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EDITORIAL

Why more attentions to fetus in cases of intrahepatic cholestasis of pregnancy?

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Abstract

Intrahepatic cholestasis of pregnancy (ICP) is a peculiar disease in middle-late pregnancy with the pathological characteristics of hepatic capillary bile duct silts and is accompanied by clinical presentations of pruritus and bile acid (BA) elevation in serum. Maternal outcomes for patients diagnosed with ICP are usually good. However, fetal outcomes can be devastating with high frequencies of perinatal complications. Patients with ICP generally have an early delivery due to fetal complications. The current hypothesis is that ICP has higher frequencies of fetal complications due to high concentrations of BA which has toxic cellular effects to many organs. In lungs, it destroys the AT-II cells, decreasing phospholipids synthesis leading to the alveolar capillary permeability to increase and pulmonary surfactant to decrease. In heart, cholate can cross into the fetal compartment and causing fetal arrhythmias and decreased contractility. In the nervous system, high BAs can cause nerve cell denaturation and necrosis, mitochondria edema and membrane dissolve. In the placenta, high BA concentration can cause edema of the villous, decrease number of villous, intervillous thickening and balloon formation. In addition, high total BA can result in chorionic vein constriction and impaired fetal adrenal function.

Key words: Intrahepatic cholestasis of pregnancy; Bile acid; Perinatal outcome; Fetal lung; Fetal heart

Core tip: Fetal outcomes for patients diagnosed with intrahepatic cholestasis of pregnancy can be devastating with serious complications. Advances in our understanding of the reasons that can cause severe fetal complications, such as sudden fetal death, slowed fetal lung maturity, perinatal nervous system injury, distress, and neonatal asphyxia, will provide some hints towards the basic etiology of this disorder. We look forward to a time that early diagnosis will be made and laboratory tests will be carried out to monitor these fetal conditions. I would suggest that more attention should be paid to the fetus which contributes to improve fetal outcomes.

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a maternal metabolic disease affecting up to 5% of pregnancies[1]. It occurs in the second and third trimester, and is characterized by intense pruritus and an elevation in serum bile acid (BA) concentrations. Maternal outcomes for patients diagnosed with ICP are usually good. However, fetal outcomes can be devastating with complications of pre-

mature delivery, fetal distress, neonatal asphyxia, neonatal respiratory distress syndrome, neonatal multi-system damage, and fetal death[2,3]. Thus, early recognition, treatment, and timely delivery are imperative. From the maternal viewpoint, the main symptom is the intense pruritus, which may become intolerable leading to an early delivery[4]. On the fetal viewpoint, it is more concerning since the high risk of perinatal complications which can result in fetal demise. Thus, many doctors would advocate induction at 37 wk[5].

SEVERE INFLUENCES OF ICP TO FETUS

Sudden fetal death

One of the most worrisome aspects of ICP is the possibility of sudden fetal death[6]. Possible explanations for sudden fetal death are taurocholate crossing into the fetal compartment and causing fetal arrhythmias and decreased contractility[7]. Other studies have noted an increased P-R interval in human fetuses affected by ICP[8]. Intrauterine fetal demise is also associated with ICP, especially when the total BA (TBA) level is critically elevated, but it rarely occurs prior to 36 weeks' gestation. With the risk for sudden fetal death, it becomes a dilemma how to monitor and when to deliver. Since fetal death rarely occurs before 36 weeks' gestation, many doctors favor delivery when it reaches to 37 wk gestation[9].

