

Reviewer #1:

Overall the manuscript title is interesting and the authors did a very good job,

1. Major issue: most of the data were represented in the text which might confuse the reader, thus tables summarizing the data should be added including the safety and efficacy other than the table summarizing radiation free ERCP during pregnancy.

Response to Comment 1 of Reviewer 1: As suggested, the following new Table (labelled Table 3) has been added to the paper:

Table 3. Literature review of relatively large clinical studies on safety of ERCP during pregnancy

First author, year [reference]	Study characteristics	Findings
Tsang SJ, 2009 [44]	Large retrospective study of 68 ERCPs performed during 65 pregnancies.	Pancreatitis occurred in 11 pregnant patients (16%) after ERCP. No other major maternal complications occurred during pregnancy. No fetal deaths and no fetal malformations occurred. After ERCP 53 patients had deliveries at term (90% rate for known delivery outcomes). However, ERCP performed during first trimester had less favorable outcomes: preterm delivery=20%, and low-birth-weight infants =21%.
Ludvigsson JF, 2017 [38]	National cohort study in Sweden of 58 pregnant patients undergoing ERCP included in a much larger study of 3,052 patients undergoing any gastrointestinal endoscopy during pregnancy.	Of 58 pregnant patients undergoing ERCP unfavorable fetal outcomes included: 3 (5.2%) preterm births, 0 (0%) stillbirths, 0 (0%) neonatal deaths, 12 (20.7%) Cesarean sections, 1 (1.7%) Apgar score <7 at 5 min., 1 (1.7%) small for gestational age, and 3 (5.2%) with any major

		congenital malformation. All these pregnancy outcomes were similar to that of pregnancy outcomes for mothers not undergoing endoscopy during pregnancy.
Jamidar PA, 1995 [45]	Retrospective study of therapeutic ERCPs performed during 20 pregnancies.	Two significant complications: 1 spontaneous abortion 3 weeks after ERCP, and 1 neonatal death 26 hrs. post-partum that occurred after the expectant mother underwent 3 therapeutic ERCPs during pregnancy with pancreatic stenting at each session complicated by post-ERCP pancreatitis; and. No other significant maternal or fetal complications.
Gupta R, 2005 [46]	Retrospective study of therapeutic ERCPs performed during 18 pregnancies for choledocholithiasis.	Complications: 1 mild postsphincterotomy bleed; and 1 mild pancreatitis and preterm labor after ERCP. All fetal outcomes were favorable. This study had long-term follow-up after intra-partum ERCP: all 18 infants had normal child development at 6 years.
Cappell MS, 2011 [42]	Systematic literature review of 296 pregnant patients undergoing therapeutic ERCP including 254 (86%) in which fetal outcome was reported.	Fetal outcomes as reported in 254 cases included: healthy infants at birth in 237, prematurely born infants with low-birth-weight in 11, late spontaneous abortions in 3, infant death soon after birth in 2, and voluntary abortion in 1. Perinatal mortality was only about 1% despite pregnant mothers undergoing therapeutic ERCP mostly for major gallstone complications, such as obstructive jaundice, ascending cholangitis, or gallstone pancreatitis. No congenital anomalies were reported in the infants. These favorable data must be interpreted cautiously: in the literature review, fetal outcome data were missing in 42 (15%) of the

	mothers undergoing ERCP during pregnancy.
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ERCP – endoscopic retrograde cholangiopancreatography.

2. Minor issue: in page number 11, please correct table 3 and not "30".

Response to #2: Corrected to “Table 4” instead of “Table 30”.

CHANGE TO:

Altogether 147 ERCP's have been performed during pregnancy without fluoroscopy in 8 clinical series, reflecting endoscopist ingenuity and technological progress (Table-4)^[64,68-75]. These clinical data are extremely promising, with a very high rate of technical success (clearing of CBD stones), low rate of maternal complications, delivery of predominantly healthy babies, mostly normal birth weights, and typical delivery at term (Table-4)^[64,68-75].

