

Long-term follow-up after fetal radiation exposure during endoscopic retrograde cholangiopancreatography



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ABSTRACT

Background and study aims The main concern about endoscopic retrograde cholangiopancreatography (ERCP)

during pregnancy is the risk of radiation exposure to the fetus. The potential exists not only in the short-term, but also in the long-term and includes growth and development problems and the possibility of childhood cancer. Little is known about the long-term effects of fetal radiation exposure at the time of ERCP. The aim of the study was to report the long-term outcome of babies born after radiation exposure to mothers who underwent ERCP during pregnancy.

Patients and methods This was a single-center retrospective cohort study. We included 24 consecutive pregnant patients who underwent ERCP due to choledocholithiasis and their children, between June 1997 and June 2015. All patients and their babies were followed up until birth to assess their short-term outcome. To assess long-term outcomes, from September 2014 to September 2015, a comprehensive medical interview was conducted with the mothers and their children. We also evaluated medical records, lab tests, school report cards, and the families completed a questionnaire inquiring about perceived health status of the children.

Results Fifteen patients had full-term pregnancies. One patient had a preterm delivery (32 weeks) due to preeclampsia. There were no cases of miscarriage, stillbirth or fetal malformations. Long-term follow-up was performed at a mean age of 11.08 years (range 1–18) for the children, with no developmental delays, poor school performance, or malignancies found.

Conclusions Long-term outcome in children born after radiation exposure during ERCP was unremarkable.

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is an important therapeutic tool in the management of biliary choledocholithiasis [1, 2]. Symptomatic common bile duct stones are infrequent during pregnancy, but they may cause complications such as cholangitis and gallstone pancreatitis and are prone to relapse during pregnancy and potentially life-threatening diseases for both mother and fetus [3, 4]. ERCP is an established method for treatment of choledocholithiasis and there are numerous case series and case reports about its safe-

ty during pregnancy, at least in the short term [5–9], but there is little information about the long-term outcome of these babies [10].

The major concern during pregnancy is the risk of radiation exposure to the fetus because of the increased radiosensitivity of their developing organs and tissues [11, 12]. These risks include fetal death, malformations, and the possibility of long-term late effects on the growth and mental development or future malignancies, mainly leukemia [13–16]. Although there is acceptable data on the short-term outcome, long-term outcomes in children born after ERCP have not been well docu-

mented [10, 17]. The aim of this study was to investigate long-term outcomes in babies born after radiation exposure to mothers who underwent ERCP during index pregnancy.

Patients and methods

Patients

We conducted a single-center retrospective cohort study. We included all pregnant women who underwent ERCP due to biliopancreatic pathologies whose babies were exposed to radiation at the time of ERCP between June 1997 and June 2015 at Hospital C. Bocalandro, an institution affiliated with the University of Buenos Aires. The study was approved by the Institutional Review Board of the Hospital and written informed consents were obtained from all the patients. Two ERCP procedures were done without fluoroscopy and were excluded.

ERCP techniques

ERCPs were performed with the patients lying in the left lateral decubitus position. The pelvis and lower abdomen of the mothers were lead-shielded. The fluoroscopic unit was a General Electric Stenoscop C-arm. Fluoroscopy was done at 75–80 kVp with a tube filtration of 2 mm Al. Before brief “snapshots” fluoroscopy for the cholangiogram, we tried to verify cannulation by aspiration of bile in the endoscopy catheter. Continuous fluoroscopy was avoided as well as hard copy radiographs. After the cannulation of the common bile duct, a biliary sphincterotomy was performed if indicated and/or a plastic stent was placed if needed. Moderate or deep sedation was achieved using a combination of propofol, midazolam or fentanyl given by an anesthesiologist. Continuous fetal monitoring was done by an obstetrician. The fetal radiation exposure was not measured during any of the procedures but the total fluoroscopy time was recorded.

