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MATERNAL-FETAL MEDICINE

Early induction of labor in high-risk intrahepatic cholestasis of pregnancy: what are the costs?

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Abstract
Purpose Induction of labor among pregnant women with high levels of total bile acid (TBA) is common among clinicians. We examined, if women with intrahepatic cholestasis of pregnancy (ICP) and TBA $\geq$ 40 µmol/l have a higher risk of maternal–fetal complications, when labor is induced at 37 weeks of gestation, compared with induction of labor at term in women with low-risk ICP.
Methods Retrospective cohort study of 16,185 women delivering at Roskilde University Hospital in the period 2006–2011. Women with high-risk ICP (TBA $\geq$ 40 µmol/l) had labor induced at 37 weeks of gestation; women with low-risk ICP (TBA $<$ 40 µmol/l) at term.
Outcomes Mode of delivery, duration of induction procedures, highest level of TBA and alanine aminotransferase (ALT) and for the neonates: Apgar scores at 5 min, umbilical cord pHs and SBEs, NICU admissions and birthweights.
Results The incidences of ICP was 1.2 % (95 % CI 1.05–1.39 %) altogether and for high-risk ICP 0.4 % (95 % CI 0.27–0.46 %). No difference was found in mode of delivery, length of induction of labor nor in neonatal outcomes, except for an expected difference in birthweight. In high-risk ICP, ALT was not raised in 10.3 % (95 % CI 2.5–18.2 %).
Conclusion Early induction of labor at 37 weeks of gestation seems justified in high-risk ICP, as, except for abbreviating gestational age by 9 days with 296 g smaller babies, induction of labor was not followed by detectable maternal–fetal disadvantages and is favored by an expected major reduction in ICP stillbirth risk.

Keywords Intrahepatic cholestasis of pregnancy · Total bile acid concentration · Induction of labor · Cesarean section

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific condition of pruritus and raised serum total bile acids (TBA) and/or liver enzymes that normalises quickly after delivery and is not explained by hepatitis or other liver disorders [1–3].

The incidence of ICP differs among populations, with the highest incidences in Chile: 6.5 % [4] and in Scandinavia: 1.5 % [1].

ICP is associated with several maternal–fetal complications including preterm delivery, meconium staining of the amniotic fluid, fetal asphyxia, post partum haemorrhage and most important significantly increased risk of intrauterine fetal death (IUFD) [1, 2, 4–8]. Thus, in a recent, huge British study, IUFD in high-risk ICP (TBA above 40 µmol/l) pregnancies was found to be 1.5 % i.e., increased three times above normal. Furthermore a recent study has found that pregnant women women with ICP are in higher risk of having other pregnancy-related disorders like gestational diabetes and pre-eclampsia [9]. The treatment of ICP is mainly symptomatic. Ursodeoxycholic acid is widely used, is well tolerated and data suggests that treatment can reduce pruritus and lower TBA levels [10, 11].

The etiologies of the fetal complications are not fully understood. However, an increased response to oxytocin

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may partly explain the mechanism behind preterm labor [12], and early onset of pruritus and high TBA have been shown to predict preterm delivery [13]. Furthermore, large prospective studies have shown an increased risk of IUFD as well as of preterm delivery, asphyxial events and meconium staining of the amniotic fluid with increased levels of TBA [1, 6, 14].

ICP-related IUFD occurs suddenly and is not associated with intrauterine growth restriction [2], though placentas from women with ICP show morphological abnormalities suggesting oxidative stress [15]. In the absence of clinical ICP symptoms, monitoring TBA is of no use explaining cases of stillbirths [16]. Cardiotocography has not been proven safe predicting fetal complications, and IUFD has occurred within 24 h of a normal non-stress test [2]. Doppler investigation of the umbilical artery might be of some value in the recognition of the specific risk of fetal compromise in pregnancies with ICP [17].

The risk of IUFD seems to increase with gestational age and in a report of mothers with ICP and related IUFD only 10 % of stillbirths in singleton pregnancies occurred before 37 weeks of gestation [18].

A newly published study finds that among women with ICP, delivery at 36 weeks gestation would reduce the perinatal mortality risk as compared with expectant management. The risk of expectant management remains higher than delivery and continues to rise by week of gestation beyond 36 weeks [19].

