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Safety of Endoscopic Retrograde Cholangiopancreatography (ERCP) in Pregnancy: A Systematic Review and Meta-Analysis

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Systematic Review/Meta-analysis

Safety of endoscopic retrograde cholangiopancreatography (ERCP) in pregnancy: A systematic review and meta-analysis

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Abstract

Background/Aims: Endoscopic retrograde cholangiopancreatography (ERCP) is a technically challenging procedure rarely associated with severe postprocedure complications. Hormonal changes during pregnancy promote cholelithiasis, but there are limited clinical data available on the outcomes of ERCP in pregnant women. ERCP techniques without irradiation were recently introduced as potential alternative. We performed a systematic review and meta-analysis to assess the safety of ERCP in pregnancy and to compare outcomes of radiation versus nonradiation ERCP.

Materials and Methods: A systematic search of PubMed, Medline/Ovid, Web of Science, and Google Scholar through April 18th, 2018 using PRISMA and MOOSE guidelines identified 27 studies reporting the outcomes of ERCP in pregnancy. Random effects pooled event rate and 95% confidence intervals (CIs) were estimated. Heterogeneity was measured by I^2, and meta-regression analysis was conducted. Adverse outcomes were divided into fetal, maternal pregnancy-related, and maternal nonpregnancy-related.

Results: In all, 27 studies reporting on 1,307 pregnant patients who underwent ERCP were identified. Median age was 27.1 years. All results were statistically significant ($P < 0.01$). The pooled event rate for overall adverse outcomes was 15.9% (95% CI = 0.132–0.191) in all studies combined, 17.6% (95% CI = 0.109–0.272) in nonradiation ERCP (NR-ERCP) subgroup and 21.6% (95% CI = 0.154–0.294) in radiation ERCP subgroup. There was no significant difference in the pooled event rate for fetal adverse outcomes in NR-ERCP 6.2% (95% CI = 0.027–0.137) versus 5.2% (95% CI = 0.026–0.101) in radiation ERCP group. There was no significant difference in maternal pregnancy-related adverse outcome event rate between NR-ERCP (8.4%) (95% CI = 0.038–0.173) and radiation ERCP (7.1%) (95% CI = 0.039–0.125). Maternal nonpregnancy-related adverse outcome event rate in NR-ERCP was 7.6% (95% CI = 0.038–0.145), which was half the event rate in radiation ERCP group of 14.9% (95% CI = 0.102–0.211).

Conclusions: ERCP done by experienced endoscopists is a safe procedure during pregnancy. Radiation-free techniques appear to reduce the rates of nonpregnancy-related complications, but not of fetal and pregnancy-related complications.

Keywords: Endoscopic retrograde cholangiopancreatography, gallstones, pregnancy

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INTRODUCTION

Physiologic changes during pregnancy are known to predispose to biliary disease.[1,2] High levels of estrogen stimulate hepatic production and secretion of cholesterol.[3,4] Rising progesterone also delays emptying of the gallbladder, which causes bile stasis and slows the release of bile acids that bind cholesterol.[3,4] Together, these lead to the development of cholesterol gallstones. This risk is higher with each pregnancy, and multiparous women are 10 times more likely to develop biliary complications [Figure 1].[5] In a prospective study of 3,200 pregnant women without cholelithiasis on baseline abdominal ultrasound (US), new cholelithiasis or bile sludge was observed in 7.1% at second trimester, 7.9% at third trimester, and up to 10.2% at 6 weeks postpartum.[6] Of these, about 1.2% developed symptoms, and 10% of those with symptoms later developed serious complications such as acute cholecystitis, cholangitis, symptomatic choledocholithiasis, biliary strictures, or biliary pancreatitis that would necessitate therapeutic intervention.[6,7]

Although the physiology of pregnancy itself increases the risk of biliary pathology, the management of these conditions in this patient population is poorly studied thus far. The mainstay in biliary intervention is endoscopic retrograde cholangiopancreatography (ERCP), which is therapeutic for many of these diseases.[8] In addition to the usual risks associated with ERCP, some inherent concerns arise in a pregnant female, including but not limited to exposure to radiation, medication teratogenicity, anesthesia, and changes in maternal anatomy.[3] The specific relative risks of these effects are not well established because current case studies are limited by small sample size. As opposed to esophagogastroduodenoscopy (EGD) or colonoscopy, ERCP requires real-time prolonged X-ray with significant amount of fluoroscopic radiation, which is a potential cause of developmental complications *in utero*. One study with 15 patients showed that on average, fluoroscopy time was 3.2 min [standard deviation (SD) ± 1.8 min] with total 3.1 millisievert (mSV) (SD ± 1.64 mSV) of radiation; in general, it is recommended during first trimester to limit exposure to less than 1 mSV, and over the entire pregnancy less than 5 mSV.[4]

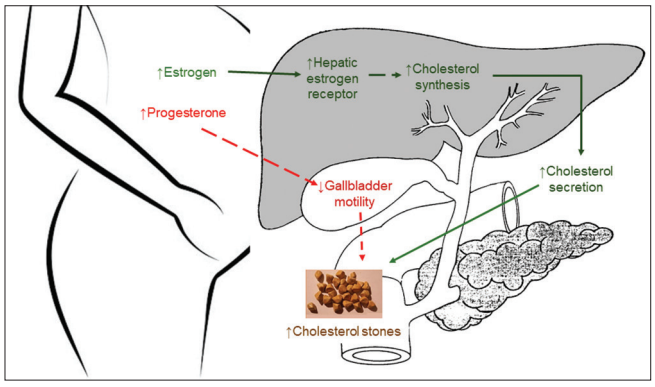

Figure 1: Pathophysiology of gallstone formation in pregnancy

Another concern is that the usual medications for sedation used during endoscopy are poorly studied in pregnant women. The most commonly used agents are propofol and ketamine.[9,10] Both drugs at moderate doses are category B drugs and considered relatively safe to use in pregnancy due to rapid onset and short duration of effect.[9,10] Of note, they require strict monitoring of levels by an experienced anesthesiologist and have not been well studied during first trimester pregnancy.[9] Other commonly used endoscopy agents such as benzodiazepines, meperidine, and narcotics are usually avoided due to their lower threshold for causing fetal neurobehavioral depression and potential birth defects.[4,9] Finally, the usual post-ERCP adverse outcomes including postsphincterotomy bleeding (PSB), infection, pancreatitis, and perforation can have greater consequences in a pregnant woman.[3] Even less documented are any potential causal links between ERCP and induction of early labor, premature rupture of membranes, or even spontaneous abortion.[11]

