

Intrahepatic Cholestasis of Pregnancy: Relationships Between Bile Acid Levels and Fetal Complication Rates

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Intrahepatic cholestasis of pregnancy (ICP), characterized by pruritus in the second half of pregnancy, entails an increased risk to the fetus. This study was designed to determine the incidence and fetal complication rates in ICP, and to define groups at increased risk. In an prospective cohort study conducted between February 1, 1999, and January 31, 2002, all 45,485 pregnancies in a defined region of Sweden (Västra Götaland) were screened for ICP, defined as otherwise unexplained pruritus of pregnancy in combination with fasting serum bile acid levels $\geq 10 \mu\text{mol/L}$. Pruritus was reported by 937 (2.1%) women, and ICP was diagnosed in 693 (1.5%). Simple logistic regression analyses showed that the probability of fetal complications (spontaneous preterm deliveries, asphyxial events, and meconium staining of amniotic fluid, placenta, and membranes) increased by 1%–2% per additional $\mu\text{mol/L}$ of serum bile acids. Complementary analyses showed that fetal complications did not arise until bile acid levels were $\geq 40 \mu\text{mol/L}$. Gallstone disease and a family history of ICP were significantly ($P < .001$) more prevalent in the group of ICP patients with higher bile acid levels. **In conclusion, we found an incidence of ICP in our population of 1.5%. From complication rates recorded prospectively, we could define a mild (81%) and a severe (19%) form of ICP, the latter with bile acid levels $\geq 40 \mu\text{mol/L}$. No increase in fetal risk was detected in ICP patients with bile acid levels $< 40 \mu\text{mol/L}$, and we propose that these women be managed expectantly, which would significantly reduce the costs of medical care. (HEPATOLOGY 2004;40:467–474.)**

Intrahepatic cholestasis of pregnancy (ICP) is a condition characterized by pruritus in the second half of pregnancy. It persists until delivery, after which it ceases promptly. A genetic background is suggested by family clustering and demographic variations, with the highest incidences reported from Chile-Bolivia (6%–27%) and Sweden (1–1.5%).¹ ICP is associated with an increased risk of preterm delivery in 19%–60%,^{2–5} intrapartum fetal distress in 22%–41%, and intrauterine fetal death (IUFD) in 0.75%–1.6% of the affected pregnancies.^{3–6} The diagnostic criteria for ICP have varied over time in different reports, making

complication rates difficult to compare. When, in addition to pruritus, clinical jaundice was used to define ICP, higher fetal complication rates were reported than when diagnosis was based only on elevated bile acid and transaminase levels.^{2,3,6–8} The Swedish ICP incidence figure is taken from a study using only pruritus in pregnancy as the inclusion criterion, and that study did not report increased fetal risk associated with ICP.⁹

Nowadays, elevation of serum bile acids is considered to be the most appropriate laboratory parameter for diagnosis of the condition.^{8,10–12} It is reasonable to believe that ICP constitutes a continuum, ranging from light to severe forms, but there has been an absence of algorithms to identify pregnancies entailing increased fetal risk. The aims of this prospective cohort study were to determine the incidences of pruritus of pregnancy and ICP, and to investigate whether fetal complication rates correlated to the severity of the disease, measured by bile acid levels in maternal serum.

Patients and Methods

The incidences of pruritus in pregnancy and ICP were studied prospectively in the Västra Götaland region of

Abbreviations: ICP, intrahepatic cholestasis of pregnancy; IUFD, intrauterine fetal death; CTG, cardiotocography.

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Sweden between February 1, 1999, and January 31, 2002. The area had 1,500,462 inhabitants in February, 2001, and all women with pregnancies leading to delivery in the region during the study period were screened for ICP.

In Sweden, all normal pregnancies are monitored by midwives at local antenatal clinics. If pregnancy complications occur, the women are referred to an obstetrician at the nearest department of obstetrics. All 106 local antenatal clinics and the 6 departments of obstetrics with delivery wards in the region participated in the study.

Pruritus in pregnancy without any obvious dermatological explanation was the inclusion criterion. Women were consecutively included in the study. Verbal and written informed consent was obtained from all participants.