Since 2006 all women with ICP giving birth at Roskilde University Hospital have been treated according to a local guideline that advices delivery at 37 weeks for high-risk ICP women and delivery before term for low-risk ICP women.

Acknowledging the higher risk for fetal complications with increasing TBA [1, 6–8], we set out to examine the clinical outcomes of early induction of labor in pregnant women with TBA $\geq$ 40 μmol/l. This limit was chosen as Glantz et al. [1] in the large Swedish study found that fasting TBA $\geq$ 40 μmol/l was followed by significantly increased clinical effects. Later, after our study was finished, it was also confirmed in the huge British study by Geenes et al. [6] using non-fasting TBA. We thus compared the mode of delivery and time of induction in women with high-risk ICP induced at 37 weeks with those with low-risk ICP induced at term. By choosing women with low-risk ICP as the control group, we obtained fairly comparable groups in terms of discomfort and avoided the ethical dilemma of a randomised study with detailed information of the reported 1.5 % risk of IUFD in high-risk ICP [6].

Materials and methods

Since 2006 the local guideline for ICP in Roskilde University Hospital has classified ICP following TBA:

- Low-risk ICP: fasting serum TBA $\geq$10 and <40 μmol/l., and/or serum alanine aminotransferase (ALT) $\geq$45 mmol/l.
- High-risk ICP: fasting serum TBA $\geq$40 μmol/l.

Furthermore, the guideline has instructions concerning induction of labor [or, for other reasons, a planned cesarean section (CS)] in pregnant women with ICP according to severity:

- High-risk ICP: induction of labor (or CS) at gestational age 37 0/7.
- Low-risk ICP: induction of labor (or CS) before term.

Inclusion criteria: All pregnant women with pruritus and elevated TBA and/or ALT as stated above, without any other liver disorder, could be included. Women were excluded, if they could not be followed-up to delivery, e.g., because of referral to another hospital.

The TBA concentration from all pregnant women with pruritus from January 1st 2006 to December 31st 2011 were gathered. All blood samples were taken when fasting. All women were categorized as either high- or low-risk ICP according to the highest measured TBA. The onset of ICP in this study was defined as the time of the first measured TBA. All women with pruritus had TBA examined within a few days, usually before initiating any medical treatment.

All women with pruritus were followed with weekly TBA levels for at least 3 weeks. Women in the high-risk group were also followed with weekly biophysical scans and cardiotocography two times weekly after 32 weeks of gestation.

According to the guideline, all women with low- or high-risk ICP were offered 250 mg deoxycholic acid tablets three times a day following the diagnosis of ICP (elevated TBA and/or ALT). The dose could be increased, when needed, to 500 mg three times a day or at the highest 500 mg four times a day.

Induction of labor was initiated with cervical ripening with one tablet of misoprostol 25 μg on the first day. Subsequently, induction of labor was performed with one tablet twice a day, if neccesary.

Each woman with high-risk ICP was randomly matched according to age and measurement-kit with a woman with low-risk ICP as, for each kit-period, women from the high-risk ICP list were systematically age-matched with low-

risk women by drawing alternately from the top and from the bottom of the low-risk ICP list.

All other data concerning outcomes were collected manually from patient files.

Fasting TBA was measured by the Laboratory of Biochemistry at the hospital.[1]

Statistical analysis

All data were analysed using Chi^2 test or Fischer's exact test for catogorical data, Mann–Whitney test for ranked data and Student *t* test for continous data. We used SPSS for MAC, version 20 (SPSS Inc, Chicago, IL, USA). *P*-values <0.05 was considered to be statistically significant.

Results

During the 6-year period from 2006 to 2011 there were 16,185 delivering women at the hospital. In the same period 59 women were diagnosed with high-risk ICP and 139 had low-risk ICP. These 198 women with ICP confined an incidence of ICP of 1.2 % (95 % CI 1.05–1.39 %). The incidence of high-risk ICP was 0.4 % (95 % CI 0.27–0.46 %).

