OBSTETRICS

Intrahepatic cholestasis of pregnancy: maternal and fetal outcomes associated with elevated bile acid levels

Laura Brouwers, BSc; Maria P. H. Koster, MD, PhD; Godelieve C. M. L. Page-Christiaens, MD, PhD; Hans Kemperman, PhD; Janine Boon, MD, PhD; Inge M. Evers, MD, PhD; Auke Bogte, MD; Martijn A. Oudijk, MD, PhD

OBJECTIVE: The primary aim of this study was to investigate the correlation between pregnancy outcome and bile acid (BA) levels in pregnancies that were affected by intrahepatic cholestasis of pregnancy (ICP). In addition, correlations between maternal and fetal BA levels were explored.

STUDY DESIGN: We conducted a retrospective study that included women with pruritus and BA levels ≥10 μmol/L between January 2005 and August 2012 in 3 large hospitals in the Netherlands. The study group was divided in mild (10-39 μmol/L), moderate (40-99 μmol/L), and severe (≥100 μmol/L) ICP. Main outcome measures were spontaneous preterm birth, meconium-stained amniotic fluid, asphyxia, and perinatal death. Univariate and multivariate logistic regression analysis was used to study associations between BA levels and adverse outcome.

RESULTS: A total of 215 women were included. Gestational age at diagnosis and gestational age at delivery were significantly lower in the severe, as compared with the mild, ICP group ($P < .001$). Spontaneous preterm birth (19.0%), meconium-stained fluid (47.6%), and perinatal death (9.5%) occurred significantly more often in cases with severe ICP. Higher BA levels were associated significantly with spontaneous preterm birth (adjusted odds ratio [aOR], 1.15; 95% confidence interval [CI], 1.03−1.28), meconium-stained amniotic fluid (aOR, 1.15; 95% CI, 1.06−1.25), and perinatal death (aOR, 1.26; 95% CI, 1.01−1.57). Maternal BA levels at diagnosis and at delivery were correlated positively with umbilical cord blood BA levels ($P = .006$ and .012, respectively).

CONCLUSION: Severe ICP is associated with adverse pregnancy outcome. Levels of BA correlate between mother and fetus.

Key words: adverse pregnancy outcome, bile acid, intrahepatic cholestasis, perinatal death

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Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-associated liver disease. It is the most common liver disease in pregnant women, with incidence figures of 0.1-1.5% in Central/Western Europe and North America and up to 1.5-4% in Chile and Bolivia.[1-4] ICP is a reversible illness that is characterized by pruritus, predominantly on the palms and soles, in the second or third trimester, combined with elevated serum bile acid (BA) levels (≥10 μmol/L). Usually, there are also abnormal transaminase levels. Symptoms and laboratory abnormalities disappear spontaneously after delivery.[5-9]

ICP is a relatively nonthreatening condition to women but is associated with fetal complications. It is linked with a higher risk of preterm delivery, meconium passage, fetal distress, and fetal death.[1,2,7-9] The underlying mechanisms of these complications are unknown. First, research in animals has shown a detrimental effect of high BA levels on cardiomyocytes, which cause arrythmia.[10-12] If these potentially lethal arrhythmias also occur in the fetus, it possibly could explain the increased incidence of stillbirth. Second, a vasoconstrictive effect of BA on placental chorionic veins has been shown, possibly explaining the occurrence of fetal distress, asphyxia and death.[13] Finally, several studies have shown BA to increase the sensitivity and expression of oxytocin receptors in the human myometrium, possibly

From the Departments of Obstetrics (Ms Brouwers and Drs Koster, Page-Christiaens, and Oudijk) and Gastroenterology and Hepatology (Dr Bogte) and the Clinical Chemistry and Hematology Laboratory (Dr Kemperman), University Medical Center Utrecht, and Department of Obstetrics and Gynecology, Diakonessenhuis (Dr Boon), Utrecht, and Department of Obstetrics and Gynecology, Meander Medical Center, Amersfoort (Dr Evers), the Netherlands.

