangitis, and acute pancreatitis occur in less than 10 % of the symptomatic patients [7]. Following appendectomy, acute cholecystitis is the second most common indication for non-obstetric-related surgical intervention. The incidence of acute cholecystitis in pregnant women with gallstones is 0.05-0.08 % [8]. Generally, conservative management is provided while safely delaying any intervention until after delivery or the second trimester when surgical intervention is relatively safer.

Patients with symptomatic choledocholithiasis relapse frequently (58−72 %) and usually require repeated hospitalization [9]. Choledocholithiasis during pregnancy is uncommon and occurs in 1 out of every 1200 deliveries [10]. Choledocholithiasis and its related complications are the most common indications for ERCP during pregnancy. The rate of performing ERCP in pregnancy has been reported as 1 in 1415 births [11]. Due to the relapsing nature of biliary symptoms, performing ERCP in the setting of choledocholithiasis may be indicated to decrease the chance of recurrences and potential fetal and maternal complications.

Case Presentation

A 20-year-old Hispanic woman, gravida 1 para 0 at 35 weeks of gestation, was transferred to our institution for further evaluation and management of biliary colic.

She developed abdominal pain 5 days prior to transfer. The pain was located in the epigastric and right upper quadrant areas without radiation, and was worse with food and associated with nausea. She presented to her local emergency department with worsened pain and vomiting. She denied any fever, chills, jaundice, or diarrhea.

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P. R. Tarnasky (✉)
Methodist Dallas Medical Center, 221 West Colorado Blvd., Pavilion II, Suite #630, Dallas, TX 75208, USA
e-mail: paultarnasky@mhd.com

B. Madani
Methodist Dallas Medical Center, 1441 North Beckley Ave, Dallas, TX 75203, USA
e-mail: baharmadani@mhd.com

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Her pregnancy course had been without any complications, and she denied any prior episodes of similar symptoms. Her past medical history was otherwise unremarkable.

Her initial laboratory evaluation revealed: WBC 6300/mm^3, hemoglobin 12.4 g/dl, platelet 128×10^3/mm^3, albumin 3.2 g/dL, AST 126 IU/L, ALT 102 IU/L, alkaline phosphatase 234 IU/L, total bilirubin 1.4 mg/dL, lipase 58 IU/L, amylase 96 IU/L, and PT/INR 12.8/1.0 s. Urinalysis was negative for urine protein and WBC. She was admitted to the obstetric antepartum service.

What Is the Differential Diagnosis of Abdominal Pain and Elevated Liver Function Tests During Pregnancy?

The differential diagnosis of abdominal pain and increased LFTs during pregnancy is broad; clinical presentation, diagnostic imaging, and laboratory findings can help to discern the various causes. The presenting features of biliary disease may include abdominal pain, nausea, vomiting, jaundice, pruritus, and liver biochemical test abnormalities. Presentation of gallstone disease in pregnancy is similar to nonpregnant patients. However, other complications that may occur during pregnancy should be considered as they can mimic the clinical presentations of biliary disease [12]. The differential diagnoses can be categorized according to the trimester of the pregnancy and specific abnormal laboratory findings as outlined below (Table 19.1).

Hyperemesis gravidarum usually occurs during early pregnancy and resolves before 20 weeks gestation. Elevations in the serum transaminases occur in more than half of the cases and are typically less than 1000 IU/L with serum ALT usually higher than AST. Intrahepatic cholestasis of pregnancy is characterized by pruritus and should be considered in pregnant patients during the 2nd or 3rd trimester. High levels of serum transaminases up to 500 IU/L and serum bile acids (4–10 times normal) with a normal GGTP are the usual laboratory findings. The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) is characterized by abdominal pain and occurs during late pregnancy or shortly thereafter. Transaminase elevations can occur in the several thousand ranges but the prothrombin time is normal unless complicated by disseminated intravascular coagulation. Acute fatty liver of pregnancy also usually presents in the 3rd trimester of pregnancy. Elevation of serum transaminases up to 1000 IU/L and hepatic synthetic dysfunction, such as elevated prothrombin time and hypoglycemia in severe cases, are observed. Preeclampsia can occur in both HELLP syndrome and acute fatty liver of pregnancy, but the pathophysiology is different and sometimes it is difficult to differentiate among these conditions. Preeclampsia presents with hypertension and proteinuria and elevated transaminases signifies severe disease and usually occurs in the third trimester. Acute viral hepatitis (A, B, C) and hepatitis E (in endemic countries) should always be considered in any pregnant patient with elevated serum transaminases. A prospective

Table 19.1 Differential diagnoses of abnormal liver function tests in pregnant patients

Disease	Pregnancy trimester	Laboratory abnormalities
Hyperemesis gravidarum	First	Elevated AST, ALT
Intrahepatic cholestasis of pregnancy	Second and third trimester and postpartum	Elevated serum bile acids Elevated AST, ALT, Bilirubin Normal GGTP
Acute fatty liver of pregnancy	Third trimester and postpartum	Elevated AST, ALT, Bilirubin Elevated PT/INR Hypoglycemia
HELLP syndrome	Second half of pregnancy and postpartum	Elevated AST, ALT Decreased PLT Increased LDH
Preeclampsia	Third trimester and immediate postpartum	Elevated AST, ALT HTN, proteinuria
Viral hepatitis	Any trimester	Elevated AST, ALT, bilirubin

study from the UK revealed liver dysfunction in 3% of the deliveries during a 15-month period. Preeclampsia was the most common abnormality (48%) followed by HELLP syndrome (22%), intrahepatic cholestasis of pregnancy (16%), hyperemesis gravidarum (8%), and acute fatty liver of pregnancy (4%) [13].

It is important to remember that a slight increase or decrease in some liver function tests may be seen during a normal pregnancy and may not be clinically significant. Serum protein concentrations decrease due to hemodilution in pregnancy; and therefore, serum albumin levels are significantly lower during all three trimesters. Serum alkaline phosphatase levels usually increase late in pregnancy due to production of the placental isoenzyme and an increase in the bone isoenzyme. Serum ALT, AST, and total bile acids level usually remain the same but total serum bilirubin levels decrease during pregnancy [14].

Biliary Colic

Biliary colic is characterized by recurrent postprandial episodes of abdominal pain in the epigastrium or right upper quadrant. It is caused by contraction of the gallbladder against an obstructed outlet due to a stone. The stone may fall back from the cystic duct and the pain resolves temporarily. During pregnancy, 28−31% of the patients may experience biliary colic [1, 2]. Almost two thirds of the patients who experience pain have stones larger than 10 mm in diameter [2]. Biliary pain is significantly more frequent among women with gallstones (5 of 17 patients, 29%) than among women with biliary sludge (2 of 42 patients, 5%). Disappearance of biliary sludge and stones after delivery is common and occurs in about two-thirds and one-third of women, respectively [1, 2]. Pre-pregnancy obesity and elevated serum leptin have been shown to be risk factors for development of gallbladder disease during pregnancy [3]. Biliary colic without bile duct stones is usually not associated with abnormal liver function tests.