Due to these concerns and the precarious nature of pregnancy itself, ERCP has historically been avoided in pregnancy. With the elevated risk of biliary disease that can occur in this patient population, avoidance of therapeutic measures can also become a cause of significant morbidity and mortality.[3] Currently, the management of these complications is poorly defined, and each case is decided on an individual basis – which can lead to clinician bias and postponement of critical care. Misunderstanding and misrepresentation of best standard of practice can lead to recurrent pain symptoms, high emergency department visits, more frequent hospitalization, or even death.[12] Fear of intervention stems from lack of access to information about the exact benefits versus risks. Available studies are few and scattered, so here we present a meta-analysis of retrospective case studies on ERCP in pregnancy to compare outcomes, establish methods to minimize risk of the procedure, and have better understanding of the procedure outcomes that can be used by gastroenterologists and physicians in future patient care.

MATERIALS AND METHODS

Search strategy

We performed a literature search using the keywords "ERCP," "endoscopic retrograde cholangiopancreatography,"

"pregnancy," "endoscopy," and "fluoroscopy" in various combinations to identify original studies published in English from PubMed, Medline/Ovid, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, and Google Scholar databases, through April 18th, 2018.

Inclusion and exclusion criteria

We included studies that reported outcomes of pregnant patients who underwent ERCP. We excluded studies that reported other endoscopic procedures in pregnancy.

Study selection and data extraction

Two authors (M.A. and M.J.) independently screened titles and abstracts. They obtained full articles that met the inclusion and exclusion criteria, and after an independent review, they extracted the data. For all phases, discrepancies were resolved in consultation with two other authors (M.M. and A.H.). We also hand-searched the eligible articles. Forty-seven studies relevant to inclusion criteria were added. The actual numbers of ERCP cases were collected from tables and manuscript text in each study. When actual data were not presented in certain studies, two authors (J.Y. and M.A.) directly contacted the corresponding authors of their studies to obtain the data. Since data were from previously published studies, an institutional review board approval was waived. Finally, 27 studies were selected. Figure 2 presents the study selection process in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13] A summary of studies is shown in Table 1.[11,14-39]

Study outcomes

We divided outcomes of ERCP in pregnancy into three categories. First, fetal outcomes, which included any fetal adverse outcomes reported during pregnancy, labor, or the follow-up period like intrauterine growth retardation, congenital malformations, fetal demise, and low birth weight. Second, maternal pregnancy-related outcomes, which included any pregnancy adverse outcomes reported after the ERCP procedure such as preterm labor, preeclampsia, or bleeding. Third, maternal nonpregnancy-related outcomes, which included all ERCP-related adverse outcomes that are not related to pregnancy, such as post-ERCP pancreatitis (PEP), PSB, or cholecystitis.

Quality assessment

We used the Newcastle–Ottawa Scale (NOS) to assess the risk of bias in the included studies.[40,41] Risk of bias in relation to selection, comparability, and assessment of the exposure/outcome was assessed according to nine items using a star allocation scheme. Stars were allocated if a study was deemed to have a low risk of bias within each item, according to the coding manual provided.[42] A study was categorized as being of low risk of bias if a total of 8–9 stars were allocated, medium risk of bias if 6–7 stars were allocated, and of high risk of bias if the study was given ≤5 stars.

