OBSTETRICS

Severe intrahepatic cholestasis of pregnancy is a risk factor for preeclampsia in singleton and twin pregnancies

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OBJECTIVE: Intrahepatic cholestasis of pregnancy (ICP) is known to be associated with fetal complications. It recently was suggested to be associated possibly with preeclampsia (PET) as well. The objective of this study was to investigate that possibility.

STUDY DESIGN: The study group included 78 women (54 singleton and 24 twin pregnancies) who had been diagnosed with ICP based on clinical presentation, elevated liver enzymes, and elevated total bile acids (>10 μmol/L). Disease severity was based on total bile acids levels as being severe (>40 μmol/L), moderate (20-40 μmol/L), or mild (10-20 μmol/L). The course of disease was reviewed carefully in each case. The control groups were comprised of apparently healthy women with singleton (n = 200) and twin (n = 100) pregnancies that were drawn randomly from a computerized registry of all the deliveries in our institution during the study period.

RESULTS: The total incidence of PET was significantly higher for the patients with ICP who had singleton and twin pregnancies compared with the control groups (singletons: 7.4% vs 1.5%; $P < .05$; twins: 33.3% vs 6.2%; $P < .05$, respectively). The incidence of severe PET was also significantly higher in both singleton (11-fold) and twin (8-fold) pregnancies compared with control subjects. Severe ICP, but not mild ICP, was a major risk factor for PET among women with either singleton or twin pregnancies. The timing of the initial presentation of ICP had no effect on PET incidence rates. Preeclampsia occurred usually 2-4 weeks after the diagnosis of ICP, and proteinuria preceded elevated blood pressure in all cases. Moreover, the total bile acid levels among 33 women who were diagnosed as having PET, but not ICP, were within normal range.

CONCLUSION: ICP increases the incidence of PET; severe disease was a major risk factor for preeclampsia. Therefore, we strongly suggest including routine evaluation for preeclampsia in the treatment of women with moderate and severe ICP.

Key words: bile acid, intrahepatic cholestasis of pregnancy, liver enzyme, preeclampsia, twins

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Intrahepatic cholestasis of pregnancy (ICP) is characterized by pruritus, elevated liver enzymes, and elevated total bile acids (TBA). The latter is considered to be the diagnostic test for ICP.[1-4] The incidence of ICP ranges from 0.1% in Canada and western Europe[5] to 22% in Indian women in Chile.[6] A higher incidence was shown in women with gestational diabetes mellitus (GDM)[7] and women who conceived after in vitro fertilization treatment.[8] The cause of ICP is multifactorial, with gene mutations in the hepatocellular transporters of bile acids to the bile canaliculi playing a role in the pathogenesis.[1,9,10] The suggestion was that the excessive bile acid levels are the basis of both the maternal and the fetal complications based on the correlation between TBA levels and the frequency and the severity of these complications.[11-13] Brouwers et al[14] recently showed that every 10 μmol/L increase in serum bile acid concentrations increases the probability of certain fetal complications. Several studies concluded that ICP is associated with increased risk for spontaneous premature labor,[11,13,15-17] meconium-stained amniotic fluid,[11,15,16,18,19] nonreassuring fetal heart rate,[15,20] fetal distress,[13,21,22] and increased risk for perinatal deaths, almost always after 37 weeks of pregnancy.[11,13,15,18,19] Therefore, active management that includes ursodeoxycholic acid administration, antenatal surveillance, and induction of labor at 37 weeks of pregnancy became common practice, although its influence

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on fetal complications is currently under debate.[7,12,23,24] Over the last few years, we have had several cases in which ICP was followed by preeclampsia. A similar phenomenon was reported in only a small number of sporadic case reports[25,26] until recently, when Wikström Shemer et al[7] demonstrated an increased incidence of preeclampsia among women with singleton pregnancies and ICP (adjusted odds ratio, 2.62). The aim of the current study was to investigate the association between ICP and preeclampsia in both singleton and twin pregnancies.

Materials and Methods

Setting

This study was conducted at the Tel Aviv Sourasky Medical Center, which is a tertiary referral center with >11,000 deliveries per year. The study was approved by the Institutional Review Board, which waived informed consent.