Acute Cholecystitis

Acute cholecystitis is an inflammatory process with infection of the gallbladder as a result of cystic duct obstruction and bile stasis. The incidence of acute cholecystitis is between 1 and 8/10,000 pregnancies [8, 11]. Severe right upper quadrant pain in addition to other symptoms such as fever, tachycardia, nausea, vomiting, anorexia, and Murphy's sign should raise the suspicion for acute cholecystitis. The diagnosis is usually confirmed with ultrasonography findings. Uncomplicated cholecystitis is not often associated with hyperbilirubinemia. However, mild elevation of serum aminotransferases and amylase, along with hyperbilirubinemia, is seen in the setting of the passage of small stones and/or sludge. Marked elevation of the liver function tests indicates the possibility of a common bile duct stone, cholangitis, or Mirizzi's syndrome.

Acute Cholangitis

Acute cholangitis is a clinical syndrome characterized by fever, jaundice, and abdominal pain that develops as a result of stasis and infection in the biliary tract.

Laboratory tests typically reveal an elevated white blood cell count with neutrophil predominance, and a cholestatic pattern of liver test abnormalities with elevations in the serum alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), and bilirubin (primarily conjugated) concentration [15–17]. However, a pattern of acute hepatocyte necrosis can occur with aminotransferases as high as 2000 IU/L [18]. Cholangitis can be a common indication for ERCP during pregnancy.

Acute Pancreatitis

Acute pancreatitis is an acute inflammatory process of the pancreas, which is associated with severe epigastric abdominal pain, elevated serum

amylase, and/or lipase three times greater than the upper limit of normal. Any significant elevation of serum pancreatic enzymes should be considered clinically relevant since serum amylase and/or lipase do not normally increase during the course of a normal pregnancy [18].

When uncertain, the diagnosis may be established by further radiologic findings such as focal or diffuse enlargement of the pancreas and/or peripancreatic inflammatory changes seen on contrast-enhanced abdominal computed tomography (CT) or magnetic resonance imaging (MRI). The incidence of acute pancreatitis during pregnancy is fortunately uncommon (<10 in 10,000) [19]. In a 5-year study of over 46,000 pregnancies, the frequency of acute pancreatitis was 0.07% at one institution [9]. Acute pancreatitis in pregnancy is most often associated with gallstones, which are responsible for over 70% of the cases [8, 9, 19, 20]. Elevation in serum ALT to more than three times the upper limit of normal has been reported to be a very sensitive biomarker of biliary pancreatitis [21]. The pathogenesis of biliary pancreatitis is related to impaction or passage of a stone or crystals via the ampulla of Vater with pancreatic ductal obstruction causing activation of intra-acinar trypsinogen to trypsin. Biliary pancreatitis can occasionally be severe and associated with significant maternal morbidity [22]. Fetal loss is not uncommon (7%) in biliary pancreatitis and is as high as 30% when associated with recurrent pancreatitis [23, 24].

The second most common cause of acute pancreatitis during pregnancy is hypertriglyceridemia. In the third trimester, serum triglyceride levels rise three-fold, likely due to estrogen-induced increase in triglyceride synthesis [25]. Treatment of hyperlipidemic acute pancreatitis during pregnancy is mostly supportive.

What Are the Diagnostic Imaging Options?

Ultrasonography

Ultrasonography is a safe initial step for identifying gallbladder stones and sludge in pregnancy. Despite its high sensitivity for detection of cholelithiasis, it lacks sensitivity for identifying CBD stones. Dilated biliary ducts in the setting of abnormal liver function tests or pancreatitis raise the suspicion for choledocholithiasis.

Magnetic Resonance Imaging (MRI) and Magnetic Resonance Cholangiopancreatography (MRCP)

MRI and magnetic resonance cholangiopancreatography (MRCP) provide large field view images of the body with excellent soft-tissue contrast and images of the pancreatobiliary system [19]. Gallstone pancreatitis is often associated with small stones and sludge, which can be missed even by MRCP especially if located in the distal CBD and smaller than 5–6 mm [26–28]. MRCP is an accepted alternative imaging modality for pregnant women when more information is needed about the biliary system. Because no contrast is given during MRCP, there is no risk of renal injury. It is important to examine several views as different projection images may provide complementary information as shown in Fig. 19.1. Based on the American College of Radiology (ACR) guidance document for safe MR practice published in 2013, MRI is only indicated during pregnancy if the information cannot be acquired through other nonionizing diagnostic imaging studies, and the data will potentially affect the care of the patient or fetus during pregnancy [26]. There are no special considerations regarding performing MRI in the first compared to any other trimester of pregnancy.

Endoscopic Ultrasonography (EUS)

Endoscopic ultrasonography is highly sensitive (89–94%) and specific (94–95%) for detecting CBD stones [29, 30]. EUS has high diagnostic accuracy for detecting CBD stones; however, compared to other imaging modalities it requires sedation, an expert endoscopist, and specialized equipment. Although EUS does not allow therapeutic intervention, it is generally safe and does

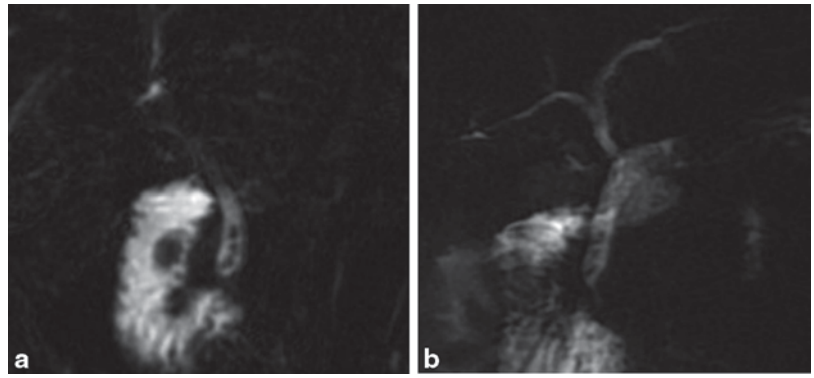

Fig. 19.1 A 21-year-old at 8 weeks gestation was referred for evaluation of suspected biliary colic due to RUQ pain, nausea, vomiting, and increased LFTs. MRCP showed several stones in the distal bile duct that are best appreciated when examining different projected images as shown here. ERCP was performed without fluoroscopy with sphincterotomy and removal of stones

not involve radiation exposure. Performing EUS prior to ERCP in patients with suspected CBD stones can help to avoid unnecessary ERCP and its complications in near two thirds of the patients [31, 32]. If a common bile duct stone is detected by EUS (Fig. 19.2), an ERCP with sphincterotomy can be performed during the same session [33, 34].

Case Continued

Abdominal ultrasonography showed cholelithiasis and moderate extrahepatic biliary duct dilation. There was no evidence of cholecystitis. A subsequent MRCP showed a dilated bile duct to 1.3 cm in diameter and multiple stones in the common bile duct. Based on the imaging findings, elevated transaminases, and her symptoms of abdominal pain and nausea, the likely diagnosis was biliary colic due to choledocholithiasis. The decision was made to proceed with ERCP.

What Are the Indications for ERCP in Pregnancy?