CHANGE FROM:

Altogether 147 ERCP's have been performed during pregnancy without fluoroscopy in 8 clinical series, reflecting endoscopist ingenuity and technological progress (Table 30)^[64,68-75]. These clinical data are extremely promising, with a very high rate of technical success (clearing of CBD stones), low rate of maternal complications, delivery of predominantly healthy babies, mostly normal birth weights, and typical delivery at term (Table-30)^[64,68-75].

Reviewer #2:

Dear authors, thank you for the report of difficult thema. This thema is difficult, therefore I hope you modify the report easier to understand.

1. Some concerns about the risks of ERCP during pregnancy were redundant. Please revise the structure, if you can. For, example: Introduction, Methods, Epidemiology, adaptive criterion of ERCP, the ERCP method of each pregnancy term, therapeutic procedures and outcomes, adverse effects or risk factor of each pregnancy term, etc.

Response: As suggested, the paper is separated into the following headings: Introduction, Methods, Results, Discussion, and Conclusions.

Moreover, as suggested, the Results section is revised to have the following subheadings:

Pathophysiology of cholelithiasis & choledocholithiasis

Epidemiology

Special concerns & modifications of ERCP during pregnancy

Outcomes & complications of therapeutic ERCP during pregnancy

2. Which position was more recommended for ERCP during pregnancy? Left side or supine position?

As suggested, the following discussion of patient positioning is modified.

Page 5. CHANGED TO:

The unique maternal and fetal physiologic requirements during pregnancy affect the usual practice of ERCP. ERCP in non-pregnant patients is usually performed with the patient in the prone position to aid in selective bile cannulation and to provide better fluoroscopic imaging compared to other positions. However, this position is not recommended during advanced pregnancy for the following reasons: to avoid patient discomfort from the enlarged, gravid uterus pressing against the hard x-ray platform, to avoid decreased systemic and uterine perfusion from the enlarged gravid uterus compressing the aorta, and to avoid decreased venous return from the enlarged gravid uterus compressing the inferior vena cava (Jamidar 1995). Patients may also require supporting cushions during advanced pregnancy to minimize patient discomfort. Rapid intraprocedural infusion of IV fluids is generally recommended.....

CHANGED FROM:

The unique maternal and fetal physiologic requirements during pregnancy affect the usual practice of ERCP. ERCP is usually performed with the patient in the prone position or occasionally on the back, but is best performed during pregnancy with the mother on the left side, especially during advanced pregnancy, to avoid the enlarged gravid uterus compressing the aorta which would decrease systemic and uterine perfusion, and compressing the inferior vena cava which would decrease venous return. Rapid intraprocedural infusion of IV fluids is generally recommended.....

Reviewer #3:

Based on substantial and reliable literature on ERCP during pregnancy, this article systematically reviewed the topic: “safety and efficacy of therapeutic ERCP during pregnancy, including studies of radiation-free ERCP”. The reasonable recommendations about ERCP indications,

special ERCP techniques during pregnancy, maternal and fetal outcomes after ERCP, and prospects for future research were given by the author. It's a good review and may have some help for ERCP endoscopist, and should be publish quickly.

Response: No changes required in response to reviewer #3 comments.

Reviewer #4:

First, performance of therapeutic ERCP during pregnancy is challenging due to concerns about pregnancy-related changes in the mother, fetal viability, fetal teratogenicity, premature delivery, and future development of the infant after parturition. Second, therapeutic ERCP has a very high rate of technical success in clearing the bile duct of gallstones, and has a relatively low and acceptable rate of maternal and fetal complications. The great majority of births after therapeutic ERCP are full-term, have normal birth weights, and are healthy. Fetal radiation exposure is a significant concern because of its potential teratogenic effects and subsequent carcinogenetic effects. Fetal radiation exposure and toxicity depends upon multiple factors, including maternal size, maternal distribution of fat, volume of amniotic fluid, fetal gestational age, and radiation delivery method. The most important factors determining fetal exposure are total radiation time and dosage, both of which should be minimized. Third, the endoscopist should frankly discuss procedural risks versus benefits with the patient. Radiation safety measures are paramount, as is the endoscopist's experience and technical skills. Various strategies and technologies may enhance biliary cannulation and ductal clearance during ERCP. Radiation-free ERCP is ideal, but should not unduly increase procedural time and risk of complications, especially pancreatitis.

