

## Continued evidence for safety of endoscopic retrograde cholangiopancreatography during pregnancy

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### Abstract

**AIM:** To report the safety of continued use of endoscopic retrograde cholangiopancreatography (ERCP) during pregnancy at various maternal ages.

**METHODS:** A retrospective chart review of pregnant patients who underwent ERCP at a tertiary academic center was undertaken between 2002 and 2012. Pertinent past medical history and initial presenting laboratory data were collected. Review of the procedure note for each ERCP performed provided documentation of lead shielding, type of sedation, fluoroscopy time, and post-procedure complications. Patients' clinical courses were reviewed until the time of delivery and pregnancy complications with fetal outcomes were examined. Data was stratified based upon the mother's age at the time of ERCP: 18-21, 22-29, and  $\geq 30$  years of age.

**RESULTS:** Twenty pregnant patients who underwent ERCP between 2002 and 2012 were identified. The mean age at the time of ERCP was 26.4 years (18-38 years) and the average trimester was the second. The indications for ERCP were choledocholithiasis in 17 patients, gallstone pancreatitis in 2 patients, and cholangitis in 1 patient. The mean fluoroscopy time of ERCP was 3.8 min (0.3-23.6 min). Sphincterotomy was performed in 18 patients with therapeutic intent and not as a prophylactic measure to prevent recurrences. Clinical documentation of use of protective shielding was found in only 8 notes (40%). Post procedure complications were limited to two cases of post-ERCP pancreatitis (10%). Elective cholecystectomy was performed shortly after ERCP in 11 of the pregnant patients. Birth records were available for 16 patients, of which 15 had full-term pregnancies. Cesarean sections were performed in 5 (31%) patients. Term birth weight was greater than 2500 g in all cases except one in which the mother had a known hypercoagulable state.

**CONCLUSION:** ERCP during pregnancy is both safe and efficacious regardless of maternal age or trimester.

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**Key words:** Endoscopic retrograde cholangiopancreatography; Pregnancy; Choledocholithiasis; Pancreatitis; Cholecystectomy; Caesarean section

**Core tip:** The incidence of choledocholithiasis during pregnancy has been estimated to be 1 in 1000. Although Endoscopic retrograde cholangiopancreatography (ERCP) remains the gold standard for treatment of symptomatic choledocholithiasis during pregnancy, there still remain safety concerns about its use. Women who conceive at "extremes of age" are at an increased risk for complications during pregnancy. Our study supports the safety and efficacy of ERCP during the peripartum period for both mothers and their newborns. Neither advanced age nor trimester in which the pro-

cedure was performed carried a higher risk for adverse outcomes during pregnancy.

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## INTRODUCTION

Pregnancy carries an increased risk for gallstone formation. Hormonal changes lead to imbalances of bile composition and secretion. Estrogen is thought to increase cholesterol secretion leading to supersaturation, while progesterone both decreases bile acid secretion and gallbladder motility<sup>[1]</sup>. Studies have shown increasing amounts of biliary sludge with trimester<sup>[2]</sup> with a rate of gallstone formation to occur in up to 12% of pregnant women<sup>[3]</sup>. It is estimated that 1 in 1000 pregnancies are complicated by choledocholithiasis<sup>[4]</sup>. Immediate and safe intervention in symptomatic choledocholithiasis has proven to be vital in preventing life-threatening outcomes to both the mother and fetus. Endoscopic retrograde cholangiopancreatography (ERCP) is currently the gold standard to treat choledocholithiasis<sup>[5]</sup>. However, there continues to be expected concern around the procedure in regards to safety of radiation exposure to the pregnant patient and unborn fetus. Furthermore, women at “extremes of maternal age” have been shown to have different risk profiles during pregnancy; young women carry a higher risk for pre-term delivery while older women are more prone to cesarean section or offspring requiring neonatal unit admission<sup>[6]</sup>. We therefore investigated the safety of ERCP during pregnancy and outcomes in regards the patient’s age during which the procedure was performed.