Choledocholithiasis and its complications are far and away the most common indication for performing ERCP during pregnancy. It is most important to understand that ERCP should only be considered when there is absolute certainty that endotherapy is necessary. The indications for performing an ERCP during pregnancy are

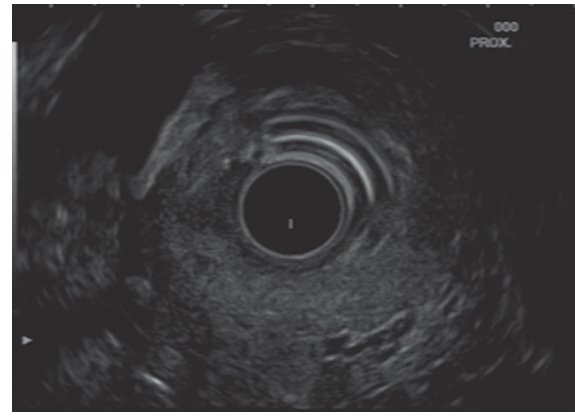

Fig. 19.2 A 26-year-old at 8 weeks gestation was referred for suspected choledocholithiasis based on increased ALT and dilated bile ducts on transabdominal ultrasonography. Endoscopic ultrasound showed a hyperechoic shadowing stone (*arrow*) in the bile duct that was removed at the same session during ERCP

Table 19.2 Indications for ERCP during pregnancy

Urgent
Acute cholangitis
Biliary pancreatitis with suspected impacted stones
Elective
Suspected symptomatic choledocholithiasis
Post-operative complications, e.g., bile leak
Relapsing pancreatitis
Pancreatic duct disruption

similar but more restricted when compared to the nonpregnant state (Table 19.2). Furthermore, if possible, ERCP should be postponed until the second trimester or postpartum.

Development of biliary disease during the pregnancy, especially in the first trimester, can result in maternal and fetal physiologic dysfunction leading to adverse pregnancy outcome such as preterm labor or low birth weight. It is important to identify complications of choledocholithiasis early during pregnancy and determine if there is a need for intervention as promptly as possible.

Not surprisingly, early reports of ERCP during pregnancy were performed for urgent indications. Baillie et al. reported the first case series of five patients in 1990. The indications were acute cholangitis in four and gallstone pancreatitis in one patient. All five patients delivered healthy babies at term [35]. Since then, ERCP during pregnancy is still almost always performed for biliary indications, but sometimes under more elective settings.

Historically, the care of pregnant patients with acute biliary related disease entailed conservative management with the hope of delaying intervention until after pregnancy or the second trimester when organogenesis is completed. While this still remains true, currently, urgent ERCP with sphincterotomy and clearance of bile duct stones is indicated in patients with cholangitis and in those with severe acute pancreatitis and evidence of persistent biliary obstruction. Elective ERCP with biliary sphincterotomy +/− stenting may be indicated when there is evidence of symptomatic CBD stones and cholecystectomy needs to be delayed due to the pregnancy or for less common reasons such as postoperative complications like bile leak (Fig. 19.3). Rarely, it may be reasonable to consider ERCP for management of pancreatitis that is not due to a biliary etiology. In the report by Jamidar et al., only 2 of the 23 pregnant patients underwent ERCP to treat a purely pancreatic indication including pancreas divisum and pancreatic duct stricture [36].

Pre-Procedure Considerations

Informed Consent

Performing ERCP in a pregnant patient is appropriate only when there are clear indications for endotherapy. The benefits and risks of the procedure should be clarified for the patient, spouse, and any other relevant family members.

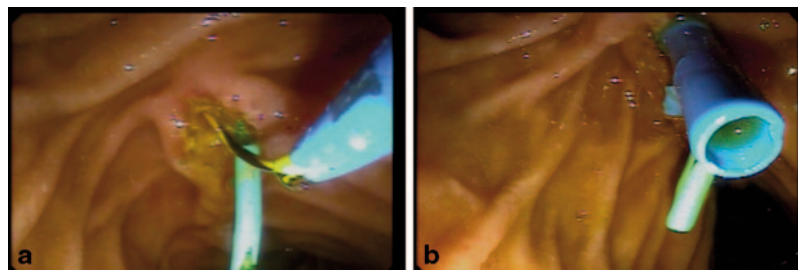

Fig. 19.3 A 42-year-old with a 21-week gestation underwent open cholecystectomy for gangrenous cholecystitis. Due to the persistent bile drainage via a percutaneous drain, she was referred for ERCP for treatment of a suspected bile leak. **a** Biliary access was obtained without use of fluoroscopy after a needle-knife access sphincterotomy over a pancreatic stent. **b** A bile duct stent was placed to ensure drainage. A postpartum ERCP was normal and the bile duct stent was extracted

The risks include not only those to the mother but also to the fetus. Complications of ERCP in general are pancreatitis, hemorrhage, perforation, infections (cholangitis, cholecystitis), cardiopulmonary complications (arrhythmia, hypoxemia, aspiration), stent-related complications (stent migration, stent occlusion, liver abscess, bile duct or pancreatic duct injury, and subsequent duct stricture), and death [37]. The fetus is sensitive to maternal hypoxia and hypotension, which can lead to fetal distress and demise. Other risks to the fetus include teratogenicity from medications and/or radiation exposure and premature birth. A full review of radiation issues will be discussed below. An informed consent for ERCP during pregnancy should include a discussion of potential risks of radiation, methods to reduce risk as well as an alternative for ERCP without any radiation. It should be clarified that ERCP without use of fluoroscopy is more difficult and therefore potentially associated with more risk from a technical aspect. Whether or not the endoscopist is comfortable with no radiation techniques (see below) should also be discussed. If patient and family are completely opposed to use of any radiation, then it is appropriate to discuss options for transfer to another expert center, if conditions allow.

Patient Positioning

Patient positioning for ERCP during pregnancy is typically different from the customary prone position used in the nonpregnant state. During pregnancy, the patient's position for ERCP depends on the trimester of her pregnancy and whether or not fluoroscopy is planned. Maintaining a prone position may be difficult during the second and third trimester, so a left lateral position with the use of a pelvic wedge, if needed, is preferable. It is generally recommended that the patient should not be completely supine since the gravid uterus can compress the vena cava or the aorta causing maternal hypotension and decreased placental perfusion [10, 38, 39]. Nonetheless, outcome of the pregnancy was not adversely affected in a study of all patients who underwent ERCP in a supine position.[38] If ERCP is performed without any fluoroscopy, then all patients regardless of pregnancy stage can remain in the left lateral position.

When monopolar electrocautery is anticipated for purposes of sphincterotomy, the return electrode (cautery pad) should be placed on the trunk or upper abdomen. This is to ensure that the uterus is not between the active and return electrodes to avoid fetal effects [40–42].

Patient Monitoring

Standard American Society of Anesthesiologists (ASA) monitoring should be utilized throughout the procedure. In the setting of a viable fetus, fetal heart rhythm should be monitored continuously or at a minimum before and after general anesthesia depending on the gestational age. Before 24 weeks, Doppler can be used to document the presence of fetal heart rate before and after the procedure. Continuous fetal heart and uterine contraction monitoring before, during, and after the endoscopy should be performed for fetuses older than 24 weeks. This should be discussed and coordinated with the obstetric team who should be consulted in all cases involving pregnant patients.