Response: No changes required in response to this reviewer's critique.

Reviewer #5: **A good and innovative idea of a quite difficult theme (ercp-pregnancy). The study covers the whole question and idea that wanted to test without to tire. The results section would be slightly separated from the other discussion. A big part of the discussion would fit better in the conclusion that is slightly limited.**

Response: As suggested, a part of the discussion is placed in the conclusion. The results section is also modified.

CHANGES MADE ACCORDING TO EDITOR'S CRITIQUES

1. A short running title of less than 6 words should be provided.

The following running title is provided:

Therapeutic ERCP during Pregnancy: Safety & Efficacy

2. Authors' full names should be given first, then the complete name of the institution, city, province and postcode.

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3. Author contributions: All the authors' work should be given in this section

As required the following has been added:

Dr. Cappell had the most important contributions to the organization, writing, and editing of the manuscript. Drs. Friedel and Stavropoulos contributed very significantly to all aspects of the paper, including the organization, writing, and editing of the manuscript. The final manuscript was reviewed, corrected, and approved by all three authors.

4. Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, detail of address (to street or avenue), city, postcode, province, country, and institute email.

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6. The signed Biostatistics Statement is submitted as a separate pdf document labelled: (4)39594-Biostatistics Review Certificate-ERCP in Pregnancy

7. Conflict of interest statement. Please offer signed pdf format: A conflict-of-interest statement is required for all article and study types. In the interests of transparency and helping reviewers to assess any potential bias in a study's design, interpretation of its results or presentation of its scientific/medical content, the BPG requires all authors of each paper to declare any conflicting interests (including but not limited to commercial, personal, political, intellectual, or religious interests) in the title page that are related to the work submitted for consideration of publication. In addition, reviewers are required to indicate any potential conflicting interests they might have related to any particular paper they are asked to review, and a copy of signed statement should be provided to the BPG in PDF format.

The signed conflict-of-interest statement is submitted as a separate pdf document labelled: (5)39594-ERCP-Pregnancy-conflictsofinterest .

8. Data Sharing Statement

Basic research and clinical research studies require a data sharing statement. The data sharing statement will be provided in the title page, and will be presented in the following form: Technical appendix, statistical code, and dataset available from the corresponding author at Dryad repository, who will provide a permanent, citable and open-access home for the dataset. In addition, a copy of the signed statement should be provided to the BPG in PDF format.

This publication as a review of the literature does not present any original data. It does not, therefore, require or have a technical appendix, statistical code, or dataset placed at a computer repository for data sharing.

9. Abstract. An informative, structured abstract of no less than 246 words should accompany each manuscript. The Abstract will be structured into the following sections, adhering to the word count thresholds indicated in parentheses:

AIM (no more than 20 words)

The purpose of the study should be stated clearly, with no or minimal background information, following the format of: “To investigate/study/determine...”

METHODS (no less than 80 words)

You should present the materials and methods used for all of the data presented in the proceeding Results section of the abstract.

RESULTS (no less than 120 words)

You should present *P* values where appropriate. You must provide relevant data to illustrate how the statistical values were obtained, *e.g.*, 6.92 ± 3.86 vs 3.61 ± 1.67 , $P < 0.001$.

CONCLUSION (no more than 26 words)

You should present your findings and implications that are within the scope of the data you have presented in the preceding Results section. The conclusion should be written in the present tense.

ABSTRACT

AIM: To systematically review safety/efficacy of therapeutic ERCP performed during pregnancy, considering risks of fetal viability, fetal teratogenicity, premature delivery, and future maldevelopment of the infant after parturition.

