OPTIMIZATION OF EARLY DIAGNOSIS AND PREVENTION OF INTRAHEPATIC CHOLESTASIS IN PREGNANT WOMEN

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Abstract: Intrahepatic cholestasis of pregnancy is a rare group of severe inflammatory skin diseases with itching, specifically associated with pregnancy and/or the immediate postpartum period. Clinical diagnosis based on morphological criteria is still very important for specific dermatoses of pregnancy, since only some of them have definitive diagnostic tests available. The study of dermatoses in pregnant women is very important for the field of obstetrics, given environmental changes and the many carcinogens in the diet of pregnant women.

Background: Dermatoses of pregnancy are a rare group of severe inflammatory skin diseases with itching, specifically associated with pregnancy and/or the immediate postpartum period. Moreover, all these diseases are united by a common symptom - severe skin itching, which significantly worsens the quality of life of a pregnant woman. As in the general population, pregnant women experience a high prevalence and annual increase in the incidence of AD. According to the latest data, the frequency of dermatosis among pregnant women ranges from 5 to 20%, and in industrial cities and megalopolises this figure is even higher.

Purpose of the study: To identify prognostic predictors of the development of intrahepatic cholestasis in pregnant women and to develop early preventive.

During pregnancy, all organs and systems undergo some restructuring. From the first weeks of pregnancy, functional changes occur in the skin, manifested in changes in microcirculation with increased venous stagnation, decreased sweating, increased sebum secretion and pigmentation [3,4].

The problem of allergic dermatoses is closely related to the polyvalent sensitization of the population, the widespread use of polymer materials in production and at home, the unfavorable environmental situation on the planet, high solar activity that stimulates their growth, and is one of the most pressing in modern medicine [5,6].

The mechanisms of occurrence and characteristics of these diseases are different and not fully understood. The main thing, according to [1,2,] is the

change in hormonal ratios in the pregnant woman's body, which in turn affects the functionality of the immune and nervous systems, the state of the gastrointestinal tract, kidneys, cardiovascular activity, water-salt exchange, etc.

There are no sufficiently effective methods for treating these diseases, which makes it urgent to develop and use new methods for early diagnosis and prevention of intrahepatic cholestasis in pregnant women.

The incidence of allergic diseases has increased significantly over the past decade, especially in economically developed countries and in countries with unfavorable environmental conditions. According to the forecasts of a number of authors, the twenty-first century will become the century of allergic diseases. Currently, more than 20 thousand allergens are known, and their number continues to increase [8,9].

One of the first reasons for the increase in the frequency of allergic diseases in pregnant women is hereditary and exogenous factors. Genetic predisposition to allergies is polygenic in nature.

The increase in the incidence of allergic diseases is also caused by environmental factors. In recent years, it has been shown that exhaust gases and tobacco smoke, due to the content of pollutants such as NO2, S02, or NO, enhance the function of type 2 T-helpers and the production of immunoglobulin E. By affecting the epithelial cells of the airways, they contribute to their activation and the production of anti-inflammatory cytokines, which in turn have a toxic effect on cells that contribute to the development of allergic inflammation [9,11,14].

In recent years, individual effects on the mother's body during pregnancy and feeding of the newborn have been considered as factors contributing to the development of predisposition to allergies. The influence on the maternal body during pregnancy of smoking, alcohol, drugs, medications, infections, and certain foods creates conditions that contribute to the predisposition of the unborn child to allergies [10,12,13].

Currently, there has been an increase in allergic reactions in pregnant women of different gestational ages who have a family history of allergies. Therefore, there is an urgent need for early detection and prevention of allergies in pregnant women, which determined the purpose of this study.

Today, a generally accepted risk factor and predictor of allergies is a family history of allergies, and its marker is an increased level of IgE [14,15]. However, sensitization does not always have clinical manifestations of allergy. Moreover, a non-allergic history or low levels are not a contradiction in making a diagnosis of an allergic disease.

Cases have been described in which healthy children were born to parents with allergies, and at the same time, allergies were noted in children who did not have a burdened allergic history [3,5]. This phenomenon dictates the need to analyze the multiple effects of ante-, intra- and postnatal factors to determine the most significant of them in the development of not only clinical manifestations of allergy, but also corresponding changes in cellular-humoral immune reactions.

However, to date, the options for the immune response during the formation of an allergic/atopic status in the neonatal period, when potentially reversible changes become irreversible, remain poorly understood. The fragmentary coverage in publications of the problem of the early development of allergic/atopic status or its coverage from the perspective of a later age of the child leaves the onset and dynamics of atopy in the neonatal period poorly studied, and therefore modern recommendations for the primary prevention of allergies are not very specific.

The dynamics of allergic processes during the first year of a child's life have not been sufficiently studied, which is important for substantiating the strategy and tactics of secondary prevention of atopy, which prevents the clinical implementation of atopic processes when sensitization has occurred.

Diseases of the liver and biliary tract occupy a significant place among extragenital pathological conditions in pregnant women and can often contribute to the development of obstetric pathology. Pregnancy can lead to severe, irreversible liver damage, since this organ, which plays an exceptional role in the life of the body, experiences significant functional stress during pregnancy [10].

Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy-related liver disorder. Maternal effects of ICP are mild; however, there is a clear association between ICP and higher frequency of fetal distress, preterm delivery, and sudden intrauterine fetal death. The cause of ICP remains elusive, but there is evidence that mutations in genes encoding hepatobiliary transport proteins can predispose for the development of ICP. Recent data suggest that ursodeoxycholic acid is currently the most effective pharmacologic treatment, whereas obstetric management is still debated. Clinical trials are required to identify the most suitable monitoring modalities that can specifically predict poor perinatal outcome. This article aims to review current achievements and unsolved problems of ICP.[17,19]

The incidence of ICP varies throughout the world. The highest incidence is considered to be in Chile and Bolivia (5%-15%). In these countries, the incidence of ICP has decreased more recently, whereas it has increased in other parts of Europe, the USA, Asia, Australia and some Latin American countries. In

Scandinavian and Baltic countries ICP occurs in up to 2% of pregnancies, while in other countries of Europe and North America the incidence is less than 1%, and in South Asian populations the incidence is 0.8%-1.46%. In Lithuania, a retrospective analysis disclosed a rate of 0.4% of ICP in 16 252 pregnant women over a period of five years. The low incidence of ICP may reflect an underestimation of the problem, and growing awareness of the condition will probably increase the numbers[22,24]

ICP occurs mainly during the third trimester, when serum concentrations of estrogens and progesterone reach their peak. ICP is also more common in twin pregnancies, which are associated with higher levels of hormones than singleton pregnancies. All hormones are metabolized by the liver, and an excess of metabolites influences the activity of biliary canalicular transporters. The cholestatic potential of some D-ring estrogens, in particular glucuronides like estradiol-17β-*d*-glucuronide, and mono- or disulfated progesterone metabolites, mainly 3α, 5α-isomers, is supported by experimental and clinical data.

The formation of large amounts of sulfated progesterone metabolites, possibly related to greater 5-α and 3-α reduction, may result in saturation of the hepatic transport system (s) utilized for biliary excretion of these compounds in some genetically predisposed women[19,20,21]e function of hepatocellular transporters such as ABCB11 and ABSB4 has been shown to be impaired at the posttranscriptional level *in vitro* by high loads of estrogen glucuronides and progesteron. In addition, estrogens impair basolateral as well as canalicular bile acid transporter expression of liver cells *in vitro* by transcriptional mechanisms [19]. ICP is characterized by pruritus starting in the second or third trimester of pregnancy, and disappearing after delivery. It is often generalized but predominates on the palms and the soles of the feet, and is worse at night. Skin lesions are characteristically absent except for excoriations due to scratching. In approximately 80% of patients pruritus starts in late pregnancy, but there can be unusual forms of ICP: (1) early onset, even in the first weeks; (2) typical pruritus without the usual serum abnormalities; (3) pruritus may fade spontaneously before delivery with or without an improvement in serum liver tests; (4) the disorder exacerbates postpartum with no signs of liver failure, and may last 1-2 mo after delivery, subsiding spontaneously without sequelae.

Mild jaundice occurs in 10% to 15% of cases, typically within 4 wk of the onset of itching. Subclinical steatorrhea may be seen along with fat malabsorption, which may lead to vitamin K deficiency. Abdominal pain is uncommon. Encephalopathy or other features of liver failure are unusual and their presence should initiate a search for other causes of liver disease.

The most sensitive laboratory abnormality in ICP is an increase in serum TBA concentrations, which may be the first or only laboratory abnormality. Serum cholic acid increases more than chenodeoxycholic acid, resulting in a marked elevation of the cholic/chenodeoxycholic acid ratio compared to pregnant women without ICP. Whereas, a study from Argentina has shown that asymptomatic hypercholanemia of pregnancy, defined as TBA > 11 μmol/L in healthy pregnant women, does not necessarily lead to ICP. Serum aminotransferases are elevated, and may reach values greater than 1000 U/L, making distinction from viral hepatitis important. Hyperbilirubinemia, up to 100 μmol/L is observed in 10% to 20% of the cases. During a 3-year period in a prospective study of 84 women with ICP, elevation of aminotransferase activities from 2-fold to 15-fold were noticed in 85% of patients, bilirubin concentration from 2-fold to 4-fold in 14%, fasting serum bile acids from 1.5-fold to 20-fold in 78%, γ-GT was elevated up to 3-fold in 11% and alkaline phosphatase up to 2-3-fold in 60% of patients.

Although a sensitive marker of other types of cholestasis, serum γ-GT is usually normal or modestly elevated. Alkaline phosphatase is of poor diagnostic value due to placental and bone production. The prothrombin time is usually normal. When present, prolonged prothrombin times reflect vitamin K deficiency due to cholestasis or to the use of anion exchange resins (such as cholestyramine) rather than liver dysfunction. Dann et al reported significantly increased levels of low-density lipoprotein cholesterol in ICP, and proposed that this test might be useful to distinguish between ICP and pruritus gravidarum. An upper abdominal ultrasound is considered in patients with biliary colic or other manifestation of gallstone disease. Liver biopsy is rarely necessary for diagnosis. Histology is characterized by cholestasis without inflammation, and bile plugs in hepatocytes and canaliculi predominate in zone 3[23,24].

Thus: Studying the early diagnosis and prevention of intrahepatic cholestasis in pregnant women will reduce the incidence and prevent complications in pregnant women.

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