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ERCP in the Management of Choledocholithiasis in Pregnancy

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Abstract The physiological changes of pregnancy increase the risk of gallstone formation, and choledocholithiaisis is the most common indication for endoscopic retrograde cholangiopancreatography (ERCP) during pregnancy. ERCP has been performed during pregnancy for over 20 years. Despite the apparent efficacy and lack of adverse fetal outcomes in published case series and reports, there remains a concern for the use of fluoroscopy during pregnancy. Recent focus has centered around avoidance of the use of fluoroscopy during ERCP, including the use of alternative techniques to confirm biliary cannulation and ductal clearance. The benefits of these techniques over traditional ERCP technique are unclear. In this article, we will review the epidemiology of gallstone disease during pregnancy, outline the risks of ERCP during pregnancy, and describe recent novel techniques in endoscopic biliary intervention for biliary drainage and ductal clearance.

Keywords ERCP · Bile duct · Pregnancy · Gallstones

Introduction

Management of gallstone-related complications in pregnancy will always remain a pertinent issue, since the physiological changes of pregnancy predispose maternal gallstone and biliary sludge formation. Endoscopic retrograde cholangiopancreatography (ERCP) has been performed during pregnancy for over 2 decades and, when performed appropriately, appears to be safe, with maternal outcomes similar to those in a nonpregnant cohort and with no significant fetal adverse outcomes. However, the theoretical risks associated with radiation during fluoroscopic exposure to the fetus, the lack of high-quality prospective studies in this domain, and the lack of long-term fetal outcome data still raise questions as to the optimal management strategy for choledocholithiasis in pregnancy. Few advances have been made in recent years to alter management in this patient subgroup. While newer endoscopic techniques that accompany or complement ERCP in the management of choledocholithiasis have recently been described, its role is largely dependent on operator expertise, and its advantage over traditional techniques is yet to be established. This review will focus on the critical issues surrounding ERCP during pregnancy and will explore how recent studies may impact on current clinical practice.

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Gallstone Disease in Pregnancy

Gallstone-related complications are relatively common during pregnancy, being the second most common indication for non-obstetric-related surgical intervention. Reports have found the incidence of biliary sludge and cholelithiasis to be 5 %–31 % and 2 %–11 %, respectively [1, 2]. Maringhini et al. prospectively followed 272 pregnant women from Italy and found that 67 of these women developed biliary sludge and 6 developed gallstones during pregnancy. Only two patients with biliary sludge developed biliary pain, as compared with five with gallstones [1]. The physiological changes of pregnancy increase the risk of development of cholesterol stones through estrogen-induced increase in cholesterol secretion and progesterone-induced reduction in bile acid secretion. Progesterone also reduces gallbladder

contraction, promoting biliary stasis [3]. Complications of gallstones, including acute cholecystitis, cholangitis, and acute pancreatitis, are thought to occur in only 10 % of symptomatic patients [4]. Therefore, the true incidence of choledocholithiasis is low during pregnancy [5]. Pancreatitis was noted to occur in 0.07 % of pregnancies over a 6-year period of over 46,000 pregnancies at one institution [6].

Choledocholithiasis and Pregnancy

Choledocholithiasis and its associated complications remain the most common indication for ERCP during pregnancy. Tang et al. retrospectively identified all ERCPs performed in pregnant patients over a 6-year period and found their rate of ERCPs in pregnancy to be 1 in 1,415 births [7•]. Similar to the nonpregnant population, acute pancreatitis remains a highly morbid complication of choledocholithiasis during pregnancy. While maternal and fetal death as a consequence of complications of choledocholithiasis is uncommon, relapse of symptoms is common and is found to occur in 58 %–72 % of cases [6–8], usually associated with repeated hopsitalizations [6]. It is therefore recommended that ERCP be performed when choledocholithiasis arises to minimize risk of relapse.

Risks of ERCP During Pregnancy

Data on the safety of any procedure during pregnancy are largely based on retrospective case series, due to the difficulty of conducting trials in this patient cohort. For this reason, limitations relating to publication bias may underestimate the risks. Risks to the patient are theoretically similar to those in the nonpregnant state. The additional risks of ERCP during pregnancy center around potential complications to the fetus. The risks to the fetus with endoscopic intervention must therefore be weighed against the risks to the fetus and patient in the absence of intervention.