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Corresponding author: M.A. Oudijk, MD, PhD. m.a.oudijk-3@umcutrecht.nl

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clarifying the mechanism behind spontaneous preterm labor in pregnancies that are complicated by ICP.[14,15]

The diagnosis of ICP is based on the presence of pruritus in combination with elevated BA levels. Although specific predictors for poor fetal outcome have not been identified consistently, higher BA levels (especially those >40 μmol/L) were found to be associated with higher rates of fetal complications.[16] Maternal treatment with ursodeoxycholic acid has been proved to provide significant relief of symptoms, to reduce serum BA levels, and to prolong pregnancy duration. However, it has not been documented to improve fetal outcome.[17,18]

The aim of this study was to investigate the association between BA levels and adverse pregnancy outcomes. In addition, the relationship between fetal and maternal BA levels at the time of delivery was investigated.

Materials and Methods

Patient selection and data collection

A retrospective study was conducted with data from January 2005 until August 2012 in 1 academic and 2 affiliated teaching hospitals in the Utrecht region, the Netherlands. All cases of ICP were identified through the laboratory computer systems. ICP was diagnosed when BA levels were ≥10 μmol/L and signs of pruritus during pregnancy where found in the hospital records. All pregnancies that were complicated by severe congenital malformations, which consisted of chromosomal abnormalities and/or multiple congenital anomalies, and all twin pregnancies were excluded from the study. Enzymatic colorimetric determination of total bile acids in serum was performed with Sentinel reagents using an AU5811 analyzer (Beckman Coulter, Brea, CA). BA levels were measured at diagnosis and on average 2-3 times per patient; there is no current standardized protocol for this in the Netherlands. In this study, the highest measured value throughout the pregnancy and the value before delivery were used for analysis.

Data on maternal demographics (ie, maternal age, parity, ethnicity), obstetric and medical history, biochemical parameters (ie, aspartate transaminase, alanine transaminase, bilirubin), treatment, and pregnancy outcomes (ie, birthweight, mode of delivery, Apgar score) were retrieved from the hospital records of all ICP cases.

This study was reviewed and approved by the local Institutional Ethical Review Board of the University Medical Center Utrecht, reference number: WAG/om/14/0005544.

Definitions

A history of ICP was positive if the disease had been present in any previous pregnancy in that particular woman. *History of hepatobiliary disease* was defined as cholecystectomy for cholelithiasis, hepatitis A, B, C, or a history of elevated liver transaminases with a different cause.

Three ICP severity groups (mild, BA 10-39 μmol/L; moderate, BA 40-99 μmol/L; severe, BA ≥100μmol/L) were constructed based on the highest measured BA throughout the pregnancy, according to international literature to perform subgroup analyses.[16]

Analysis of adverse pregnancy outcome included mode of delivery, meconium staining of the amniotic fluid, spontaneous and induced preterm birth (defined as <37 weeks of gestation), postpartum hemorrhage (defined as >1000 mL), small for gestational age (defined as birthweight <10th percentile), asphyxia (defined as a pHa <7.05 and base deficit of >12 mmol/L or pHa <7.00), low Apgar score (<7 after 5 minutes), admissions to medium care unit and neonatal intensive care unit, and perinatal death (24 weeks of gestation to 7 days after delivery). *Late preterm birth* was defined as birth between 34 and 36-6/7 weeks of pregnancy. Outcome measures were based on previous large studies on ICP and national guidelines.[3,5,16,19,20]

Statistical analysis

For baseline comparison between the ICP groups (mild, moderate, severe) medians and interquartile range were calculated for continuous variables; numbers and percentages were calculated for categoric variables. Differences between groups were analyzed with the nonparametric Kruskal-Wallis test and the Fisher exact test for continuous and categoric variables, respectively. Pairwise comparisons were performed with the Mann-Whitney *U* tests or by pairwise chi-square tests if variables were categoric. Correlations between BA levels in maternal and neonatal blood were calculated with Spearman's correlation coefficient.