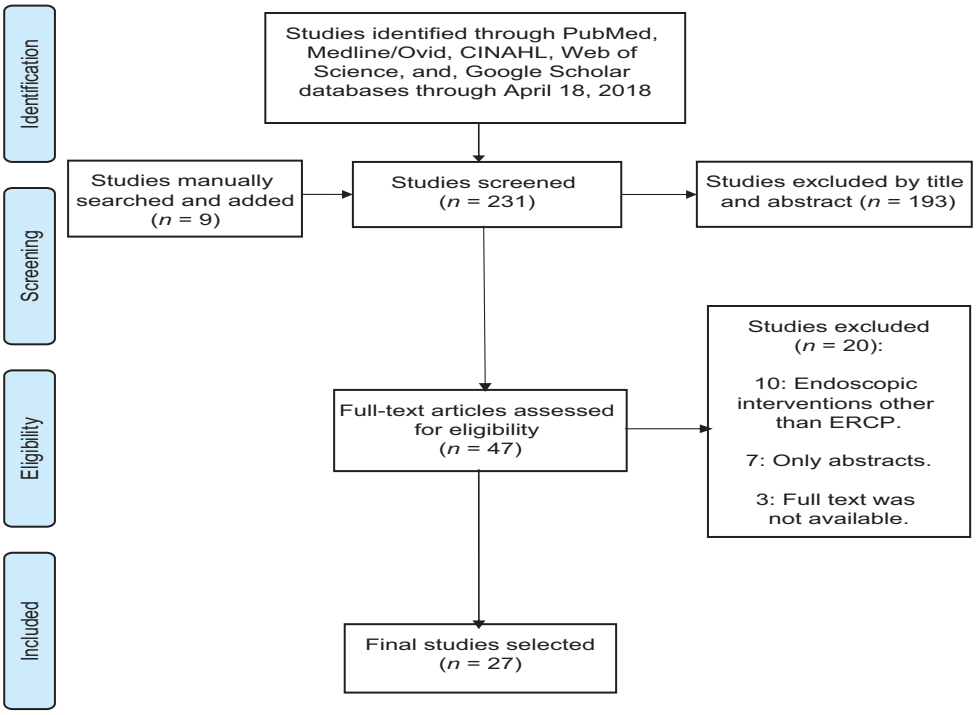

Figure 2: Study selection process

Table 1: Summary of studies

Studies	Duration	Location	Type	No. of patients	Intervention	Mean age	Mean gestational age	No of ERCP in 1st, 2nd, 3rd trimester	Fetal complications	Maternal nonpregnancy-related complications	Maternal pregnancy-related complications	Duration of FU
Ludvigsson *et al*.[14] 2017	1992-2011	Sweden	Cohort	58	ERCP unspecified	Unspecified	Unspecified	Unspecified	3 major congenital malformations	0	3 Preterm labor	Unspecified
Mali[15] 2016	1994-2014	USA	Cohort	6	ERCP unspecified	25.7	24.4 weeks	0, 1, 5	0	1 PEP	0	Unspecified
Inamdar *et al*.[16] 2016	2008-2009	USA	Cohort	907	ERCP unspecified	26.06	Unspecified	Unspecified	Unspecified	109 PEP	16 Preterm labor	Unspecified
İlhan *et al*.[17] 2016	2010-2015	Turkey	Cohort	4	NR-ERCP	Unspecified	Unspecified	Unspecified	0	0	0	Unspecified
Ersoz *et al*.[18] 2016	2002-2013	Turkey	Cohort	22	NR-ERCP	26	26	2,3,17	0	2 PEP	0	6 months
Lee *et al*.[19] 2015	2002-2013	Korea	Cohort	10	Rad-ERCP and NR-ERCP	30.7	16.8 weeks	4, 8, 1	0	1 Hyperamylasemia	0	Unspecified
Fine *et al*.[20] 2014	2002-2012	USA	Cohort	20	Rad-ERCP	26.4	second trimester	Unspecified	0	2 PEP	0	Unspecified
Yang *et al*.[21] 2013	2003-2008	China	Cohort	24	NR-ERCP	28.5	Unspecified	Unspecified	0	2 PSB	4 Preterm labor	Unspecified
Vohra *et al*.[22] 2013	2008-2012	USA	Cohort	6	NR-ERCP (ERCP w EUS)	29	25 weeks	Unspecified	0	0	0	Unspecified
Smith *et al*.[23] 2013	2001-2009	USA	Cohort	35	Rad-ERCP	25	18.9 weeks	14, 11, 10	0	2 PEP, 2 PSB, 1 ARDS (fatal) and 1 cholecystitis	0	Unspecified
Agcaoglu *et al*.[24] 2013	2007-2012	Turkey	Cohort	5	NR-ERCP	26	20 Weeks	Unspecified	0	0	0	30 days
García-Cano *et al*.[25] 2012	2002-2012	Spain	Cohort	11	Rad-ERCP and NR-ERCP	30.6	Unspecified	1, 4, 6	0	1 Hyperamylasemia	0	Unspecified
Krishnan *et al*.[26] 2011	2006-2010	India	Cohort	6	Rad-ERCP and NR-ERCP	28.3	24 weeks	1, 2, 3	0	0	0	30 days
Tang *et al*.[27] 2009	2000-2006	China	Cohort	65	Rad-ERCP	25.8	Unspecified	17, 20, 31	4 LBW	11 PEP	5 Preterm labor	Unspecified
Bani Hani *et al*.[28] 2009	2002-2007	Jordan	Cohort	10	Rad-ERCP	24.3	18.4 weeks	2, 5, 3	0	1 PEP	0	1 week
Daas *et al*.[29] 2009	2005-2009	USA	Cohort	10	Rad-ERCP and NR-ERCP	23.5	20 weeks	Unspecified	0	0	0	30 days
Akcakaya *et al*.[30] 2009	2000-2008	Turkey	Cohort	6	NR-ERCP	28	23 weeks	Unspecified	0	0	0	Unspecified
Sharma and Maharshi[31] 2008	1996-2005	India	Cohort	11	NR-ERCP (2-step ERCP)	Unspecified	Unspecified	2, 6, 3	0	0	0	4 weeks after delivery
Shelton *et al*.[32] 2008	2000-2007	USA	Cohort	21	NR-ERCP	27	19 weeks	Unspecified	1 LBW	1 PEP	1 Preterm labor	Unspecified
Gawrychowski *et al*.[33] 2007	2007	Poland	Cohort	4	NR-ERCP	36	33 weeks	0, 0, 4	0	0	0	Unspecified
Quan *et al*.[34] 2006	1997-2004	Singapore	Cohort	3	Rad-ERCP	27.8	21.5 weeks	0, 2, 2	0	0	0	Unspecified
Gupta *et al*.[35] 2005	1994-2004	India	Cohort	18	NR-ERCP (ERCP w EUS)	Unspecified	Unspecified	4, 6, 8	0	1 PEP and 1 PSB	1 Preterm labor	6 years
Kahaleh *et al*.[11] 2004	1995-2003	USA	Cohort	17	Rad-ERCP	Unspecified	18.6 weeks	Unspecified	0	1 PEP and 1 PSB	2 Preeclampsia	Unspecified
Simmons *et al*.[36] 2004	2001-2002	USA	Cohort	6	NR-ERCP	27	16 weeks	Unspecified	1 IUGR	0	2 Preterm labor	Unspecified
Tham *et al*.[37] 2003	1998-2003	USA	Cohort	15	Rad-ERCP	28.9	25 weeks	1, 5, 9	0	1 PEP	0	Unspecified
Sungler *et al*.[38] 2000	1994-1998	Austria	Cohort	5	Rad-ERCP	Unspecified	Unspecified	0, 4, 1	0	0	0	Unspecified
Barthel *et al*.[39] 1998	1991-1998	USA	Cohort	3	Rad-ERCP	20	24 weeks	Unspecified	0	1 PEP	0	6 months-2 years

ERCP: Endoscopic retrograde cholangiopancreatography; FU: Follow-up; Rad-ERCP: Radiation ERCP; NR-ERCP: Nonradiation ERCP; EUS: Endoscopic ultrasound; PEP: Post-ERCP pancreatitis; PSB: Postsphincterotomy bleeding; ARDS: Acute respiratory distress syndrome; LBW: Low birth weight; IUGR: Intrauterine growth restriction

Data synthesis and analysis

We combined individual study results to calculate the pooled odds ratio (OR) and 95% confidence intervals (CIs) using the random effects method.[43] Between-study heterogeneity was assessed using the I^2 static values of 50%, representing extensive statistical inconsistency. Subgroup analysis was performed to examine effects of irradiation on fetal and maternal outcomes. All analyses were performed using Comprehensive Meta-Analysis version 3 (Biostat Inc., Englewood, NJ, USA; 2014). A two-sided *P* value <0.05 was considered statistically significant.