One of the 59 women with high-risk ICP was excluded because of referral to another hospital. Three women with low-risk ICP were excluded: one because of IUFD in gestational week 19, who subsequently had a (probably non-fasting) high TBA, but who never experienced pruritus, one was referred to another hospital and one woman had elevated TBA, detected only after delivery, and she was examined solely because of high alcalic phosphatases as she did not have pruritus during pregnancy. See Fig. 1.

The compared groups did not differ considering age, parity or proportion of twin pregnancies (Table 1).

We found a significant difference in gestational age at diagnosis of ICP, with median debut age in the high-risk ICP group 17 days earlier (37 0/7 weeks vs 34 4/7 weeks; $p < 0.01$). Also, as could be expected, there was a significant difference in the highest measured TBA between the two groups ($p < 0.001$). However, in contrast, we found no difference in the highest measured ALT, and diagnostics using ALT alone failed in 10.3 % (95 % CI 2.5–18.2 %) of high-risk ICP and in 16.4 % (95 % CI 6.6–26.1 %) of low-risk ICP.

[1] Until November 25th 2009 the Reactionlab A/S—BIO-STAT Bile Acid kit (Cat.no. 495000) was used. The kit was calibrated by performing measurements in parallel with the laboratorium in Gothenburg that performed the analyses in the large Swedish prospective study by A. Glantz (1) and was accordingly corrected by a factor 40/30; later a Sentinel Bile Acids TBA (REF 6K9001) were used and calibrated against its standard.

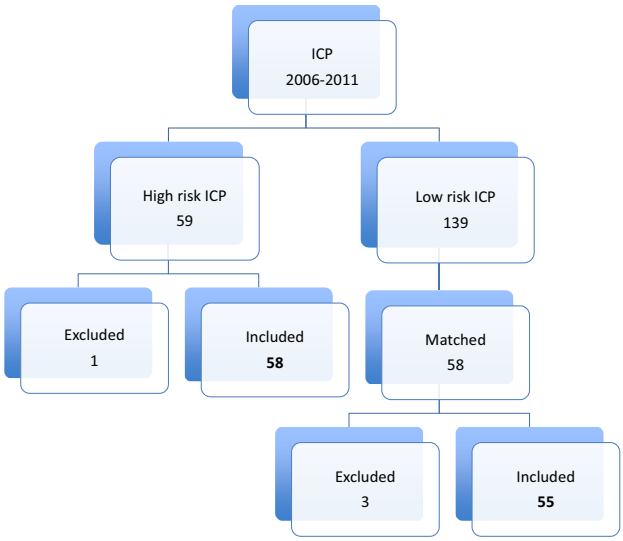

Fig. 1 Flowchart of included women with intrahepatic cholestasis of pregnancy at Roskilde University Hospital from 2006 to 2011

There was no difference in the amount of women treated with deoxycholic acid, but more women in the high-risk ICP group were treated with higher doses ($p < 0.001$).

A significant difference in median gestational age at delivery was measured (38 4/7 weeks (low risk) and 37 1/7 weeks (high risk); $p < 0.001$) (Table 2) and accordingly, a significant difference in mean neonatal birthweigth was recorded as well (3439 and 3143 g; $p < 0.01$) (Table 3).

No difference was recorded in mode of delivery (Table 2). We found a non-significant trend in the distribution between antepartum and intrapartum cesarean sections with more antepartum cesareans in the low-risk group (73.7 %) as compared with the high-risk group (50.0 %). The majority of intrapartum sections (90.0 %), in the high-risk ICP group, was performed due to dystocia rather than to asphyxia.

There was a trend towards more spontaneous preterm deliveries in the high-risk group [5:58 vs 0:55 ($p < 0.06$)]. No difference was observed in neither the length of induction period, the proportion of meconium stained amniotic fluid nor in the proportion of women with significant postpartum haemorrhage.

Most important, there was no IUFDs, and we found no difference in neonatal outcome (Table 3), except for 9 days difference in gestational age and 296 g difference in birthweight.