Sources of information

One of the staff members in the Gastroenterology Department followed up with all all of the mothers and their babies after ERCP until birth to obtain information on maternal and fetal outcome. Outcome measurements included miscarriage, stillbirth, preterm delivery, and fetal malformations. Deliveries were classified as: preterm (before 37 weeks), early term (37–38 weeks), full term (39–40 weeks), late term (41 weeks), and post term (42 weeks and beyond). Trimesters were divided into first trimester (weeks 1–12), second trimester (weeks 13–26) and third trimester (≥ 27 weeks). Low birth weight was defined as a weight < 2500 g at delivery. An Apgar score at 5 minutes ≥ 8 was considered normal.

Long-term follow-up

Because follow-up after delivery spanned a period up to 18 years, information concerning the long-term outcome was obtained from multiple sources to ensure complete and accurate data collection. Between September 2014 and September 2015, we conducted a comprehensive medical interview with the mothers and their children inquiring about the children’s health, medications, personal, social, and family history as well

as a review of systems to obtain information about the children’s outcomes. We also reviewed medical records (pediatric and/or adult), laboratory examinations, and diagnostic tests, if they were done, and we contacted the children’s pediatricians. In addition, we evaluated the school performance of the children (relative school level, repeats, and dropout frequency) during the family interview and School Report Card review. Finally, families were asked to complete a questionnaire inquiring about the perceived health status of the children (answer options were: very good, good, fair, bad, very bad). Outcomes evaluated included normal development of the children, neurological, hearing, and visual impairment, premature or delayed puberty, and childhood cancers.

Statistical analysis

We used descriptive statistics to compare the different findings of the study. The data collected were pooled by corresponding trimester and presented as whole numbers (n) followed by percentage (%).

Results

We included 24 pregnant women with a mean age of 24.5 years (range 19–34) at time of ERCP. Gestational age corresponded with first trimester (n = 1), second trimester (n = 10) and third trimester (n = 13). The indications for ERCP were acute cholangitis (n = 8), obstructive jaundice due to cholelithiasis (n = 12), and gallstone pancreatitis (n = 4). The only patient in the first trimester had acute cholangitis. The mean fluoroscopy time during ERCP was 1.30 minutes (range: 0.30–2.5). Twenty-two patients had biliary sphincterotomy with stone extraction. Multiple stone extractions were performed in 16 of 22 patients. One patient in the second trimester had a large common bile duct stone and required temporary stenting; definitive resolution was performed after delivery.

One patient had a normal cholangiogram. There were three adverse events, two mild pancreatitis and one acute cholecystitis, which was resolved with medical treatment.

Pregnancy and perinatal outcomes.

There were 15 full-term pregnancies, six early term pregnancies, and two late-term pregnancies (► **Table 1**). One mother had a preterm delivery at 32 weeks due to preeclampsia (the patient with temporary stenting) and her newborn had an Apgar score < 8 and low birth weight. Fortunately, he recovered uneventfully. Cesarean section was performed on 10 patients. We did not find any miscarriage or stillbirth cases. There were no fetal malformations detected.

Long-term outcomes.

Data from the 24 children (10 male) at mean age 11.08 years (range 1–18) were collected. In all cases, growth and development were according to the age. Physical examinations, including neurological, visual and hearing evaluations, were normal. Physical changes and signs of puberty were evaluated to address the outcome of premature or delayed puberty. Normal puberty was observed in 15 children (9 girls). The two children

► **Table 1** Pregnancy and perinatal outcomes.

Outcomes	All pregnancies n = 24	First-trimester ERCP (n = 1)	Second-trimester ERCP (n = 9)	Third-trimester ERCP (n = 14)
Full-term pregnancy	15 (62.5%)	0	6	9
Early-term pregnancy	6 (25%)	1	2	3
Late-term pregnancy	2 (8.3%)	0	0	2
Preterm delivery	1 (4.1%)	0	1 (temporary stent-pre-eclampsia)	0
Cesarean section	10 (41.6%)	0	4	6
Miscarriage, stillbirth	0	0	0	0
Apgar score < 8 at 5 min	1 (4.1%)	0	1	0
Low birth weight (<2500 g)	1 (4.1%)	0	1	0
Perinatal death	0	0	0	0
Fetal malformations	0	0	0	0

ERCP, endoscopic retrograde cholangiopancreatography.