Study population

In our institution, pregnant women with elevated liver enzymes and/or pruritus are tested routinely for serum TBA levels. In addition, we perform an investigation to rule out preeclampsia, TORCH infection (Toxoplasmosis, Rubella, Cytomegalovirus, Parvo virus, Herpes virus, Syphilis), viral hepatitis (hepatitis B, C), Epstein Barr virus, and liver or biliary disease. The diagnosis of ICP is based on clinical presentation, elevated liver enzymes, and elevated TBA levels (>10 μmol/L) in the absence of other possible causes.

Between January 2008 and February 2014, a total of 83 women were diagnosed with ICP. Five cases were excluded (1 triplet pregnancy and 4 lost to follow up), which resulted in a study population of 78 women (54 singleton and 24 twin pregnancies).

The control groups consisted of 200 women with singleton pregnancies and 100 women with twin pregnancies who were apparently healthy and who were drawn randomly from a computerized registry of all the deliveries that occurred during the study period in our institution.

To determine whether preeclampsia manifests with elevated TBA levels, we sampled the TBA levels of 33 consecutive women who were diagnosed initially with preeclampsia, but not ICP (25 singleton and 8 twin pregnancies).

Study design

This was a retrospective cohort study whose primary outcome was the incidence of preeclampsia among women with ICP. Although we are aware of the executive summary on hypertension in pregnancy published on November 2013,[27] preeclampsia was defined according to the criteria of the American College of Obstetrics and Gynecology that were published on 2002.[28] These criteria were in use during the study period and determined the diagnosis and treatment of women with preeclampsia. *Preeclampsia* was defined as blood pressure values of ≥140/90 mm Hg accompanied by proteinuria of ≥0.3-g protein in a 24-hour urine specimen first diagnosed at >20 weeks of gestation. *Severe preeclampsia* was defined as preeclampsia accompanied by 1 of the following events: blood pressure values of ≥160/110 mm Hg on 2 occasions that were at least 6 hours apart while on bed rest, proteinuria of ≥5 g in a 24-hour urine collection or ≥3+ on 2 random urine samples that were collected at least 4 hours apart, oliguria of <500 mL in 24 hours, cerebral or visual disturbances, pulmonary edema or cyanosis, epigastric or right upper-quadrant pain, impaired liver function, thrombocytopenia, or fetal growth restriction.

ICP severity was defined according to TBA levels as severe (>40 μmol/L), moderate (20-40 μmol/L), or mild (10-20 μmol/L).[11-13] All women who were diagnosed with ICP at <37 weeks of pregnancy were hospitalized in our Maternal and Fetal Medicine Department and placed under active treatment until labor .We adopted this protocol to provide an intensive care protocol that could not be provided in community health care services in our country. The follow-up evaluation in the department included daily vital sign measurements, fetal monitoring 3 times per day, liver enzyme evaluation every other day, and weekly evaluation of TBA levels. All women with ICP before term received ursodeoxycholic acid 300 mg (Ursolit; CTS Chemical Industries Ltd, Kiriat Malachi, Israel) 3 times per day. In addition, our common practice is to induce labor at 37 weeks of gestation in all women with ICP before term, in line with the widely accepted guidelines.[29-31]

In cases of ICP and subsequent preeclampsia, the decisions regarding induction of labor were made according to criteria similar to those applied to patients with preeclampsia alone and were guided by American College of Obstetricians and Gynecologists recommendations that were accepted at that time.[28] Women with ICP and mild preeclampsia were treated conservatively until term and induced at 37 weeks of gestation. Women with ICP and severe preeclampsia at ≥34 weeks of gestation or those with unstable maternal or fetal conditions at any gestational age were delivered after maternal stabilization. Women with ICP and severe preeclampsia remote from term with stable maternal and fetal conditions received conservative treatment with daily evaluation. The preferred mode of delivery was induction of labor and vaginal birth and was determined by fetal gestational age, fetal presentation, cervical status, and maternal and fetal conditions. Maternal and neonatal data were obtained from the computerized database and included maternal age, gravidity, parity, body mass index, obstetric and medical history, diagnosed GDM, in vitro fertilization treatment, onset of pruritus, gestational age at diagnosis and at admission, gestational age at first administration of Ursolit (CTS Chemical Industries Ltd), complete blood count and liver function tests, proteinuria, blood pressure values, gestational age at delivery, mode of delivery, induction of labor, and the diagnosis of preeclampsia. In addition, after the first cases of preeclampsia in patients with ICP, we added weekly measurements of urine protein/creatinine ratio and complete blood count. Perinatal data included birthweight, birthweight percentiles according to the Israeli