In this single center study we report our experience with 20 pregnant patients who underwent therapeutic ERCP by experienced endoscopist.

## MATERIALS AND METHODS

### Patient population

The patient’s history, laboratory data, hospital course, ERCP procedure, and delivery/fetal outcomes were obtained through chart review through both Rhode Island and Women and Infants Hospitals. The study was approved by both hospitals Institutional Review Board. We divided the patients into three different groups based on what has previously been performed in obstetric studies investigating outcomes/adverse events in regards to age<sup>[6]</sup>. Given the limited number of patients, we created three age brackets based on the age of the patient at the time of the ERCP procedure; teens to young twenties (18-21), mid-upper twenties (22-29), and  $\geq 30$  years old.

Term pregnancy was considered to be equal to or greater than 37 wk at time of delivery. Trimesters were broken down into the following: first trimester weeks 1-14, second trimester weeks 15-28 and third trimester weeks greater than or equal to 29. Small for gestational age when baby’s weight was less than 2500 g at delivery. Apgar scores at 5 min were used as data points, considering a score of 7 or above to be normal. Lastly, any documentation of birth defects was also noted. In regards to the maternal adverse events, documentation of post-procedure or antenatal complications was reported when available.

All laboratory data used in this study were values collected on initial presentation to the hospital. A skilled endoscopist performed all ERCPs with a therapeutic intent based on abnormal abdominal ultrasound or magnetic resonance cholangiopancreatography (MRCP).

### Endoscopic procedure

ERCP was performed with the patient lying in the left lateral decubitus position. Standard maternal monitoring during the procedure took place largely by an endoscopy nurse or by anesthesiologist if monitored anesthesia care (MAC) was administered. Sedation was largely achieved through the use of conscious sedation using combinations of intravenous fentanyl, midazolam, or meperidine. In 3 cases, an anesthesiologist administered MAC. Continuous fetal monitoring was performed by a delivery nurse on all patients at 24 wk of gestation or later. Standard practice during the procedure was that the gravid pelvis was shielded using a lead drape to limit radiation exposure to the fetus. Biliary cannulation was achieved by using a sphincterotome and was confirmed by aspiration of bile. Contrast cholangiogram was performed to visualize the presence of stones/obstruction and removal was accomplished by either balloon or retrieval basket. Sphincterotomy, when indicated, was performed by a monofilament short-tip traction sphincterotome using blended current. If indicated, plastic stents were placed. In cases of mild post sphincterotomy bleeding, epinephrine was injected or tamponade performed. Lastly, the diagnosis of post-ERCP pancreatitis consisted of the combination of abdominal pain and elevated lipase.

### Statistical analysis

This study used descriptive statistics to compare the different findings of the study. The data collected was pooled into corresponding age groups and presented as whole numbers followed by (%) or as means followed by the standard deviation (SD).

## RESULTS

### Study population

Twenty pregnant patients were identified between 2002-2012. Five patients were Caucasian, six were African American, and nine of other ethnicities. The mean age of all patients at the time of procedure was 26.4 years (18-38

