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Risks of emergency cesarean section and fetal asphyxia after induction of labor in intrahepatic cholestasis of pregnancy: A hospital-based retrospective cohort study

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ABSTRACT

Objectives: Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy liver-specific disease. Induction of labor in gestational weeks 37–39 is commonly performed with the perspective to avoid the complication of stillbirth. We aimed to study whether this practice increases the risks of emergency cesarean section (CS) and fetal asphyxia.
Study design: We assessed the risk of emergency CS and fetal asphyxia in ICP among women with spontaneous and induced onset of labor in comparison to women without ICP. We performed a hospital based retrospective cohort study with 25,870 singleton pregnancies, 333 with ICP (1.3%), of which 231 gave birth in weeks 37–39. Obstetric outcome was assessed through linkage of the Swedish Medical Birth Registry and a local obstetrical database based on the patient's medical files.
Main outcome measure: Risk for emergency CS; fetal asphyxia and postpartum hemorrhage.
Results: The risk of emergency CS in ICP with spontaneous onset of labor (12.5%) did not differ from non ICP women with spontaneous onset of labor (9.3%; aOR, 1.33; 95% CI 0.60–2.96). When labor was induced, risk of emergency CS was significantly lower among women with ICP than among without ICP (aOR, 0.47; 95% CI 0.26–0.86). Exclusion of women with preeclampsia, gestational hypertension or diabetes mellitus did not alter the result. The risk for fetal asphyxia was not significantly associated with ICP status.
Conclusion: Induction of labor in women with ICP gestational weeks 37–39 did not increase the risks of emergency CS or fetal asphyxia.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is characterized by otherwise unexplained pruritus, raised bile acids and/or liver transaminases [1,2]. ICP commonly presents in the third trimester and affected 1.5% of pregnancies of a large Swedish observational trial [3]. Older observational studies of ICP reported a stillbirth rate up to 10%, however, recent international literature report stillbirth rates of 3.5% or less [2]. In the Swedish trial, severe ICP, defined as maternal serum bile acids above 40 μmol/L, was associated with an increased risk for intrapartal asphyxia but not with stillbirth [3].

Since stillbirth in ICP in previous studies tended to cluster at gestational weeks 37–38 [2] and is unpredictable by conventional fetal surveillance [4] such as increased fetal heart rate monitoring, frequent biochemical testing, induction of labor at gestational weeks 37–38 has been advocated to prevent obstetric complications by prolonged pregnancy and to possibly reduce the risk of stillbirth [2,5–7]. However, data from randomized prospective trials to support this concept are lacking [8,9] and are probably difficult to obtain due to today's practice recommendations of induction of labor in ICP, besides pragmatic treatment with ursodeoxycholic acid (UDCA) [5–7], and in particular, the overall low incidence of stillbirth. In Stockholm, after 28 weeks of gestation, 3–4 stillbirths/1000 births were recorded in 2002–2005, but only 0.04 stillbirths/1000 births were attributed to ICP [10]. Thus, as long as randomized control trials are lacking, the potential benefit

Abbreviations: ICP, intrahepatic cholestasis of pregnancy; OR, odds ratio; aOR, adjusted odds-ratio; CI, confidence interval; CS, cesarean section; MBR, Swedish Medical Birth Register; BMI, body mass index; UDCA, ursodeoxycholic acid.

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of avoiding stillbirth by induction of labor has to be weighed against the risk for delivery complications caused by this procedure, in particular, the increased risk for and associated with emergency cesarean section (CS) [11,13–15].

The aim of this study was to analyze delivery outcomes of women with ICP at our hospital, compared to women without ICP, and to assess the risk for emergency cesarean section (CS), fetal asphyxia and postpartum hemorrhage following spontaneous onset of labor and after induction of labor in gestational weeks 37–39, i.e., the period when induction of labor in ICP is advocated.

Methods

The population of this hospital-based retrospective cohort study consisted of 25,870 women with singleton pregnancies who delivered during the period 2002–2006 at Danderyd Hospital, Stockholm, Sweden (Fig. 1). Of these, 333 (1.3%) had a diagnosis of ICP and 25,537 (98.7%) had no such diagnosis. Of women with ICP, 39 (12%) had an elective CS and the corresponding figure for women without ICP was 2727 (9%). The indications for elective CS in women with ICP included previous CS ($n = 9$), psychosocial indication ($n = 11$), breech presentation ($n = 10$), back pain ($n = 3$), anal sphincter injury in previous pregnancy ($n = 3$), in vitro fertilization ($n = 2$), and macrosomia ($n = 1$).

The diagnosis of ICP was made in the presence of otherwise unexplained pruritus and elevated serum bile acids (>10 μmol/L) and/or aminotranferases (ALT/AST) in at least one of serial evaluations (Table 1). Management of ICP consisted of fetal monitoring by weekly non-stress cardiotocography (CTG) test and oral administration of UDCA (10–15 mg/kg/day) if pruritus was intolerable or if maternal bile acids exceeded 30 μmol/L. ICP women were considered for induction of labor at 37–39 weeks of gestation or without delay if diagnosed with ICP later than gestational week 37. In cases of severe maternal disease unresponsive to therapy, obstetric complications or non-reassuring fetal testing, immediate induction of delivery was considered. However, according to the patients' preference, spontaneous onset of labor could be awaited in uncomplicated cases.