Each participant received a study protocol and was instructed to bring it to every appointment during pregnancy, including the stay at the delivery ward. A medical history, including heredity for pruritus in pregnancy, outcome of prior pregnancies, skin disorders, atopic and allergic conditions, liver/gallbladder disorders, and other relevant illnesses, was taken. At weekly visits until parturition, a fasting blood sample for analysis of total bile acids was drawn from an antecubital vein, and the patient was instructed to estimate her pruritus on a 100-mm-long visual analogue scale with the endpoints "no pruritus at all" (0 mm) and "worst possible pruritus" (100 mm). If the total bile acid levels were normal ($<10 \mu\text{mol/L}$), the patient was scheduled for checkups at the local antenatal clinic. If the total bile acid level was $\geq 10 \mu\text{mol/L}$ at any time, the patient was referred to the nearest department of obstetrics for further care. The study protocol instructed the managing obstetricians to take fasting blood samples for analysis of bile acids, aminotransferases, and bilirubin in serum once a week until delivery, to ask the patients to estimate their pruritus on a visual analogue scale, and to monitor fetal well-being by cardiotocography (CTG) at the same appointments. No other specific instructions were given to the obstetricians regarding how to manage the pregnancies or whether to time the deliveries. Data recorded at delivery included gestational age, mode of delivery, spontaneous or induced labor, blood loss, frequency of asphyxial events (operative delivery due to asphyxia; Apgar score <7 at 5 minutes; postpartum pH <7.05 in umbilical arterial blood), and meconium staining of amniotic fluid or green staining of placenta and membranes, indicating a longer period since meconium passage. All data concerning patient history, laboratory results, and estimation of pruritus on the visual analogue scale as well as delivery data were recorded in the study protocol.

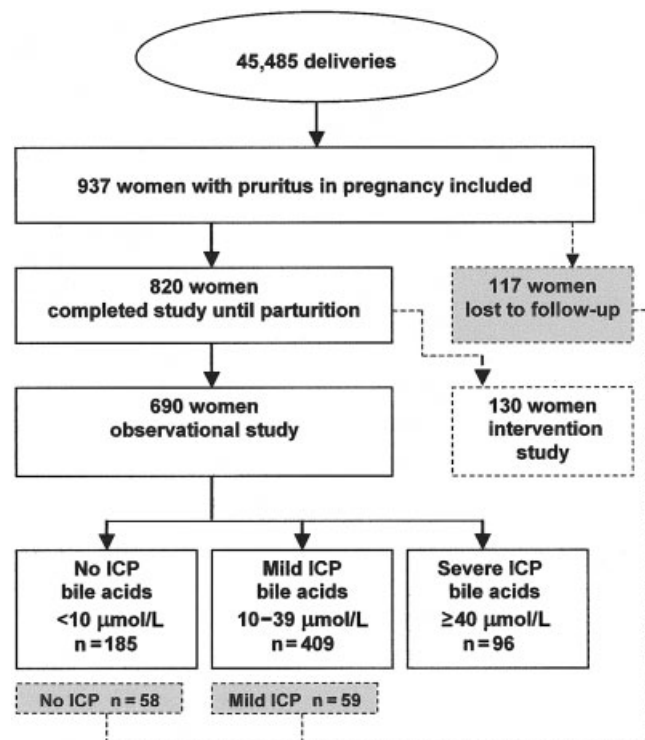


Fig. 1. Total number of deliveries in women with pruritus of pregnancy in a defined area. Women in the observational study were categorized according to bile acid levels in serum.

Participants who did not attend the weekly visits or who did not return their study protocol to the delivery ward were considered as "lost to follow-up." Of the 937 women registered, 820 women completed the study, and 117 were lost to follow-up (12.5%). Data from these women were included in the calculation of the incidences of pruritus in pregnancy and ICP but were excluded from the analyses of patient history and outcome of the present pregnancy (Fig. 1).

