The role of Doppler ultrasonography in intrahepatic cholestasis of pregnancy

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Abstract

Introduction. Intrahepatic cholestasis of pregnancy (ICP) is a systemic disease which is unique to pregnancy and linked to cellular and receptor dysfunctions, and genetic mutations. ICP affects not only the mother, but also the course of pregnancy, labor and delivery with significant fetal outcomes.

Discussion. Conventional monitoring of fetal well-being is not sufficient to detect and prevent potential complications associated with ICP. The superiority of obstetric ultrasonography combined with Doppler assessment of the fetal circulation and liver function tests in the mother is discussed based on published reports.

Conclusion. With the wide availability of Doppler blood flow studies, umbilical artery Doppler assessment should be performed in all pregnancies complicated by intrahepatic cholestasis in order to improve fetal outcomes.

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Introduction

During pregnancy, the pregnant mother undergoes several physiological changes to adapt her body to pregnancy and allow normal development of the fetus. When these adaptive changes depart from normal, they may have adverse effects on both the mother and the fetus. When transient liver impairment occurs during pregnancy, pregnancy-specific liver dysfunction is diagnosed which falls into three categories [1-3]:

- disorders which develop exclusively during pregnancy and are related to its course;
- pre-existing hepatobiliary disease which affects the course of pregnancy;
- disorders which worsen during pregnancy and run a more severe course than in the non-pregnant state.

The first group includes hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy and HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome [4].

The second group includes viral hepatitis, cholelithiasis and Budd-Chiari syndrome.

The thirds group includes autoimmune hepatitis, Wilson's disease and Dubin-Johnson syndrome [5,6].

Intrahepatic cholestasis of pregnancy (ICP) is typically specific to pregnancy [3,5,7-13]. An association between cholestasis and pregnancy was first observed by Ahfeld in 1883 [5,14]. In 1932, Schwalm reported the recurrence of intrahepatic cholestasis in the same patient during her consecutive pregnancies [1954]. The biochemical and clinical features were described by Svanborg in 1954 while the very term intrahepatic cholestasis of pregnancy was first used by Hammerli in 1967 [5].

The prevalence of ICP is highly geographically variable [3-5,12,15,16]. ICP seems somewhat more common in Scandinavia, Bolivia and China than in Central Europe. In South America, it affects from 6.5% to 22% of pregnant women compared to 0.2% to 3% in Central Europe, i.e. 1case per 2000-8000 deliveries.

The development of cholestasis is associated with the maternal age (ICP is more frequent in women over 35 years of age) and multiplicity of pregnancy [12] but the exact cause of ICP remains unclear [5,11,12,17].

At present, it is known that ICP is a systemic disorder which usually occurs in the third trimester [2,18-22] although single cases of ICP as early as the first trimester have been reported [6]. Cholestasis of pregnancy is a mild, reversible disorder which may recur in subsequent pregnancies [5,23,11,12,17]. The pruritus of the palms of the hands and soles of the feet is the most common manifestation. The itching gradually becomes generalized to involve the whole body, substantially decreasing the patient's quality of life [18]. Although during pregnancy the volume of body fluids and vascular bed filling are altered, the blood flow through the liver remains unchanged or even, according to some authors, decreases [14]. The hepatic metabolism, however, is substantially more active [16].

In cholestasis, there is a decrease in bile flow which triggers pruritus and increases in the enzymatic measures of cholestasis, e.g. alkaline phosphatase (ALP), leucine aminopeptidase (LAP), gamma-glutamyl transpeptidase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), glutamate dehydrogenase (GLDH), α-hydroxybutyric dehydrogenase (HBD), beta-glucuronidase (RRG), acetylcholinesterase (AchE), ceruloplasmin (Crpl) or alanyl aminopeptidase (AAP) [23,24,14] and an increase in bile acid levels [25].

Cholestasis may result from a mechanical obstruction impairing the flow of bile at the level of the hepatocyte [6]. The hepatocyte dysfunction is caused by increased levels of estrogens and progesterone during pregnancy and occurs in women who are carriers of a genetic mutation responsible for disorders of bile formation and bile acid metabolism [4,8]. Increases in the levels of estrogens and progesterone are most evident in the third trimester of pregnancy. Estrogens which accumulate in the hepatocyte reduce the permeability of its membrane. A thickening of the bile results followed by its stasis in all pregnant women, but intrahepatic liver dysfunction is actually diagnosed in only a very small proportion of pregnancies [5,14,16]. That is why a variety of causes are suggested to contribute to ICP [5,15,13,17].

Approximately 50% of women with diagnosed ICP have a positive family history. Genetic mutations associated with intrahepatic cholestasis of pregnancy are usually a missense mutation or a deletion of the genes encoding some transport proteins. The process of bile transport across the cell membranes is active and involves transport proteins and therefore mutations which are responsible for alterations in the transport protein structure may play a role in the development of ICP [26,18].