Univariate logistic regression analyses were performed to calculate crude odds ratios (ORs) with 95% confidence intervals (95% CIs) with the use of the highest measured BA levels as a continuous predictor for several dichotomous adverse pregnancy outcomes. In a multivariate logistic regression analysis, ORs were adjusted for maternal age, gestational age, and birthweight.

Statistical analyses were performed with SPSS software (release 20.0; SPSS Inc, Chicago, IL). Probability values of < .05 were considered statistically significant.

Results

During the study period, 215 cases of ICP were diagnosed in women with singleton pregnancies. Of these 215 women, 108 had mild ICP; 86 had moderate ICP, and 21 had severe ICP. Eleven women had >1 ICP-affected pregnancy in the study period and were included as separate cases in this study.

Baseline characteristics of the study population are shown in Table 1. A large number of women (70.2%) received oral medication (ursodeoxycholic acid or in 2 cases cholestyramine) to treat ICP. In the severe ICP group, 90.5% of patients were treated with ursodeoxycholic acid; 2 patients were not treated with any medication because they were induced for labor immediately after diagnosis. In this population, 82.8% of the women were white. There was a relatively large proportion of patients with a history of ICP in a previous pregnancy (14.9%); only 6 patients (2.8%) had a history of hepatobiliary disease.

TABLE 1
Maternal demographics within the study population

Baseline demographic	Population (n = 215)	Intrahepatic cholestasis of pregnancy			P value
		Mild (n = 108)	Moderate (n = 86)	Severe (n = 21)	
Maternal age, y[a]	31 (29-34)	32 (29-36)	31 (29-33)	33 (30-36)	.072
Gravidity, n[a]	2 (1-3)	2 (1-3)	1 (1-2)	2 (1-3)	.218
Parity, n[a]	0 (0-1)	1 (0-1)	0 (0-1)	1 (0-1)	.287
White, n (%)	178 (82.8)	89 (82.4)	75 (87.2)	14 (66.7)	.142
Smoking, n (%)	8 (3.7)	6 (5.6)	1 (1.2)	1 (4.8)	.206
History of intrahepatic cholestasis of pregnancy, n (%)	32 (14.9)	19 (17.6)	8 (9.3)	5 (23.8)	.127
History of hepatobiliary disease, n (%)	6 (2.8)	2 (1.9)	2 (2.3)	3 (14.3)	.179
Gestational age at diagnosis, d[a]	252 (238-265)	259 (244-266)	248 (239-263)	234 (207-248)	.001[b,c,d]
Use of medication, n (%)[e]	151 (70.2)	69 (63.9)	63 (73.3)	19 (90.5)	.042[d]
Laboratory measurements[af]					
Bile acid, μmol/L	39 (21–66)	21 (15–29)	60 (51–73)	149 (109–200)	< .001[b,c,d]
Aspartate transaminase, IU/L	55 (34–86)	41 (27–71)	68 (40–133)	71 (38–183)	< .001[b,d]
Alanine transaminase, IU/L	90 (37–162)	66 (26–123)	130 (46–222)	100 (66–208)	< .001[b,d]
Gama-glutamyl transpeptidase, IU/L	24(16–43)	23 (15–34)	28 (17–54)	20 (16–41)	.113
Alkaline phosphatase, IU/L	220 (165–268)	190 (135–249)	237 (195–279)	226 (164–287)	.002[b]
Lactate dehydrogenase, IU/L	247 (196–379)	240 (187–374)	253 (214–439)	216 (180–298)	.055
Bilirubin, μmol/L	11 (8–14)	10 (8–12)	11 (8–15)	16 (11–22)	.002[c,d]

Three levels of severity of intrahepatic cholestasis of pregnancy: mild, bile acid levels of 10-39 μmol/L; moderate, bile acid levels of 40-99 μmol/L; severe, bile acid levels of ≥100 μmol/L.

[a] Values are presented as median (interquartile range); [b] Significant difference between mild and moderate levels; [c] Significant difference between moderate and severe levels; [d] Significant difference between mild and severe levels; [e] Mainly ursodeoxycholic acid (in 2 cases cholestyramine); [f] Highest measured laboratory data throughout the pregnancy were used.

