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Serum Bile Acids in Intrahepatic Cholestasis of Pregnancy: Not just a Diagnostic test

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The first descriptions of intrahepatic cholestasis of pregnancy (ICP) may be those of Ahlfeld in 1883 and Eppinger in 1937, although Scandinavian clinicians began more detailed description of ICP in the 1950's (1). ICP, sometimes also termed obstetric cholestasis, is thought to occur in women with increased susceptibility to the cholestatic effects of estrogen, or higher levels of estrogen, as evidenced by ICP's occurrence mainly in the third trimester when pregnancy hormone levels are highest, and its increased frequency in multiple pregnancies, which have higher levels of hormones compared to singleton pregnancies. The prevalence of ICP varies between populations, as well as within populations over time and between seasons, suggesting presence of both genetic and environmental effects. The increased incidence of ICP in some populations with some Native American ancestry, from different regions of the Americas, suggests the existence of one or more genetic variant(s) that increase susceptibility to ICP, and which is/are at increased frequency in Native American populations (2).

The most commonly accepted definition of ICP includes pruritus with a characteristic pattern of distribution, with palms and soles of the feet especially affected, together with elevation of total serum bile acids (SBA) and/or transaminases, and absence of other liver disease to which these manifestations can be attributed; also, skin lesions are absent, except for excoriations due to scratching. Occasional women with ICP have elevated serum bilirubin (total and direct). Physicians have relied on the characteristic clinical presentation coupled with an elevation in SBA and/or transaminases to make the diagnosis of ICP. SBA increase after meals; however, non-fasting values are still useful for clinical purposes in ICP, as values among women with ICP remain significantly elevated in comparison to those in pregnant women without ICP (3, 4). The precise cut-off for the level of SBA considered high and diagnostic of ICP varies between sites and studies, but is often chosen to be ≥ 10 μmol/liter.

Diagnosis of women who manifest the characteristic pattern of pruritus, but have SBA and transaminases in the normal range, is controversial; in some places where ICP is relatively

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common, and healthcare resources limited, diagnosis is routinely made without SBA measurement, based only upon characteristic pruritus, in the absence of other causes of liver disease. Onset of ICP usually occurs in the 2nd or 3rd trimester. The disorder clears up within a few days (typically 1–3) after delivery; if cholestasis is persistent after delivery, diagnosis of ICP is likely incorrect.

For the mother, ICP is a transient, generally benign condition that resolves promptly after delivery. However, ICP appears associated with increased risks to the fetus, including preterm delivery, meconium staining of the amniotic fluid, fetal distress (defined by Apgar scores or hypoxemia/acidemia in umbilical cord gases), respiratory distress, bradycardia, and intrauterine fetal demise (IUFD) (5–7). The extent to which these risks have been quantified in well-controlled studies is variable. Ursodeoxycholate is now the preferred pharmacological treatment used in management of ICP; it decreases maternal symptoms and SBA, and may also improve fetal outcomes, although the latter has not been proven (8).

As the risk of IUFD appears greatest late in pregnancy (6, 9), induction of labor at approximately 37 weeks gestation, or at diagnosis if after 37 weeks gestation, is typically recommended in ICP, regardless of the levels of SBA; this recommendation is made in consideration of the relatively small risks conferred by iatrogenic prematurity at this gestational age, weighed against the possibility of the terrible outcome of IUFD. The study reporting the largest number of stillbirths in ICP where gestational age at demise was known derived from a population of women contacting an obstetric cholestasis support group, and reported on 20 IUFDs in singleton pregnancies, of which 18 were at ≥ 37 weeks gestation. The diagnosis was made retrospectively in all but two of these cases, and they therefore had not been actively managed (9).

Efforts have been made to identify factors which influence the risk of poor fetal outcomes in ICP. The largest previous study, of a Swedish population, found no evidence of substantial increase in fetal complication rates in pregnancies with ICP unless the mothers' SBA were ≥ 40 μmol/l; however, this study may have missed more subtle increase in risk in pregnancies with moderate elevations of SBA (10–40 μmol/l), as the control group was formed of women who had reported pruritus, but had normal SBA levels; some women fitting this category may have mild ICP, and therefore are not an optimal control group (7).

For decades, obstetricians have pondered what antenatal fetal surveillance strategies to use in the management of ICP in order to avoid or decrease the possibility of a stillbirth. Fetal death usually occurs suddenly, without warning. Autopsy studies have shown otherwise structurally normal, normally grown fetuses with signs of acute anoxia (10). Intervention trials that have used antepartum electronic fetal heart monitoring, growth ultrasound, or Doppler ultrasound, have not yielded encouraging results in the prevention of IUFD among patients with ICP (11). Thus, the standard methods used to ascertain fetuses at risk of in-utero death among high risk pregnancies, aimed primarily at detecting placental insufficiency, have not proved to be helpful in the management of obstetric cholestasis.

In this issue of Hepatology, Geenes *et al.* report results of a prospective population-based case-control study examining perinatal outcomes in severe ICP, defined as SBA ≥ 40 μmol/l

(12). The outcomes studied included preterm birth, presence of meconium in amniotic fluid, neonatal unit admission, and stillbirth. To perform this study, the authors made good use of the UK Obstetric Surveillance System (UKOSS), which facilitates efficient collection of data from patients across the UK with relatively rare pregnancy-related disorders, while minimizing the time burden on reporting clinicians. UKOSS was launched in 2005, and has been used to generate data for over 2 dozen publications on pregnancy-related disorders (https://www.npeu.ox.ac.uk/ukoss/completed-surveillance).