TABLE 1
Obstetric and demographic characteristics of women with and without intrahepatic cholestasis of pregnancy

Characteristic	Singleton pregnancy			Twin pregnancy		
	Intrahepatic cholestasis of pregnancy (n = 54)	No intrahepatic cholestasis of pregnancy (n = 200)	*P* value	Intrahepatic cholestasis of pregnancy (n = 24)	No intrahepatic cholestasis of pregnancy (n = 100)	*P* value
Maternal age, y[a]	33.42 ± 5.48[b]	31.67 ± 5.11	.029	34.41 ± 5.27	33.41 ± 4.75	.36
Pregestation body mass index, kg/m^2[a]	23.7 ± 4.43	23 ± 4.72	.35	23.51 ± 6.04	23.04 ± 4.72	.71
Parity, n[a]	0.77 ± 0.9	0.96 ± 1.2	.3	0.33 ± 0.63	0.45 ± 0.7	.44
Gravity, n[a]	2.35 ± 1.33	2.46 ± 1.58	.63	1.95 ± 1.26	1.9 ± 1.26	.86
Birthweight, g[a]	2888 ± 498[b]	3221.5 ± 448	.0001	2046 ± 523[b]	2332 ± 536	.001
Birthweight percentile, %[a]	50.27 ± 27.39	51.64 ± 25.14	.72	41.93 ± 28.72	49.6 ± 26.78	.08
Gestational age at delivery, wk[a]	37.16 ± 1.3[b]	39.49 ± 1.54	.0001	34.84 ± 2.25[b]	36.3 ± 2.69	.016
Cesarean deliveries, % of total	29.6	18.7	.091	66.7	74.2	.45
Gestational diabetes mellitus, % of total	16.7	5.6	.019	8.3	4.1	.34
In vitro fertilization, % of total	7.4	5.6	.53	75	55.7	.1

[a] Data are given as mean ± SD; [b] $P < .05$ (a *t*-test was used to compare means).

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birthweight curves,[32] Apgar scores at 1 and 5 minutes, cord blood pH, meconium-stained amniotic fluid, nonreassuring fetal heart rate monitoring, and neonatal complications.

TBA assay

The quantitative determination of TBA was performed on the ADVIA 2400 Clinical Chemistry System (Siemens Healthcare, Erlangen, Germany) with the use of the Diazyme Laboratory Total Bile Acids Assay Kit (DZ042A-K; Diazyme Lab, Poway, CA) by 2 experienced technicians.

Statistical analysis

Statistical analysis was performed with the use of the IBM SPSS statistics software (version 22; IBM Corporation, New York, NY). Univariate analysis was used to determine the relationships between each explanatory variable and preeclampsia occurrence in the 2 groups. The Pearson χ^2 test or Fisher exact was used to compare between the study and control groups with respect to categoric variables. Independent-samples *t*-test was used to compare the means of the 2 groups. Multivariate logistic regression analysis was also performed. A probability value of $< .05$ was considered statistically significant.

Results

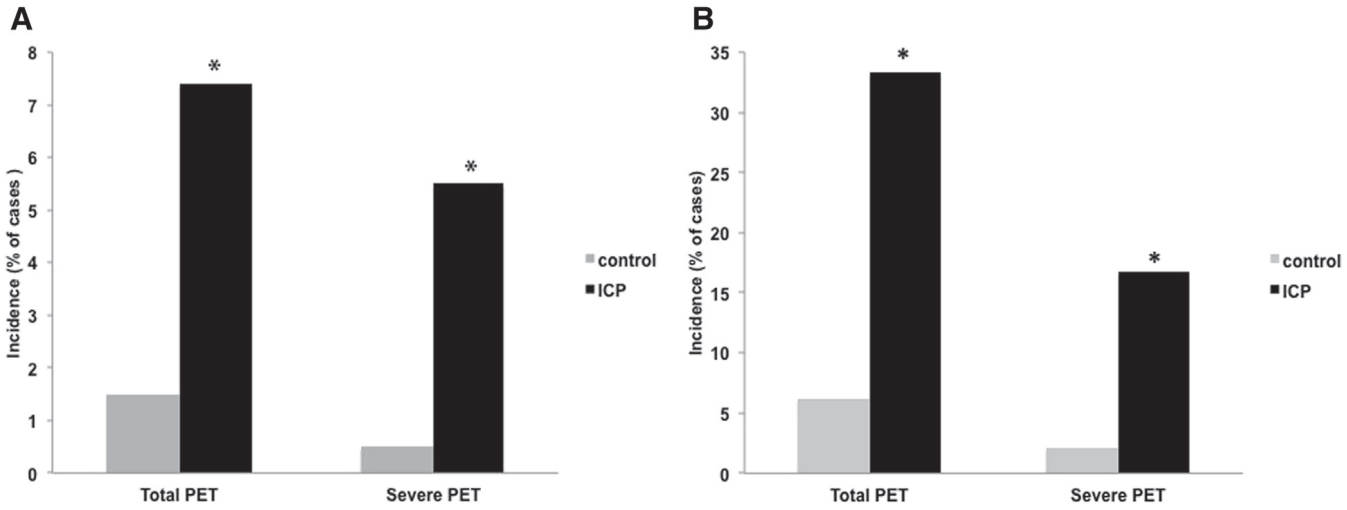
The incidence of ICP in our population, (overall −0.1%; 9 per 10,000 deliveries and 121 per 10,000 deliveries for singleton and twins, respectively) is similar to that reported from Canada.[5]