► **Table 2** Full research papers on ERCP and pregnancy with fluoroscopy.

Author	Year	n	Mean fluoroscopy	Estimated fetus radiation	Long-term follow up
Tham [9]	2003	15	3.2 minutes	3.1 mGy (1.02–5.77)	Not reported
Kahaled [5]	2004	17	14 seconds	0.4 mGy (0.01–1.8)	Not reported
Gupta [29]	2005	18 (F11)	8 seconds	Not reported	11 children; healthy at median age 6 years
Tang [7]	2009	65	1.45 minutes	Not reported	Not reported
Garcia-Cano [35]	2011	11	30 seconds	Not reported	Not reported
Smith [23]	2013	35	0.15 minutes	23 patients < 0.1 mGy	Not reported
Fine [8]	2014	20	3.8 minutes	Not reported	Not reported
Konduct [30]	2019	25 (F18)	6 seconds	Not reported	21 children. Healthy at 1–7 years
Current study	2020	24	1.30 minutes	1.25–1.38 mGy	24 children. Healthy at mean age 11.08 years

ERCP, endoscopic retrograde cholangiopancreatography; F, ERCP done with fluoroscopy.

under age 5 had expected development. Good or very good were the answers to the questionnaire asking families about the perceived health status of their children.

In 22 children over age 5 years (12 in elementary school and 10 in high school), a normal relative school level was observed. The two children under age 5 years had expected development.

We did not detect any childhood cancer.

Discussion

The first report on ERCP during pregnancy was in 1990 [6]. Since then, several studies have addressed the efficacy and safety of ERCP in pregnancy (► **Table 2**). The majority of these studies concluded that ERCP is safe and effective during pregnancy at least in the short term and at delivery. However, little is known about the long-term outcome of children born after radiation exposure at the time of ERCP. Many authors suggest

that long-term follow-up data would be worthwhile on outcomes of children who received ERCP radiation in utero [17]

In utero exposure to ionizing radiation can be teratogenic, carcinogenic, and mutagenic and is directly related to the level of radiation. The fetus is most susceptible during the organogenesis period (first trimester) and the risk is diminished in the second and third trimesters [18]. The American College of Obstetricians and Gynecologist guideline states that “Fetal risks of anomalies, growth restriction, or abortion have not been reported with radiation exposure of less than 50 mGy” [19]. This radiation level is below the general radiological studies. Exposure to a radiation dose < 50 mGy has not been shown to affect pregnancy outcomes compared with control populations exposed to background radiation [20] Spontaneous abortion, growth restriction, and mental retardation may occur at higher exposure levels. Unlike the deterministic radiation effects, which have a threshold dose, stochastic radiation effects do not seem to have a threshold dose. Prenatal exposure to ioniz-

ing radiation at any dose could be associated with an increased risk of childhood malignancy. The lifetime cancer risk is largely unknown [21, 22]

The International Commission on Radiological Protection (ICRP) recommends monitoring fetal radiation exposure when the dose is expected to exceed 10 mGy [18]. Different authors tried to evaluate fetal radiation exposure during ERCP using thermoluminescent dosimeters (TLD) placed on the mother's skin over and above the uterus.

Kahaleh et al [5] estimated the fetal radiation exposure at 0.4 mGy in 17 pregnant women, with a mean fluoroscopy time of 14 seconds (range 1–48 seconds). With the same methodology, Smith and Kahaleh et al [23] studied 35 pregnant women and estimated the fetal radiation exposure almost negligible (<0.1 mGy) for the majority of patients, with mean fluoroscopy time of 0.15 minutes (range 0–1 minute). One patient died after ERCP due to acute respiratory distress syndrome and two mothers gave birth preterm and fetal outcomes were not reported. The authors suggested that for routine ERCP, estimating fetal radiation fetal exposure is not necessary because these values are below the maximum allowed dose of radiation to the fetus of 0.005 Gy. They recommended monitoring fetal radiation exposure in complicated long-lasting ERCPs such as patients with altered anatomy, failed prior ERCP or complex bile leak. But that measurement is only an approximate value because the principal radiation source for the fetus is the scattered radiation from maternal tissues. TLD taped to the skin may underestimate fetal radiation exposure [24].