In patients with ICP in their first pregnancy, the risk of recurrence in subsequent pregnancies is

40-100%. In subsequent pregnancies, however, the symptoms tend to appear earlier and are considerably more severe [5,11].

Intrahepatic cholestasis of pregnancy is characterized by numerous biochemical abnormalities including disorders of carbohydrate metabolism, renal tubular and glomerular dysfunction, subclinical acidosis, disorders of hormonal regulation of lipid metabolism and disorders of erythrocyte metabolism [27-29].

According to Niespodziański, 3-beta-hydroxycholic acid produced by the immature fetal liver with limited enzymatic activity also induces maternal cholestasis [16]. Additionally, in vitro studies have demonstrated that bile acids have a vasoconstrictive effect on the human placenta chorionic veins thus contributing to the development of cholestasis [27,19].

The first symptoms of cholestasis usually appear between Weeks 25 and 32 of pregnancy [5,12]. Pruritus and jaundice persist for about one week after delivery while the biochemical parameters slowly return to normal [5,11,13,16,17,30]. To diagnose ICP, at least three of the following manifestations must be present:

- **Pruritus** occurs in most patients and usually affects the trunk, the palms of the hands and soles of the feet. Pruritus may severe enough to disrupt sleep with adverse effects on the patient's general well-being [12]. Pruritus may precede the biochemical abnormalities of cholestasis by four weeks [10].
- **Elevated serum bilirubin levels** up to 2-8 mg% are observed in 70% of patients and clinically evident jaundice is observed in approximately 10% to 25% of pregnant women with cholestasis [30]. Jaundice typically follows the onset of pruritus by 1 to 4 weeks [12].
- **Elevated alkaline phosphatase (ALP)** is a marker of damage to the liver cells. Maternal serum total ALP levels are raised by approximately 100-300% of the normal while there is only a slight increase in placental ALP levels.
- **Elevated AST and ALT levels** are markers of damage to the liver cells and in cholestasis they rise up to 2-3 times the upper limit of normal. ALT is a more sensitive marker of ICP than AST. The **De Ritis ratio (AST/ALT**) is important for evaluation of liver injury. The normal range is 1.0 – 2.75, while in pregnacy it decreases to 0.5.
- **Other signs** include dark urine, loss of appetite, steatorrhea and vomiting [5,12,16].

Apart from the above, abnormalities of 24-hour glycemic profiles are observed (increased postprandial glucose levels and abnormal 24-hour glucose curves) [2,18,19,21,22,27,32,33].

When confirming the diagnosis of ICP, it is necessary to exclude

patients with characteristic symptoms and signs of intrahepatic cholestasis which may be due to another underlying condition such as viral hepatitis or are found in liver transplant recipients [24].

Bile acid measurements are not routinely performed because of the involved high cost and frequent delays in obtaining the results [5]. However, the levels of cholic acid and chenodeoxycholic acid are known to increase up to 100-fold in ICP.

According to the Obstetric Cholestasis Guideline of the Royal College of Obstetricians and Gynaecologists of the United, the diagnosis of intrahepatic cholestasis of pregnancy should be confirmed by abnormal liver function tests, i.e. elevated aminotransferases and gamma-glutamyl transpeptidase (GGT), bilirubin and (or) bile acid salts [7].

Other abnormalities, of a lesser diagnostic value, include elevated activities of ceruloplasmin, GGT, 5-nucleotidase (5'NT) and leucine aminopeptidase (LAP), serum iron increased by approximately 100%, increased serum copper, reduced cholinesterase activity, decreased levels of total protein, albumins and gamma globulins with the resulting decrease in oncotic pressure and edema, subclinical acidosis, elevated cholesterol levels, hemostatic disorders (a prolonged prothrombin time due to the impaired synthesis of vitamin K-dependent clotting factors II, V, VII, X) [5,12,16,30]. Some authors report an increased risk for postpartum hemorrhage in women with ICP and an increased risk for intracranial hemorrhage in the fetuses [16].

ICP predisposes to blood clotting disorders and vomiting and may lead to water-electrolyte imbalance which may adversely affect fetal well-being.

Cholestasis usually resolves within a few weeks after delivery.