The authors compared outcomes in women with severe ICP as compared to unaffected pregnant women, and also evaluated the relationship of SBA and other biochemical parameters to outcomes in ICP. They confirmed the increased risk of late preterm delivery, stillbirth, neonatal unit admission, and meconium staining of amniotic fluid in ICP, compared to unaffected pregnancies; they also found that the rate of these complications (including total and spontaneous late preterm delivery) in ICP increased with increasing concentrations of SBA.

The mean gestational age at delivery in the study was 37.5 weeks among cases. The majority of women with ICP had induced labors; 17% of patients were induced at gestational age < 37 weeks, and 58% of patients were induced at 37 weeks or later in gestation. The Royal College of Obstetricians and Gynecologists recommends that clinicians discuss the benefits and risks to induction of labor after 37 weeks gestation with women affected by ICP (13). For women with ICP and markedly elevated SBA, defined as >40 μmol/L, the case for delivery at 37 weeks, or potentially even earlier among women with co-morbidities, is strengthened by the present study (12); a stillbirth rate of 1.5% (OR 3.05; 1.29 to 7.21) was found among such ICP patients, and doubling of the levels of SBA correlated with a 200% increase in risk of IUFD, based upon logistic regression analysis. The mechanism leading to fetal death in ICP remains elusive, but some studies suggest that increased levels of SBA trigger either vasoconstriction of the umbilical cord (14) or cardiac arrhythmia (15). Results reported in this study confirm that induction of labor at 37 weeks gestation does not fully prevent IUFD, as 6 of the 10 stillbirths in ICP pregnancies occurred before 37 weeks gestation. This observation is in keeping with data indicating that the majority of IUFD cases among women with known, actively managed ICP occur at less than 37 weeks gestation (13). The results of the current study add further support for monitoring of serum biochemical abnormalities, especially SBA, and use of SBA levels to inform decision-making regarding management of pregnancies affected by ICP.

The majority of women with ICP have SBA levels < 40 μmol/L. Patients with SBA levels < 40 μmol/L were not included in the study by Geenes *et al.* by virtue of having a relatively common condition and thus not meeting criteria for a UKOSS study (12). Until more large prospective studies that include women with this milder presentation of ICP are available, it is likely that physicians will continue to advise women in favor of delivery at 37-38 weeks, despite accumulating evidence of substantially less risk of IUFD among ICP patients with mild elevations of SBA levels.

The data from the study by Geenes *et al.* support broadening the use of SBA in the management of ICP beyond diagnostic purposes, to use in assessment of disease severity

and in assisting patients and physicians in deciding the optimal timing of delivery to decrease the possibility of stillbirth.

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REFERENCES

1. Reyes H, Simon FR. Intrahepatic cholestasis of pregnancy: an estrogen-related disease. Semin Liver Dis. 1993; 13:289–301. [PubMed: 8235718]
2. Arrese M, Reyes H. Intrahepatic cholestasis of pregnancy: a past and present riddle. Annals of hepatology. 2006; 5:202–205. [PubMed: 17060884]
3. Lee RH, Goodwin TM, Greenspoon J, Incerpi M. The prevalence of intrahepatic cholestasis of pregnancy in a primarily Latina Los Angeles population. Journal of perinatology : official journal of the California Perinatal Association. 2006; 26:527–532. [PubMed: 16761011]
4. Lee RH, Ouzounian JG, Goodwin TM, Incerpi MH, Miller DA, Zhang K, Caulfield MP, et al. Bile acid concentration reference ranges in a pregnant Latina population. Am J Perinatol. 2013; 30:389–393. [PubMed: 23161351]
5. Pusl T, Beuers U. Intrahepatic cholestasis of pregnancy. Orphanet journal of rare diseases. 2007; 2:26. [PubMed: 17535422]
6. Pathak B, Sheibani L, Lee RH. Cholestasis of pregnancy. Obstetrics and gynecology clinics of North America. 2010; 37:269–282. [PubMed: 20685553]
7. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: relationships between bile acid levels and fetal complication rates. Hepatology. 2004; 40:467–474. [PubMed: 15368452]
8. Bacq Y, Sentilhes L, Reyes HB, Glantz A, Kondrackiene J, Binder T, Nicastri PL, et al. Efficacy of ursodeoxycholic acid in treating intrahepatic cholestasis of pregnancy: a meta-analysis. Gastroenterology. 2012; 143:1492–1501. [PubMed: 22892336]
9. Williamson C, Hems LM, Goulis DG, Walker I, Chambers J, Donaldson O, Swiet M, et al. Clinical outcome in a series of cases of obstetric cholestasis identified via a patient support group. BJOG. 2004; 111:676–681. [PubMed: 15198757]
10. Fisk NM, Bye WB, Storey GN. Maternal features of obstetric cholestasis: 20 years experience at King George V Hospital. Aust N Z J Obstet Gynaecol. 1988; 28:172–176. [PubMed: 3233079]
11. Kondrackiene J, Kupcinskas L. Intrahepatic cholestasis of pregnancy-current achievements and unsolved problems. World J Gastroenterol. 2008; 14:5781–5788. [PubMed: 18855975]
12. Geenes V, Chappell LC, Seed PT, Steer PJ, Knight M, Williamson C. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: A prospective population-based case-control study. Hepatology. 2013
13. RCOG. Obstetric Cholestasis. Green Top Guideline No. 43. 2011
14. Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. World J Gastroenterol. 2009; 15:2049–2066. [PubMed: 19418576]
15. Sheikh Abdul Kadir SH, Miragoli M, Abu-Hayyeh S, Moshkov AV, Xie Q, Keitel V, Nikolaev VO, et al. Bile acid-induced arrhythmia is mediated by muscarinic M2 receptors in neonatal rat cardiomyocytes. PLoS One. 2010; 5:e9689. [PubMed: 20300620]