All women with ICP at a gestational age less than 37 weeks were invited to participate in a double-blind, placebo-controlled intervention study comparing treatment effects of dexamethasone and ursodeoxycholic acid. Data from the 130 women enrolled were analyzed regarding incidence of pruritus and ICP, and patient history, but they were not included in the calculations concerning the outcome of the present pregnancy.

Total serum bile acids were analysed with an enzymatic, colorimetric method (Enzabile, Biostat Diagnostic Systems, Stockport, UK). Aminotransferases were analyzed with standard laboratory methods.

The study protocol was conformed to the ethical guidelines of the Helsinki Declaration, and the study was approved by the Swedish Medical Products Agency and the local Ethics Committee of the Faculty of Med-

icine at the University of Göteborg, Göteborg, Sweden.

Statistical Analyses and Stratification. In a first step, the relationship between serum bile acid levels and fetal complications was analyzed with logistic regression analyses. In the next step, logistic regression was combined with spline functions. This approach resulted in smooth curves with a higher degree of freedom, allowing a piecewise analysis of subintervals in the curves. It was thus possible to estimate the relationship between serum bile acid levels and fetal risk in each subinterval. This approach allowed stratification of the patient material into three groups: "no ICP" (bile acid levels $<10 \mu\text{mol/L}$), "mild ICP" (maximum bile acid levels of 10–39 $\mu\text{mol/L}$), and "severe ICP" (bile acid levels $\geq 40 \mu\text{mol/L}$ at any time) (Fig. 1). The stratified groups were used when data regarding the patient's history was analysed and for presentation of fetal complication rates. Differences between groups were calculated according to the chi-square method. *P*-values $<.05$ were considered to be statistically significant.

Correlation between bile acid and alanine transaminase levels was estimated using Pearson's correlation test. Correlation between bile acid levels and pruritus was calculated using Kendall's τ_b .

Results

All 45,485 pregnancies leading to delivery in the region during the study period were screened for ICP. A total of 937 women, comprising 2.1% of the pregnant population, complained of pruritus in pregnancy and were included in the study. ICP, defined as pruritus in pregnancy in combination with serum bile acids $\geq 10 \mu\text{mol/L}$, was found in 693 women (1.5%). The distribution of maximum bile acids during pregnancy is illustrated in Figure 1.

The 117 women lost to follow-up stated that spontaneous relief of pruritus ($n = 45$), discomfort from repeated venous punctures ($n = 18$), or the long distance between home and hospital ($n = 11$) were major reasons for discontinuation. Thirty-eight women did not explain why they stopped attending, and 5 women moved to another region of Sweden. Some patients lost to follow-up were tested for total bile acids only once, while others were tested as many as 8 times. Of the women lost to follow-up, 58 had bile acid levels $<10 \mu\text{mol/L}$, and 59 had bile acid levels 10–29 $\mu\text{mol/L}$.

Patient History

Medical histories were taken from all 820 women who completed the study (Fig. 1).

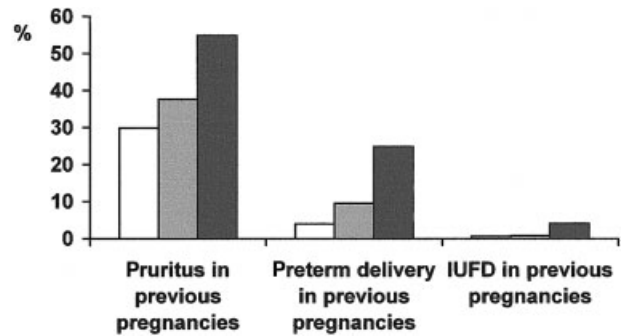


Fig. 2. Frequencies of pruritus, preterm deliveries and IUDF in previous pregnancies categorized according to severity of ICP in the present pregnancy. **White bar** indicates no ICP (serum bile acids $<10 \mu\text{mol/L}$); **gray bar** indicates mild ICP (bile acids 10–39 $\mu\text{mol/L}$); and **black bar** indicates severe ICP (bile acids $\geq 40 \mu\text{mol/L}$).