ICP poses no risk to the mother, but it may increase the risk of perinatal mortality to the infant. According to the older data, ICP had a perinatal mortality rate of 10% and according to newer reports it is 2-4% [16]. From 12% to 44% to even 60% of pregnant women with ICP are thought to be at risk of pre-term delivery [5,12,13,15-17,20,32], which is associated with the enhanced uterine sensitivity to oxytocin. This sensitization to oxytocin reflects oxytocin augmentation in the myometrium as high levels of the oxytocin receptor are expressed at the messenger RNA and protein levels [31]. The presence of meconium in the amniotic fluid is reported in approximately 30% of pregnant women with ICP [32]. Bile acid concentrations in the meconium are high and probably produce direct damage to the walls of the umbilical vessels [19]. Additionally, meconium present in the amniotic fluid increases the risk for meconium aspiration syndrome in the fetus [6]. According to Geenes, meconium aspiration syndrome occurs in 16-58% of all pregnancies with ICP and in 100% of pregnancies affected by ICP and complicated by intrauterine fetal death [30]. High concentrations of taurocholic acid in the fetal circulation may induce acute fetal arrhythmia [18].

According to some authors, the fetuses of women with ICP are more frequently female, the birth weight is lower than in fetuses of mothers without ICP and the placenta bigger [6,15,33]. Additionally, women with ICP more frequently experience a complicated delivery (premature or abnormal placenta separation and hemorrhage in the third stage of labor, increased uterine contractility due to enhanced uterine sensitivity to oxytocin and precipitate delivery) [5,12,15]

The role of ultrasonography in women with ICP

According to a number of authors, undiagnosed cholestasis is a likely cause of intrauterine fetal death [5, 12, 13, 15] while the risk of ICP is largely underestimated. Traditional methods of fetal well-being monitoring are not very helpful in this respect and ultrasonography in pregnancy, in addition to laboratory investigations and cardiotocography, is a very useful diagnostic tool [34-36].

Ultrasonography with a Doppler blood flow study to assess fetal circulation was first performed by FitzGerald and Drumm in 1977 [33]. Nowadays, it is considered a useful method for a prenatal evaluation of fetal well-being in high-risk pregnancies. The study reflects the hemodynamics of fetal circulation in normal and complicated pregnancies [34-36] and allows non-invasive and safe assessment of the fetus [36-38]. The accuracy and reliability of fetal Doppler ultrasound depend on the examiner's experience and the device sensitivity [39]. Assessment of the blood flow in the aorta, and the umbilical artery and vein is especially important. Doppler ultrasound allows visualization of fetal blood vessels and measurement of such parameters as the blood flow velocity, vessel diameter and blood flow volume. During normal pregnancy, with development of the fetus blood flow indices change. The total blood flow in the aorta and the umbilical vein as well as their diameters increase while towards the end of gestation, the velocity of blood flow and the vascular resistance are decreased in the aorta and the umbilical artery. The quantitative values of fetomaternal vascular resistance change in the course of pregnancy and that is why establishing and applying nomograms of blood flow for a given population throughout the weeks of pregnancy is so important [40]. Disorders of blood flow in the fetomaternal circulation visualized by Doppler ultrasonography may detect potentially life-threatening fetal hypoxia and prevent further more severe complications. According to some authors, abnormalities of the umbilical artery blood flow may precede by 7 days changes recorded by cardiotocography [41].

Some obstetricians are of the opinion that women with ICP should have delivery induced at 36 weeks of gestation and not later than 37 weeks of gestation [42].

To date, the topic of fetal circulation in pregnancies complicated by intrahepatic cholestasis of pregnancy has been of research and clinical interest to only a few authors in Poland and other countries [6,43,44]. Published studies of ICP and fetal circulation often report results which are inconsistent and inconclusive. There seems to be no clear answer as

to the actual usefulness of blood flow parameters for standard monitoring of pregnancies complicated by cholestasis. Previous studies show that cholestasis in the course of pregnancy leads to decreases in the total blood flow in the aorta and umbilical vein, which do not occur in normal pregnancies.

The use of accurate diagnostic techniques and methods based on the image analysis and evaluation of quantitative values of blood flow pressures and the resistance to the flow in the maternofetal circulation in ICP may prompt the justified decision to undertake the induction of labor to prevent the intrauterine death of the high-risk fetus.

Fetal outcomes in ICP and the assessment placental circulation

Some authors do not observe any correlation between the severity of intrahepatic cholestasis of pregnancy in the mother and the general condition of the newborn [5,12,16]. However, Łoziński has convincingly demonstrated a worse general condition of these babies at birth [6]. The underlying mechanism of fetal death in pregnancies complicated by ICP is not fully understood. Post-mortem examinations of dead fetuses born to mothers with ICP found acute hypoxia with petechiae in the pericardium, pleura and peritoneum [12,18,20]. It is believed that conventional fetal monitoring, i.e. cardiotocography, amnioscopy and ultrasonography without Doppler flow studies, does not adequately assess fetal well-being and cannot properly identify fetal distress in ICP [12].