Lung maturity

ICP usually accompanied with slowed lung maturity. It is associated with fetal distress, neonatal asphyxia, neonatal respiratory distress syndrome, and cholic acid pneumonia[10]. In Glantz's study, fetal asphyxia was related to BA concentration with the critical level of 40 mmol/L or greater[11]. The pulmonary pathological changes consist with neonatal pulmonary hyaline membrane disease, light transmittance of the lung reducing, swelling, widely atelectasis, diffuse pulmonary hyaline membrane disease[12,13]. In one of our case control studies, amniotic fluid surfactant and lamellar body was significantly decreased and fetal lung area/body weight ratio was significantly reduced in ICP patients. In addition, fetal blood TBA showed a negative correlation to the surface active substances-phospholipids production. In Shi *et al*[14] study, cholic acid can cause a dysfunction in the synthesis of surface active substances in the lung. He found that high BA can lead to immature fetal rat lung with the pulmonary morphological changes of smaller alveolar cavities, thickening alveolar intervals, local atelectasis, and most cells fall off from the wall. Furthermore, pulmonary tissue was found to have heavy density and diffuse bleeding lesions.

Nervous system

Severe and moderate ICP can cause perinatal nervous system injury and the severity of injury is associated with the TBA level. Pathological changes include immaturity of the hepatoencephalic barrier and presents with endothelial holes, thinning of the base membrane leading to an increase in permeability[15]. Animal experiments demonstrated that high BAs can cause nerve cell denaturation and necrosis, mitochondria edema and membrane damage[16]. By measuring umbilical artery blood pH, lactic acid, and color Doppler on fetal cerebral artery blood flow, it was found that ICP can cause fetal acidemia and reduced fetal cerebral blood flow[17].

Fetal distress and neonatal asphyxia

ICP has higher frequencies of fetal distress and neonatal asphyxia. It is considered these may be associated with the pathological changes in the placenta. The morphology of placentas from the rodent model of ICP is markedly abnormal. Human and rodent studies have shown that transplacental transfer of BAs is impaired in ICP. High BA concentration results in placental alteration with increased syncytial knots, reduced collagen, edema of the villous, decreased number of villous, intervillous thickening and balloon formation[18]. Geenes found that ICP placentas have an increase in the number of syncytial knots, and that these can be reproduced in an *in vitro* model exposed to the BAs taurocholic acid and taurochenodoexycholic acid[19]. Ding studied the morphologic ultrastructure of human placental syncytial cells and reported that ICP placenta has impaired cellular organelle, resulting in the abnormal physiological function of syncytial cells, and affecting the synthesis and transportation functions of the placenta[20].

Vascular system

In addition, high TBAs can increase the intracellular calcium concentration resulting in chorionic vein constriction and can lead to the increase of placental circulation resistance[21]. It can cause fetal adrenal dysfunction and influence the production of vascular aldosterone and corticosterone[22].

LABORATORY MONITORING OF ICP

Many laboratory abnormalities can be seen in ICP. The most specific and sensitive marker of ICP is TBA levels greater than 10 μmol/L[23]. In addition, the cholic acid level is significantly increased while the chenodeoxycholic acid level is mildly increased, resulting in an elevation in the cholic/chenodeoxycholic acid level ratio[24,25].

Recommended laboratory studies for the diagnosis of ICP include monitoring total serum BA levels, cholic acid, chenodeoxycholic acid (to evaluate the cholic/chenodeoxycholic acid ratio), total bilirubin, transaminases, GGT, PT, PTT, and INR. These laboratory studies are used in conjunction with physical examination and symptoms to make a diagnosis of ICP. Once a diagnosis of ICP has been made, TBA levels can be followed every 2-3 wk to guide therapy and timing of delivery. In addition, coagulation studies and transaminase levels should be monitored to measure progression of the disease.

MANAGEMENT OF FETUS

More attention should be placed on the fetus. Tests for the fetus, including umbilical artery Doppler studies, bio-

physical profile, and nonstress tests, should be performed to reduce the risk of stillbirth[26]. One study demonstrated that increased fetal testing and scheduled induction with documentation of fetal lung maturity in patients with ICP lessened perinatal mortality rates compared with patients who were not tested[27]. Delivery should be induced at 37 wk. If deliver prior to 37 wk occurs, amniocentesis for fetal lung maturity is necessary. If meconium is present at the time of amniocentesis, delivery is indicated regardless of the fetal lung maturity results. Delivery should proceed without an amniocentesis if the fetal monitoring is nonreassuring.

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