RESULTS

A total of 1,307 patients from 27 retrospective studies were analyzed. Baseline characteristics from pooled study participants are reported in Table 1. The characteristics were grouped by adverse outcomes (fetal, maternal pregnancy-related, and maternal nonpregnancy-related): fetal adverse outcomes ($n = 9$), maternal pregnancy-related outcomes ($n = 22$), maternal nonpregnancy-related outcomes ($n = 143$).

Figure 3 presents the meta-analysis results of the overall adverse events in pregnant patients; the pooled event rate was 15.9% (95% CI = 0.132–0.19). The results were statistically significant ($P < 0.01$). Heterogeneity was low ($Q = 26$, $P = 0.370$, $I^2 = 6.3\%$). Inamdar *et al*.'s study could be an outlier resulting in increasing the degree of heterogeneity.[16] When this study was removed from current meta-analysis, the magnitude of pooled event rate slightly increased to 18.1% (95% CI 0.144–0.226) and heterogeneity dropped to near zero ($I^2 < 0.01\%$).

The large number of patients in Inamdar *et al*. generated the outlier effect [Figure 4].[16]

Figure 5 presents the meta-analysis results of the fetal adverse outcomes; the pooled event rate was 5.4% (95% CI = 0.035–0.083). The pooled event rate for maternal pregnancy-related adverse events in pregnant patients was 6.1% (95% CI = 0.040–0.093). The pooled event rate for maternal nonpregnancy-related adverse events in pregnant patients was 11.9% (95% CI = 0.102–0.138). The quality of evidence started low because analyzed studies were all observational. Symmetrical funnel plot was consistent with

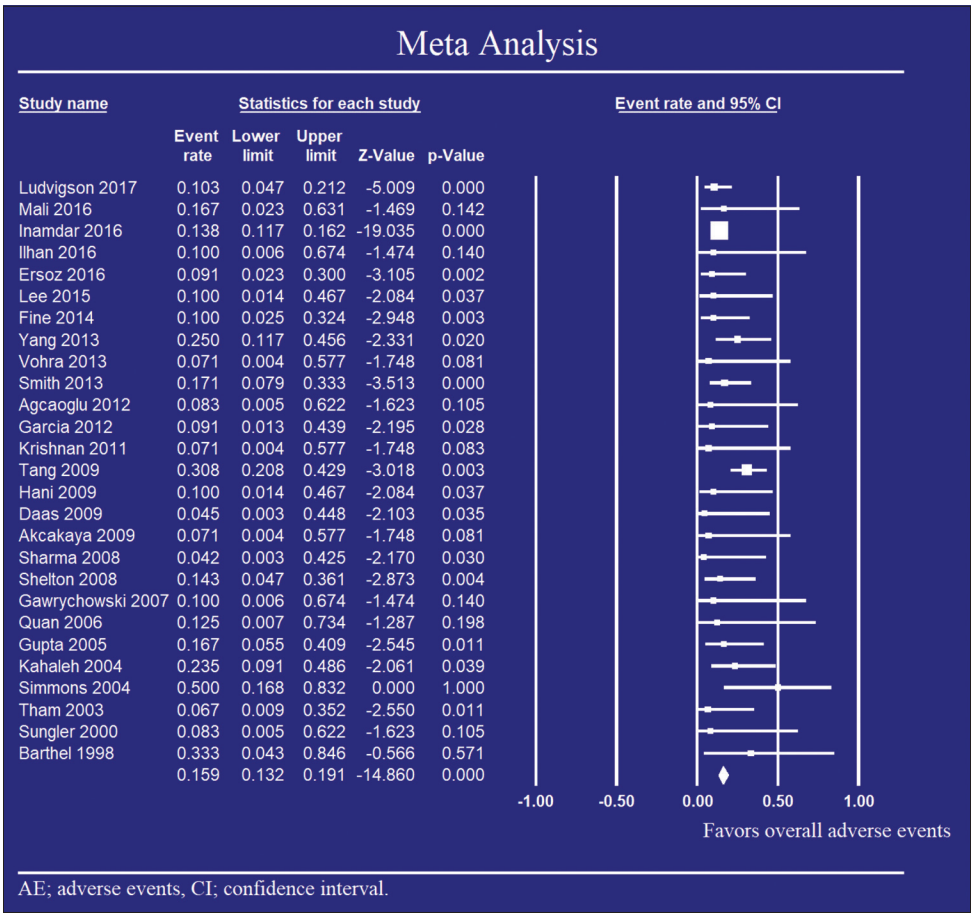

Figure 3: Meta-analysis result of overall adverse events in pregnant patients undergoing ERCP

the absence of publication bias. No evidence of publication bias by Egger's regression test for all-cause was found. The final quality of evidence was high because no serious limitation was found in the NOS as shown in Table 2.