METHODS: Systematic computerized literature search performed using PubMed with the key words “ERCP” and “pregnancy”. Two clinicians independently reviewed the literature, and decided on which articles to incorporate in this review based on consensus and pre-arranged priorities. Large clinical trials, meta-analyses, systematic reviews, and controlled trials were assigned higher priority than review articles or small clinical series, and individual case reports

were assigned lowest priority. Dr. Cappell has formal training and considerable experience in conducting systematic reviews, with 4 published systematic reviews in peer-reviewed journals indexed in PubMed during the last 2 years, and with a Ph.D. in neurophysiology that involved 5 years of training and research in biomedical statistics.

RESULTS: Advances in imaging modalities, including abdominal ultrasound, MRCP, and EUS, have generally obviated the need for diagnostic ERCP. Clinical experience with performing therapeutic ERCP during pregnancy is burgeoning, with >500 cases of therapeutic ERCP reported in the literature, aside from a national registry study of 58 patients. These studies show that therapeutic ERCP has a very high rate of technical success in clearing the bile duct of gallstones, and has a relatively low and acceptable rate of maternal and fetal complications. The great majority of births after therapeutic ERCP are full-term, have normal birth weights, and are healthy. A recent trend is performing ERCP without radiation to eliminate radiation teratogenicity. Systematic literature review reveals 147 cases of ERCP without fluoroscopy in 8 clinical series. These studies demonstrate extremely high technical success in endoscopically removing choledocholithiasis, favorable maternal outcomes with rare maternal ERCP complications, and excellent fetal outcomes. ERCP without fluoroscopy generally confirms proper biliary cannulation by aspiration of yellow bile per sphincterotome or leakage of yellow bile around an inserted guide-wire.

CONCLUSIONS: This systematic literature review reveals ERCP is relatively safe and efficacious during pregnancy, with relatively favorable maternal and fetal outcomes after ERCP. Recommendations are provided about ERCP indications, special ERCP techniques during pregnancy, and prospects for future research.

13. Please separate the paper into four parts: introduction, methods, results, discussion. Thank you.

As suggested by the editor, the paper is separated into: Introduction, Methods, Results, and Discussion. The Conclusion has been eliminated. A Results section has been added to the paper to help the reader navigate through the paper.

14. **ARTICLE HIGHLIGHTS**

ARTICLE HIGHLIGHTS

The guidelines for writing and formatting Article Highlights are as follows:

1. Research background

The background, present status, and significance of the study should be described in detail.

Endoscopic retrograde cholangiopancreatography (ERCP) is currently the standard technique for treating choledocholithiasis and associated complications, such as cholangitis, biliary pancreatitis, and biliary stricture, in the non-pregnant population. The approach in pregnant women with suspected choledocholithiasis, however, differs somewhat from that for non-pregnant patients because of concerns about the pregnant mother and the fetus, including procedure time, teratogenicity of intraprocedural medications, and fetal radiation exposure. This work systematically reviews ERCP during pregnancy, with a particular focus on differences between the pregnant versus non-pregnant patient in patient indications, patient preparation, procedural medications, complications, reducing fetal radiation exposure, and maternal and fetal outcomes.

2. Research motivation

The main topics, the key problems to be solved, and the significance of solving these problems for future research in this field should be described in detail.