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Maternal age, parity, and ethnicity had no effect on the severity of ICP. Gestational age at diagnosis of ICP was significantly lower in the moderate and severe ICP groups ($P = .001$). Almost all laboratory data could be retrieved; however, in approximately 15% of cases, liver function parameters were not determined. Aspartate transaminase, alanine transaminase, bilirubin, and alkaline phosphatase levels all were elevated significantly, related to the severity of ICP (Table 1).

Perinatal pregnancy outcomes are shown in Table 2. Patients in the moderate and severe groups had a lower average gestational age at delivery ($P <$ .001). Preterm birth occurred in 28 cases (13.0%), of which 8 cases (38.1%) were in the severe ICP group ($P = .003$). Labor was induced in 159 cases (74.0%), and 14 patients (6.5%) had an elective cesarean delivery.

Birthweight was significantly lower in the more severe cases of ICP ($P = .009$), but no difference was seen in the percentage of small-for-gestational-age children ($P = .831$). Apgar scores were comparable between groups ($P = .263$ and 0.45 after 1 minute and 5 minutes, respectively). Spontaneous preterm birth was more common with increasing severity of ICP ($P = .023$). In addition, meconium-stained amniotic fluid was found more often in the more severe cases ($P = .003$). Postpartum hemorrhage was present in 7.4% of all cases, with the highest percentage seen in the moderate group ($P = .019$). Asphyxia was seen in 2 cases throughout the study period; both cases were in the moderate ICP group. In this study population, perinatal death occurred in 2 cases (0.9%). Both intrauterine deaths were found in the severe ICP group ($P = .009$), which amounts to 9.5% of the severe ICP cases. In 1 of these patients, placental histopathologic examination showed a small placenta (<p10) with villitis.[21] In the other patient, no placental abnormalities were found. Both women declined autopsy.

Higher maternal levels of BA were also seen at time of delivery in the more severe group compared with the mild and moderate groups ($P < .001$). However, in all groups, the average level of BAs at delivery was lower than the highest measured level during the entire pregnancy.

In 35 cases, the umbilical cord BA levels were tested. Umbilical BA levels were elevated in patients with severe

TABLE 2
Obstetric outcomes within the study population

Obstetric outcome	Population (n = 215)	Intrahepatic cholestasis of pregnancy			P value
		Mild (n = 8)	Moderate (n = 86)	Severe (n = 21)	
Gestational age at delivery, d[a]	267 (260–275)	272 (264–279)	265 (260–270)	259 (252–267)	< .001[b,c,d]
Bile acid levels at time of delivery, μmol/L[a]					
Maternal	27 (15–56)	17 (12–23)	50 (24–68)	100 (22–141)	< .001[b,d]
Umbilical[e]	8 (5–14)	6 (4–8)	9 (5–15)	14 (10–24)	.076
Fetal sex (male)	115 (53.5)	54 (50.0)	48 (55.8)	13 (61.9)	.544
Apgar scores[a]					
1-Minute	9 (8–9)	9 (8–9)	9 (9–9)	9 (8–9)	.263
5-Minute	10 (10–10)	10 (10–10)	10 (10–10)	10 (9–10)	.45
pH[a]	7.26 (7.21–7.32)	7.27 (7.20–7.32)	7.26 (7.21–7.32)	7.27 (7.20–7.30)	.923
Birthweight, g[a]	3210 (2900–3550)	3290 (2950–3680)	3180 (2980–3480)	2930 (2710–3360)	.009[c,d]
Small for gestational age, n (%)[f]	13 (6.0)	8 (7.3)	4 (4.7)	1 (4.8)	.831
Preterm birth, n (%)[g]	28 (13.0)	9 (8.3)	11 (12.8)	8 (38.1)	.003[c,d]
Start of labor, n (%)			0.081		
Spontaneous	42 (19.5)	28 (25.9)	10 (11.6)	4 (19.0)	
Induced	159 (74.0)	74 (68.5)	68 (79.1)	17 (81.0)	
Elective caesarean delivery	14 (6.5)	6 (5.6)	8 (9.3)	—	
Mode of delivery, n (%)			0.409		
Vaginal delivery	185 (86.0)	94 (87.0)	72 (83.7)	20 (95.2)	
Cesarean delivery	30 (14.0)	14 (13.0)	14 (16.3)	1 (4.8)	
Adverse neonatal outcome, n (%)					
Spontaneous preterm birth	10 (4.7)	3 (2.8)	3 (3.5)	4 (19.0)	.023 [cd]
Meconium-stained fluid	44 (20.5)	15 (13.8)	19 (22.1)	10 (47.6)	.003[cd]
Postpartum hemorrhage[h]	16 (7.4)	3 (2.8)	11 (12.8)	2 (9.5)	.019[b]
Asphyxia[i]	2 (0.9)	—	2 (2.3)	—	.345
Perinatal death[j]	2 (0.9)	—	—	2 (9.5)	.009[cd]
Admission medium care	49 (22.8)	21 (19.4)	21 (24.4)	7 (33.3)	.374
Admission neonatal intensive care unit	5 (2.4)	1 (0.9)	2 (2.3)	2 (9.5)	.062