Subgroup analysis results were done by radiation exposure. Nine of 27 studies included both ERCP with radiation and NR-ERCP. They did not specify the outcomes based on radiation exposure. Nine studies included only NR-ERCP and another nine studies included radiation ERCP. NR-ERCPs were performed using three different techniques: abdominal US-guided ERCP, endoscopic ultrasound (EUS)-guided ERCP, and choledochoscopy-guided ERCP. Overall adverse events were less prevalent in the NR-ERCP group (pooled event rate of 17.6%, 95% CI = 0.109–0.272) versus radiation ERCP group (pooled event rate 21.6%, 95% CI = 0.154–0.294). There was no significant difference in the fetal adverse outcomes between the radiation ERCP group (pooled event rate 5.2%, 95% CI = 0.026–0.101) and the NR-ERCP group (pooled event rate 6.2%, 95% CI = 0.027–0.137).

Maternal pregnancy-related adverse outcomes were less prevalent in the radiation ERCP group (pooled event rate 7.1%, 95% CI = 0.039–0.125) in comparison to the NR-ERCP group (pooled event rate 12.0%, 95% CI = 0.065–0.211). However, the overlap in CI makes the results less statistically significant. Maternal nonpregnancy-related outcomes were more prevalent in the radiation ERCP group (pooled event rate 14.9%, 95% CI = 0.102–0.211) in comparison to 7.6% (95% CI = 0.038–0.145) in the NR-ERCP group. Again, the CI overlap affects the statistical significance despite the low *P* value. All results were statistically significant with *P* value <0.01.

DISCUSSION

To our knowledge, this is the first meta-analysis of the ERCP outcomes in pregnancy and the first to provide a head-to-head comparison between radiation ERCP and NR-ERCP. In this systematic review and meta-analysis, we found ERCP to be a relatively safe procedure during pregnancy. Intraoperatively, no complications were reported. Maternal post-ERCP adverse events included

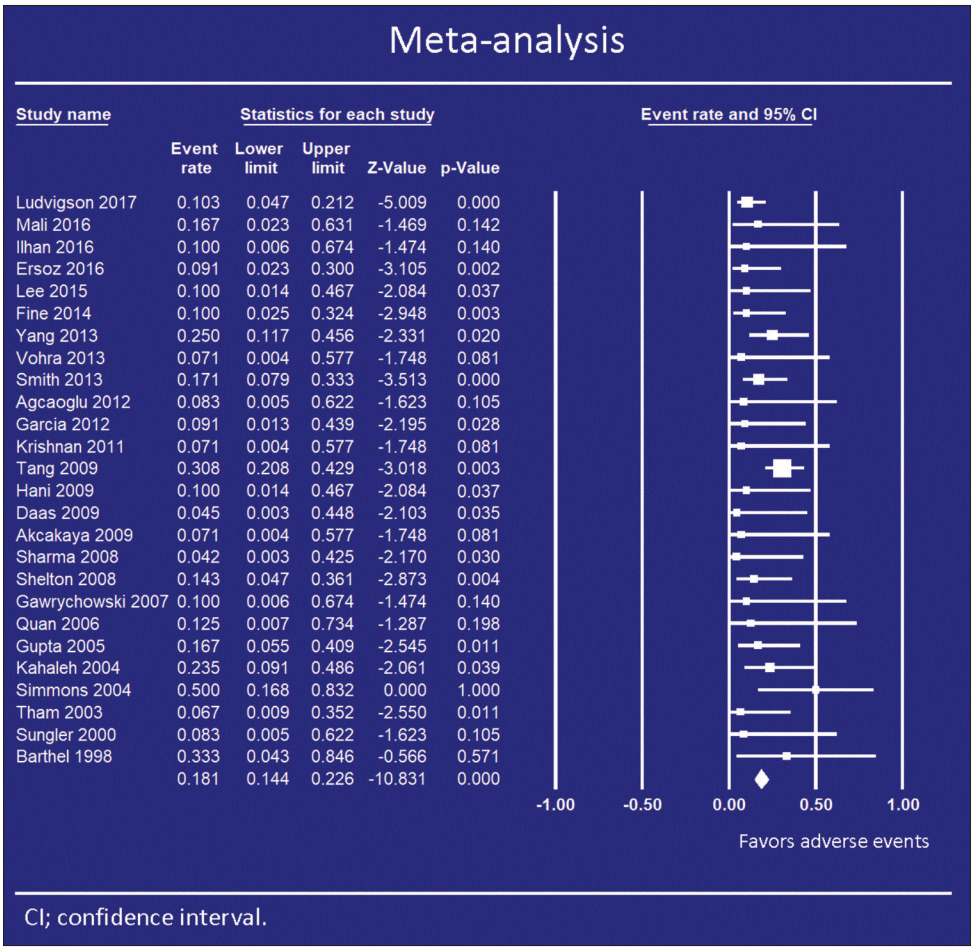

Figure 4: Overall adverse events in pregnant patients undergoing ERCP without outlier effect