**Table 1** Baseline characteristics and laboratory data

	All patients (n = 20)	Age 18-21 (n = 7)	Age 22-29 (n = 8)	Age ≥ 30 (n = 5)
Age (yr)	26.4 (6.18)	20.1 (1.21)	26.5 (2.26)	35 (3.08)
Race (Caucasian/African American/other)	5/6/9	0/2/5	2/3/3	3/1/1
Parity	2.25 (1.16)	1.42 (0.78)	3 (0.92)	2.2 (1.3)
Past medical history				
Hypertension	2	0	1	1
Hypothyroidism	1	0	1	0
History of latent tuberculosis	2	0	2	0
Depression	4	2	2	0
Asthma	1	0	1	0
Coagulopathy	1	0	0	1
Prior hepatitis B infection	2	1	0	1
Reflux disease	1	1	0	0
History of gallbladder disease	6	1	3	2
White blood cell (4.0-11.0 × 10 <sup>9</sup> /L)	8.6 (2.28)	8.42 (2.54)	9.61 (2.53)	7.54 (1)
Hemoglobin (11.7-16 g/L)	12 (1.29)	11.9 (0.88)	11.8 (1.93)	12.32 (0.23)
Platelet count (150-440 × 10 <sup>9</sup> /L)	261.1 (62.63)	263.1 (62.6)	255 (75.9)	267.2 (50.32)
AST (20-30 units/L)	163 (111.38)	127.4 (100.3)	162.1 (129.8)	214.2 (93.8)
ALT (5-32 units/L)	213.5 (214)	183.4 (165.3)	228.8 (299.7)	231 (135.5)
Total bilirubin (0.1-1.1 mg/dL)	2.6 (1.9)	2.84 (2.37)	2.36 (1.68)	2.64 (1.99)
Alkaline phosphatase (16-100 units/L)	189.1 (96)	162.8 (39.2)	223 (142.2)	171.6 (47.36)
Lipase (4-57 units/L)	1105 (1736.5)	519.7 (1258)	1669 (2104)	1025 (1719.2)

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

years). Eight patients were in the age bracket 18-21, seven in 22-29, and five ≥ 30 years old. The past medical history, parity, and initial presenting laboratory data were collected for each of the patients on admission and were then separated based on specific age groups (Table 1).

#### Indication/preventative measures/procedure outcomes

All ERCPs were performed with a therapeutic intent. The mean trimester at which ERCP was performed was in the second. The indications for ERCP were choledocholithiasis in 17 patients, gallstone pancreatitis in 2 patients, and cholangitis in 1 patient. (Table 2). The overall mean fluoroscopy time during ERCP was 3.8 min (Range: 0.4-23.6 min). The mean fluoroscopy times with respected ranges in parenthesis for the different age groups were: 6.5 min (0.4-23.6 min) Age 18-21, 2.2 min (0.4-9.1 min) Age 22-29, and 2.7 min (0.3-7.6 min) for ≥ 30 years (Table 2). Eighteen patients (90%) had biliary sphincterotomy performed during ERCP. Of the 2 remaining cases, sphincterotomy was not performed because one patient was noted to have had a prior sphincterotomy and the second patient had a normal cholangiogram. Four (20%) patients had plastic stents placed. The indication for stent placement in 3 cases was evidence of pus and to allow for ample drainage, while the last stent was placed due to prolonged procedure time (23.6 min) with an inability to completely remove the stone. Five (25%) patients were noted to have two or more stones removed from the common bile duct at the time of procedure (Table 2). Lastly, our clinical practice refers patients to a general surgeon for elective cholecystectomy after evidence of biliary obstruction and resolution with ERCP. Three (15%) patients had a prior history cholecystectomy being performed. Eleven (55%) patients had documented

cholecystectomy after having had ERCP, while six (30%) patients had no record of having the follow-up procedure (Table 2).

#### Sedation/procedure complications/antibiotic use

Seventeen patients received conscious sedation that consisted of a combination of midazolam with either fentanyl or meperidine. In the other 3 cases, MAC was administered. Regardless of the type of sedation used, there were no observed complications in regard to maternal or fetal well being. Though it was common practice in our endoscopy suite to use lead shielding to the pelvis and optimal positioning, there were only 8 (40%) instances of these preventative practices being documented in the procedure note. Post procedure complications in our patient population were limited to 2 (10%) cases of post-ERCP pancreatitis and both patients were noted to have multiple stones on ERCP (Table 2). Minor post sphincterotomy bleeding was seen in 2 cases (10%). Bleeding in both cases was controlled by either balloon tamponade or epinephrine injection at the site. Lastly, Piperacillin/Tazobactam was administered post-ERCP in 2 cases for either frank pus or suspected infectious debris post clearance of the common bile duct.