A total of 78 women with ICP (54 singleton and 24 twin pregnancies) were included in the study group. The obstetric and demographic characteristics of the women in the study and control groups are presented in Table 1. The maternal age of women with singleton pregnancies and ICP was significantly higher than that of the control group. The mean birthweights of neonates born to women with ICP in both the singleton and twin pregnancy groups were significantly lower than that of the control groups. Because their average birthweight percentiles are similar to those of the control groups, this is mainly a result of their significantly younger gestational age at delivery. The latter is, at least partially, the result of the widely accepted induction of labor at 37 weeks of gestation as part of the active treatment of patients with ICP. The prevalence of GDM was significantly higher in singleton pregnancies with ICP, as previously reported.[7]

There was a significant increase in the incidence of preeclampsia among women with ICP and singleton pregnancies compared with control subjects (7.4% vs 1.5%, respectively; $P < .05$; Figure 1, A). Women with twin pregnancies and ICP also had a significantly higher incidence of preeclampsia compared with control subjects (33% vs 6%, respectively; $P < .05$; Figure 1, B).

The incidence of severe preeclampsia was significantly higher in both singleton (11-fold) and twin (8-fold) pregnancies compared with control pregnancies (Figure 1). Furthermore, among the women with singleton pregnancies, preeclampsia was diagnosed only when ICP was severe (Figure 2, A) and, among the women with twin pregnancies, the incidence of preeclampsia correlated with the severity of ICP (Figure 2, B). No patient with mild ICP in either the

FIGURE 1
Preeclampsia incidence in women with intrahepatic cholestasis of pregnancy



A, singleton pregnancies; the *asterisk* indicates $P < .05$. **B,** twin pregnancies; the *asterisk* indicates $P < .05$.

ICP, intrahepatic cholestasis of pregnancy; *PET*, preeclampsia.

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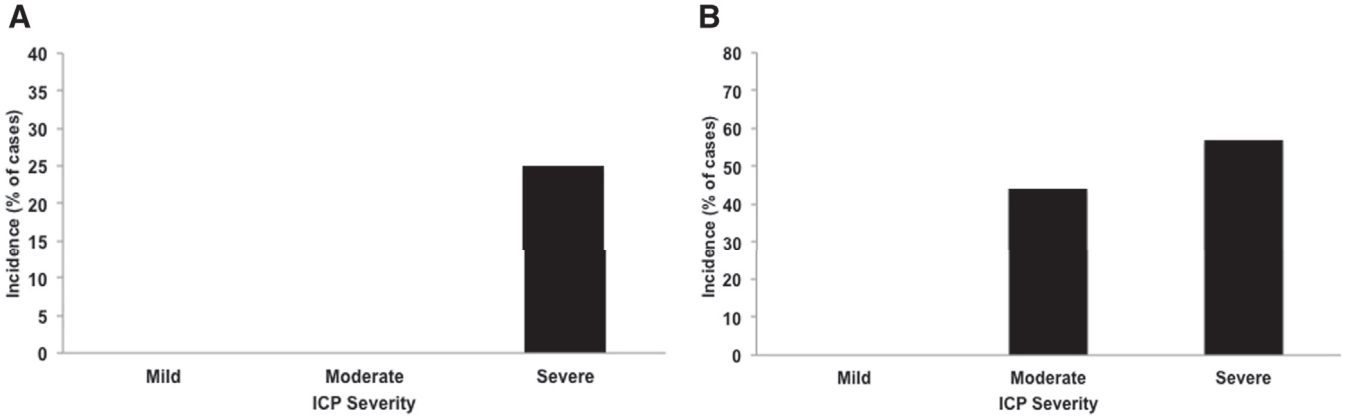
singleton or twin pregnancy groups later experienced preeclampsia.