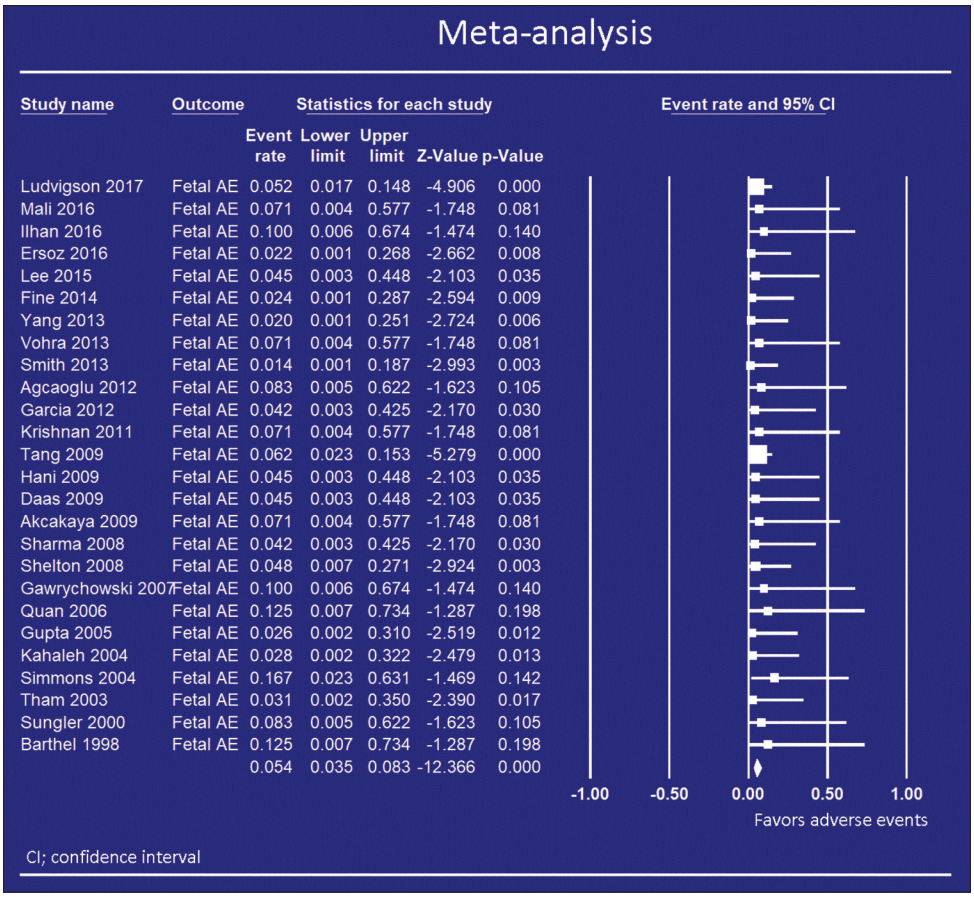

Figure 5: Fetal outcomes' meta-analysis

pancreatitis, PSB, cholecystitis, and one incidence of acute respiratory distress syndrome resulting in the only case of maternal death. The rate of ERCP-related maternal adverse outcomes was found to be slightly higher than the usual ERCP outcomes.[16] ERCP was also associated with an increased risk of preterm labor and preeclampsia, but there were no reported cases of abortion, bleeding, or intrauterine fetal death. With regard to fetal outcomes, ERCP was found to be relatively safe on the fetus without any reported cases of fetal congenital malformation or stillbirth, despite the increased risk of preterm labor and low birth weight. A subgroup analysis was performed to compare the outcomes of radiation ERCP versus NR-ERCP. NR-ERCP had a higher safety profile in terms of maternal nonpregnancy-related outcomes with lower rates of PEP and PSB. Regarding fetal outcomes, NR-ERCP showed no superiority to radiation ERCP. No congenital malformations were reported in both groups. However, both groups had an increased risk of preterm labor and intrauterine growth retardation.

Radiation exposure during fluoroscopy time in ERCP is used to visualize the anatomy of the biliary tract and ensure safe and successful biliary cannulation, stone extraction, and sphincterotomy. Different NR-ERCP techniques have recently been introduced to avoid possible radiation exposure fetal malformations. However, these techniques were not associated with better fetal outcomes in comparison to the radiation ERCP. This may be attributable to the fact that radiation exposure in ERCP is lower than the exposure needed to cause congenital fetal anomalies.[44] Fetal risk of anomalies, growth restriction, or abortion has not been reported with radiation exposure of less than 50 mGy, a level above the range of exposure in ERCP according to the American College of Obstetrics and Gynecology.[44] In one study, the estimated fetal radiation exposure in 17 cases of ERCP with limited fluoroscopy time (range 1–48 s) is 0.4 mGy (range 0.01–1.8 mGy).[11] Other factors that can affect the fetal absorbed dose of irradiation include orientation of the fetus, fetus size, procedure position, and body composition of the mother.[45] Although most of the fetal irradiation exposure comes from the radiation diffused from the maternal tissue, application of a lead apron is still routinely recommended.[11] Several other strategies are recommended to reduce the fetal irradiation exposure and complications, including decreasing fluoroscopy time, minimizing exposure areas, and application of electric grounding pad higher in the posterior thoracic wall level

Table 2: Newcastle-Ottawa Scale for the included studies

Reference	Selection				Comparability	Outcome			Overall quality assessment score (of a maximum of 9)
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was FU long enough for outcomes to occur	Adequacy of FU of cohorts	
Agcaoglu *et al.*[24] 2013	Not representative	Nonexposed cohort: N/A	*NR- ERCP	*No comments regarding patient's pre-ERCP history	Controls N/A	*Independent blind assessment	Long-term FU N/A (maternal; postprocedure, fetal: at delivery, 30 days post-delivery)	*No maternal/fetal adverse events and complications	4
Akcakaya *et al.*[30] 2009	Not representative	Nonexposed cohort: N/A	*NR-ERCP	One patient with biliary fistula	Controls N/A	*Independent blind assessment	Long-term FU N/A (until discharge)	*1 maternal complication (fistula persistent, which was present before the 1st ERCP) No fetal complication	3
Barthel *et al.*[39] 1998	Not representative	Nonexposed cohort: N/A	*Endoscopic sphincterotomy	*No comments regarding patient's pre-ERCP history	Controls N/A	*Independent blind assessment, phone FU for 1 patient	FU 6 months to 2 years	1 PEP, 1 preterm birth	3
Daas *et al.*[29] 2009	*Somewhat representative	Nonexposed cohort: N/A	*ERCP (limited use of fluoroscopy in 6 cases)	*No comments regarding patient's pre-ERCP history	Controls N/A	*Independent blind assessment	Maternal: post-ERCP FU Fetal: at delivery and 30 days post-delivery	*No maternal/fetal adverse events and complications	5
Ersoz *et al.*[18] 2016	*Somewhat representative	Nonexposed cohort: N/A	*NR-ERCP	*No comments regarding patient's pre-ERCP history except 1 patient with GDM	Controls N/A	*Independent blind assessment	*Maternal: FU for 6 months for post-ERCP late complications Fetal: at delivery and 6 months post-delivery	Maternal: mild post-ERCP complication (bleeding, pain, mild pancreatitis) No fetal complication	5
Fine *et al.*[20] 2014	*Somewhat representative	Nonexposed cohort: N/A	* ERCP with or without fluoroscopy	*No comments regarding patient's pre-ERCP history	*Controls for age and sex	*Independent blind assessment	Long-term FU N/A	* 2 PEP but both had multiple stones on ERCP	6
García-Cano *et al.*[25] 2012	*Somewhat representative	Nonexposed cohort: N/A	* ERCP with or without fluoroscopy	*No comments regarding patient's pre-ERCP history except showing symptoms for CBDS	Controls N/A	*Independent blind assessment	Long-term FU N/A	1 hyperamylasemia	4
Gawrychowski *et al.*[33] 2007	Not representative	Nonexposed cohort: N/A	*ERCP with papillotomy	* 1 patient with previous cholecystectomy	Controls N/A	*Independent blind assessment	Maternal: postprocedure Fetal: at delivery	*Minimal risk of PEP No increase in fetal loss	4