Sedation

There are potential risks to the fetus from the use of specific medications for sedation (Table 19.3). None of the medications that are used for sedation during ERCP are in category A of Food and Drug Association of the United States (FDA), so category B or C drugs may be used [10]. Category B medications are considered relatively safe while category C drugs are likely safe and category D medications should be avoided unless absolutely needed with no safer alternatives. Most ERCPs are performed using a combination of benzodiazepine and opiates or propofol and opiates. Meperidine is a category B drug and does not appear teratogenic. However, meperidine can be considered as category D when used for long periods (>36 h) in high doses at term due to concerns

Table 19.3 Medication Safety in ERCP during pregnancy

Medications	FDA category	Comment
Meperidine	B	Safe in pregnancy, avoid use at term
Propofol	B	Safe in pregnancy
Fentanyl	C	Safe at low doses
Morphine	C	Crosses fetal blood–brain barrier rapidly
Naloxone	B	Use with caution, one reported case of neonatal fatality
Flumazenil	C	Use only if clearly indicated
Benzodiazepines (diazepam)	D	Possible association with mental retardation and congenital anomalies
Midazolam	D	Preferred over diazepam, no reports of congenital anomalies, avoid in 1st trimester
Glucagon	B	Safe in pregnancy

about accumulation of its mildly toxic metabolite, normeperidine. During routine endoscopy, the maximum suggested dose for meperidine is 75 mg. Fentanyl is a category C drug as it has embryocidal effects in rats, but appears safe in humans at low doses. Propofol is classified as category B, but its use in the first trimester has been inadequately studied [7]. Benzodiazepines, including midazolam and diazepam, are category D drugs. Midazolam has not been associated with congenital abnormalities like cleft palate malformations and is preferred over diazepam when sedation with meperidine is inadequate, but if possible it should be avoided in the first trimester due to the potential fetal harm at that time. Glucagon and lidocaine are considered category B, whereas flumazenil and simethicone are rated as category C [10].

Endotracheal intubation is generally recommended for any upper endoscopy procedure due to the potential concern for aspiration as well as to maintain the airway and for a potentially prolonged, complicated procedure. Physiologic changes during pregnancy include swelling of the oropharyngeal tissue and narrower glottis opening [43].

Antibiotics

An appropriate antibiotic should be administered in cases with evidence for acute cholangitis or cholecystitis; however, selecting the right antibiotic during pregnancy can be complicated (Table 19.4). There are potential concerns regarding the transplacental passage of antibiotics leading to possible teratogenic effects on the fetus. Initial antibiotic choice is empiric and should be subsequently modified based on the organisms found in the blood and bile cultures. Most of the penicillin derivatives (amoxicillin, ampicillin, ampicillin-sulbactam, piperacillin-tazobactam), clindamycin, erythromycin, and cephalosporins are classified as category B drugs and are safe during pregnancy [19]. Metronidazole crosses the placenta and should be avoided in the first trimester [43]. Imipenem, which belongs to carbapenem class, is a category C drug, and while animal studies showed no teratogenic risks, there are no available human data [19]. Quinolones are category C with reports of adverse effects to the fetus, therefore their use should be avoided during pregnancy.

Case Continued

The decision of proceeding with ERCP was discussed with the patient's obstetrician, and we were assured of staff availability during the procedure in case of fetal distress or pregnancy related complications. Informed consent was obtained after the risks, benefits, and alternatives of the procedure were thoroughly explained. She and her husband wished to have the ERCP performed without any fluoroscopy, if possible. Standard ASA monitors were placed with the addition of fetal heart monitoring. A labor and delivery nurse was present before, during, and after the ERCP to monitor fetal heart rate and rhythm, and to monitor for uterine contractions. Preoxygenation and rapid sequence

Table 19.4 Antibiotic safety in ERCP during pregnancy

Antibiotics	FDA category	Comment
Penicillins	B	Safe in pregnancy
Cephalosporines	B	Safe in pregnancy
Erythromycin	B	Safe in pregnancy
Clindamycin	B	Safe in pregnant patients with penicillin allergy
Ampicillin- sulbactam	B	Safe in pregnancy
Piperacillin-tazobactam	B	Safe in pregnancy
Metronidazole	B	Avoid in first trimester
Quinolone	C	Avoid in pregnancy
Imipenem	C	Avoid in pregnancy
Tetracycline	D	Avoid in pregnancy
Sulfonamide	C	Avoid in third trimester

induction was then performed followed by a standard general endotracheal anesthetic. The patient was positioned in the left lateral position.

Radiation and Pregnancy

What Are the Potential Effects of Fluoroscopy During Pregnancy?

Use of fluoroscopy and spot radiography is inherent to standard ERCP procedures. Any ERCP during pregnancy that utilizes fluoroscopy will expose the fetus to potential risks of ionizing radiation with the greatest risk during 8–15 weeks gestation. There are a number of excellent and comprehensive reviews on the topic [7, 10, 38, 39, 41, 44–46].

X-ray exposure or the amount of ions per unit mass of air is measured in roentgens (R). The radiation dose of energy deposited in tissue is measured in gray (Gy) that is equal to 1 J of energy per kilogram of tissue. An equivalent of approximately 0.01 (Gy) is generated by 1 R. Ionizing radiation is measured in radiation absorbed dose (rads) and radiation equivalent man (rem), and in the international units as gray (Gy) and seivert (Sv) (1 rad = 1 rem = 0.01 Gy = 0.01 Sv).

Radiation damage is classified into stochastic and deterministic effects. The stochastic (carcinogenic) effects include childhood cancer, leukemia, and genetic effects. The probability, but not the severity, of stochastic effects increases with dose and does not have a threshold value. Conceptus dose radiation up to 1 mGy is considered insignificant but doses higher than 10 mGy (1 rad or 0.01 Sv) will require measurement of associated risks. The National Council on Radiation Protection (NCRP, 1977) raised this threshold and suggested that fetal radiation doses up to 50 mGy (5 rad) would still be considered a minor teratogenic factor and did not, by itself, justify therapeutic abortion [47].

Deterministic effects, such as growth and mental retardation depend on gestational age and conceptus radiation dose. The threshold dose is 100 mGy, above which fetal growth retardation and malformations may develop, and the severity of the effects varies with the dose. Below this level there is no risk of deterministic effects. It is recommended that fetal radiation dose should not exceed 0.5 mSv per month or 1 mSv during the first trimester with 5 mSv being the maximum permitted over the entire gestation.