Evaluation of safety and efficacy of ERCP during pregnancy is clinically important because patients occasionally, but not rarely, develop during pregnancy cholelithiasis associated with cholangitis, biliary pancreatitis, or choledochal strictures that would normally necessitate therapeutic ERCP in non-pregnant patients. The critical clinical question is whether ERCP is relatively safe during pregnancy because of potential teratogenicity of radiation and medications, and premature delivery induced by the procedure. Clinical experience with ERCP during pregnancy is burgeoning, with >500 cases of therapeutic ERCP reported in the literature, including several hundred reported during the last few years, with publication 1 year ago of a

national Swedish registry study of 58 patients undergoing ERCP during pregnancy, and publication of 8 relatively recently published clinical series, incorporating 147 cases of ERCP without fluoroscopy. Moreover, much of the work on safety and efficacy of ERCP during pregnancy is scattered in very small clinical series. This work systematically collates the clinical data from the clinical studies including the numerous small clinical series to render the data accessible to clinicians. This work provides a systematic review of the rapidly evolving literature in this clinically booming field to provide highly important and clinically relevant updates on ERCP safety, efficacy, and recent technical improvements in pregnant patients.

3 Research objectives

The main objectives, the objectives that were realized, and the significance of realizing these objectives for future research in this field should be described in detail.

The prevalence of cholelithiasis during pregnancy varies according to study population, with ranges 5% to 10% in high risk populations, such as American Hispanics, with about 1 in a 100 of this cohort developing symptomatic cholelithiasis. Cholelithiasis and choledocholithiasis are not infrequently encountered during pregnancy because female gender, concurrent pregnancy, hyperlipidemia from cholestasis during pregnancy, and prior pregnancy are risk factors for cholelithiasis. Clinical management of this problem is important during pregnancy because symptomatic choledocholithiasis would generally require therapeutic ERCP in non-pregnant patients, but might theoretically be dangerous to the fetus due to potential radiation and medication teratogenicity and premature labor induced by the procedure. This work assesses the very sizeable clinical research in this field involving several relatively large clinical series and numerous very small clinical series to demonstrate that ERCP may be extremely efficacious in eliminating choledocholithiasis while involving a relatively low and generally acceptable risk of fetal complications. This work reports numerous techniques to reduce radiation exposure and other safety precautions to decrease fetal risk from ERCP during pregnancy. Indeed, this work discusses in detail radiation free ERCP during pregnancy to completely eliminate teratogenic risks of radiation.

4. Research methods

The research methods (*e.g.*, experiments, data analysis, surveys, and clinical trials) that were adopted to realize the objectives, as well as the characteristics and novelty of these research methods, should be described in detail.

Systematic computerized literature search was performed using PubMed with the key words “ERCP” and “pregnancy”. Two clinicians independently reviewed the literature, and decided on which articles to incorporate in this review based on consensus using pre-agreed prioritization criteria. Large clinical trials, meta-analyses, systematic reviews, and controlled trials were assigned higher priority than review articles or small clinical series, and individual case reports were assigned the lowest priority. This review encompassed more than 500 cases published in small clinical series and scattered reports, in addition to 58 cases recently reported in a retrospective Swedish registry study. In particular, this work focuses on the safety and efficacy of the novel, recently introduced technique of radiation-free ERCP to completely eliminate radiation teratogenesis during ERCP.

The first author, Dr. Cappell, has formal training and considerable experience in conducting systematic reviews, with 4 published systematic reviews in peer-reviewed journals indexed in PubMed during the last 2 years, and with a Ph.D. in neurophysiology that involved 5 years of training and research in biomedical statistics. Use of a systematic review of the literature permits analysis of clinical data from numerous very small clinical series as well as the several relatively large clinical series to increase the reviewed study population and thereby obtain more sound conclusions.

5. Research results

The research findings, their contributions to the research in this field, and the problems that remain to be solved should be described in detail.

This systematic review reports data from the few relatively large clinical studies of therapeutic ERCP during pregnancy, including 4 studies of 65, 58, 20, and 18 pregnant patients undergoing ERCP, but supplements these data from 254 cases consisting mostly of very small clinical series to maximize the available data and improve the reliability of the conclusions. This work focuses on techniques to improve ERCP safety during pregnancy, including analysis of the relatively recently introduced radiation-free ERCP to completely eliminate the potential for radiation

teratogenicity. Radiation-free ERCP is shown to be a relatively safe, and efficacious technique. However, more clinical data are required on this promising technique.

