Intra-Hepatic Cholestasis of Pregnancy

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Key points

- What is Intra-hepatic cholestasis and it's causes.
- How the increase in bile acids effect the fetus.
- Treatments to minimize the harmful effects of ICP on the growing fetus

Intrahepatic cholestasis of pregnancy is a pregnancy-specific liver disease which compromises symptoms like skin pruritus (itching) and elevated level of bile acids. Symptoms in the pregnant woman appear in the second or third trimester but in some cases, they emerge in the first trimester and goes back to normal after delivery. This disease arise in around 0.5-2% pregnancies.1

Causes

One of the several causes of ICP includes genetic mutation of the hepatobiliary transport protein-multidrug resistance protein 3 (MDR3). These transport proteins are involved in the secretion of phospholipids. This kind of mutation is appreciated in almost 16% of the ICP patients that have bile acid level higher than 40 µmol/L. MDR3 disorder, however, can also be seen in people having low phospholipid level by birth or even due to induced cholestasis. In some cases, intrahepatic cholestasis can also be caused by change in BSEP (bile salt export pump) gene in which amino acid on 444 position is substituted. In addition to the mutations in MDR3 and BSEP genes, rare mutations in the FIC1 gene (ATP8B1) which is present inside the bile duct membrane and the FXR gene (NR1H4) were also detected in the patients in Caucasus and steroid hormones or their metabolites are said to be the cause of such mutations.2

Another major cause is the increase in bile acid level which accumulate in hepatocytes and damage the cell membranes which in turn releases aminotransferases, bilirubin, γ- glutamyl transpeptidases, and alkaline phosphatase into the blood serum. In ICP patients, the bile acid flow is reversed from mother to fetus which enhances the levels of bile acids in the fetus. In Laatikainen, a higher concentration of BAs (bile acids) was found in the umbilical cord blood of fetuses from ICP (approximately 5.6 µg/mL) as compared to fetus from normal pregnancy (1.8 µg/mL). The stimulus of this reversal is said to be the structural and functional change in placenta. In an advanced pregnancy, when the mother's liver is exposed to high levels of sex hormones, an increase in the level of BAs in both the mother and the fetus along with abnormal functioning of the placenta will make it impossible to synthesize water-soluble BAs, that will cause disturbances in BA transport across the placenta and ICP development.The accumulation of BAs in the maternal and fetal liver in ICP may lead to oxidative stress and hepatocyte apoptosis, which may affect time period of the pregnancy.3

The sex hormones are metabolized in the liver. A number of studies confirmed the effects of gestational hormones on the metabolism of bile acids; however, many of these studies were conducted in animal (mainly murine) models for ethical reasons. Glucuronates, estrogens, and progesterone disturb the function of hepatobiliary transport proteins that are involved in the excretion of bile acids into the hepatic bile ducts. It changes the composition of bile, and the ratio of hydrophilic and hydrophobic bile acids is also disturbed. This results in the impairment of water-soluble bile acids being transported across the placenta and excreted by maternal kidneys. Balance of BAs in maternal and fetal blood plays an important role in ICP.4

Effect on the fetus

Intrahepatic cholestasis may gravely threaten fetal growth and development, resulting in intrauterine fetal distress and death, premature delivery, neonatal hypoxia-ischemia (brain damage) and asphyxia (deficiency of oxygen). Long-term high bile acid level, especially high CG (chorionic gonadotropin) level will cause contraction in vessels on the surface of placental villi and decreased flow of blood and oxygen level and lesser exchange of nutrients from the mother. This will finally terminate in intrauterine fetal distress and affect growth and development of the fetus.5

Treatment

Treatment of ICP can be accomplished in several ways to minimize the harmful effects on the fetus. Non-pharmacological treatment (without the involvement of drugs) includes satisfactory bed time routine which leads to improvement of hepatic blood flow, monitoring the fetus by using biophysical methods like ultrasound examination, monitoring the fetal movements by the pregnant woman, and monitoring of concentrations of hepatic functional tests. Weekly tests to note the bile acid levels are also suggested

according to which time of delivery is recommended. For example:

- at the concentration of <40 µmol/L total bile acids, childbirth is recommended between 37 and 38 weeks of pregnancy.
- at the concentration of 40–99 µmol/L total bile acids, childbirth is recommended between 36 and 37 weeks of pregnancy.

In pharmacological treatment, UDCA is the main medication for intrahepatic cholestasis. It is a hydrophilic, naturally occurring, tertiary bile acid formed in the gastrointestinal tract through the bacterial metabolism of primary bile acids. After taking it orally, the maximum blood concentration is reached after about 30–60 min. UDCA reduces the rate of cholesterol absorption, reduces hepatic synthesis and secretion of cholesterol, corrects bile acid transport through the placenta and reduces concentration of primary bile acids in the umbilical cord.

Ornithine aspartate, phospholipids, dexamethasone, and cholestyramine are some medications used for Intrahepatic cholestasis.3

References

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