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

Cite this article as: Raz Y, Lavie A, Vered Y, et al. Severe intrahepatic cholestasis of pregnancy is a risk factor for preeclampsia in singleton and twin pregnancies. Am J Obstet Gynecol 2015;213:395.e1-8.

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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Received Dec. 11, 2014; revised Feb. 27, 2015; accepted May 7, 2015.

The authors report no conflict of interest.

Preliminary data were presented at the 61st Annual Scientific Meeting of the Society for Gynecologic Investigation, Florence, Italy, March 26-29, 2014.

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0002-9378/$36.00 • http://dx.doi.org/10.1016/j.ajog.2015.05.011

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