Tham et al [9], using a Plexiglas phantom, estimated fetal radiation exposure at 3.10 mGy (range 1.02–5.77 mGy) in 15 pregnant women, with a mean fluoroscopy time of 3.2 minutes (range 1.1–6.1 minutes) with spot films obtained in 12 of 15 patients. Only one patient was in the first trimester and 11 infants had been delivered uneventfully at the time the paper was written.

Samara et al [24] estimated radiation delivery to a potential conceptus in 24 patients (11 male, 13 female) using the Monte Carlo methodology and physical anthropomorphic phantoms that simulate a pregnant women at different trimesters and concluded that conceptus dose from ERCP may occasionally exceed the 10 mGy dose in the case of a complicated long-lasting ERCP procedure, raising the possibility of high fetal dose levels during ERCP.

In a recent study, Huda et al [25] using TLDs, Kerma-area product (KAP) meter and a voxel-based phantom connected to the Monte Carlo codes estimated in a pregnant woman the fetal absorbed dose. The fetal gestational age was 32 to 34 weeks; fluoroscopy time 2.67 minutes, KPA 7.128 Gy cm² and the fetal absorbed dose was estimated at 2.85 mGy.

Taking all of the above into account, estimating fetal radiation exposure during ERCP is not easy. Although measurements from studies during pregnancy are clearly below the 10 mGy level, fetal radiation exposure depends on multiple factors, such as gestational age, size and body composition of the mother, patient position, orientation of the fetus, and the endoscopist experience.

Therefore, special attention must be paid to radiation dose reduction. Fetal radiation exposure must be kept to a minimum according to the ALARA principle (as low as reasonably achievable) by limiting the fluoroscopy time. Several strategies are recommended, including decreasing fluoroscopy time, minimizing exposure areas, short “taps” of fluoroscopy, and low-dose-rate pulsed fluoroscopy. In addition, protective radiation shields under and over the table of the x-ray system and copper filters in the x-ray beam or a drape hanging over the image intensifier can be used to minimize radiation to the mother and the fetus [26].

Non-radiation ERCP has been proposed during pregnancy [27], but with this technique, stones could be missed, which may lead to recurrent cholangitis or pancreatitis with more serious effects on the mother and the fetus. In addition, a recent systematic review/meta-analysis showed that a radiation-free ERCP did not reduce fetal and pregnancy-related complications [28].

Long-term follow-up data are scarce and to our knowledge, only two studies have attempted to address this topic. Gupta et al [29] reported on the first long-term follow up data in 11 of 18 pregnant women who underwent therapeutic ERCP. Eleven procedures were done with fluoroscopy, with a median fluoroscopy time of 8 seconds and the majority in the second and third trimesters. In two of 18 procedures, adverse events were recorded, one pancreatitis and one post-sphincterotomy bleeding. One woman had a preterm delivery. The median age of the 11 babies at the follow up was 6 years (range 1–11) and all the children were healthy. Unfortunately, the authors did not mention the type of contact and assessment they did and not all of the procedures included were done with fluoroscopy.

The other study conducted by Konduk et al. [30] included 25 pregnant patients who underwent ERCP due to biliopancreatic pathologies, the majority in the second trimester. Eighteen procedures were performed with fluoroscopy with an average duration of 6 seconds. There were no major complications. Preterm labor was not observed. Regarding long-term follow-up data, they contacted and obtained information about 21 of 25 patients who had healthy newborns for a follow-up period of 1 to 7 years. Once more, the authors did not mention the type of contact and assessment they did and not all of the procedures included were done with fluoroscopy.

