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Intrahepatic cholestasis of pregnancy: A past and present riddle

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Abstract

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific disorders that occurs mainly in the third trimester of pregnancy and is characterized by pruritus and elevated bile acid levels. ICP is regarded as a benign disease with no meaningful consequences to the mother but associated to an increased perinatal risk with increased rates of fetal morbidity and mortality. The pathogenesis of disease is unknown but likely involves a genetic hypersensitivity to estrogen or estrogen metabolites. Mutations or polymorphisms of some hepatobiliary transport proteins may contribute to disease pathogenesis or severity. Treatment is focused on a) reducing symptoms in the mother and b) to provide an adequate obstetric management in order to prevent fetal distress. Currently, only Ursodeoxycholic acid treatment has been proven to be useful and should be considered mainly in patients with severe pruritus or complications in previous pregnancies.

Key words: Bile acids and bile salts, cholestasis, intrahepatic, estrogens, pregnancy complications, hepatic progesterone, ursodeoxycholic acid, high-risk pregnancy.

Intrahepatic cholestasis of pregnancy (ICP) is a unique disorder of pregnancy characterized by skin pruritus and mild to moderate biochemical cholestasis appearing during pregnancy (mainly in the third trimester) and rapidly resolving after delivery.[1-3] Although its clinical course is usually benign with regard to the mother, it is associated to unexplained fetal death and premature delivery and therefore patients with this diagnosis are considered to have a high-risk pregnancy.[4,5] The present article summarizes current concepts of the disease.

Epidemiology

ICP has been diagnosed in almost all ethnic groups.[1,6] The prevalence of this disease ranges from 1 case out of 1,000 to 1 case out of 10,000 deliveries in North America, Asia, and Australia.[2,7] An intriguing higher prevalence (10 to 100-fold) has been reported between 1950 and 1980 in Chile (particularly in the native southern [Mapuche] population) and in Sweden and other Scandinavian countries.[3,8] Reported figures reached up to 14% of pregnant women in Chile.[2] Interestingly, in the following years the prevalence of the disease has markedly decreased in both regions.[6,9] The estimated current prevalence in Chile ranges from 1.5 to 4% of all pregnancies.[6] The reason for this variation remains unclear and unidentified environmental factors may be responsible. This is also suggested by the seasonal variation observed in Chile, in Finland and in Sweden.[2,9]

Advanced maternal age and multiple gestations are associated to an increased incidence of ICP. The disease may also cluster in families with around 16% of cases being familial. The reported recurrence rate of ICP varies between 40 and 60% of pregnancies with a great variations in the intensity of the disease in subsequent pregnancies and in a random fashion.[1,10]

Etiology and pathogenesis

Despite intense research in the field the cause of ICP remains unknown although its pathogenesis appears to be related to the effects of sex hormones in the liver of genetically predisposed women.[7] As mentioned above, the expression of the diseases may be modulated by non-genetic/environmental factors.

Role of sex hormones: Several lines of evidence suggest that estrogens are involved in the pathogenesis of ICP.[11,12] First, the disease appears in the third trimester when the estrogen production reaches its maximum. Moreover, the prevalence of ICP is five times greater in

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twin pregnancies which are characterized by higher levels of estrogens than single pregnancies.[13] Second, ICP closely resembles the cholestatic picture developed in some women using oral contraceptives with a high estrogen content.[12] And third, administration of an estrogen derivative to experimental animals is able to induce cholestasis which appears related to impaired expression and/or function of specific transporter proteins such as the Na+/taurocholate cotransporting polypeptide [Ntcp, Slc10a1], the bile salt export pump (Bsep, Abcb11) and the multidrug resistance associated protein-2 (Mrp2, Abcc2).[14] These transporters, among others, are critical for the generation of bile flow as well as for the excretory function of the liver.[15] Interestingly, the changes observed in transporter expression in estrogen-induced cholestasis are very similar to those observed during normal pregnancy in the rat.[14] Therefore, it can be speculated that if similar changes in hepatic transporter expression occur in humans they might explain the functional alterations described in pregnant women and would support an old postulate that pregnancy is a physiological cholestatic-prone condition.

Progesterone metabolites may also play a role in the pathogenesis of ICP. Bacq et al. observed that administration of progesterone in early pregnancy may be a risk factor for ICP.[16] In addition, alterations of progesterone metabolism have been shown to occur in ICP patients (see ref. (17) and references herein). However, it is not clear if those changes are of pathogenic relevance or merely represent. In the experimental setting, administration of progesterone to rodents has little effect on bile secretion but in vitro data suggests that several progesterone metabolites are able to induce trans-inhibition of the canalicular bile salt transporter Bsep[18] thus playing a role in the pathogenesis of ICP.

Role of genetics: The importance of a genetic predisposition in the occurrence of ICP is enforced by both familial clustering of the disease, the higher prevalence of ICP in Mapuche Indians, and the exaggerated response to an estrogen challenge that was observed in both nulliparous sisters and brothers of ICP patients.[19] However, the search for a specific genetic defect has not been successful. In recent years, different research groups have sought mutations in genes encoding biliary transport proteins.[20] Thus, mutations in the hepatic phospholipid transporter (MDR3, ABCB4), in the aminophospholipid transporter ATP8B1 and in the bile salt export pump (BSEP, ABCB11) have been found in patients diagnosed as ICP.[21-23] However, the precise role of these mutations remains unclear since they have been identified in only a small proportion of patients. Moreover, the available information comes from a rather heterogeneous population of patients, which may not all of them represent true cases of ICP. Of note, some reports include patients diagnosed in the first trimester of pregnancy,[24] patients with markedly elevated serum levels of gamma-glutamyl transpeptidase (GGT)[25] and some patients later diagnosed as having biliary cirrhosis.[26] Clinical features of ICP are well characterized and indicate that the disease generally starts during the third trimester, most patients have normal GGT levels and the disease implies a benign long term prognosis of the mother.[2] Therefore, the occurrence of cholestasis during pregnancy does not always imply the clinical diagnosis of ICP.[27] Rather, consideration must be given to the possibility that other underlying hepatic disorders may be unmasked during pregnancy appearing with cholestasis as its first manifestation (see article by Arrese M. in this issue).