Three levels of severity of intrahepatic cholestasis of pregnancy: mild, bile acid levels of 10-39 μmol/L; moderate, bile acid levels of 40-99 μmol/L; severe, bile acid levels of ≥100 μmol/L.

[a] Values are presented as median (interquartile range); [b] Significant difference between mild and moderate; [c] Significant difference between moderate and severe; [d] Significant difference between mild and severe; [e] Umbilical levels of bile acid at time of delivery (micromoles per liter) that was determined for only 35 neonates; [f] Defined as birthweight <10th percentile; [g] Defined as <37 weeks of gestation; [h] Defined as >1000 mL; [i] Defined as pHa <7.05 and base deficit of >12 μmol/L or pHa <7.00; [j] Defined as 24 weeks of gestation to 7 days after delivery.

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ICP; however, this was not statistically significant ($P = .076$). As shown in Table 3 and the Figure, there was a significant positive correlation between the highest measured maternal BA and umbilical BA ($r = 0.453$; $P = .006$) and between maternal BA at delivery and umbilical BA ($r = 0.425$; $P = .012$).

Table 4 shows the regression analysis in which the highest measured BA levels were used as a continuous predictor for adverse pregnancy outcome. After adjustment for maternal age, gestational age, and birthweight, every 10-μmol/L increase of BA increased the probability

of spontaneous preterm birth (OR, 1.15; 95% CI, 1.03−1.28; $P = .016$), the likelihood of perinatal death (OR, 1.26; 95% CI, 1.01−1.57; $P = .039$), and the chance of meconium-stained fluid (OR, 1.15; 95% CI, 1.06−1.25; $P = .001$). There was no significant association between higher BA levels and postpartum hemorrhage or asphyxia.

Comments

This relatively large study of characteristics and perinatal outcome in women with a pregnancy that was complicated by ICP shows a significantly increased risk for iatrogenic preterm delivery, spontaneous preterm delivery, meconium-stained amniotic fluid, postpartum hemorrhage, and sudden intrauterine death, when ICP is severe (≥100 μmol/L). This confirms the results of a recent large study from the United Kingdom.[20]

A relatively large proportion (13.0%) of women delivered at <37 weeks gestation; 10 patients (4.7%) had a spontaneous onset of preterm labor. In the severe group, 19% of patients had a spontaneous preterm birth, as opposed to the overall national preterm birth rate in the Netherlands of 7.7%, of which approximately 5% were spontaneous.[22] These spontaneous preterm births are thought to be caused by the increase in sensitivity and expression of oxytocin receptors in the myometrium.[14,15] The number of late preterm births and births just after 37 weeks of gestation is in accordance with the national Dutch guideline on ICP that advocates an induction of labor at 37 weeks of gestation when BA levels are >40 μmol/L.[3,16,20]