Discussion

Our retrospective cohort study found 198 women with ICP in a population of more than 16,000 delivering women, which corresponds to an 1.2 % incidence of ICP (95 % CI

Table 1 Patient characteristics and biochemistry

	Low-risk ICP ($n = 55$)	High-risk ICP ($n = 58$)	p
Age mean (SD)	31.3 (±1.2)	31.2 (±1.3)	NS[b]
Parity			
Primiparas *n* (%)	28 (50.9)	33 (56.9)	NS[a]
Multiparas *n* (%)	27 (49.1)	25 (43.1)	NS[a]
Twin gestations *n* (%)	9 (16.4)	11 (19.0)	NS[a]
Diagnosis of ICP:			
GA median (weeks) (min, max)	37 0/7 (24 2/7; 40 0/7)	34 4/7 (24 0/7; 41 0/7)	<0.01[b]
TBA (μmol/L) mean (95 % CI)	21 (±2)	84 (±14)	<0.001[b]
ALT (mmol/L) mean (95 % CI)	208 (±52)	218 (±41)	NS[b]
Number (%) of patients with ALAT > 45 mmol/l	46 (83.6)	52 (89.7)	NS[a]
Deoxycholic acid: Number of patients treated (%)	41 (74.5)	48 (82.8)	NS[a]

Measured values of ALT and TBA are shown

GA gestational age

Statistical tests used: [a] Chi^2-test, [b] Mann–Whitney's test

Table 2 Maternal outcome

	Low-risk ICP ($n = 55$)	High-risk ICP ($n = 58$)	p
Duration of pregnancy			
Median weeks (min, max)	38 4/7 (33 1/7; 40 2/7)	37 1/7 (33 1/7; 41 3/7)	<0.001[c]
Spontaneous vaginal delivery n (%)	9 (16.4)	7 (12.1)	NS[b]
Before 34 weeks *n* (%)	0 (0)	1 (1.7)	NS[a]
Before 37 weeks *n* (%)	0 (0)	5 (8.6)	<0.06[a]
Induced labor *n* (%)	32 (58.2)	38 (65.5)	NS[b]
Mode of delivery following induction			
Vaginal delivery *n* (%)	27 (84.3)	31 (81.6)	NS[b]
Cesarean section *n* (%)	5 (15.6)	7 (18.4)	NS[b]
Duration of induction Mean (95 % CI)			
Hours	16 (±8)	17 (±6)	NS[c]
Minutes	982 (±503)	1070 (±374)	NS[c]
Overall CS rate *n* (%)	19 (34.5)	20 (34.5)	NS[b]
Antepartum *n* (%)	14 (73.7)	10 (50.0)	NS[b]
Intrapartum *n* (%)	5 (26.3)	10 (50.0)	NS[b]
Meconium staining *n* (%)	6 (10.9)	13 (22.4)	NS[b]
Postpartum haemorrhage *n* (%)			
<1000 mL	53 (96.4)	53 (91.4)	NS[b]
>1000 mL	1 (1.8)	3 (5.2)	
Blood transfusion	1 (1.8)	2 (3.4)	

Duration of induction is defined as the time from cervical ripening until delivery (vaginal/CS)

Statistical tests used: [a] Fishers exact test, [b] Chi^2-test, [c] Mann–Whitney's test

1.05–1.39 %). We found 59 women with high-risk ICP which equals an incidence of 0.4 % (95 % CI 0.27–0.46 %).

Our policy of inducing labor (or performing a, for other reasons planned, CS) already at 37 weeks in high-risk ICP was compared with the intended completion of pregnancy at term in the low-risk ICP group. The earlier induction of labor, of course led to babies being born earlier (in this study 9 days) and smaller (here 296 g); however, the comparison did not reveal any significant difference in neonatal safety nor in maternal discomfort due to long

Table 3 Neonatal outcome (for single borns only)

	Low-risk ICP ($n = 46$)	High-risk ICP ($n = 47$)	p
Birthweight (g) mean (95 % CI)	3439 (±139)	3143 (±127)	<0.01[b]
Apgar score <7/5 min n (%)	1 (2.2)	1 (2.1)	NS[a]
Umbilical artery pH <7.10 or sBE <−10 n (%)	0 (0)	1 (2.1)	NS[a]
Days at NICU mean (95 % CI)	0.7 (±1.2)	0.8 (±1.4)	NS[b]

Outcomes are only shown for single born neonates as ICP provide special problems in twin pregnancies. However, comparing the same outcomes in twin neonates did not reveal any statistical difference either

Statistical tests used: [a] Chi^2-test, [b] Mann-Whitney's test

induction periods or in higher risk of cesarean sections. As could be expected and hoped for, no IUFD was detected in the high-risk group of 59 women.