Radiation

The main concern for performing ERCP during pregnancy centers around radiation exposure to the fetus during fluoroscopy. Ionizing radiation is considered a teratogen, and ERCP therefore poses additional risks to the fetus, when compared with gastroscopy (EGD) alone, which is considered to be safe. In general, the radiation dose used in pregnancy is significantly lower than the threshold dose required for fetal malformation, otherwise known as the deterministic effect. Above this threshold, the likelihood and severity of radiation-induced effects increase. The carcinogenic effect of radiation is thought to occur at a lower radiation dose, of which the exact value is uncertain.

Measuring Radiation Exposure

X-ray exposure is measured in units called roentgens (R), the amount of ions per unit mass of air. The dose of energy deposited by X-rays in tissue is measured in gray (Gr), which is equal to 1 joule of energy per kilogram of tissue. One R generates an equivalent of approximately 0.01 Gr. Ionising radiation exposes patients to other forms of radiation in addition to X-rays. The unit for equivalent doses of radiation is known as the sievert (Sv). The Sv and Gr are equivalent in diagnostic X-rays [9].

Factors affecting the total absorbed dose of X-rays include the energy and size of the X-ray beam, the skin surface exposure to the mother, the depth of the fetus, and the size of the mother. While lead shielding over the fetus can minimize direct X-ray beam and external scatter exposure, internal scatter of radiation from the mother remains a major risk. Therefore, minimizing overall radiation use with collimation and short exposure time remain key. Fetal exposure is estimated to be around one third of the mother's if no shield is used. It is estimated that if the fetus is 5 cm from the edge of the radiation field, the dose to the fetus is 10 % of the entrance dose to the mother [10].

Estimated Radiation Exposure

In general, the determinisitic effects threshold has been estimated to be around 100 mSv [11•]. In the first trimester, exposure of less than 1 mSv is recommended, with a total recommended exposure of less than 5 mSv during the entire gestation. Published series on estimated dose exposure to fetus during ERCP have ranged from 0.1 to 3 mSv [12–14]. There are some concerns that this could be an underestimation due to lack of detection of scatter radiation. Samara et al. have used mathematical and physical anthropomorphic phantoms to mimic patients during various stages of pregnancy in an effort to estimate conceptus dose exposure during routine ERCP. This model factored scatter radiation into the equation. On the basis of their model, exposure of more than 10 mGy can easily occur if extra precautions are not taken to minimize radation [11•]. Kahaleh et al. highlighted the linear relationship between fluoroscopy time and fetal radiation exposure. However, it was also noted that there was up to a threefold difference in the estimated radiation exposure for a given fluoroscopy time [12], making estimates of radiation exposure based on fluoroscopy time alone difficult. However, this work supports the principle of minimizing fluoroscopy time as a variable in reducing overall radiation exposure.

Sedation

None of the most common medications used for sedation during ERCP have been given category A in the U.S. Food

and Drug Association categories for drugs used in pregnancy. However, cautious use of sedation appears to be safe [15]. Most ERCPs are performed using a combination of benzodiazepines and opiates or propofol and opiates. Meperidine is rated category B drug during pregnancy but category D when used for long periods (>36 h) at high doses at term, due to concerns about accumulation of its mildly toxic metabolite, normeperidine. Fentanyl is classified category C but has been used at low doses without any untoward effects. There are limited human data on propofol, but it has been classified as category B drug. Its use in the first trimester has been inadequately studied. There have been concerns in the past about a possible association between diazepam and cleft palate [16], but this finding has not been duplicated in subsequent studies [17, 18]. There have also been reports associating diazepam and mental retardation and neurological and cardiac defects, and this drug has therefore been rated category D. Data on midazolam are limited, but there has been no reported association with cleft palate. Midazolam has also been rated category D but is preferred over diazepam due to its relative paucity of reported problems. Naloxone is rated category B but should be used sparingly since there has been one report of a neonatal fatality associated with its use [19]. Flumazenil is rated a category C drug, with minimal published literature and, therefore, unclear long-term effects.

Clinical Series

There are multiple case series, the majority being retrospective, reporting outcomes of ERCP during pregnancy. Overall, they report favorably, although lack of extended longitudinal data may potentially underestimate complications. Baillie et al. reported the first case series, of 5 patients, in 1990. Fluoroscopy was kept to <10 s. All patients underwent biliary sphincterotomy. One premature, and four healthy full-term deliveries were observed [20]. The only prospective study to date involved 10 patients who underwent biliary stenting without sphincterotomy. One patient required a second ERCP for an impacted stone that was subsequently removed after sphincterotomy. No maternal or fetal complications were seen [21].

