

Cholestasis of pregnancy



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ABSTRACT

Cholestasis of pregnancy is a dysfunction of the liver characterized by pruritus and increased concentration of bile acids in the plasma during the second and third trimester. The cause of cholestasis of pregnancy is unknown, but it is believed to be connected to genetic factors and high values of the pregnancy hormone, which causes a disorder in the transport of bile acids in liver ducts. The leading symptom is pruritus, which is often generalized, but dominant on the palms and soles of the feet, and worsens during the night. Cholestasis of pregnancy is dangerous because it increases the risk of spontaneous preterm birth, meconium stained amniotic fluid, fetal distress, and intrauterine fetal death.

KEYWORDS: bile acids; cholestasis; pregnancy; pruritus

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INTRODUCTION

Cholestasis of pregnancy is a dysfunction of the liver characterized by pruritus and increased concentration of bile acids in the plasma during the second and third trimester. Intrahepatic cholestasis syndrome was first described by Ahlfeld in 1883 as itching and jaundice in the third trimester of pregnancy, which disappeared after delivery. In literature it is referred to as obstetric cholestasis, recurrent jaundice in pregnancy, hepatitis of pregnancy, jaundice in late pregnancy, etc (1).

ETIOLOGY

The cause of cholestasis of pregnancy is unknown, but it is believed to be connected to genetic factors and high values of the pregnancy hormone,

which causes a disorder in the transport of bile acids in liver ducts (2). Etiology is therefore explained through genetic, hormonal, and environmental factors. Genetic factors explain cases of frequent illness in certain families and some ethnic groups. Although the genetic background of cholestasis of pregnancy has yet to be completely explained, it has been discovered that in certain families there is a mutation of the gene that codes the transport protein in the membrane of hepatocytes (ABCB4/MDR3), thereby disrupting the transport of bile acids (3,4). When it comes to the hormonal background of cholestasis of pregnancy, it is believed that an increase in the levels of estrogen and progesterone may slow down the normal flow of bile from the liver. It is known that estrogen causes cholestasis in experimental and clinical conditions (5). This is

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supported by the fact that cholestasis of pregnancy most commonly occurs in the third trimester of pregnancy, when serum concentrations of estrogen reach the highest values. Also, it has been shown that cholestasis is more common in twin pregnancies, which are connected to higher levels of estrogen (6). When it comes to environmental factors, in certain countries it has been noted that the prevalence of cholestasis differs depending on the season. For example, in Finland, Switzerland, and Chile it is much more common in colder months (4).

CLINICAL PRESENTATION

The leading symptom is pruritus, which is often generalized, but dominant on the palms and soles of the feet, and worsens during the night (7). As a result of the itching, excoriations are often visible on the skin of the pregnant woman. Other symptoms and signs include a pale stool and dark urine, and more rarely jaundice, nausea, steatorrhea, abdominal pain, and loss of appetite.

DIAGNOSTICS

Laboratory tests show high values of bile acids, over 10 $\mu\text{mol/L}$ (8). In most cases there is an increase in the values of liver enzymes alanine transaminase (ALT) and aspartate transaminase (AST). Although ALT is more specific to the cholestasis of pregnancy, the values of both enzymes may vary from a mild elevation to several thousand U/L (8). Unlike liver transaminases, the level of gamma-glutamyl transpeptidase (GGT) is within the reference range or only mildly elevated. As part of cholestasis there are also increased concentrations of bilirubin in the plasma, usually from 35 to 55 $\mu\text{mol/L}$, and elevated concentration of alkaline phosphatase (ALP). However, considering the placental excretion of ALP, increased concentrations of that enzyme are non-specific to the cholestasis of pregnancy. An ultrasound of the liver shows a normal parenchyma with no liver duct dilatation. The final diagnosis of cholestasis of pregnancy is made on the basis of itching with increased values of bile acids and/or transaminases, with no other liver diseases present.

The differential diagnosis needs to exclude other liver dysfunctions during pregnancy, such as the hyperemesis gravidarum, acute fatty liver of pregnancy, preeclampsia, the HELLP syndrome, and changes of the skin plaques, urticaria and papules of pregnancy (PUPPS), pruritus gravidarum, pemphigoid gestationis, atopic dermatitis, and allergic reactions.