6. Research conclusions

The following questions should be briefly answered: What are the new findings of this study? What are the new theories that this study proposes? What are the appropriate summarizations of the current knowledge that this study provided? What are the original insights into the current knowledge that this study offered? What are the new hypotheses that this study proposed? What are the new methods that this study proposed? What are the new phenomena that were found through experiments in this study? What are the hypotheses that were confirmed through experiments in this study? What are the implications of this study for clinical practice in the future?

This work systematically collates the available literature in this clinically burgeoning field to show that therapeutic endoscopy is a reasonably safe therapy to the mother and the fetus during pregnancy, and should be performed when indicated for choledocholithiasis and its associated complications. Before ERCP, maternal resuscitation should including fluid repletion and correction of metabolic and hematologic abnormalities, and institution of antibiotics to manage cholangitis. These conclusions are based on analysis of reports of >500 cases of therapeutic endoscopy during pregnancy and several moderately large retrospective studies of 65, 58, 20, and 18 pregnant patients. This work describes important procedural maneuvers and techniques to improve fetal safety of ERCP during pregnancy.

An important consideration is use of radiation-free ERCP during pregnancy to completely avoid radiation teratogenicity. In this technique, successful bile duct cannulation is guided and confirmed by visualizing bile drainage after wire insertion and bile aspiration after catheter cannulation. Shortcomings of this method include wires or catheters can inadvertently enter the cystic duct, chronically obstructed biliary systems may yield “white bile” that leads to falsely confirming correct catheter placement, and curled wires may cause bile duct injury that complicates proper stent insertion.

Altogether 147 ERCP’s have been performed during pregnancy without fluoroscopy in 8 clinical series, reflecting endoscopist ingenuity and technological progress. These clinical data

are extremely promising, with a very high rate of technical success (clearing of CBD stones), low rate of maternal complications, delivery of predominantly healthy babies, mostly normal birth weights, and typical delivery at term. However, these case series from tertiary academic centers may not be necessarily extrapolated to community hospitals. Moreover, brief fluoroscopy with “ultra-short” (<60 seconds) radiation exposure may produce as favorable fetal results as radiation-free ERCP.

Diagnostic ERCP is being increasingly replaced by less invasive techniques in the non-pregnant population due to improved accuracy and much less invasiveness of alternative tests including magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS). This work confirms that solely diagnostic ERCP should generally not be performed during pregnancy due to the risks of fetal radiation teratogenesis and induction of early labor, and should be replaced by diagnostic MRCP or endoscopic ultrasound.

ERCP should not be performed during pregnancy for asymptomatic stones because of potential fetal risks; ERCs can often be delayed to postpartum because patients have minimal clinical findings, or patients can directly undergo cholecystectomy without antecedent ERCP for acute cholecystitis.

7. Research perspectives

What experiences and lessons can be learnt from this study? What is the direction of the future research? What is/are the best method/s for future research?

This systematic review of the rapidly evolving literature demonstrates that therapeutic ERCP during pregnancy is relatively safe to the mother and the fetus. This finding is clinically important. It demonstrates that therapeutic ERCP is clinically indicated in the management of choledocholithiasis and its attendant complications of cholangitis, gallstone pancreatitis, and biliary stricture during pregnancy. This work provides an up-to-date review of radiation-free ERCP which shows its potential advantages during pregnancy. However, radiation-free ERCP is technically demanding, and may not be yet ready for ERCP specialists who perform a low volume of ERCs, or in the setting of community hospitals, which have limited experience with high-risk ERCs. More data are needed on radiation-free ERCs. This work describes technique modifications for therapeutic ERCP during pregnancy. It is hoped that clinicians adapt

these technique modifications during ERCP to further improve ERCP safety and efficacy during pregnancy.

15. As suggested by the editor, Figure 2 is submitted as a decomposable figure submitted as a computer file.

Thank you for thorough review and careful criticisms of this paper. We will be delighted to perform more revisions if so requested by the editors.

Warm regards,

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