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Intrahepatic cholestasis of pregnancy (ICP)

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Introduction

The first chapter of the article presents the general evidence, the clinical manifestation, the pathogenesis and diagnosis of the intrahepatic cholestasis, together with the risks involved for the mother and the fetus. The second chapter presents the treatment goals and the pharmacologic treatment during pregnancy, the management during and after delivery, as well as the risk of recurrence and future goals.

Discussion

The intrahepatic cholestasis of pregnancy (ICP) is the most frequent liver disease during pregnancy. The frequency rate in Europe is estimated to 0,5-1%. The regions with the highest frequency rates are Scandinavia, Chile, Bolivia, India and Pakistan.

Clinical manifestations of the disease include pruritus (which is usually intense and more severe during night hours) in the limbs, and in the main body (more frequently in the palms and the soles of the feet). It appears mostly during the second part of pregnancy (80% of manifestations occur after the 30th week). It is also combined with intense discomfort and sleep deprivation. There may be skin scratches but no skin rashes. Icterus is manifested in 15% of cases, always after the manifestation of pruritus. Anorexia, urine hyperpigmentation and steatorrhea (because of the malabsorption) are also possible manifestations of ICP. In women with HCV antibodies, the symptoms appear much earlier (average value: 29 weeks). A full relief of symptoms occurs within 48 hours after delivery. After 2-3 weeks, the Liver Function Tests (LFTs) return to normal standards. Rarely and in case of recurrence after delivery, LFTs return to normal within 4-8 weeks.

In 35% of patients this disease is associated with family incidence. Studies conducted in genealogical tables of patients have shown an autosomal dominant inheritance pattern, concerning the gene ABCB4/MDR3 (7q21.12) which helps the transfer of phospholipids to liver cells. They are attached to bile acids and they reduce their toxic action. Gene ABCB11 (2q31.1) serves to pump bile acids respectively. This particular polymorphism causes the reduced excretion of bile acids and the reaction of estrogens and progesterone in pregnancy. High levels of estrogens are associated with significant reduction of the possibility of bile acid sulfation. Sulfation is very important in reducing the cholestatic capacity of acids. They affect the function of bile acid transporters in liver cells and they diminish the membrane fluidity of liver cells. According to recent evidence, Peroxisome Proliferator-Activated Recep-

tors (PPARγ) are transcription factors expressed mostly in the adipose tissue[1]. As blockers of the NF-kb pathway, they cause anti-inflammatory action. Low PAPP-A values in women with ICP may be a probable mechanism through the IGF pathway which may be used as a predictive marker[2].

ICP diagnosis is a diagnosis of exclusion. The necessary data for this diagnosis is the intense pruritus without skin rashes, the abnormal liver function tests and the exclusion of other causes of pruritus and liver malfunction. The affected LFTs include small increase (<3x) of transaminases (ALT being the most susceptible), increased alkaline phosphatase, more than expected in pregnancy, normal GGT or increased only by 20%), rarely increased chelerythrine, increased serum bile acids (10-100x), which may be the first or the only finding. The affected values of liver function appear before or after the clinical manifestation.

The exclusion of other causes is done by a liver ultrasound, viral tests and detection of liver auto-antibodies. As to the liver ultrasound, the existence of gallstones does not exclude ICP diagnosis, unless it is combined with an imaged etiology for hepatic venous outflow obstruction. In fact, gallstones are a common finding in ICP patients. As to the viral tests (HBV, HCV) and in case of clinical semiology of active hepatitis, tests for HAV, HEV, EBV and CMV are also required. Liver auto-antibodies include auto-antibodies against smooth muscles (Anti-Smooth Muscle Antibodies - ASMA, Autoimmune Hepatitis) and Anti-Mitochondrial Antibodies (AMA, Primary Biliary cirrhosis). Maternal risks are various. Vitamin K deficiency (because of malabsorption), increased risk of bleeding after labor, gestational diabetes (especially in twin pregnancies), increased rate of future liver diseases (cirrhosis) and increased probability of cholestasis after taking contraceptives[3,4]. The fetal risks, whose mechanisms are still unknown, include discomfort during labor (pathologic cardiotocography with fetal bradycardia, distress or continuous loss, 12-22%), meconium staining of amniotic fluid (25-45%), pre-term delivery (12-44%), intrauterine death and intracranial hemorrhage of the fetus. The risk of complications gets higher when labor is close. There is no correlation with the intensity of symptoms or the levels of transaminases. However, there is a probable correlation with bile acids in mother's serum (<40μmol/L: no increase, >40μmol/L: 1-2% higher risk for complications for every μmol/L).

Treatment goals include a less intense pruritus, weekly tests of liver enzymes including bile acids (<40μmol/lt) and PT measurements before labor or in case of liver function disorder, especially when combined with icterus. There is no evidence connecting the regular fetal tests (cardiotocography, umbilical arterial Doppler and middle cerebral arterial Doppler, prenatal development control) with better prediction of an intrauterine fetal death (D RCOG guidelines)[5]. Inducing labor at 37-38 weeks to women with bile acid rates >40μmol/lt does not increase Cesarean Section rates (A RCOG)[5]. Pregnant women should therefore be informed about the risks of complications and the need for continuous monitoring. Pharmaceutical treatment consists of administering Vitamin K (because of malabsorption), which is necessary to women with persistent PT (5-10mgx1), and antihistamines such as chlorphenamine (4mg x3) or promethazine in order to reduce pruritus. Administering ursodeoxycholic acid (UDCA) is a first-line therapy. This is a hydrophilic bile salt contributing in reducing the hydrophobic bile acids rate and in increasing the placental transport proteins. The daily administration of 1000-1500 mg (or 10-15mg/kg) offers pruritus reduction, low levels of liver enzymes and bile acids in 80-90% of patients, decrease of pre-term delivery rates, of fetal malaise and fetal complications (A RCOG)[5]. Even though there is no evidence for their

safe administration, no adverse effects have been recorded to pregnant women or the fetus (C RCOG, non FDA approved)[5,6]. Refampicin reacts with UDCA: it deactivates the bile acids (action in CYP450) and enhances the extraction of bile acids pumped by UDCA. There are case reports where refambicin has been administered additionally to UDCA (150-300mg x1) improving symptomatology and the biochemical markers of cholestasis. The continuous monitoring of transaminases is therefore required.