Factors that can affect fetal radiation dosage depend on the energy and size of the x-ray beam, the skin surface exposure to the mother, the depth of fetus, and the size of the mother. It is estimated that the fetal dose may range between 10 and 30 % of the mother's exposure. However, fetal radiation exposure may be underestimated due to an inability to detect scatter radiation. Samara et al. developed a method for assessing the conceptus dose from ERCP procedures based on mathematical and physical phantom models. Their study revealed that the conceptus dose from ERCPs might occasionally exceed 10 mGy, the limit above which an accurate determination of conceptus dose is required by placing a dosimeter on the abdomen over the uterus. They

emphasized that the main source of radiation to the fetus during an ERCP is scattered radiation that is absorbed within the mother's body; therefore, they concluded that external shielding is unnecessary since the dose reduction is trivial. The normalized dose data derived from this study may be used for accurate estimation of conceptus dose from an ERCP performed on a pregnant patient, regardless of body size, gestational age, operating parameters, and equipment used [41]. Kahaleh et al. found a linear relationship between fluoroscopy time and fetal radiation exposure although there was up to a three-fold difference in the estimated exposure for a given fluoroscopy time. This difference makes the estimation of radiation exposure based on fluoroscopy time difficult. They concluded that fetal exposure to ionizing radiation must be kept to the absolute minimum [38]. Consultation with a radiation physicist who can provide assistance in protecting the fetus and estimating fetal exposure is helpful.

What Are the General Principles for Safe and Effective Fluoroscopy in Pregnancy?

The following strategies and general techniques to minimize radiation and maximize safety should be considered for fluoroscopy use during ERCP (Table 19.5) [40]. Short taps of fluoroscopy instead of continuous operation will limit x-ray beam exposure. Use of the last-image-hold or fluoroscopy loop-recording feature for image study, instruction, etc. will also decrease radiation exposure. The number of recorded images should be minimal or even avoided all together. Collimate the x-ray beam to the smallest field possible. This technique will decrease the amount of scatter radiation striking the fetus in proportion to the exposure area. The image quality will also improve by reducing the amount of scatter radiation reaching the image receptor. The x-ray tube should be placed as far as possible from the patient with the image receptor as close as possible to the patient. This action will not only improve image quality but also decrease patient dose. Magnification mode should be used sporadically and if absolutely necessary. Placing a lead shield over the uterus can prevent direct fetal exposure. However, because the fetus is exposed to scatter radiation, this will provide only a diminutive amount of dose reduction [41]. If digital fluoroscopy is available, it is preferred over film-screen radiography because it requires significantly lower dose of radiation during image acquisition. The fluoroscopy store feature to save the last-image-hold images instead of acquiring a separate digital image should be used. A low-dose-rate setting is recommended with digital fluoroscopy. Advances in ERCP cannulation techniques are probably most important toward the goal of minimizing or eliminating risk of radiation (see next section).

Table 19.5 Techniques to reduce radiation exposure during ERCP in pregnancy

Use short taps of fluoroscopy instead of continuous operation
Use digital fluoroscopy if available
Collimate the x-ray beam to the smallest field possible
Avoid magnification of fluoroscopic image
Use fluoroscopic videotaping for documentation when needed instead of spot radiographs
Position patient as close as possible to the image receptor and as far as possible from the x-ray tube
Adjust patient position and use shielding to minimize fetal radiation exposure
If possible delay ERCP from first trimester to second trimester to avoid fetal radiation exposure during organogenesis
Minimize procedure time

ERCP Strategies and Techniques in Management of Pregnant Patients

Normally, fluoroscopy is used during ERCP to evaluate biliary anatomy, confirm, and monitor stone(s) and guidewire, catheter, or sphincterotome positions in the bile duct, and document ductal clearance. Some modified ERCP strategies and techniques are required in the setting of pregnancy as outlined in the algorithm (Fig. 19.4). Such techniques are focused on limiting or eliminating the use of fluoroscopy and replacing it with alternative means of confirming biliary access and duct clearance.

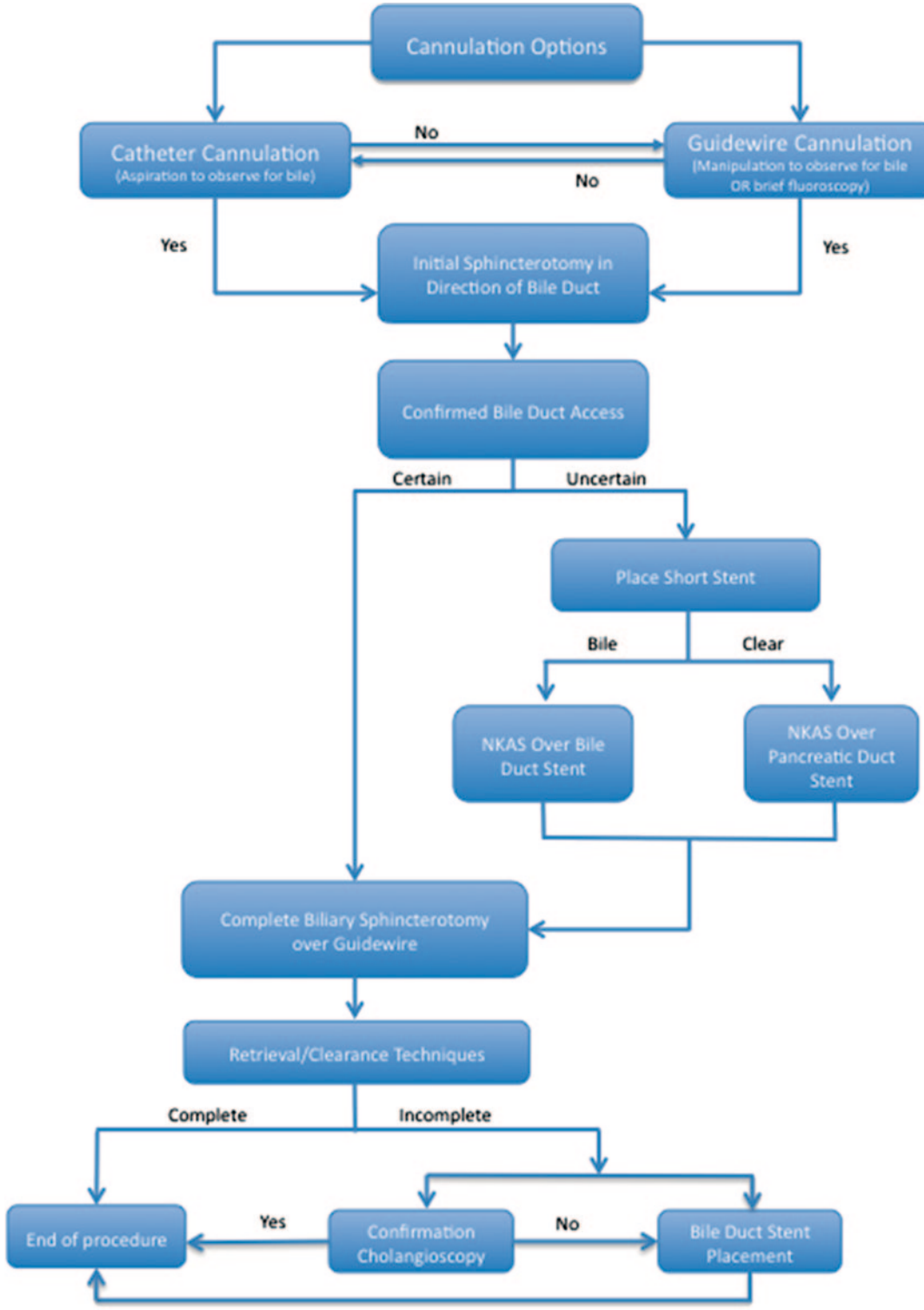

Fig. 19.4 Suggested algorithm for cannulation and confirmation of biliary access and ductal clearance for ERCP during pregnancy. *NKAS*: needle-knife access sphincterotomy