Of these, 365 were nulliparas, 280 were primiparas, and 175 were multiparas. The parous women ($n = 455$) had a total of 684 pregnancies leading to delivery in their histories. The frequencies of pruritus, preterm deliveries, and IUDF in previous pregnancies varied, as shown in Figure 2. Four percent of the no ICP group had a history of preterm delivery, compared to 25% of the severe ICP group ($P < .001$). IUDF had occurred in 1 previous pregnancy in the no ICP group (0.6%) and had not been associated with pruritus of pregnancy. However, a history of previous IUDF was found in 4.1% of women in the severe ICP group ($P < .001$). In this group, all prior cases of IUDF had been associated with pruritus of pregnancy.

The prevalence of gallstone disease (defined as prior cholecystectomy or ultrasound-verified gallstones) and heredity for pruritus of pregnancy also varied among the groups. Gallstone disease was reported by 24 women (2.9%). The prevalence in the different groups were: no ICP 0.5%, mild ICP 2.3%, and severe ICP 7.4%, respectively (no ICP vs. severe ICP, $P < .001$). Heredity for pruritus of pregnancy was reported by 173 women (21%), of which 13% did not have ICP, 21% had mild ICP, and 30% had severe ICP (no ICP vs. severe ICP, $P < .001$).

Previous allergic reactions with skin manifestations had occurred in a total of 25% and did not vary among the groups. The total frequency of other atopic conditions such as asthma and eczema was 8.8%, but a variation among the groups was noticed. In the no ICP group, 15% of the patients reported atopy, while 8% in the mild ICP group and 3% in the severe ICP group had this condition (no ICP vs. severe ICP, $P < .001$). The frequency of psoriasis was 1.2%, with no difference among the groups.

A total of 733 women were ever-users of oral contraceptives, of which 14 women (1.7%) had experienced pruritus during use.

Table 1. Bile Acid Level-Correlated Probability of Fetal Complications

Variable		β	SE	Odds Ratio* (95% CI)	P Value
Preterm delivery	Constant	-3.7836	0.2631		
	Bile acids	0.0209	0.0041	1.02 (1.01-1.03)	<.001
Asphyxial events	Constant	-2.8940	0.1916		
	Bile acids	0.0117	0.0037	1.01 (1.00-1.02)	.0016
Meconium passage	Constant	-1.5962	0.1245		
	Bile acids	0.0159	0.0032	1.02 (1.01-1.02)	<.001
Green staining of placenta/membranes	Constant	-2.4675	0.1612		
	Bile acids	0.0148	0.0034	1.01 (1.01-1.02)	<.001

*The odds ratio corresponds to the comparisons of risk between two levels of bile acids, where the second value is one unit ($\mu\text{mol/L}$) higher than the first. The odds ratio 1.02 states that the risk of an event increases by 2% for each additional unit of bile acid.

Present Pregnancy

Data concerning the present pregnancy were collected from the 690 women completing the observational study (Fig. 1).

Fetal Complications. The frequency of spontaneous, preterm birth in singleton pregnancies was 4.3%, and asphyxial events occurred in 7.1%. Meconium staining of amniotic fluid was noted in 24.8% of the deliveries, and green staining of placenta and/or membranes was observed in 12.2%.

A correlation was found between bile acid levels and fetal complication rates. Analysis with simple logistic regression showed that the probability of preterm delivery, asphyxial events, meconium staining of amniotic fluid, and green-staining of placenta and membranes increased by 1%–2% for each additional $\mu\text{mol/L}$ of bile acid. Analysis by a combination of spline functions and logistic regression revealed that the probability of preterm delivery, asphyxial events, and green staining of placenta and membranes did not increase until bile acid levels exceeded 40 $\mu\text{mol/L}$, while the probability of meconium staining of amniotic fluid started to rise when bile acid levels exceeded 20 $\mu\text{mol/L}$ (Table 1 and Fig. 3A-D).