No significant differences were found in demographic and obstetric characteristics of women with ICP who experienced preeclampsia and those who did not (Table 2). There was no difference in the average gestational week of ICP presentation between women who later experienced preeclampsia and those who did not in both the singleton (32.5 ± 2.64 vs 33.34 ± 2.78, respectively; $P = .58$) and twin (30.62 ± 3.54 vs 31.5 ± 3.4, respectively; $P = .57$) pregnancy groups.

The multivariate analysis showed that, although significant in the univariate analysis for singleton pregnancies with ICP, maternal age and GDM did not affect preeclampsia incidence and the only parameters that affected the incidence of preeclampsia among women with ICP in both singleton and twin pregnancies were ICP presence and ICP severity.

We found that the incidences of total preeclampsia and of severe preeclampsia among women with ICP that were diagnosed at<32 weeks of gestation were similar to those of women with ICP diagnosed at >32 weeks of gestation for

FIGURE 2
Correlation between intrahepatic cholestasis of pregnancy severity and preeclampsia incidence



A, Singleton pregnancies. **B,** Twin pregnancies.

ICP, intrahepatic cholestasis of pregnancy.

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TABLE 2
Obstetric and demographic characteristics of women with intrahepatic cholestasis of pregnancy isolated or followed by preeclampsia

Characteristic	Singleton pregnancies, mean ± SD			Twin pregnancies, mean ± SD		
	No preeclampsia (n = 50)	Preeclampsia (n = 4)	*P* value	No preeclampsia (n = 16)	Preeclampsia (n = 8)	*P* value
Maternal age, y	33.16 ± 5.50	36.75 ± 4.57	.21	33.56 ± 4.69	36.12 ± 6.26	.27
Pregestation body mass index, kg/m^2	23.7 ± 4.55	23.66 ± 2.42	.98	23.74 ± 6.82	23.01 ± 4.38	.81
Parity, n	0.82 ± 0.91	0.25 ± 0.5	.22	0.43 ± 0.72	0.12 ± 0.35	.17
Gravity, n	2.36 ± 1.36	2.25 ± 0.95	.87	2.18 ± 1.42	1.5 ± 0.75	.13

A *t*-test was used to compare means.

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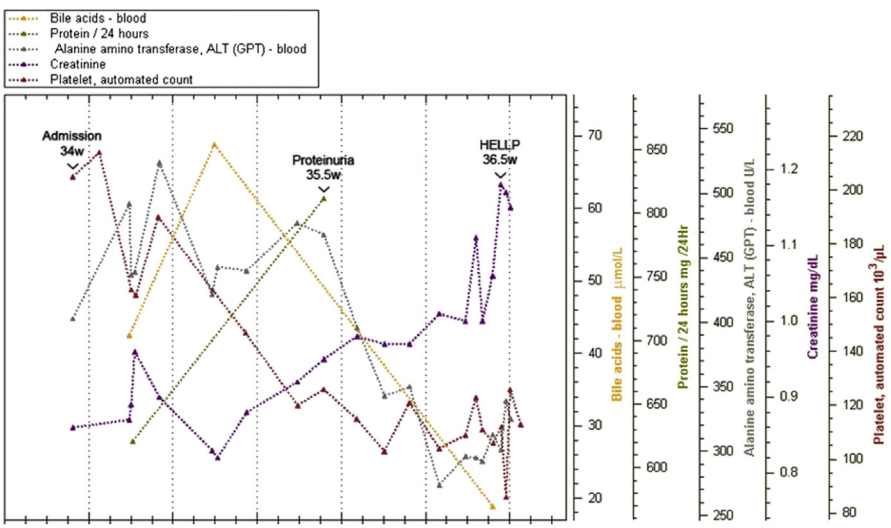
both the singleton and twin pregnancies (15.3% vs 2.5% and 38% vs 33%, respectively; $P > .05$).