More recently, Tang et al. published one of the largest series, involving 65 patients. Of the patient cohort, 85 % were of Hispanic ethnicity. Six patients underwent MRCP prior to ERCP, 4 being positive for choledocholithiasis. Median fluoroscopy time was 1.45 min. All patients underwent biliary sphincterotomy. Choledocholithiasis was found in 51.5 %, 3 patients had biliary strictures, and 2 patients had Mirrizi's syndrome. Biliary stenting was performed in 15 patients for biliary strictures or concern for retained stone. Two patients had a repeat ERCP during the same pregnancy: One was performed for concern of a postcholecystectomy bile leak, another for ongoing biliary obstruction secondary to an impacted stone despite the presence of a biliary stent. A third patient had two ERCPs in consecutive pregnancies for stone disease after failing to follow up after a biliary stent was inserted during the first ERCP. Eleven cases (16 %) of acute pancreatitis were seen. Of the 59 patients who had records available postpartum, there were five premature births, with no fetal abnormalities evident [7•]. Only one of the five preterm births had post-ERCP pancreatitis; another patient required cholecystectomy during pregnancy. Both of these patients were in their first trimester.

Tang et al.'s study has merit in being a "real-world" study, with "traditional" ERCP technique being performed. While acute pancreatitis rates were higher than standard, the authors argued that several patients may have had atypical pain related to pregnancy with a hyperlipasemia that may not have truly represented pancreatitis. Preterm birth rates were comparable to those in matched controls.

Cappell et al. pooled 46 studies involving 296 patients in a comprehensive review of published maternal and fetal outcome data. This included the study of Tang et al. While such summative data has its limitations, the lack of high-quality controlled studies in this area makes this observational data valuable. In the 296 cases, 235 sphincterotomies were performed, and 52 stents were placed. Maternal complications were rare; they are outlined below. Twenty-four patients required repeat ERCP or surgery during pregnancy, due to recurrence of biliary complications. Four patients underwent repeat ERCP for biliary obstructive complications. One patient required a repeat ERCP for biliary obstruction secondary to stent migration. Sixteen patients underwent cholecystectomy. Two patients had biliary ascariasis and required open surgery after failed attempts at ERCP. Fourteen patients had failed ERCPs, and 13 had a successful ERCP at a subsequent attempt, 12 of which were performed post partum.

Since Cappell's review, two small series have been published, both reporting positive outcomes for both patients and fetus. The use of fluoroscopy was kept to a minimum. Garcia-Cano et al. reported 6 of 11 cases without the use of fluoroscopy [22], and Krishnan et al. used fluoroscopy in only 1 of 6 cases [23]. The most recently published case series on ERCP during pregnancy involving more than five patients are outlined in Table 1.

Maternal Risks

The main patient risks relating to ERCP include acute pancreatitis, cholangitis, postsphincterotomy bleeding, and perforation. Reported complication rates in literature for ERCP during pregnancy do not differ from those for the nonpregnant

Table 1 Summary of most recently published case series on pregnancy in ERCP

Author	Year	Pt no.	Gestation	Intervention	Fluoroscopy	Complication	Fetal outcomes
Garcia- Cano [22]	2012	11	1st Tri 1 2nd tri 4 3rd tri 6	Sphincterotomy 9 Stent 2	5 cases (mean 30 s)	Hyperamylasemia 1	Nil adverse
Daas [39]	2011	10	1st tri 6 2nd tri 5 3rd tri 6 20 (8–34)	Sphincterotomy 10 Stent 4	6 cases (mean 8 s)	nil	Nil adverse
Shelton [28]	2008	21	1st tri 7 2nd tri 7 3rd tri 7 19 mean	Sphincterotomy 21 EUS 6 Choledochoscopy 5	nil	Pancreatitis 4.8 %	Preterm 1/18
Tang [7•]	2009	65	1st tri 17 2nd tri 20 3rd tri 31	Sphincterotomy 64 Stent 16	1.45 min (med)	Pancreatitis 16 % Bleed 7.4 %	Preterm delivery 5
Krishnan [23]	2011	6	1st tri 1 2nd tri 2 3rd tri 3	Sphincterotomy 6	1 case (3 s)	nil	Nil adverse
Sharma [30]	2008	11	?	Sphincterotomy 11 Stent 11	nil	Nil 1 surgery postpartum for CBD stone	Nil adverse
Bani Hani [40]	2008	10	1st tri 2 2nd tri 5 3rd tri 3	Sphincterotomy 10	10 cases ?duration	Pancreatitis 10 %	Nil adverse
Chong [41]	2010	8	1st tri 2	Sphincterotomy 5	5 cases (median 12 s)	1 lost to F/U Represent with cholangitis leading to caesarian section.	1 spontaneous abortion
			2nd tri 5	Stent 6		HELLP, PE	1 SIDS at 40 days
			3rd tri 2				
Akcakaya [29]	2009	6	1st tri 0 2nd tri 5 3rd tri 1	Sphincterotomy5 Stent 1	nil	Repeat ERCP for persistent fistula	Nil adverse