Increased concentrations of bile acids are likely to produce vasoconstriction of the chorionic and other veins [5,6,16,46]. Bile acid metabolites, which as demonstrated in the animal model are fetotoxic, are transported across the placenta to the fetus [12]. Increased concentrations of bile acids were found in the umbilical blood of neonates born to mothers with ICP and bile acid concentrations were significantly elevated in fetal peripheral blood [4,9,19]. This may decrease blood flow to the placenta resulting in fetal asphyxia. In view of these reports, it may be presumed that bile acid concentrations also have an effect on blood flow in the umbilical artery [44] and the severity of cholestasis should correlate with the magnitude of changes in maternal bile acid concentrations and abnormalities of blood flow in the umbilical artery. Bile acids stimulate intestinal motility and meconium passage in utero while meconium staining of the amniotic fluid is associated with an increased risk of fetal distress [5,13,16,30]. Elective cesarean section when the signs of fetal hypoxia become evident prevents fetal distress or fetal death.

The studies discussed above emphasize the importance of close monitoring of fetal well-being using conventional ultrasound combined with Doppler flow imaging. Methods of fetal monitoring vary. Roncgalia et al. [3] monitored fetal well-being using cardiotocography (non-stress test), contraction stress test, amniotic fluid volume determinations, amnioscopy or amniocentesis. Heinonen used a similar approach to fetal surveillance [43]. Fetal movement counting by mother may help to reveal deterioration in fetal well-being hours before it becomes evident, when the count is reduced or fetal movements are absent, but this evaluation is subjective.

The blood flow in some segments of the fetal circulation was studied by Dmoch-Gajzlerska in normal and complicated pregnancies, who found that Doppler assessment of the blood flow in the aorta, and umbilical artery and vein is especially important in surveillance of fetal well-being. Her study demonstrated decreases in the umbilical vein diameter and decreased total blood flow in the aorta and umbilical vein in pregnancies complicated by cholestasis compared to normal pregnancies. Dmoch-Gajzlerska demonstrated that in several pathological conditions complicating pregnancy, such as intrauterine growth restriction, intrahepatic cholestasis, gestational diabetes, renal disease and pregnancy-induced hypertension or the serological conflict, towards the end of pregnancy the vascular resistance increases in both the aorta and the umbilical artery while the other Doppler parameters may vary depending on a complicating factor [8]. Fifteen years later, Sieroszewski et al. assessed Doppler parameters of vascular resistance in the fetal circulation in several disorders such as arterial hypertension, renal disease with proteinuria,

fetal hypotrophy and non-reactive cardiotocography, but not intrahepatic cholestasis of pregnancy [42]. Their study confirmed the results of Dmoch-Gajzlerska as they found that Doppler parameters were significantly altered in all conditions they investigated [8,42].

Williams et al. compared the umbilical artery Doppler testing with the non-stress testing [29]. The study was conducted in 1360 women with various disorders of pregnancy, including postdates, decreased fetal movement for longer than 24 hours, diabetes mellitus and arterial hypertension, and in cases of intrauterine growth restriction. No pregnant patients with intrahepatic cholestasis of pregnancy were included in the study. The authors proved the superiority of umbilical artery Doppler over the non-stress testing confirming that this method of screening for fetal well-being in high-risk pregnant women reduces the incidence of cesarean delivery, with no increase in neonatal morbidity [29].

Also in other studies abnormalities found by the umbilical artery Doppler testing prompted induction of labor and delivery, which was not associated with increases in the incidence of cesarean delivery. Since the risk for the fetus increases with gestational age, labor and delivery were induced once the fetus had achieved maturity but before the estimated date of delivery [5,12,13,15,16,42].

In 1991 Zimmermann et al. assessed Doppler umbilical artery velocimetry in 15 pregnancies complicated by intrahepatic cholestasis and in 129 normal pregnancies. The authors did not find any significant correlation between Doppler flow velocities and serum levels of bile acids and alanine aminotransferase and considered the umbilical artery Doppler testing to be of little value in assessing the risk to the fetus associated with maternal cholestasis [44]. Łoziński, on the other hand, emphasizes the relationship between some blood flow indices measured in the umbilical artery and maternal intrahepatic cholestasis [6].

As early as 1987, Dmoch-Gajzlerska in her study of aortic blood flow in 156 fetuses convincingly demonstrated significant sensitivity of fetuses to increased vascular resistance and marked tendency to fetal distress produced by vasoconstriction and leading to intrauterine death [8].

Summary

Liver function tests should be performed in pregnant patients with suspected intrahepatic cholestasis to minimize the risk of fetomaternal complications. At the same time, fetal well-being should be monitored by ultrasonography to assess the gestational age, and fetal and placental size. Especially important are the umbilical artery Doppler assessment and the biophysical profile including the amniotic fluid index (AFI).

Establishing any correlations between the liver function tests and ultrasonography in pregnancy, especially umbilical artery resistance index, may improve monitoring and management of pregnancies complicated by intrahepatic cholestasis and surveillance of fetal well-being.

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