The presence of meconium staining of the amniotic fluid increased with the severity of ICP. It has been shown that BAs have a vasoconstrictive effect on the placental chorionic veins, which leads to fetal distress and explains the occurrence of intrauterine meconium passage in these pregnancies.[13] Though not sufficiently proved in humans, it may also be explained by a negative effect of high BA levels on cardiomyocytes, which cause arrhythmias and thus fetal distress.[10-12] On the other hand, some research in animals suggests that BAs stimulate fetal colonic motility. The presence of meconium in the amniotic fluid in patients with ICP therefore may not be a sign of fetal distress, but rather a physiologic reaction.[23]

As mentioned previously, there are various ways in which intrauterine deaths are thought to be related to high levels of BAs, one of which is a damaging effect on fetal cardiomyocytes that results in fatal arrhythmias. Another reason is that BA triggers vasoconstriction in the chorionic veins and causes fetal distress and possibly sudden intrauterine death.[10-13]

A high percentage (n = 2/21; 9.5%) of perinatal death was seen in the severe ICP group ($P = .009$). When BA levels was used as a continuous predictor, a significantly increased risk of perinatal death was found ($P = .039$) for each 10-μmol/L increase of BA. Regular check-ups were performed in all patients with ICP, which included weekly visits to the out-patient clinic with antenatal ultrasound scanning (biometry, amniotic fluid assessment, assessment of fetal movements), cardiotocography monitoring, and maternal monitoring of fetal movement. Doppler investigation of fetal vessels is not part of the standard work up. Unfortunately, no predictive findings for these sudden fetal deaths were present; both pregnancies had undergone tests for the assessment of fetal condition by ultrasound scanning and maternal monitoring of fetal movements. One patient had additional cardiotocography performed that showed a reassuring fetal condition the day before the intrauterine death was diagnosed. The only indication of a

TABLE 3
Correlations between maternal and fetal bile acid levels

Variable	n	Spearman correlation coefficient	*P* value
Highest measured maternal[a] vs umbilical bile acid,[b] μmol/L	35	0.453	.006
Maternal bile acid at time of delivery[c] vs umbilical bile acid, μmol/L	34	0.425	.012

Correlations between maternal and fetal measurements using Spearman's correlation coefficient.

[a] Highest value found throughout the pregnancy; [b] In a sample of umbilical blood directly after delivery; [c] Measured <7 days before delivery.

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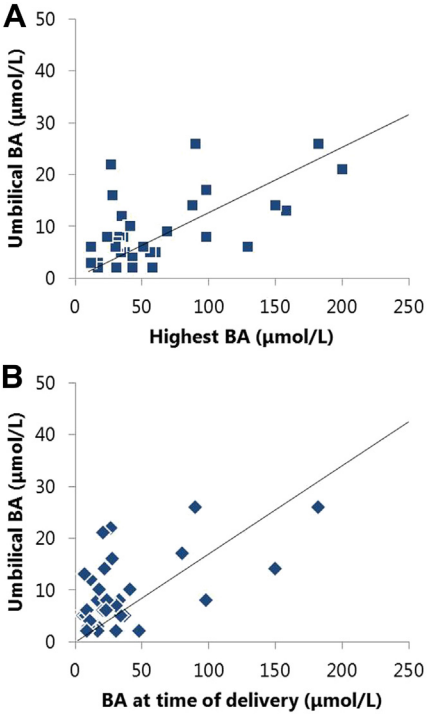
FIGURE
Correlations between maternal and fetal bile acid levels



Graphic diagram shows the correlations between maternal and fetal bile acid (*BA*) levels. **A,** Correlations between the highest measured maternal and umbilical bile acid levels (micromoles per liter). **B,** Correlations between maternal bile acid levels at delivery and fetal bile acid levels (micromoles per liter).