population. On the basis of the most recent pooled data published by Cappell et al. including 46 studies, the overall rate of acute pancreatitis was 6.4 %. Only one reported case of acute pancreatitis was severe, and no case required surgical intervention. Postsphincterotomy bleeding incidence was 1 %, with hemostasis achieved without surgery in all cases. No perforations were reported. Twenty-four patients required repeat ERCP or surgery. Only 4 patients developed ductal complications requiring repeat ERCP; 16 patients underwent cholecystectomy with resolution of biliary symptoms [24••].

Fetal Risks

Fetal safety includes issues related to preterm labor, teratogenicity, and fetal trauma. On the basis of animal studies and observational studies of humans exposed to radiation from the atomic bombs in Japan and the Chernobyl nuclear accident, the greatest risk to the fetus appears to occur in the first trimester [25, 26], when organogenesis occurs. There is also a high spontaneous rate of fetal loss during the first trimester. The general recommendation is, therefore, to avoid ERCP during the first trimester. The threshold for fetal malformations after 16 weeks is thought to be much higher [27]. In Tang et al.'s series, 17 first-trimester ERCPs were performed. Fetal outcome of 15 of these patients was identified. Although there were no perinatal deaths or stillbirths, the rate of preterm delivery was higher at 20 % (as compared with 4 % for the remaining patients) [7•].

Fetal outcomes of 254 patients were reported in Cappell et al.'s review; there were 234 healthy term births, 11 preterm births, 3 late spontaneous abortions, 2 infant deaths soon after birth, and 1 voluntary abortion. No associated congenital malformations have been identified [24••]. However, as the teratogenic effects of radiation to the fetus are essentially unknown, lack of longitudinal data limits weighting of risk in this situation.

ERCP Techniques

Advances in ERCP technique in the pregnant population centers around minimizing the use of fluoroscopy and radiation exposure to the fetus. Despite the lack of significant adverse fetal outcomes in published literature, the uncertainty of long-term effects of radiation on the fetus and the likely publication bias in this area still poses a significant concern to clinicians. Many variations on biliary cannulation have been described. Most have focused on avoiding the use of fluoroscopy and replacing it with an alternative form of biliary access confirmation. The decision to modify traditional ERCP techniques must be weighed against operator expertise in the modified technique and the realistic benefit one would expect when it is likely that this new technique will be less familiar to the operator.

Bile Aspiration/Visualization Techniques

There are multiple reports describing the technique of aspirating after deep cannulation into the biliary tree to confirm positioning. More recently, a modification of this technique has been described whereby wire-guided cannulation is followed by wire manipulation without engagement of the sphincterotome, assessing for bile flow along the wire. If no bile is seen to flow, a 5 Fr stent is placed over the wire, and needle knife sphincterotomy is performed over the stent, either to act as a precut technique or as direct biliary sphincterotomy [28, 29]. Others have described a two-step technique whereby a biliary stent is placed to ensure drainage, followed by completion stone clearance postpartum [30].

While these techniques may be effective in achieving biliary cannulation without the use of fluoroscopy, it does not help in ensuring adequacy of ductal clearance. Stent occlusion remains a potential complication in patients stented without attempted ductal clearance. Without the use of fluoroscopy, further imaging techniques are still required to ensure ductal clearance and biliary drainage.

Ancillary Imaging Modalities

MRCP

There are no recent reports on the safety of MRI in pregnancy. While there is a theoretical risk of tissue heating from radiofrequency pulses at higher field strengths and the effects of acoustic noise on the fetus are still unknown, there are still no reports of any adverse effect of MRI to the fetus. MRCP should be used with caution in the first trimester of pregnancy, due to the possibility of unknown adverse effects during organogenesis. However, the use MRI should not be avoided if the clinical indication is strong [31, 32].

Cholangioscopy

Direct vision of the biliary tree by cholangioscopy has recently been described by several authors as an alternative to fluoroscopy for stone visualization [28, 33, 34]. These have been case reports and small case series only. Shelton et al. included five cases of cholangioscopy-assisted ERCP in his cohort [28]; there was no comment on the procedure time in these cases. No adverse outcomes have been described in relation to cholangioscopy. Its benefit is clearly its ability to obviate the need for fluoroscopy in confirming clearance of stones from the CBD. Its use is largely limited by a prolonged procedure time (and by association, greater need for sedation), lack of operator expertise, and the need for two operators in a "mother and daughter" setup.