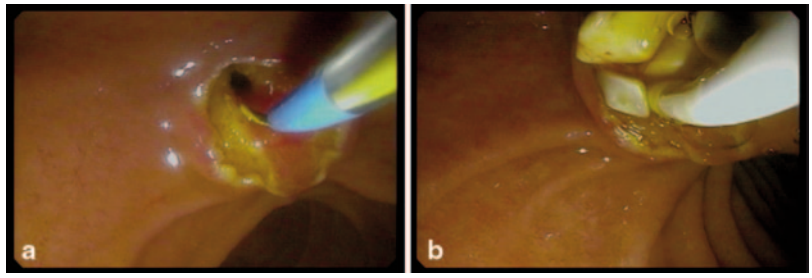

Fig. 19.5 A 27-year-old at 21 weeks gestation presented with jaundice and numerous stones were noted on MRCP. ERCP was performed without fluoroscopy with sphincterotomy and removal of stones. Biliary access and drainage becomes obvious after a complete biliary sphincterotomy (**a**) and then stone retrieval (**b**) can be accomplished

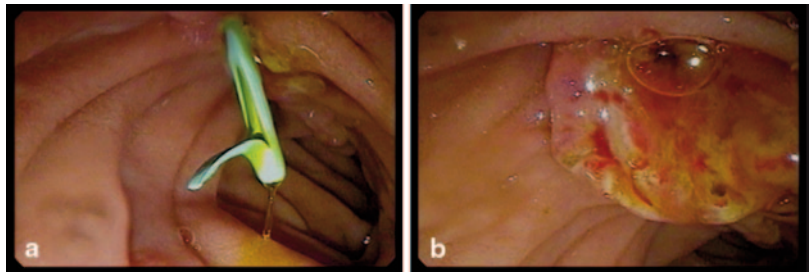

Fig. 19.6 A 29-year-old at 9 weeks gestation presented with her second attack of biliary pancreatitis in 2 weeks. The papilla was prominent and biliary cannulation could not be confirmed after manipulation of the guidewire. **a** A short 5F stent was placed, which appeared to angle in the direction of the bile duct, and bile was observed draining from the stent. **b** Sludge was noted to drain after completing the biliary sphincterotomy

As almost all ERCP procedures during pregnancy are therapeutic with interventions that include sphincterotomy, most endoscopists begin cannulation attempts using a sphincterotome preloaded with a guidewire. Usually wire-guided cannulation is performed without contrast injection, and the wire is carefully advanced to an observed distance of approximately 10–15 cm over which the sphincterotome is introduced into the duct. [48] Alternatively, cannulation can be performed by advancing the sphincterotome with or without a guidewire several centimeters into the duct. The standard method to confirm biliary cannulation is by applying manual suction using a syringe attached to the sphincterotome and observing for bile. An alternative approach to confirm bile duct cannulation entails manipulation of the guidewire to open the sphincter and promote bile drainage around the guidewire [34]. If biliary cannulation is confirmed, then sphincterotomy can be started along the intraduodenal segment in the direction of the bile duct (Video 19.1 and Fig. 19.5).

If biliary cannulation is uncertain after either guidewire access or manipulation or an initial sphincterotomy, then we typically place a short (2–3 cm) 5F stent over the guidewire and observe the stent direction and color of drainage via the tip and side flaps. The stent may or may not have proximal flaps. If the stent does not have proximal flaps, it may migrate out during the procedure. If the stent angles in the direction of the bile duct and/or bile clearly drains from the stent, then biliary access is certain (Fig. 19.6). Biliary sphincterotomy can be initiated with a sphincterotome after cannulating alongside the indwelling stent with a guidewire or with a needle knife using the stent as a guide. The biliary stent can be removed following guidewire access if it has not already migrated out spontaneously.

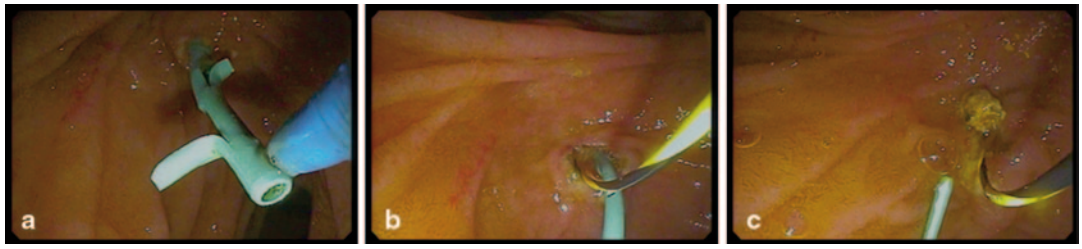

Fig. 19.7 A 21-year-old at 8 weeks gestation was referred for evaluation of suspected biliary colic due to RUQ pain, nausea, vomiting, and increased LFTs. MRCP showed several stones in the distal bile duct (See Fig. 19.1). Guidewire cannulation was obtained without any fluoroscopy. **a** A short 5F stent without internal flaps was placed, which appeared to angle in the direction of the pancreatic duct and drained clear fluid. **b** A needle knife access biliary sphincterotomy was performed, **c** followed by stone extraction. The pancreatic stent migrated out spontaneously while extracting stones

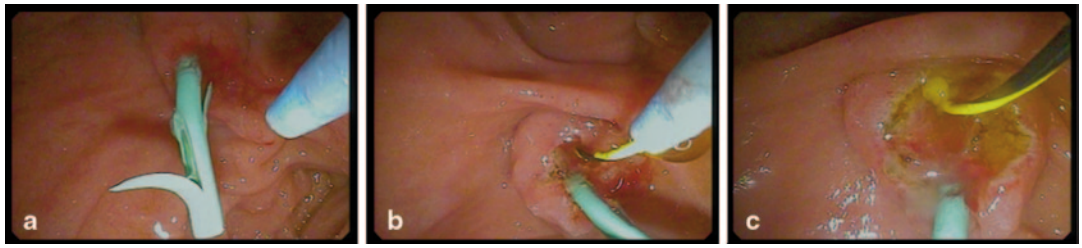

Fig. 19.8 A 16-year-old with a 6-week intrauterine pregnancy presented with biliary colic, marked elevations in LFTs, and an MRCP showing a distal bile duct stone. Guidewire cannulation was obtained without fluoroscopy and a short 5F stent without internal flaps was placed. **a** The stent appeared to angle in the direction of the bile duct but only drained clear fluid from the side flap. **b** Biliary access was obtained after needle knife sphincterotomy over the pancreatic stent. **c** The biliary sphincterotomy was completed with a papillotome followed by stone extraction

If the stent angles in the direction of the pancreatic duct and/or only clear fluid or no fluid drains from the stent, then biliary access should be considered unlikely, and instead, one should assume that the pancreatic duct has been entered (Fig. 19.7). Sometimes the stent may appear to angle in the direction of the bile duct but with clear and not bilious fluid draining (Fig. 19.8). Again, one should assume that the pancreatic duct has been accessed. In this situation, biliary cannulation can be attempted with a guidewire over the stent. An experienced operator may consider performing an access biliary sphincterotomy with a needle knife using the pancreatic stent as a guide. The stent can be removed at the end of the procedure if it has not already migrated out, and if not, left in place to reduce the risk of post-ERCP pancreatitis. If the endoscopist does not have the expertise to proceed with a high-risk access sphincterotomy, an alternative would be to discontinue the procedure and consider repeat ERCP by another operator. The pancreatic stent may remain in situ if the repeat ERCP is planned within the next few days.