That early term delivery does not increase the rate of CS is in accordance with other recent studies: Chappel et al. randomised 62 women with ICP to either early term delivery (induction/delivery initiated between 37 0/7 and 37 6/7 weeks) or expectant management (with intended delivery shortly before term) and found no difference in cesarean section rates [11]. Shemer et al. found that women with induced labor had more than 50 % reduction in risk of emergency CS as compared to women without ICP [20]. We have not been able to find any study that has examined the length of induction of labor. It is a reassuring finding that women with high-risk ICP having labor induced do not suffer from longer induction periods compared to women with low-risk ICP having labor induced at term.

This study includes all women with ICP in a population of more than 16,000 women and includes as many as 58 women with high-risk ICP, defined as women with TBA above 40 μmol/L. In essence, it is a retrospective cohort study only; however, during the whole 6-year period, it was based on the same specific guideline for measurement of fasting TBA and performing early induction in case of high fasting TBA levels. Unfortunately, the measurement kit was changed half way in the study; nevertheless, by calibrating the kits and matching the controls according to the kit used, we minimized deviations stemming from this.

The incidence of ICP found in this study equals the incidence found in another Scandinavian study (1.5 %) [1]. A lower incidence has been found in Great Britain (0.1–0.7 %) [6, 21] and higher incidences are reported from Latin American populations (5.6–6.5 %) [4, 22]. Our incidence of high-risk ICP, based on fasting TBA, of 0.4 % is remarkable compared to an incidence of only 0.09 % in a newly published huge study from the UK were they used non-fasting TBA levels in diagnosing ICP [6]. This study prospectively registered all pregnant women with high non-fasting TBA in almost all of the UK for almost a year and compared the clinical results with those from a database of normal pregnant women. They thereby confirmed a significantly increased risk of preterm delivery, neonatal unit admissions and stillbirths (1.5 vs 0.5 %; OR 2.68; 95 % CI 1.03–6.49 %) in ICP with non-fasting TBA above 40 μmol/l. The use of non-fasting TBA levels surely have practical advantages and is surely more patient friendly; however, it has to be shown in a comparative study whether non-fasting TBA has similar sensitivity and specificity as fasting TBA to diagnose high-risk TBA. As mentioned, non-fasting TBA has already been proved to provide valuable clinical information in a huge study. However, one would expect non-fasting TBA to over-diagnose high-risk ICP, probably leading to unneccesary induction, which could be avoided by taking fasting TBA for example in only cases with high non-fasting TBA. The very low incidence of high-risk ICP found in the UK speaks against a low specificity using non-fasting TBA to diagnose high-risk ICP, provided that the authors really were succesful overcoming the immense practical difficulties diagnosing all pregnant women with ICP using a new blood test in nearly all hospitals in the UK for almost a year.

ICP has been reported to be associated with an increased risk of IUFD (0.4–4.1 %) [2, 4–6, 23, 24]. It seems that 90 % percent of this risk occurs after 37 weeks [18] and thus should be avoidable by early delivery at 37 weeks. Our study, as all other published studies, is far from having the power to prove a reduction in IUFD by abbreviating high-risk ICP pregnancies at 37 weeks. The question is, if this assumed higher safety is worth an average loss of 9 days of gestational age and 296 g of birthweight when there, as it is observed in this study, is no major difference in maternal complications and in neonatal safety. We think so.

The observation that more than 10 % of high-risk ICP are not detected by measuring ALT lead us to encourage the use of both ALT and fasting TBA levels or TBA only in diagnosing ICP.

In conclusion, early induction of labor at 37 weeks of gestation seems justified in high-risk ICP, as, except for

abbreviating gestational age by 9 days with 296 g smaller babies, induction of labor was not followed by detectable maternal–fetal disadvantages and is favored by an expected major reduction in ICP stillbirth risk.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards The Danish Data Protection Agency approved the study (file number: SN-21-2012). No ethic approval was neccesary for this study according to The National Committee on Health Research Ethics.

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