#### Fetal outcome

Birth records were available for 16 (80%) patients (Table 3). In each of the three different age groups, one patient's follow-up was lost due to delivery at an outside hospital. The additional patient, in the age group 22-29, had an elective termination of the pregnancy. Term pregnancy was seen in 15 (93%) patients. Cesarean sections were performed in 16% of patients in age brackets 18-21 and 22-29, while 75% of patients in the age bracket ≥ 30 had

**Table 2** Endoscopic retrograde cholangiopancreatography indications, outcomes, and complications

	All patients ( <i>n</i> = 20)	Age 18-21 ( <i>n</i> = 7)	Age 22-29 ( <i>n</i> = 8)	Age ≥ 30 ( <i>n</i> = 5)
Trimester	2 (0.77)	2.14 (0.89)	2 (0.92)	1.8 (0.44)
Indication for ERCP				
Common bile duct stone	17	5	8	4
Gallstone pancreatitis	2	2	0	0
Cholangitis	1	0	0	1
Protective shielding stated in note	8	3	1	4
Anesthesia				
Midazolam	17	6	7	4
Fentanyl	5	2	3	0
Propofol	3	1	1	1
Meperidine	13	4	5	4
Fluoroscopy dose/min	3.8 (5.5)	6.5 (8.5)	2.2 (2.8)	2.7 (3.0)
Spot radiographs	6	2	3	1
Sphincterotomy	18	5	8	5
Stenting	4	2	1	1
2 ≥ stones removed	5	1	1	3
Post ERCP antibiotic				
Piperacillin/tazobactam	2	0	1	1
Post-ERCP complications				
Pancreatitis	2	1	1	0
Oversedation	0	0	0	0
Perforation	0	0	0	0
Cholangitis	0	0	0	0
Contrast dye reaction	0	0	0	0
Bleeding	2	1	1	0
Cholecystectomy				
Prior history of receiving	3	0	1	2
Post ERCP	11	5	5	1

ERCP: Endoscopic retrograde cholangiopancreatography.

**Table 3** Pregnancy outcomes

	All patients ( <i>n</i> = 16)	Age 18-21 ( <i>n</i> = 6)	Age 22-29 ( <i>n</i> = 6)	Age ≥ 30 ( <i>n</i> = 4)
Term pregnancy	15	6	6	3
Caesarean section	5	1	1	3
5 min Apgar score	8.77 (0.73)	9 (0)	9 (0)	8 (1.4)
Birth weight in grams	2638 (1227)	3200 (472)	3297 (408.8)	2838 (883)
Fetal malformations	1	0	0	1

a C-section. Term birth weight was greater than 2500 g in all cases except for one which also had a cleft palate. This was attributed to the mother's significant history for clotting disorder, which had resulted in cerebral vein thrombosis in the past. This pregnancy was noted for severe intrauterine growth restriction and required induced cesarean section delivery at 36 wk. Examination of the placenta revealed extensive chronic villitis, avascular villi, and 30% of infarcted placenta. Apgar scores at 5 min were all 9, except for one score of 6 in the offspring of the patient with a known clotting disorder and required the Neonatal Intensive Care Unit (NICU) admission after birth.

## DISCUSSION

In our study, we further expound on the continued evidence for safety of ERCP during pregnancy. When management of pregnant patients with biliary tract disease can no longer be safely managed conservatively,

ERCP still proves to be an invaluable therapeutic tool for maintaining a viable pregnancy. The concern has largely focused on the fetal-radiation exposure and outcomes the procedure may have on pregnancy. The limited data of reported outcomes for ERCP during pregnancy in the current literature continues to be a barrier of comfort for even the experienced proceduralist. Although our study is limited by the number of study subjects, it nevertheless contributes to the growing body of literature that supports the continued safety of ERCP during pregnancy.