COMPLICATIONS

Cholestasis of pregnancy is dangerous because it increases the risk of spontaneous preterm birth, meconium stained amniotic fluid, fetal distress, and intrauterine fetal death (9,10). Those fetal complications correspond to the values of bile acids in the maternal serum and are not frequent when those values are under 40 $\mu\text{mol/L}$ (11). Therefore, the risk of intrauterine fetal death, which is the most severe complication, increases with the rise of bile acids, especially above 100 $\mu\text{mol/L}$, and with increasing gestational age. The cause of death remains unknown but is assumed to be connected to the sudden onset of fetal arrhythmia (12) or the vasospasm of blood vessels in the placenta caused by high levels of bile acids (13). In one large prospective cohort study of women suffering from cholestasis of pregnancy with levels of bile acids above 40 $\mu\text{mol/L}$, the incidence of intrauterine fetal death was 1.5%, more than in the control group, where it was 0.5%. The study showed that 10 out of 669 children were stillborn. Six of the ten deaths occurred before the 37th week of gestation, with the median age of 36+2 and the middle value of bile acids of 137 $\mu\text{mol/L}$ (14).

Unlike in cases of potentially severe fetal complications, a mother suffering from cholestasis of pregnancy has a very good prognosis. The itching usually disappears within a few days after birth, along with the normalization of laboratory results. It is recommended to carry out tests of blood acids and hepatograms 6-8 weeks after birth. In 60-70% of cases cholestasis reoccurs in subsequent pregnancies. Some studies suggest that women who suffered from cholestasis of pregnancy have a high risk of developing gallstones, hepatobiliary cancer, diabetes, and Crohn's disease later in life (15).

ANTENATAL FOLLOW-UP AND CARE

It is recommended that antenatal care include testing the level of bile acids, transaminases, and bilirubin in the maternal serum once a week, along with cardiotocographic monitoring of the fetal unit every day and ultrasonic monitoring once a week. It is important to emphasize that ultrasonic monitoring and cardiotocographic records are not reliable methods of preventing intrauterine fetal death because it occurs suddenly and is impossible to predict using those methods. A medicamentous therapy and a light diet are important components of the antenatal care for this type of high-risk pregnancy (16). The goal of the treatment is to reduce the symptoms, primarily the itching, and prevent maternal and fetal complications. Ursodeoxycholic

acid is very effective in the treatment of cholestasis of pregnancy because it reduces the level of bile acids by substituting toxic bile acids with a citoprotective, non-toxic ursodeoxycholic acid, thereby also reducing the itching as the most severe symptom in pregnant women suffering from cholestasis of pregnancy. It is applied in dosages of 300 mg three times per day until labor. Control studies have been carried out on other medicines (hydroxyzine, cholestyramine, dexamethasone), but have been shown to be less effective than the ursodeoxycholic acid, while also having some unwanted side-effects (17,18). A long-term corticosteroid therapy that was used earlier was shown to be unjustified. In cholestasis of pregnancy corticosteroids are only used to prevent respiratory distress in cases of premature birth. Sometimes, although rarely, supplements of vitamin K are necessary in cases of extended prothrombin time.

COMPLETION OF PREGNANCY

According to contemporary obstetric guidelines, due to increased perinatal and maternal morbidity in early induction, there are no clear guidelines for the completion of such pregnancies. Every pregnant woman and her pregnancy should receive an individualized approach. It is very important to inform every pregnant woman about the increased risk of perinatal morbidity in early induction, but also about the impossibility of predicting potential fetal complications, primarily intrauterine fetal death with increasing gestational age. According to the current recommendations in „UpToDate“ from 2017, a pregnancy should be completed from 36+0 to 36+6 weeks of gestation. According to the recommendations of the Royal College of Obstetricians and Gynaecologists (RCOG) from 2011, a pregnancy should be completed after the 37th week of gestation.

CONCLUSION

Pregnancies with cholestasis of pregnancy are high-risk and as such present a serious challenge to contemporary obstetrics. Since there are no protocols for guiding and completing such pregnancies, antenatal supervision and an individualized approach are of great importance. It is very important to inform the mother about the illness itself and its complications, and the impossibility of predicting those complications using available obstetric methods.

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