The relationship between fetal complication rates and bile acid levels could also be demonstrated by analyzing the differences in complication rates among the stratified groups, as demonstrated in Figure 4. Spontaneous preterm delivery occurred in 2.7% of the no ICP group and in 2.2% of the mild ICP group, and the corresponding figure was 16.7% in the severe ICP group. Asphyxial events occurred in 5.4% of the no ICP group, 6.3% of the mild ICP group, and 13.5% of the severe ICP group. The occurrence of meconium staining of amniotic fluid was 21% in the no ICP group, compared to 44% in the severe ICP group. Green staining of placenta and membranes also differed among the no ICP group (8%), the mild ICP group (11%), and the severe ICP group (25%). The rates of all complications differed between the severe ICP group and the other groups (preterm delivery, and meco-

nium staining of amniotic fluid, placenta, and membranes, $P < 0.001$; asphyxial events, $P < .01$).

The total prematurity rate was 11.7%, including preterm birth in multiple pregnancies and iatrogenic premature deliveries due to the severity of complications or symptoms. The total prematurity rate was higher in the severe ICP group ($P < .001$) than in the other groups. The total planned delivery rate in term pregnancies was 25%, of which 18% were planned inductions of labor and 7% were elective cesarean sections. The planned delivery rate in term pregnancies was 21% in the no ICP group, 24% in the mild ICP group, and 32% in the severe ICP group (Fig. 5).

IUFDs. Three IUFDs occurred during the observation period (3/690, or 0.4%). One was a singleton pregnancy with onset of pruritus in the 34th week of gestation. Bile acids were 94 $\mu\text{mol/L}$ at inclusion in the 36th week, and IUFD was discovered when labor started spontaneously a few days later. The second IUFD occurred in a twin pregnancy, with onset of pruritus in the 24th week of gestation. At inclusion in the 25th week of gestation, bile acids were 130 $\mu\text{mol/L}$. At the next checkup, 4 days later, 1 twin was dead, and the patient spontaneously gave birth to a vital albeit premature baby in the 28th week of gestation. The third case was also a twin pregnancy, with onset of pruritus in the 36th week of gestation. Bile acids were 27 $\mu\text{mol/L}$. At a routine checkup a few days later, the second twin was found to be dead. Spontaneous onset of labor started in the 39th week of gestation, but the patient was delivered by an acute cesarean section. A tight knot on the umbilical cord of the dead twin was found, while the other twin was healthy.

CTG. CTG-surveillance of the fetuses was performed on 1,479 occasions at scheduled checkups before onset of labor. In 52 cases, the CTG registration was assessed as pathological and required prolonged or repeated registrations. In all but 2 cases, the CTG registrations normalized spontaneously. These 2 patients were referred to the delivery ward for induction of labor and gave birth vaginally