Contd...

Table 2: Contd...

Reference	Selection				Comparability	Outcome			Overall quality assessment score (of a maximum of 9)
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was FU long enough for outcomes to occur	Adequacy of FU of cohorts	
Gupta *et al.*[35] 2005	*Somewhat representative	Nonexposed cohort: N/A	*ERCP with or without fluoroscopy	*No comments regarding patient's pre-ERCP history	Controls N/A	*Independent blind assessment	*11 of 18 patients were FU for babies (age 1-11)	Maternal: mild post-ERCP complication, 1 preterm delivery No fetal complication	5
Bani Hani *et al.*[28] 2009	*Somewhat representative	Nonexposed cohort: N/A	*ERCP	*3 patients with previous cholecystectomy	Controls N/A	*Independent blind assessment	Maternal: postprocedure Fetal: till neonatal period (screening for congenital anomalies/ malformations done)	*No maternal/ fetal adverse events and complications noted.	5
İlhan *et al.*[17] 2016	*Probable representative	Nonexposed cohort: conservative treatment	*ERCP in 4, Cholecystectomy in 15 patients	*No comments regarding patient's pre-ERCP history	Controls available, but study does not control for other factors	*Independent blind assessment	Long-term FU N/A	1 Maternal death/Perinatal complications (preterm delivery, missed abortion, LBW), no fetal abnormalities	4
Inamdar *et al.*[16] 2016	*Truly representative	Nonexposed cohort: N/A	*ERCP	*No comments regarding patient's pre-ERCP history	*Controls were available; age-matched	*Independent blind assessment	Long-term FU N/A	*No deaths in pregnant group, no difference in maternal mortality, similar fetal distress/fetal loss rate compared to national average	6
Kahaleh *et al.*[11] 2004	*Somewhat representative	Nonexposed cohort: N/A	*ERCP with Fluoroscopy performed/ Radiation exposure measured by TLD in 15 patients	*No comments regarding patient's pre-ERCP history	Controls N/A	*Independent blind assessment	Long-term FU N/A	1 PSB, 2 obstetric complications (preeclampsia ->induced labor)	4
Krishnan *et al.*[26] 2011	Not representative	Nonexposed cohort: N/A	*ERCP with or without fluoroscopy	*No comments regarding patient's pre-ERCP history	Controls N/A	*Independent blind assessment	Maternal: postprocedure Fetal: at delivery and 30 days after delivery	*No maternal/fetal adverse events and complications noted	4

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Table 2: Contd...

Reference	Selection				Comparability	Outcome			Overall quality assessment score (of a maximum of 9)
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was FU long enough for outcomes to occur	Adequacy of FU of cohorts	
Lee *et al*.[19] 2015	*Somewhat representative	Nonexposed cohort: N/A	*ERCP (with or without fluoroscopy) or EUS	*No comments regarding patient's pre-ERCP history	Controls N/A	*Independent blind assessment/ self-report for long-term FU (phone)	*Maternal: postprocedure Fetal: at delivery and long-term FU by phone	1 hyperamylasemia, 1 acute pulmonary edema (->artificial abortion) 3 preterm births, 1 LBW	5
Ludvigsson *et al*.[14] 2017	*Truly representative	*Mother without any endoscopy	*Any endoscopy (EGD, colonoscopy, sigmoidoscopy, ERCP)	outcomes likely due to disease activity	**Study controls matched for more than 3 factors	*Independent blind assessment	Long-term FU N/A	For any endoscopy: higher preterm birth percentage (but lower in ERCP group), higher SGA percentage, no difference in congenital malformations and stillbirths	6
Mali[15] 2016	Not representative	*Pregnant women with pancreatitis treated without ERCP	*ERCP	*No comments regarding patient's pre-ERCP history	Controls available, but study does not control for other factors	*Independent blind assessment	Long-term FU N/A	*No maternal/fetal adverse events and complications	5
Quan *et al*.[34] 2006	Not representative	Nonexposed cohort: N/A	*ERCP or oral gastroduodenoscopy	*No comments regarding patient's pre-ERCP history	Controls N/A	*Independent blind assessment/ telecommunication FU	*long term FU by telecommunication	*No maternal/fetal adverse events and complications	5
Sharma and Maharshi[31] 2008	*Somewhat representative	Nonexposed cohort: N/A	*2 stage endoscopic approach: 1) biliary sphincterotomy and stenting (without any fluoroscopy or US) 2) definitive ERCP and stone clearance after delivery	*No comments regarding patient's pre-ERCP history	Controls N/A	*Independent blind assessment	*8 of 11 patients: regular FU for 2-6 years after procedure	*No maternal/fetal adverse events and complications	6
Shelton *et al*.[32] 2008	*Somewhat representative	Nonexposed cohort: N/A	*NR-ERCP	*No comments regarding patient's pre-ERCP history	Controls N/A	*Independent blind assessment	Long-term FU N/A	1 mild PEP, 1 IUGR	4

Contd...

Table 2: Contd...