Endoscopic-Ultrasound-Guided ERCP

Clinical data on the safety of endoscopic ultrasound (EUS) in pregnancy are limited. Theoretically, its risks should not exceed those of standard gastroscopy, which is, overall, regarded as safe [35] (Fig. 1). There are a handful of case reports on the use of EUS during pregnancy. Shelton et al. published a series of six cases in which EUS was performed prior to ERCP in patients with suspected choledocholithiasis. CBD stones were found in two patients, and sludge in four patients [28]. It is unclear from the study how many negative EUS findings were reported from the institution. EUS seems more appropriate for patients with low to intermediate probability for choledocholithiasis, when the decision to proceed to ERCP is unclear, rather than as an

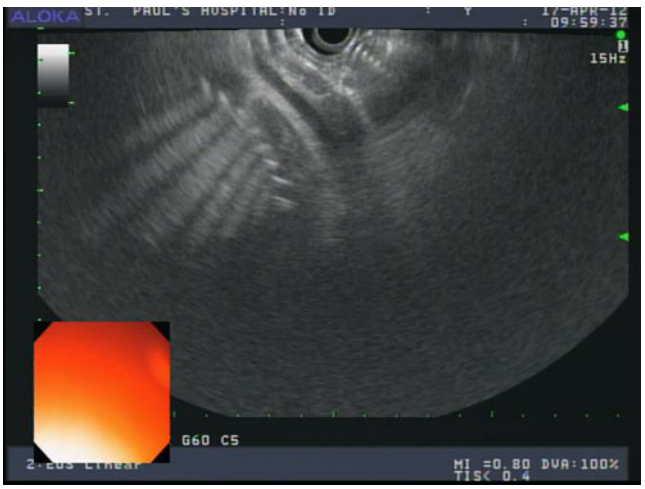

Fig. 1 Transgastric endoscopic ultrasound (EUS) image of a fetal spine at 16-weeks gestation. The mother presented with biliary colic and resolving liver function abnormalities. EUS was negative for choledocholithiasis. The patient improved without undergoing ERCP

aid to minimizing the risk associated with performing ERCP. To date, there have been no reports of EUS-guided biliary drainage or EUS-assisted rendezvous procedures in pregnancy; given the availability of less invasive options for biliary access, the risks of this approach would seem unjustifiable in its current phase of development [36].

Transabdominal-Ultrasound-Assisted ERCP

Standard transabdominal ultrasound and contrast-enhanced ultrasound have both been described in confirming placement of a guide wire or sphincterotome in the biliary tree [37, 38]. A recent case report describes confirmation of sphincterotome and guidewire position with injection of ultrasound contrast agent into the bile duct and subsequent visualization of the guidewire within the bile duct on ultrasound [38]. Resource constraints may limit the ability to perform this procedure at many institutions.

Current Clinical Practice

Due to the lack of high-quality evidence, it is difficult to make concrete recommendations on the optimal approach. However, the following principles should be considered when approaching a pregnant patient with choledocholithiasis:

- Informed consent about the risks and benefits of performing the procedure, including the alternative invasive and noninvasive options, should be thoroughly discussed and documented.
- Involvement of ancillary health care professionals, including obstetricians, anesthesiologists, and radiation physicists, should be considered.
- Published case series have varied in patient positioning (left lateral vs. supine) and use of fetal monitoring during the procedure, which depends on gestational period and severity of the patient's clinical state.
- Attempts to minimize radiation exposure include:
  - Keep fluoroscopy time to a minimum.
  - Collimate the beam to reduce scatter radiation.
  - Place the image receptor as close to the patient as possible.
  - Use digital acquisition imaging, which requires a lower radiation dose.
  - Use lead shielding over the uterus (although this does not reduce scatter radiation).

Alterations to standard technique may not necessarily result in improved outcomes. Traditional ERCP with attention to minimizing fluoroscopy use is still an accepted management option and is likely to be the technique used by the majority of endoscopists.

Conclusion

ERCP can be performed safely during pregnancy and remains the first-line modality for the management of choledocholithiasis and its associated complications. While newer techniques focus on avoiding the use of fluoroscopy, their benefits over traditional techniques employing minimal fluoroscopy are unclear. Recent published literature does not support a change in clinical practice but, rather, emphasizes the importance of minimizing fluoroscopy time. Individuals who are comfortable with ancillary techniques for biliary access and duct clearance may find these alternatives useful.

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