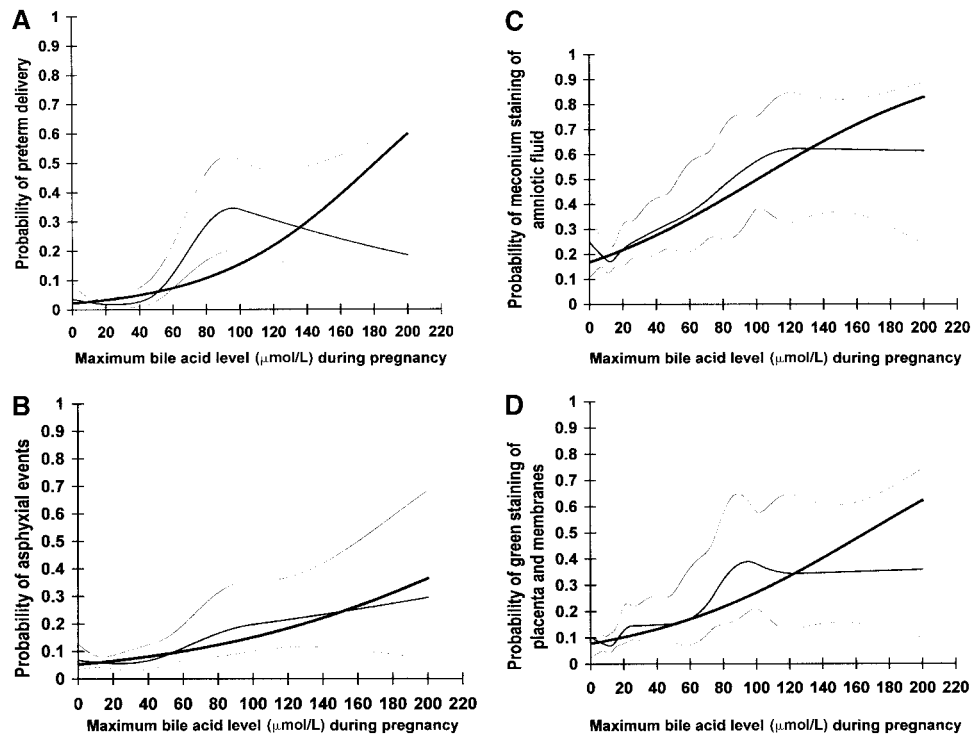


Fig. 3. Probability of (A) preterm deliveries, (B) asphyxial events, (C) meconium staining of amniotic fluid, and (D) green staining of placenta and membranes in relation to serum bile acid levels ($\mu\text{mol/L}$) analyzed with simple logistic regression (thick line) and spline functions (medium line), the latter with 95% CI (thin line).

to healthy infants without asphyxial events. No CTG abnormalities requiring immediate operative delivery were recorded.

Age, Parity, Onset of Pruritus and Blood Loss. There was no difference among the stratified groups regarding age and parity. The median gestational age at onset of pruritus was in the 31st week. A trend, not reaching statistical significance, toward later onset of pruritus in more severe ICP forms was recorded (no ICP, 27th week of gestation; mild ICP, 31st week of gestation; and severe ICP, 33rd week of gestation, respectively). Estimated blood loss in vaginal deliveries did not differ among the groups (median, 400 mL for all groups; mean, 423–484 mL).

Correlation Coefficients, Twin Pregnancies, and Pruritic Urticarial Papules and Plaques of Pregnancy. No patient presented with clinical jaundice. The correlation coefficient between serum bile acids and estimated intensity of pruritus on a visual analogue scale was 0.108 ($P < .01$). The correlation coefficient between bile acids and alanine aminotransferase was 0.349 ($P < .01$). There were 38 twin pregnancies in the observational study, comprising 5.5% of the pregnancies. Pruritic urticarial papules and plaques of pregnancy was diagnosed by a dermatologist in 11 cases, of which 10 also had ICP. The frequency of pruritic urticarial papules and plaques of

pregnancy in this study was 1/63 pregnancies, compared to an expected frequency of 1/130–1/300.^{13,14}

Discussion

In this prospective study, more than 45,000 pregnant women were screened for ICP, and the incidence of fetal complications in these pregnancies was investigated. The data were comprehensively collected, according to Swedish health care system routines.

In our experience, women with severe pruritus in pregnancy seek help and are willing to cooperate to attain relief of symptoms. It is therefore unlikely that there were many nonparticipating women with pruritus and elevated bile acid levels during the study period. We therefore believe that the patient material in this study is representative of a pregnant population in Sweden.

Pruritus occurred in 2.1% of the pregnancies. Among these cases, ICP was diagnosed when fasting serum bile acid levels were $\geq 10 \mu\text{mol/L}$, as was the case in 1.5% of the pregnancies, in concordance with a previous Swedish study.⁹ In contrast to that study, which did not include bile acids as a diagnostic criterion, we found an increased fetal risk associated with ICP and, more importantly, a bile acid level distinguishing 2 degrees of risk.

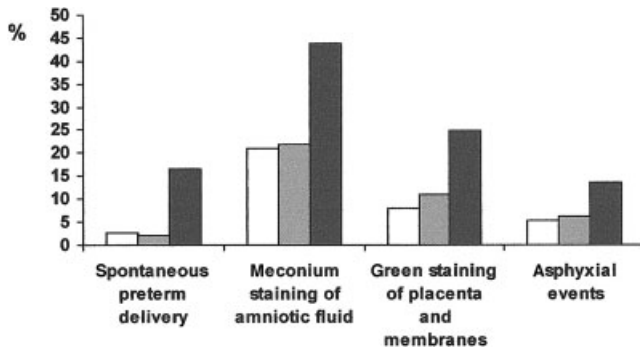


Fig. 4. Fetal complication rates in pregnant women with ICP. **White bar** indicates no ICP; **gray bar** indicates mild ICP; and **black bar** indicates severe ICP.