Comparing the results of the long-term follow-up of these series with our results is hampered by differences in data collection, length of follow-up, and type of children's evaluation of the long-term outcome.

Our series reports the long-term outcome of the babies born after radiation exposure to mothers who underwent ERCP during an index pregnancy, including 24 mothers and their children. Only ERCPs with the use of fluoroscopy were included and the vast majority of ERCPs were performed in the second and third trimesters. We follow the general recommendation to avoid ERCP during the first trimester and delay it to the second trimester whenever possible, because the fetus is more susceptible to radiation during organogenesis. Only one of the pregnant patients was in the first trimester and she had an absolutely imperative indication, acute cholangitis. The mean

fluoroscopy time in our study was 1.30 minutes (range 0.30–2.5 minutes), in the middle between the Kahaleh et al and Smith et al [5, 24] study and the Tham et al study [9]. Larkin et al [31] found that the dose area product (DAP) measurement correlated well with fluoroscopy time. Taking into consideration the measurements during pregnancy by Tham et al and Huda et al [25] and Kahaleh and Smith, we could estimate our fetal radiation exposure between 1.25 to 1.38 mGy, which is below the threshold of 10 mGy.

Conscious sedation was administered by the anesthesiologist with a combination of propofol, midazolam, and fentanyl at the lowest effective dose. Propofol was the main drug used and several times the only drug used. The U.S. Food and Drug Administration (FDA) classifies propofol as category B, fentanyl as category C (not teratogenic but it was embryocidal in rats), and benzodiazepines as category D, because their use during the first trimester has been associated with cleft palate. But midazolam, also category D, has not been associated with congenital abnormalities. No children had cleft palate malformation. Some patients received antibiotics (mainly ampicillin) due to cholangitis. Most of the antibiotics are category B and can be safely used during pregnancy [32]. Regarding indomethacin use for post-ERCP pancreatitis prophylaxis, none of the women received it after discussion with their attending obstetrician. Indomethacin is category C during pregnancy and some studies raised the issue of increased newborn complications such as oligohydramnios and premature closure of the ductus arteriosus [33]. None of the patients developed arrhythmia or respiratory depression during the procedures. Regarding maternal age, advanced maternal age (defined as ≥ 40 years) is considered a risk factor for adverse pregnancy outcome (miscarriage, preeclampsia, cesarean section, and fetal periventricular leukomalacia), but our cohort of patients were relatively young (mean age of 24.5 years, range 19–34) [34].

There were three procedural adverse events, including two cases of post-ERCP pancreatitis. There was one preterm delivery (32 weeks) due to preeclampsia in the mother and there were no cases of miscarriage, stillbirths or fetal malformations. Long-term outcomes were assessed during a comprehensive interview with families and children. The mean age of the children was 11.08 years, with 10 (41.7%) in high school, one of the longest follow-up reports. During the medical interview we inquired about the children's health, medications, personal, social, and family history as well as doing a review of systems and a physical examination. We also reviewed medical records (pediatric and/or adult), laboratory examinations and diagnostic tests, if they were done, and we contacted her or his pediatrician. Finally, families completed a questionnaire inquiring about the perceived health status of their children. Outcomes evaluated included normal development of the children, premature or delayed puberty, school performance, and childhood cancers. The results of these evaluations showed that the growth and development, general health, and the school performance of the children was normal. No childhood cancers were found.

Our study has some limitations. It represents a single-center's experience, limiting its generalizability, small sample size

with the caveat that is very difficult to recruit many patients for this specific topic. Although we could not measure fetal radiation exposure, we estimated it.

The strengths of our study include the thorough interviews conducted with children and their mothers at the long-term follow-up visit, which even included report card reviews, providing data on an important topic with little data. I

Conclusions

In conclusion, bearing in mind all relevant techniques to control and minimize fetal radiation exposure, the results of this study support the performance of ERCP during pregnancy for appropriate indications and provide endoscopists with knowledge in a field where randomized studies cannot be ethically performed. Further data may provide reassurance about these findings.

Competing interests

The authors declare that they have no conflict of interest

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