As to the administration of dexamethasone (12mg x1), it has been recorded in one case study that it improves symptomatology, it lowers the levels of bile acids and transaminases in 70% of pregnant women, but it has not been confirmed ever since. It is not considered as a first- or second-line treatment because of the side effects cause by the high doses of corticosteroids to both mother and the fetus (D RCOG)[5]. The administration of cholestyramine (4g x2) may improve the pruritus feeling in some pregnant women but it is not tolerable enough because of its bad taste and the implied gastro-intestinal disorders. It also causes a Vitamin K deficiency. S-adenosylmethionine (SAMe) results in re-establishing the levels of hepatic glutathione, in methylation and in metabolic wastes. The data for SAMe's efficacity as to the reduction of pruritus and the improvement of biochemical markers are inadequate (A RCOG)[5]. Epomediol is a synthetic terpenoid which restores the fluidity of the liver cells' membrane and it may reduce the pruritus feeling in ICP. Activated carbon lowers the levels of bile acids but it does not have an influence on pruritus. Naloxone, an opioid antagonist, has been reported to reduce the pruritus feeling. The same is true with ondansetron, a serotonin inceptor (5-HT3) antagonist. The use of some hydration creams with or without menthol has also been reported to sooth pruritus (C RCOG) and they are safe to use during pregnancy.

Conclusion

To conclude, as to the ICP management during and after labor, the induction of labor at 37-38 weeks is recommended to women with increased concern for an intrauterine fetal death (increased biomarker values) and to women with persistent high levels of bile acids (>40μmol/lt). Many companies recommend inducing labor at 36-36+6 weeks, regardless of the biomarker values. The high risk of fetal discomfort requires close monitoring of the fetus, staring from the labor's induction, during labor and until the final baby delivery (A RCOG)[5], intramuscular injection of Vitamin K to the neonate, monitoring of liver enzymes for 6-12 weeks regardless of the pruritus and further investigation in case of further increase. 90% of women will suffer from ICP in their subsequent pregnancies. It is necessary to recommend the avoidance of contraceptives which include estrogens; in case they need to be taken, a frequent monitoring of the liver function is required. The risk is reduced by progesterone pills, only if the liver enzymes levels return to normal after delivery. Hormone Replacement Therapy to post-menopause women does not increase the risk of recurrence. The future goals include better comprehension of ICP pathophysiology, an improved understanding of the intrauterine death mechanism, discovering of risk assessment methods, and verification of the accurate role of UDCA in lowering the risk of an intrauterine death and its safe administration.

RCOG guidelines present the data for fetal risks which are associated with obstetric cholestasis and they provide guidance on the different management choices and the options available for treatment. Obstetric cholestasis is diagnosed when otherwise unexplained pruritus occurs in pregnancy and abnormal liver function tests (LFTs) together with/or raised bile acids occur in the pregnant woman. Pruritus in the palms and soles of the feet is highly indicative. Other etiology of pruritus and liver dys-

function should be excluded. Women with persistent pruritus and normal biochemistry should repeat their LFTs every 1–2 weeks. Postnatal analysis of pruritus and abnormal LFTs should also be confirmed. Once the obstetric cholestasis is diagnosed, it is necessary to measure the LFTs weekly until delivery. In a hospital setting, the current additional risk of stillbirth in obstetric cholestasis above that of the general population has not been determined but is likely to be small. Obstetricians should be aware (and they also should advise women) that the incidence of preterm delivery, especially iatrogenic, is increased. Women with obstetric cholestasis should be recommended to give birth in a hospital unit with specialized equipment. Finally, there are many fields that require further research, in particular:

- the pathophysiology of obstetric cholestasis
- the mechanism of fetal death and improved detection of pregnancies at risk
- the risk levels of a fetal death and ways of prevention
- the role of UDCA, its safety profile and the probability of lowering the risk of fetal death.
- pharmaceutical therapies.

References

1. Y. Zhang, et al., PPARg provides anti-inflammatory and protective effects in intrahepatic cholestasis of pregnancy through NF-kB pathway, Biochemical and Biophysical Research Communications 2018.
2. Tayyar AT et al., Could first- and second-trimester biochemical markers for Down syndrome have a role in predicting intrahepatic cholestasis of pregnancy?, Arch Med Sci 2018.
3. Mei Y et al., Perinatal outcomes in intrahepatic cholestasis of pregnancy with monochorionic diamniotic twin pregnancy, BMC Pregnancy and Childbirth (2018) 18:291.
4. Hämäläinen et al., Intrahepatic cholestasis of pregnancy and associated causes of death: a cohort study with follow-up of 27–46 years. BMC Women's Health (2018) 18:98.
5. Obstetric Cholestasis. RCOG Green-top Guideline No.43. April 2011. Royal College of Obstetricians and Gynaecologists. NICE accredited.
6. Bacq Y, Sentilhes L, Reyes HB, et al. Efficacy of ursodeoxycholic acid in treating intrahepatic cholestasis of pregnancy: a meta-analysis. Gastroenterology 2012; 143:1492–501.