When there is evidence of an impacted stone, a needle-knife access sphincterotomy over the stone is reasonable. After biliary access and initial sphincterotomy are achieved by one of the methods described above, the sphincterotomy may be completed, if necessary, followed by stone retrieval and any other necessary maneuvers.

Ensuring ductal clearance can be difficult when performing ERCP with limited or even no fluoroscopy. Without fluoroscopy one cannot document location of the stones, balloon catheter manipulations, and confirmation of clearance.

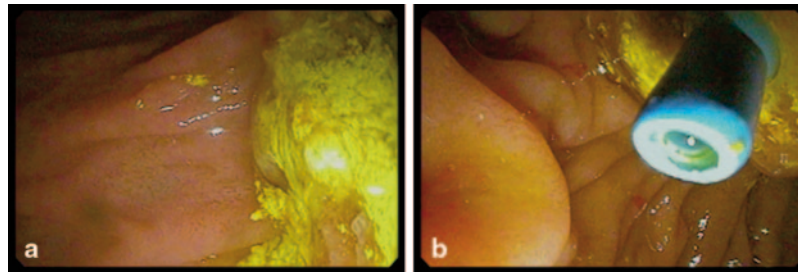

Fig. 19.9 A 23-year-old at 29 weeks gestation presented with biliary colic and multiple stones seen on MRCP. **a** An ERCP was performed without fluoroscopy and abundant stones and sludge were repeatedly removed with a balloon catheter. Cholangioscopy with a Spyglass catheter showed residual stones and sludge. **b** A 7 cm long 7F biliary stent was placed to ensure drainage. An ERCP was performed 1 month after delivering a healthy boy at which time the biliary stent and multiple stones were removed

Prior imaging can provide a reasonable estimate of the number of stones allowing some confidence of ductal clearance by observing the number of stones retrieved into the duodenum. We typically perform several "negative" balloon sweeps after stone extraction(s) before considering the procedure complete.

Cholangioscopy allows direct visualization of the biliary tree and provides an alternative to fluoroscopy for stone visualization without apparent adverse outcomes during pregnancy [33, 34, 49, 50]. Limitations include the need for proper equipment and operator expertise and prolonged procedures with longer sedation times. A mother–daughter system may require two operators [33]. The single operator SpyGlass system (Boston Scientific, Marlborough, MA) can be used as designed with the SpyGlass optical catheter inserted into the SpyScope [50, 51]. We typically use only the SpyGlass catheter [34] via a standard ERCP catheter, sphincterotome, or needle knife accessory (Video 19.2). Imaging by this method may be adequate but often inferior due to the limited ability to achieve directional control of the optical catheter.

There are some reports of bile duct stent placement to ensure drainage if uncertainty remains over stone clearance [34, 48]. This is reasonable if prior imaging demonstrated significant stone burden, repeated balloon sweeps continue to retrieve stones, and/or many stones are seen on cholangioscopy (Fig. 19.9). Because stent occlusion remains a potential complication, follow-up ERCP must be performed postpartum for stent removal and further endotherapy (Fig. 19.10).

Case Continued

A duodenoscope was introduced through the mouth and advanced to the second portion of the duodenum. Brief endoscopic survey of the stomach and duodenum was normal. The major papilla was notable for evidence of an impacted stone. The common bile duct was successfully cannulated using a straight-tipped guidewire technique (Video 19.1). Bile was noted to drain from around the guidewire, confirming biliary cannulation. Biliary sphincterotomy was performed using a papillotome over the guidewire. Following sphincterotomy, sludge drained spontaneously. No fluoroscopy was used, and neither pancreatography nor cholangiography was attempted. One bile duct stone was extracted using a balloon catheter. Several balloon sweeps were performed. Cholangioscopy using Spyglass catheter showed biliary sludge without evidence of residual stones or Mirizzi syndrome (Video 19.2).

The following day, her abdominal pain, nausea, and vomiting, had subsided. There was no concern for post-ERCP pancreatitis, and her diet was advanced without difficulty.

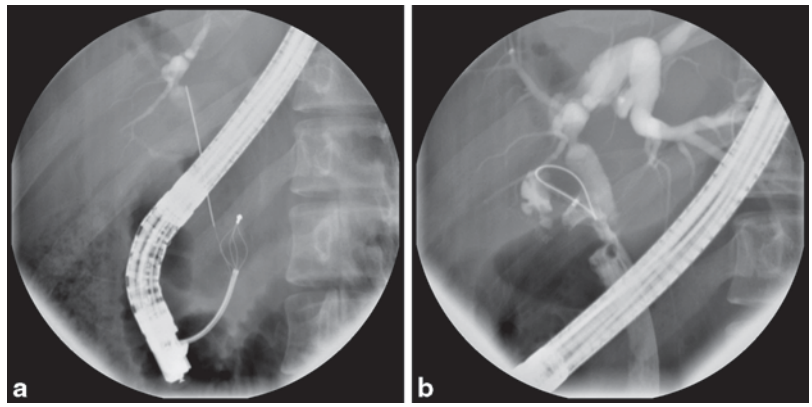

Fig. 19.10 A 22-year-old at 34 weeks gestation was referred for jaundice and suspected bile duct stones due to persistently elevated LFTs. An MRCP prior to referral showed dilation of the gallbladder, cystic duct, and bile duct with a very obvious distal filling defect. An ERCP without fluoroscopy was performed with removal of a bile duct stone. The duct did not appear clear of debris on cholangioscopy so a 7 cm long 7F biliary stent was placed. She had an uneventful delivery and underwent cholecystectomy and ERCP postpartum. **a** Following stent extraction, mechanical lithotripsy was required to remove a distal bile duct stone. **b** A second stone was removed with a balloon catheter from the cystic duct remnant

Outcomes After ERCP During Pregnancy

Technical Aspects

Many reports on ERCP during pregnancy represent anecdotal experiences from expert centers, and there are no established guidelines on the topic. As mentioned earlier, Baillie et al. published the first reported case series in 1990 of five pregnant patients who all underwent ERCP with sphincterotomy using fluoroscopy and delivered healthy babies at term. Fluoroscopy time was under 10 s, no spot radiographs were obtained, radiation exposure was measured with dosimetry badges to document fetal exposure, and lead shields were utilized [35]. In 1990, the first reported ERCP without using fluoroscopy and using needle-knife papillotomy for an impacted CBD stone in a pregnant patient was published [52]. The actual first non-radiation ERCP was performed in 1988, but reported in 1991 [53]. Gall bladder stent placement during pregnancy in addition to bile duct stone removal was reported in 1993; this procedure required about 4 min of fluoroscopy [54]. In 1994, two reports of successful ERCP without fluoroscopy described the bile aspiration technique to confirm biliary access [55, 56].