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TABLE 4
Odds ratios for every 10 μmol/L increase in bile acids

Adverse neonatal outcome	n	Crude odds ratio	95% confidence interval	*P* value	Adjusted odds ratio[a]	95% confidence interval	*P* value
Spontaneous preterm birth[b]	10	1.19	1.07–1.31	.001	1.15	1.03–1.28	.016[c]
Meconium-stained fluid	44	1.12	1.05–1.21	.002	1.15	1.06–1.25	.001
Postpartum hemorrhage[d]	16	1.02	0.96–1.09	.491	1.01	0.93–1.09	.912
Asphyxia[e]	2	0.97	0.70–1.35	.869	0.85	0.56–1.30	.463
Perinatal death[f]	2	1.08	1.00–1.17	.06	1.26	1.01–1.57	.039

Univariate and multivariate odds ratios for the association of every 10 μmol/L increase in bile acids with adverse pregnancy outcome.

[a] Adjusted for maternal age, gestational age, and birthweight; [b] Defined as <37 weeks of gestation; [c] Spontaneous preterm birth was corrected only for maternal age and birthweight; [d] Defined as >1000 mL; [e] Defined as pHa <7.05 and base deficit of >12 μmol/L or pHa <7.00; [f] Defined as 24 weeks of gestation to 7 days after delivery.

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potentially severe complication in these two patients was the increased BA level of ≥100 μmol/L. In patients with a BA level of ≥100 μmol /L, we therefore propose a more aggressive approach and elective delivery even if gestational age is 34-37 weeks of gestation. The consequences of iatrogenic preterm delivery, such as infant respiratory distress syndrome, special education needs, and poorer school performance vs the risks of ICP were not evaluated in this study. The possible iatrogenic consequences of late preterm induced labor, of course, must be balanced against the probability of the prevention of intrauterine deaths.[24,25] In mild and moderate ICP groups, the incidence of complications was significantly lower than in severe ICP cases. Elective delivery at <37 completed weeks of pregnancy therefore may not be justified in these groups. In a publication by Glantz et al,[16] a significantly increased complication rate was seen in pregnancies with ICP after 40 weeks of gestation. In accordance with this landmark research, most national guidelines advise a termination of pregnancy, before 40 weeks, in any ICP case.[3,5,16,19]

After performing a subanalysis, we found that women were treated more often with medication when they were diagnosed earlier in the pregnancy (data not shown). Women who were not treated with medication often delivered very soon after diagnosis. The treated women often showed higher BA levels throughout pregnancy and a lower BA level at delivery, which possibly shows an effect of treatment. Our data, however, did not show any significant changes on pregnancy duration or other pregnancy outcomes.

Umbilical cord BA levels showed significantly positive correlations with the highest measured maternal BA and the maternal BA at delivery, which provides evidence that BA are transported across the placenta; this correlation may imply a causal relationship between levels of BA and adverse fetal outcome. A relationship between BA levels in maternal and fetal blood samples previously has been seen in a few small studies.[26-30] However, there is no recent research on this topic. Probably because of the small sample size in our group (n = 34), significant correlations between umbilical cord BA levels and adverse outcome could not be found.

Limitations of this study were the retrospective nature of the study. First, approximately 15% of liver function parameters and 85% of umbilical BA levels were not available. The latter was not part of routine care. Fetal outcomes, however, were all well-documented in the 3 participating hospitals. A second limitation was the relatively small amount of adverse pregnancy outcomes (ie, asphyxia and perinatal death) that were found in the study. This is likely explained by the low incidence of these complications and is therefore a limitation in most perinatal studies. This limitation may result in some findings to be nonsignificant, even though previous research may show a significant correlation. For the most important outcomes (ie, preterm birth, perinatal death), the study population was large enough to show significant results. To fully assess the effect of ICP on all mentioned complications, a larger group may be favorable.

ICP is associated with spontaneous preterm delivery, meconium-staining of amniotic fluid, postpartum hemorrhage and perinatal death. In severe cases of ICP, sudden and unpredicted intrauterine death is seen. A more aggressive approach of elective delivery may be justified when BA levels are >100 μmol/L. Levels of BAs correlate between mother and fetus and imply a causal relationship between levels of BA and fetal complications and adverse outcome. ■

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