Proteinuria preceded the elevation in blood pressure in all 12 cases of women who subsequently experienced preeclampsia. Interestingly, normalization of TBA and liver function tests under treatment, which usually occurs within 1-3 weeks, did not prevent preeclampsia. Full-blown preeclampsia occurred most often 2-4 weeks after pruritus and the detection of elevated liver enzymes. A typical course of disease in one of our patients with ICP with a singleton pregnancy and subsequent preeclampsia is presented in Figure 3. Proteinuria appeared 4 weeks after the appearance of pruritus, and she experienced preeclampsia, despite the decreasing levels of liver enzymes and TBA.

Table 3 presents the adverse perinatal outcomes in the study group that are similar to those reported in different cohort studies.[12,16,18,20]

We had 1 case of intrauterine fetal death (IUFD) at 30 weeks of gestation in a woman with twin pregnancy and severe ICP. This 38-year-old woman presented to our high-risk pregnancy outpatient clinic at 29 weeks of pregnancy complaining of pruritus that had started 3 weeks earlier and normal liver function tests. A dermatologic examination concluded that her rash is compatible with PUPPP (Pruritic Urticarial Papules and Plaques of Pregnancy). A skin biopsy, liver enzymes levels, and TBA levels were taken. Her TBA results (TBA, 57 μmol/L) and liver enzymes levels revealed that she had severe ICP; she was admitted to our department for ursodeoxycholic acid administration and fetal monitoring. Three days after her admission, the routine morning fetal monitor was normal. Only 6 hours later, the following routine fetal monitor was pathologic, and she was rushed to the operating room for an emergency cesarean delivery. The birthweights were 1675 g (a female, 90th percentile, IUFD fetus) and 1369 g (a female, 56th percentile, live fetus). Thick meconium was present in the amniotic sac of the dead fetus. Autopsy of the dead fetus and placental histologic examination of both placentas did not reveal any abnormalities. The skin biopsy results that were returned after delivery indicated vasculitis.

FIGURE 3
Course of disease in a woman with intrahepatic cholestasis of pregnancy and subsequent preeclampsia



A representative case of severe ICP (bile acids: *yellow* graph) followed by later development of HELLP syndrome. Proteinuria (*green* graph) was the earliest presenting sign. HELLP developed despite normalization of bile acid concentrations and liver function tests under Ursulit (CTS Chemical Industries Ltd, Kiriat Malachi, Israel) treatment.

ALT, alanine amino transferase; *GPT*, glutamic pyruvic transaminase; *HELLP*, hemolysis, elevated liver enzymes, and low platelet count syndrome.

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TABLE 3
Adverse outcomes in neonates of mothers with intrahepatic cholestasis of pregnancy

Outcome	n	%
Meconium-stained amniotic fluid	16	20.5
Nonreassuring fetal heart rate		
Total	6	7.7
Assisted delivery	3	3.9
Nonelective cesarean delivery	3	3.9
Preterm delivery (<37 wk): spontaneous		
Total	15	19.2
Gestational age <34 wk	3	3.9
Gestational age 34 wk to <37 wk	12	15.4
Preterm premature rupture of membranes	7	9
Preterm delivery (<37 wk): induction of labor		
Total	16	20.5
Gestational age < 34 wk	3	3.9
Gestational age 34 wk to <37 wk	13	16.7
Fetal acidemia (Apgar <7 or pH <7.1)	9	11.5
Intrauterine fetal death	1	1.3

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The data presented in this study strongly suggest that ICP is associated with preeclampsia. To verify that preeclampsia itself is not associated with increased plasma bile acids concentrations, we analyzed the TBA levels in 33 subsequent women who were diagnosed with preeclampsia, but not ICP (25 singleton and 8 twin pregnancies). Notably, all 33 women had normal TBA levels (<10 μmol/L).

Comment

We have demonstrated an increased incidence of preeclampsia and of severe preeclampsia among women with ICP in both singleton and twin pregnancies, compared with control subjects, and a correlation with disease severity. The incidence of preeclampsia in our control groups is similar to that reported by Sibai et al.[33,34] Our results are further supported by a recent study in which women with ICP were more likely to experience preeclampsia than were control subjects (adjusted odds ratio, 2.62).[7] However, because the diagnosis of ICP was not based on TBA levels, it was impossible to draw conclusions about the association between the incidence of preeclampsia and severity of ICP as we have now shown.