A relatively large multicenter experience described the first reported case of post-ERCP pancreatitis during pregnancy, albeit in a patient with a primary pancreatic indication [36]. In the only prospective study, ten patients underwent biliary stenting without sphincterotomy [57]. One patient needed a second ERCP during pregnancy to remove an impacted stone after sphincterotomy. The remaining patients required postpartum ERCP for stent extractions, two of which were complicated by proximal stent migrations. Radiation exposure was carefully reported (range 30–90 s, mean 45 sec, 18 mrad). The authors proposed that this strategy might be safer than sphincterotomy with initial attempts at ductal clearance and may require less radiation exposure. This approach, however, has not become popular likely due to need for repeat procedures and potential stent-related complications.

About 10-years-ago, a single center experience reported on the safety of ERCP in 15 pregnant patients [58]. Although fluoroscopy and spot radiographs were used and more than half the patients underwent diagnostic ERCP only, the authors concluded that ERCP during pregnancy

should be performed using safety measures and only when there is a therapeutic intent. This report spurred two letters describing small series of non-radiation ERCP during pregnancy with therapy performed in all cases [59, 60]. Since then, experience with ERCP during pregnancy has dramatically expanded in the last decade.

The largest series published by Tang et al. involved 65 patients who underwent 68 ERCPs during pregnancy [11]. Nearly half the ERCPs occurred during the third trimester with a calculated rate of ERCP in pregnancy of 1 per 1415 births. Median fluoroscopy time was 1.45 min. Nearly all patients underwent biliary sphincterotomy and biliary stenting was performed in 15 patients (22%) for biliary strictures or concern for retained stone. Post-ERCP pancreatitis was diagnosed in 11 patients (17%) with one patient graded as severe, which is a higher rate than reported in other studies.

Maternal Risks

Pregnant patients are exposed to the same general risks of ERCP as nonpregnant patients. These include acute pancreatitis, cholangitis, post-sphincterotomy bleeding, and perforation. Pancreatitis is the most feared complication with isolated reports of over 10% rate of post-ERCP pancreatitis [11, 61]. Cappell pooled data on 296 patients from 46 studies of ERCP during pregnancy [44]. Fortunately, the overall rate of post-ERCP pancreatitis (6.4%) was similar to nonpregnant patients. The risk for maternal bleeding after sphincterotomy (1%) was also within the expected range. None of the cases required surgical intervention to stop bleeding. No biliary or gastrointestinal perforation occurred after sphincterotomy.

Fetal Risks

Development of hepatobiliary diseases may lead to adverse pregnancy outcome such as prematurity, fetal loss, and low birth weight. Use of ionizing radiation during ERCP will add to the fetal risks of teratogenicity and carcinogenesis, which may take years to appear. Based on several animal studies and human observational studies of atomic bomb survivors, radiation exposure in the first trimester during which organogenesis occurs has the highest risk of adverse effects on the fetus. The average reported radiation exposures from available ERCP series range from 4 to 310 mrad [35, 38, 57, 58], which falls within the acceptable range. In a study that included 17 first trimester patients who underwent ERCP, 15 patients were followed to delivery. Preterm delivery occurred in 20% of this group compared to 5% in the 44 patients who completed ERCP during the second or third trimesters [11]. None of the 59 patients who were followed until delivery had spontaneous fetal loss, perinatal death, stillbirth, or fetal malformation. In an Indian study by Gupta et al., the longest follow-up of fetal outcome with a mean of 6 years postpartum was reported in 11 patients who all had healthy babies. [62]. Fetal outcomes from 254 patients were described in a review by Cappell [44]. Healthy term babies were delivered by 234 patients. There were 11 preterm births, 3 late spontaneous abortions, 2 infant deaths after birth, 1 voluntary abortion, and no associated congenital malformations observed.

Back to Our Case

The patient was discharged and cholecystectomy with intraoperative cholangiogram in the postpartum period was recommended.

Indications for Cholecystectomy During Pregnancy or Postpartum

Patients with biliary colic should initially be managed with supportive care but those with recurrent symptoms during pregnancy will often need consideration for cholecystectomy. Indications for surgery in pregnancy also include severe symptoms, obstructive jaundice, acute cholecystitis intractable to medical management, and peritonitis [19]. More than 50% of the patients have recurrent biliary symptoms with a higher rate of fetal loss (up to 12%) in patients

managed conservatively [63, 64]. Similarly, from a study of 9714 pregnant patients who underwent cholecystectomy, those who underwent surgery had significantly lower maternal (4.3 vs. 16.5 %) and fetal (5.8 vs. 16.5 %) complications compared to patients treated nonoperatively [65]. For patients with biliary pancreatitis, the relapse rate exceeds 70 % when not treated surgically before delivery [9]. If surgery is necessary during pregnancy, the second or early third trimester are generally considered the safest. During this period, organogenesis has been completed and the uterus is not large enough to occupy the operative field. An early study from the 1980s reported that spontaneous abortion was nearly twice as likely in patients undergoing surgery during early pregnancy compared to nonpregnant patients [66]. More recent experience suggested that cholecystectomy and even common duct explorations can occur safely at any time during pregnancy although this is a minority opinion [67]. Retrospective studies comparing open and laparoscopic cholecystectomy reported no significant difference in maternal or fetal outcomes [23].

Postpartum cholecystectomy is indicated in patients who had evidence of complications of choledocholithiasis including a passed common bile duct stone or biliary pancreatitis. Since gallstones and sludge frequently resolve after pregnancy, the decision to proceed with surgery should include further imaging to confirm the presence of stones and the patient's desire for having subsequent pregnancies.

Key Points

- Pregnancy associated hormonal changes increase the risk of gallstone formation.
- Complications related to gallstones during pregnancy may benefit from therapeutic ERCP.
- Consultation from the obstetrics team should be obtained to help manage pregnant patients.
- ERCP should be performed only when there is a strong indication for endotherapy to treat choledocholithiasis and its complications, such as biliary colic, acute biliary pancreatitis, or acute cholangitis.
- Endoscopic ultrasonography and magnetic resonance cholangiography are appropriate diagnostic options in pregnant patients with suspected biliary tract disease because of their accuracy in detecting common bile duct stones and lower morbidity than ERCP.
- If possible, ERCP should be postponed to the second trimester or postpartum.
- Efforts should be taken during ERCP to minimize or completely avoid using fluoroscopy to prevent possible radiation exposure to the fetus.
- ERCP is overall a safe and successful therapeutic option in the management of gallstone-related complications in pregnant patients.

Video Captions

Video 19.1 In this pregnant patient with confirmed choledocholithiasis on MRCP, ERCP shows a stone at the biliary orifice. Guidewire cannulation is performed with bile seen subsequently emanating from the papilla. The wire is advanced into the bile duct, biliary sphincterotomy performed, and balloon extraction of the stone performed. No fluoroscopy was used during the ERCP

Video 19.2 In the same patient, cholangioscopy using the optical fiber of Spyglass preloaded into a cannula shows biliary sludge without evidence of residual stones

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