Obstetric outcome was assessed through linkage of the cohort to the Medical Birth Register and an obstetrical database at Danderyd Hospital containing information from patients' medical files. We analyzed the following entries: CS, postpartum hemorrhage and fetal asphyxia, corresponding to codes P21, O68, O72, and O82 of the 10th revision of the International Classification of Disease (ICD-10) [12], respectively. Induction of labor was also defined according to ICD-10 (O61.0). Preterm labor was defined as labor at gestational age $\leqslant$37 weeks. Data on body mass index (BMI) was registered in 60% of the patients.

All ICP patients' obstetrical files were manually reviewed to verify the indications for emergency CS and to retrieve data on maternal bile acids, liver transaminases, bilirubin and UDCA treatment. For women without ICP, due to the large cohort, data were solely obtained through the obstetrical database. The study was approved by the local Ethics' Committee at Karolinska Institutet (Dnr 2011/1586-31).

We evaluated data in two steps. First, we analyzed the association between ICP and risk of emergency CS in ICP with spontaneous onset of labor, compared to women without ICP with spontaneous onset of labor. We then estimated the risk of emergency CS in ICP with induction of labor, compared to women without ICP with induction of labor. We performed a subgroup analysis where we exclude women with the diagnoses preeclampsia, gestational hypertension, or diabetes. Risk for emergency CS after induction of labor was analyzed with emergency CS as dependent and ICP as independent variables using the logistic procedure in SAS (SAS Institute Inc., Cary, NC, USA). Since other studies have found BMI, age, use of epidural analgesia and parity to be factors affecting labor outcome, we adjusted for these potential confounders by successively adding these variables to the strata statement. Tests of heterogeneity were done by the chi-square test. Patient characteristics, fetal and maternal outcome were analyzed by chi-square and Wilcoxon signed-rank test. $P < 0.05$ was considered statistically significant.

Results

ICP was diagnosed in 333 (1.3%) of 25,870 singleton pregnancies. Gestational ages and mode of delivery onset are presented in Fig. 1. Maternal or gestational age, BMI, use of epidural analgesia, and parity did not differ between women with ICP and women without ICP (Table 1).

ICP with spontaneous or induced onset of labor did not differ in duration of ICP diagnosis, serum levels of bile acids, ALT/AST, bilirubin, or proportion treated with UDCA (Table 1). When these groups were compared, no difference in the incidence of emergency CS (7/56 vs. 13/144) or fetal asphyxia (2/56 vs. 1/144) was found (Tables 2 and 3).

For women with ICP and spontaneous onset of labor, the proportion delivered by emergency CS was 12.5% compared to 9.3% among women without ICP. Expressed in adjusted odds ratio (aOR) the risk for emergency CS was 1.33 (95% CI 0.60–2.96) (Table 2).

Among women who were induced, the proportions delivered by emergency CS were 9% for women with ICP and 16.5% in women without ICP. There was a significantly lower risk for emergency CS in induced ICP compared to induced women without ICP (aOR 0.47; 95% CI 0.26–0.86) (Table 2). There was no statistically significant difference in risk of fetal asphyxia in spontaneous and induced labor between ICP women and controls but numbers were small (Table 3). Excluding women with preeclampsia, gestational hypertension or diabetes mellitus did not change the results.

The proportion of hemorrhage was significantly increased in ICP with spontaneous onset of labor (12.5%) compared to women without ICP with spontaneous onset of labor (5.8%) (aOR 2.25; 95% CI 1.01–4.99) (Table 4). Furthermore, excluding pregnancies with missing data on BMI did not alter the results (data not shown).

Overall, dysfunctional labor was the most common indication for emergency CS in ICP ($n = 9$; 69%) as well as controls ($n = 94$; 54%). The proportion of women who had emergency CS because of fetal asphyxia did not differ between the two groups ($n = 4$, 30.7% vs. $n = 60$, 34.5%). Among women who had induction of labor, four with ICP (2.8%) and 60 (6.3%) of controls had emergency CS because of suspicion of fetal asphyxia (Table 5).

Discussion

In this study we found that women with ICP in gestational weeks 37–39 with spontaneous onset of labor had no increased risk of emergency CS as compared to women without this diagnosis (controls) and spontaneous onset of labor. In contrast, induction to labor in ICP in gestational weeks 37–39 had a more than 50% reduction in risk of emergency CS as compared to women without ICP.

The main strength of our study is that we compared delivery outcomes of ICP with spontaneous or induced delivery onset, to outcomes of women without ICP with the same delivery onset, gestational ages, and equal distributions of parity, BMI and epidural analgesia. This is in contrast to previous studies that compared the outcome of induction of labor of pre- or post-term deliveries, to normal deliveries in general [13–15].