Reference	Selection				Comparability	Outcome			Overall quality assessment score (of a maximum of 9)
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was FU long enough for outcomes to occur	Adequacy of FU of cohorts	
Simmons *et al.*[36] 2004	Not representative	Nonexposed cohort: N/A	*NR-ERCP	*No comments regarding patient's pre-ERCP history	Controls N/A	*Independent blind assessment	Long-term FU N/A	No maternal complications, 2 infants born prematurely (1 of them with IUGR, ARDS), 2 mothers: lost to FU	3
Smith *et al.*[23] 2013	*Probable representative	Nonexposed cohort: N/A	*ERCP with fluoroscopy	5 patients had cholecystectomy prior to ERCP	Controls N/A	*Independent blind assessment	Long-term FU N/A	2 PEP, 2 PSB, 1 ARDS (fatal) and 1 cholecystitis No details on the fetal complications	3
Sungler *et al.*[38] 2000	Not representative	*32 patients not exposed to ERCP	ERCP and/or laparoscopic surgery	*No comments regarding patient's pre-ERCP history	Controls available, but study does not control for other factors	*Independent blind assessment	*FU with mother and infant to date	*No maternal/fetal adverse events and complications	5
Tang *et al.*[27] 2009	*Probable representative	Nonexposed cohort: N/A	*ERCP with fluoroscopy	*No comments regarding patient's pre-ERCP history	Controls N/A	*Independent blind assessment	Long-term FU N/A	11 PEP, 5 preterm labor, and 4 LBW	4
Tham *et al.*[37] 2003	*Somewhat representative	Nonexposed cohort: N/A	*ERCP with fluoroscopy	*No comments regarding patient's pre-ERCP history	Controls N/A	*Independent blind assessment	Long-term FU N/A	1 PEP, and 3 needed laparoscopic cholecystectomy	4
Vohra *et al.*[22] 2013	*somewhat representative	*4 patients EUS	*NR-ERCP	*No comments regarding patient's pre-ERCP history	Controls available, but study does not control for other factors	*Independent blind assessment	Long-term follow-up N/A	*No maternal/fetal adverse events and complications	6
Yang *et al.*[21] 2013	*Somewhat representative	Nonexposed cohort: N/A	*NR-ERCP	*No comments regarding patient's pre-ERCP history	Controls N/A	*Independent blind assessment	Long-term follow-up N/A	2 PSB, 4 preterm labor	4

ERCP: Endoscopic retrograde cholangiopancreatography; FU: Follow-up; NR-ERCP: Nonradiation ERCP; EUS: Endoscopic ultrasound; PEP: Post-ERCP pancreatitis; PSB: Postsphincterotomy bleeding; ARDS: Acute respiratory distress syndrome; LBW: Low birth weight; IUGR: Intrauterine growth restriction; SGA: Small for gestational age; N/A: Not available

to avoid transmission of electric current to the fetus.[46,47] Gestational age at the time of irradiation exposure is also crucial. Significant irradiation exposure before 16 weeks of gestational age has a higher risk of intellectual disability.[48]

The NR-ERCP group had lower rates of PEP and PSB in comparison to the radiation ERCP. This finding is unexpected and should be interpreted cautiously due to CI overlap. It may be attributable to the fact that NR-ERCP is a more sophisticated procedure which requires more equipment and a higher level of expertise in endoscopy and is thus only performed by high-volume practitioners. NR-ERCP is achieved through empirical bile aspiration technique and can be done with imaging guidance. Bile aspiration technique allows confirmation of common bile duct (CBD) cannulation and endoscopic sphincterotomy to be carried out without radiation, while imaging guidance can be provided by EUS, transabdominal US, or choledochoscopy. US allows recognition of the CBD stone site, confirmation of wire placement, and cannulation of the CBD. An US contrast agent (sulfur hexafluoride microbubbles) was injected through ERCP to improve visualization of the CBD as an alternative to fluoroscopy in a single case report.[49] No fetal complications were reported in this case report; however, the safety profile of this contrast material on the fetus is still unclear. US-guided ERCP showed higher rate of stone clearance in comparison to empirical NR-ERCP (89% vs 60%, $P < 0.05$) and lower complication rates (14% vs 3%, $P < 0.05$).[50] EUS can be carried out in the same session before ERCP to determine the number and site of stones before NR-ERCP is carried out with bile aspiration technique to clear the CBD.[51,52] Another way to confirm biliary cannulation and stone clearance without radiation is by insertion of a choledochoscope through the working channel of EGD to directly visualize the bile duct.[53] Due to the scarcity of available literature, there are currently no available data that compare EUS-guided ERCP or peroral choledochoscopy-guided ERCP to empiric NR-ERCP.

Two-stage ERCP technique was introduced in a few reports. During pregnancy, NR-ERCP with empiric biliary aspiration and CBD stenting is performed. After delivery, a repeat ERCP is performed to remove the stent and ensure CBD clearance.[31] Extensive experience in ERCP is required in this technique as stent placement without fluoroscopy might lead to the stent misplacement either in the gallbladder or before the stone. A postprocedural US is required to confirm the position of the stent.

The following few points strengthen our confidence in the current meta-analysis results. First, statistical heterogeneity was very low. Second, the quality of the included studies was moderately high. Third, we found no evidence of publication bias. Nonetheless, we acknowledge several limitations. First, the risk of selection bias could have resulted in underreporting of ERCP adverse outcomes in pregnancy. Second, the duration of follow-up differed from one study to the other, and most patients were lost to follow-up 1 month after delivery. Third, studies were performed at different locations around the world with varying levels of expertise in endoscopy. Fourth, the heterogeneity in the NR-ERCP techniques could have affected the outcomes.

In conclusion, our findings support the notion that ERCP should continue to be the procedure of choice for bile duct decompression in pregnancy to prevent potentially life-threatening complications to both mother and fetus. Nonradiation techniques may decrease the risk of nonpregnancy-related outcomes, but do not impact fetal or pregnancy-related outcomes.

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Conflicts of interest

There are no conflicts of interest.

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