Women who conceive at a later age are at an increased risk for complications during pregnancy<sup>[7]</sup>. Advanced age carries an increased risk for spontaneous abortion, likely due to decline of oocyte quality<sup>[8]</sup>. Coexisting medical conditions such as hypertension and diabetes are more prevalent with increasing age leading to further risk during pregnancy. Older age has also been associated with increased rates of low birth weight<sup>[9]</sup>, the use of cesarean delivery<sup>[10]</sup>, increased risk of stillbirth<sup>[11]</sup>, as well as heightened pregnancy related maternal mortality<sup>[12]</sup>. Conversely, younger pregnant patients are more likely to be underweight, smoke, and have a higher risk for preterm birth<sup>[6]</sup>. The different age brackets of pregnant patients in our study did not show increased rates of spontaneous abortion, low birth rate, preterm delivery, or maternal death. One patient who was of advanced age with a significant history for pro-thrombotic state was the only patient noted to have complications requiring induction and preterm delivery due to severe low intrauterine growth



restriction and a birth weight less than 2500 g requiring NICU admission. On further analysis of the placenta she was noted to have 30% of the placental area that was infarcted, suggesting the cause of complications was due to her clotting history. Of note, the first two age brackets (18-21 and 22-29) had equivalent rates of C-section, 16%. However, in the age group  $\geq 30$ , 75% of the patients gave birth *via* C-section. We suspect that this is largely due to the already reported trend of increased rates of delivery *via* cesarean section with advancing age<sup>[6,10]</sup> and not as a result from intervention with ERCP.

Fetal radiation exposure during ERCP still remains a valid concern for the pregnant patient. Radiation exposure has been linked to congenital malformations, growth retardation, fetal death, and childhood cancer<sup>[13]</sup>. Ionizing radiation is measured in rads (radiation absorbed dose). The level that is considered to be teratogenic is between 5-10 rads<sup>[14]</sup>. The use of hard films during ERCP procedure can also be a source of radiation exposure to the fetus. The mean fluoroscopy time in our study was 3.8 min (Range: 0.3-23.6 min) that corresponded to an calculated estimated uterine dose of about 1.18 rads, well below the level of concern for teratogenic effect<sup>[15]</sup>. Furthermore, six of the patients had spot radiographs taken during the procedure. Two patients had greater than five films taken; one 7 and the other 11 and both with long fluoroscopy times of 9.1 min and 10.8 min respectively. Both patients were in the first trimester at the time of the procedure and neither pregnancy had complications documented. Efforts have been made to eliminate the need for fluoroscopy during ERCP that have relied on aspiration of bile after cannulation to confirm the location<sup>[16,17]</sup>. Fluoroscopy provides the ability to confirm complete removal of all stones and debris. This decreases the need for repeat procedures and unnecessary risk to the mother and fetus<sup>[18]</sup>. Furthermore, Smith *et al*<sup>[19]</sup> demonstrated that routine ERCP has minimal radiation exposure to the fetus and that measurement with thermoluminescent dosimeters does not appear to be necessary.

Proper positioning and shielding of the unborn fetus help to further limit radiation exposure. Having the patient in the left lateral decubitus position allows for optimal blood flow by limiting compression of the inferior vena cava and aorta by the gravid uterus<sup>[20]</sup>. Lead shielding to the uterus helps to minimize radiation exposure along with minimized procedure time. Though it was standard practice of our endoscopy unit to perform these maneuvers, documentation of these being done was found in only 40% of the procedure notes. In this era of computerized medical records, careful documentation of these preventative interventions in pregnant patients is prudent and should not be overlooked.

Performing prophylactic sphincterotomy after a normal cholangiogram is controversial. Barthel *et al*<sup>[21]</sup> performed biliary sphincterotomy in 3 patients who presented with gallstone pancreatitis and reported healthy pregnancies with no further recurrences of pancreatitis, despite no evidence of choledocholithiasis on ERCP. Tang *et al*<sup>[22]</sup> also showed that sphincterotomy could suc-

cessfully reduce recurrent pancreatitis. Though this study had high rates of sphincterotomy being performed, half of the patients who received them were also noted to have choledocholithiasis which justified its use. Prophylactic sphincterotomy can lead to biliary bacterial colonization, duodenal reflux, and may increase the risk of post-ERCP pancreatitis. In our study, sphincterotomy was only performed when clinically indicated for stone removal and was not used for prophylactic measures. Furthermore, referral to a general surgeon for elective cholecystectomy shortly after ERCP appears to be safe and does not carry a higher risk for morbidity when compared to non-pregnant patients<sup>[23]</sup>. Eleven (55%) patients had documentation of a successful cholecystectomy later on during pregnancy in our study. Heightened awareness for the safety of cholecystectomy after therapeutic ERCP, as a preventative solution to future stone complications during pregnancy, appears to be a more favorable treatment solution.