Interestingly, preeclampsia occurred most often 2-4 weeks after the diagnosis of ICP and was concomitant with ICP severity at initial diagnosis. The incidence of preeclampsia, however, did not correlate with the duration of exposure to excess TBA or with the time of ICP onset. Moreover, preeclampsia still occurred even though liver enzymes and TBA levels decreased towards the normal range. This observation suggests that the initial elevation of TBA levels may induce a cascade of events that later results in preeclampsia, even if TBA levels are decreasing.

We had 1 case of IUFD at 30 weeks of gestation in a woman with twin pregnancy and severe ICP. Similar unexpected IUFD cases have been described by Lee et al[35] and, recently, by Brouwers et al[14] that stated an increase in perinatal deaths in women with ICP in correlation with TBA levels. The authors determined that no predictive findings were present for these sudden deaths. It is suggested that these cases occur after exposure to high TBA level, but the mechanism is still unknown.

Our data suggest that preeclampsia does not lead to ICP, but most probably the opposite is the case. This is further supported by our finding that women with preeclampsia had normal TBA levels and that women with ICP had no clinical or laboratory abnormalities typical for preeclampsia in their initial presentation (eg, high blood pressure, proteinuria). Goulis et al[36]demonstrated raised TBA levels in 8% of women with preeclampsia and abnormal liver function tests results. Because bile acids were sampled from stored sera of women after they were diagnosed with preeclampsia, it is possible that these patients had coexisting ICP. Both Glantz et al[11]and Brouwers et al[14] demonstrated that ICP complications correlate with exposure to higher levels of TBA, as we have shown herein for preeclampsia. Several studies have suggested that the elevated TBA levels play a major role in the pathophysiologic condition of ICP.[11-13] We hypothesize that high TBA levels might also precipitate preeclampsia in patients with ICP. The pathophysiologic condition of preeclampsia is not understood fully, but several studies point to soluble fms-like tyrosine kinase−1 as a major contributor in the mechanism of preeclampsia.[37-40] Previously, the proposal was that excess TBA may cause endothelial injury in the kidney and lungs via generation and release of reactive oxygen species.[41] The resulting oxidative stress promotes the formation of various vasoactive mediators. Renal disturbances through these mechanisms have been documented in women with ICP,[42] and it is possible that they are also operative in the initiation of preeclampsia in patients with ICP. In addition, the accumulation of TBA may affect the placenta directly and lead to oxidative damage of the placental unit.[41] Li et al[43] showed that increased oxidative stress leads to the up-regulation of soluble fms-like tyrosine kinase−1

production by placental trophoblast cells and low placental growth factor production. Elevated soluble fms-like tyrosine kinase−1 levels in the maternal circulation contribute to the pathogenesis of preeclampsia and therefore could explain our observation.

The current study adds valuable information and further characterizes the association between ICP and preeclampsia. Although the study group was relatively small, to the best of our knowledge, this is the largest database to date in which the diagnosis of ICP, based on TBA levels, has been shown to be associated with preeclampsia, both in singleton and twin pregnancies. Our data suggest that the routine evaluation for preeclampsia should be included in the treatment of women with ICP, especially among those with moderate and severe forms of ICP and in twin pregnancies. During the study period, all women who were diagnosed with ICP before term were hospitalized in our Maternal and Fetal Medicine Department, where an intensive care protocol could be provided. Importantly, this protocol represents only our institutional policy. Obviously, if intensive care can be provided in the setting of an outpatient clinic, it is an appropriate alternative for hospitalization. Data that were obtained from recent studies and cumulative clinical experience in our department have suggested that most fetal and maternal complications occur among women with severe ICP.[11-13] Therefore, our policy has been revised, and only women with severe ICP or ICP and preeclampsia currently stay in the hospital. All other women with ICP are discharged for outpatient clinic surveillance once TBA levels and liver enzymes level normalize. The follow-up protocol in our outpatient clinic includes fetal monitoring 1-2 times each week; weekly measurements of blood pressure, blood protein/creatinine ratio, and liver function tests; and a sonographic biophysical profile once each week. Fetal growth assessment is performed once each month, unless growth retardation is suspected. TBA measurements are retaken based on clinical indications such as worsening pruritus or an elevation in liver function tests results. Application of the suggested protocol may help to diagnose preeclampsia earlier in this high-risk population and improve maternal and fetal outcomes. ■

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