There was an overall positive correlation between fetal complication rates in ICP patients and the level of total bile acids in maternal serum. Logistic regression analyses demonstrated that the probability of fetal complications such as spontaneous preterm deliveries, asphyxial events, and meconium staining of amniotic fluid, placenta and membranes increased by 1%–2% for each additional $\mu\text{mol/L}$ of bile acid. However, use of the refined technique of spline functions revealed that the probability of these events did not increase until bile acid levels exceeded $40 \mu\text{mol/L}$. Up to this level the incidence of fetal complications in ICP patients did not differ significantly from that in a normal pregnancy. A majority of the women with ICP (81%) had serum bile acids between 10 and $39 \mu\text{mol/L}$ without increased rate of fetal complications, whereas 19% were found to have serum bile acids $\geq 40 \mu\text{mol/L}$ associated with a raised fetal risk. These data actually prove for the first time a relationship between the severity of ICP and fetal complications. That low levels of serum bile acids confer minimal fetal risk is also clinically important.

ICP has been reported to be associated to an increased risk of IUFD.^{3–6} In this study, a low frequency of IUFD was recorded (3/690, or 0.4%), similar to rates found in the normal pregnant population in Sweden.¹⁵ We assume that the low incidence of IUFD was due to increased attention devoted to ICP and its symptoms during the study, which might have led to early intervention. This hypothesis may be substantiated by the high rates of induction of labor and planned cesarean section (25%). Planned delivery before term in women with ICP has been reported to protect against IUFD.^{2–5} The frequency of IUFD in previous pregnancies in the study population was 1.3%. Interestingly, there was a striking difference between IUFD in previous pregnancies reported in the no ICP group (0.6%) and in the severe ICP group (4.1%)

($P < .01$). This observation might indicate an association between severity of the disease and IUFD.

The incidence of intrapartum meconium staining of amniotic fluid varies between 17% and 24% in a normal pregnant population¹⁶ and is considered as a warning signal of possible fetal distress. It is, however, also known from animal models that high maternal bile acid levels stimulate fetal colonic motility, causing the fetus to void meconium.¹⁷ In our material, the probability of meconium passage and green staining of placenta and membranes increased gradually in relation to elevated bile acid levels in an almost linear fashion, calculated with simple logistic regression. In the stratified groups, the frequencies of meconium passage were 21% in the no ICP group and 22% in the mild ICP group, suggesting that ICP with bile acid levels below $40 \mu\text{mol/L}$ does not affect the colonic motility of the fetus. These findings were in contrast to those of the severe ICP group, in which meconium passage was observed in 44%.

The mechanisms of preterm delivery in ICP are still unclear, but they have been discussed in light of *in vitro* findings indicating that myometrial cell preparations from ICP women show a more intense response to oxytocin stimuli than do cells from healthy women.¹⁸ A recent article describes that myometrial strips from healthy women show an increased response to oxytocin and an increased oxytocin-receptor expression after being incubated with cholic acid.¹⁹

Family clustering and a large demographic variation, with the highest incidence figures of ICP reported from Chile-Bolivia and Scandinavia, support the hypothesis of a substantial hereditary component of the disease, but the molecular genetic background has yet to be determined.¹