Complications of ERCP can consist of acute pancreatitis, hemorrhage, and even perforation. In prior studies, the estimated rates of post-ERCP pancreatitis have ranged from 2.6% to 15.1%<sup>[24,25]</sup>. In our study, we had 2 (10%) cases of post-ERCP pancreatitis based on the clinical exam findings and laboratory values. Our pancreatitis occurrence rate falls in between previously reported expected study rates. Both cases were mild and resolved with supportive care. ERCP during pregnancy does not carry a higher incidence rate of pancreatitis than in the general population.

The long-term effects of ERCP on offspring have not been closely studied. This is largely due to the disconnection between the endoscopist and unborn child, as well as the difficulty of following newborns prospectively. Gupta *et al*<sup>[26]</sup> followed 11 out of 18 children for a median of 6 years post-procedure. All subjects were reported to be healthy without congenital or developmental complications. This small but important study confirms our notion that when prophylactic measures are taken to limit radiation exposure during ERCP, there seem to be no adverse effects on the developing child. However, continuing to follow children overtime with the help of their pediatricians would allow for longer observation and further confirmation of our current conceived notions.

In conclusion, our study supports the safety and efficacy of ERCP during the peripartum period for both mothers and their newborns. ERCP intervention in regards to different age brackets did not appear to confer higher risk to the pregnancy than what is already reported in the literature. Rates of C-Section appear to be more prevalent with aging patients and not as a result of having ERCP during gestation. Pregnant women who had ERCP performed are also not at a higher risk for post-ERCP pancreatitis than the general population. A skilled and well-versed endoscopist is needed in order to therapeutically intervene as well as minimizing fetal radiation. Although there appears to be no long-term effects on children, further data collection needs to continue to reaffirm this. ERCP during pregnancy should include a

multi-disciplinary team approach to ensure the safety and well being of both the mother and offspring.

## COMMENTS

### Background

Pancreaticobiliary disease during pregnancy is not only common, but may also increase the risk of peripartum complications. Therapeutic endoscopic retrograde cholangiopancreatography (ERCP) remains the gold standard for treatment of symptomatic choledocholithiasis with or without pregnancy. However, there still remain concerns about the safety of its continued use during pregnancy with regards to both the mother and unborn fetus.

### Research frontiers

Modifications to ERCP during pregnancy have been proposed in an attempt to reduce the use of radiation that may have long-term consequences on the fetus. However, these measures that do not employ fluoroscopy do not afford the same diagnostic and therapeutic yield. Continued reporting of the safety of ERCP with fluoroscopy in pregnancy allows both providers and pregnant patients to have confidence that they may safely and appropriately treat biliary disease.

### Innovations and breakthroughs

Prior studies have reported safety data by trimester of pregnancy when ERCP was performed. Conversely, this study divided groups based upon the mother's age at the time of the intervention. Extremes of maternal age may portend an elevated risk of peripartum complications. However, this study did not demonstrate that a specific maternal age bracket carried an increased risk for peripartum adverse events secondary to ERCP intervention.

### Applications

These data add to existing literature that ERCP during pregnancy is safe for both the mother and fetus. Furthermore, the patient's age at the time of the procedure does not significantly impact the risk of adverse peripartum events.

### Terminology

Protective lead shielding and left lateral decubitus positioning of the patient were standard measures taken to limit radiation exposure and fetal distress.

### Peer review

This is an interesting study that has been presented in a clear, well-written manuscript.

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