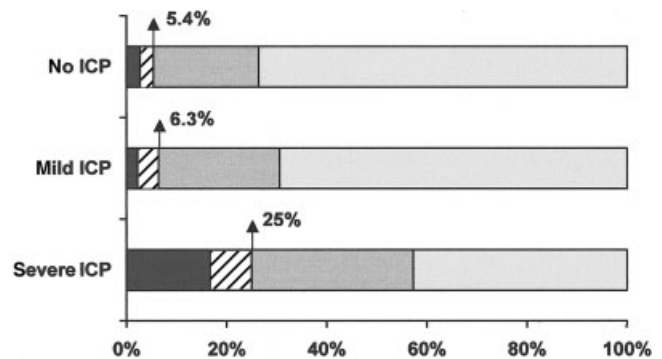


Fig. 5. Timing of spontaneous and planned deliveries in women, categorized according to severity of ICP. **Dark gray bar** indicates spontaneous singleton preterm delivery; **striped bar** indicates spontaneous twin preterm delivery/preterm induction or preterm cesarean section; **medium gray bar** indicates planned induction or planned cesarean section after 37 weeks of gestation; and **light gray bar** indicates spontaneous onset of labor after 37 weeks of gestation. The **arrows** indicate the total prematurity rate.

Our data revealed a correlation between a history of gallstone disease and the severity of ICP in the present pregnancy. In the no ICP group, 0.5% of the women reported gallstone disease, compared to 7.4% in the severe ICP group ($P < .001$). A 2-fold increase in the prevalence of gallstone disease among women with ICP has previously been reported.²⁰ A recent report stated that genetic factors were responsible for at least 30% of symptomatic gallstone disease,²¹ supporting the hypothesis that ICP and gallstone disease might at least to some extent have a common, underlying genetic explanation.

Twin pregnancies constituted 5.3% of all pregnancies in this study, which is in concordance with previous reports indicating a 5-fold increase of ICP in twin pregnancies, compared to singleton pregnancies.²²

In this study, the correlation between bile acid levels and alanine aminotransferase was poor. However, a weak correlation between bile acid levels and reported pruritus was found, but the subjective symptoms cannot predict severity of the disease in terms of bile acid concentrations. Accordingly, the clinical relevance of alanine aminotransferase for diagnosis and surveillance of ICP is questionable.

Of all pregnant women with pruritus, 26% did not show any laboratory signs of ICP. This group had an earlier onset of pruritus and reported a significantly higher frequency of atopic diseases (asthma, eczema) than the other groups, implying that pruritus might have been of dermatological origin in these cases. Atopic dermatitis is more likely to deteriorate than to remit in pregnancy.²³

In some countries, especially Sweden and Chile-Bolivia, ICP patients constitute a fairly large patient group. We suggest that pregnant women with pruritus should be surveilled with repeated determinations of serum bile acids. Patients could be managed expectantly when bile acid levels remain below 40 $\mu\text{mol/L}$. Our data do not indicate that this group would benefit from induction of labor before term. Symptomatic treatment, such as H₁-receptor blockers or ursodeoxycholic acid, should be offered to these women.²⁴ Fetuses of ICP patients with higher serum bile acids are exposed to increased risks. CTG was not proven to be of any value for detection of fetal risk in these women.

Induction of labor in the 38th week of gestation has previously been shown to reduce fetal risk.⁴ This study indicated that active management should be restricted to the group with bile acids $\geq 40 \mu\text{mol/L}$. Since this group constitutes only 19% of the ICP population, the costs of medical care could hereby be reduced significantly. If gestational age does not permit induction of labor, it seems reasonable to administer pharmacological treatment to

reduce bile acid levels and provide relief from pruritus. Ursodeoxycholic acid has yielded promising results in a small, randomized, placebo-controlled study²⁵ but has not been approved for treatment of ICP as yet.

In conclusion, pruritus of pregnancy was reported by 2.1% of pregnant women in western Sweden. The incidence of ICP, defined as pruritus in pregnancy and bile acid levels $\geq 10 \mu\text{mol/L}$, was 1.5%. The majority of ICP patients (81%) had a mild form of the condition (bile acids 10–39 $\mu\text{mol/L}$). These women were exposed to the same risk of fetal complications as an ordinary obstetrical population, and we therefore propose that these women be managed expectantly, which would significantly reduce the costs of medical care. A severe form of ICP occurred in 19%. With bile acids $\geq 40 \mu\text{mol/L}$, these patients suffered a significantly higher rate of fetal complications such as asphyxial events, spontaneous preterm deliveries, and meconium staining of amniotic fluid, placenta, and membranes, compared to women with normal bile acid levels and women with mild ICP.

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