Role of environmental factors: The observed geographical and seasonal variations of the disease suggests the involvement of environmental factors in modulation the expression of ICP in genetically susceptible individuals. Although several factors have been investigated including the long-chain monounsaturated fatty acid erucic acid and selenium, there is no definitive evidence that they play a pathogenetic role in ICP.[9,28] Further research is needed to elucidate environmental factors involved in the pathogenesis of ICP.

Pathogenesis of perinatal consequences of ICP: ICP is associated to preterm deliveries and poor perinatal outcome including intrauterine fetal death.[1,10] The mechanisms involved in the pathogenesis of premature labor as well as fetal distress and stillbirths in ICP are unclear.[6] Elevated levels of bile acids can contribute to preterm delivery by way of increased oxytocin bioaction[29] although direct proof of this hypothesis is still lacking. Bile acids may also have a role in unexplained, intra-uterine fetal death by inducing oxidative stress in the placenta[30] or impairing fetal cardiomyocyte function.[31] Elevated levels of bile acids in the fetus may result from both increased bile acid levels in mother's serum and impaired ability of the placenta to carry out vectorial bile acid transfer from the fetus to the mother.[32] In addition, immature hepatic transport systems can contribute to impaired handling of both bile acids and other organic anions in a cholestatic setting. This is based in experiments carried out in a model of experimental cholestasis in pregnant rats showing that a reversible impairment of neonatal hepatobiliary function occurs in the offspring of cholestatic mothers.[33,34]

Clinical features

ICP is characterized by pruritus and mild to moderate biochemical cholestasis appearing mainly during the third trimester of pregnancy. A hallmark of the disease is that hepatic alterations as well as pruritus rapidly resolve after delivery. Laboratory alterations usually seen in these patients include increased serum levels of aminotransferases (ranging from two to ten times over the upper normal value) and raised fasting serum total bile acids which seem to be the most sensitive serum marker of the disease. A minority of patients (about 20%) exhibits conjugated hyperbilirubinemia seldom revealing a mild jaundice. Mildly

elevated levels of gamma-glutamyl transpeptidase are observed in less than 30% of cases. Some patients may have sub-clinical steatorrhea, which seems to correlate with disease severity. Histological changes are minimal and unspecific, reported as «pure» cholestasis. Although ICP may recur in subsequent pregnancies it is regarded as a benign disorder with no meaningful consequences to the mother. When examined outside of pregnancy, patients with ICP do not have signs of chronic liver disease and display normal standard liver function tests. This description is supported in large series of patients from Scandinavia, France and Chile. Differential diagnosis of ICP includes other causes of cholestasis occurring in young women. Because of space restraints this topic will not be discussed here and the interested reader is referred to previous reviews on the topic.[1,35]

As mentioned earlier, ICP implies an increased risk of both preterm delivery and perinatal mortality. In some series, the risk of spontaneous preterm delivery is as high as 44%.[6] An early onset (e.g. second trimester) and greater biochemical severity seem to be risk factors for these events. According to published data, fetal mortality can range from 11% to 20%. Unfortunately, this event is unpredictable.[6]

Management

Treatment of ICP focuses on a) reducing symptoms in the mother and b) to provide an adequate obstetric management in order to prevent fetal distress or sudden fetal death. The main maternal symptom to be treated is pruritus although proper attention must also be given to fatigue and anxiety, and malabsorption of fat and fat-soluble vitamins.[1,35] Thus, rest, mild sedation and a low fat diet can be considered, with parenteral supplementation of vitamin K in cases with ICP of early onset. Management of pruritus may include cholestyramine and antihistamines, however their efficacy is debated and some adverse effects may occur.[36] Current pharmacological therapy consist mainly in the administration of the hydrophilic bile acid ursodeoxycholic acid (UDCA) which has proven efficacy documented in randomized controlled trials and in several open uncontrolled clinical trials [see ref. (37) and references herein]. UDCA exercises its effect thanks to a number of mechanisms including stimulation of impaired biliary secretion, protection of hepatocytes and cholangiocytes against toxic effects of bile acids, stimulation of detoxification of hydrophobic bile acids.[38] Clinically, UDCA alleviates pruritus and reduces serum levels of aminotransferases and bile acids toward normal values with no adverse effects in the mother or in the fetus. A reduction in intrauterine fetal death after UDCA treatment has been suggested but not demonstrated due to a lack of statistical power of published studies. Other drugs have been postulated to be useful in ICP management including dexamethasone,[39] phenobarbital[40] and S-Adenosylmethionine.[41] However, larger studies are required before these agents can be recommended as a universally safe and effective treatment of ICP.

Although there is no consensus regarding prenatal surveillance of ICP patients, active management is preferred by most obstetricians.[6,10] This includes close fetal monitoring using nonstress testing and search for meconium and elective delivery at 37 weeks. This seems to reduce the stillbirth rate. Recently, a study by Glantz et al prospectively identified a serum bile acid level higher than 40 μM as predictive of fetal risk.[42] They therefore proposed that women that do not meet this criterion be managed expectantly to reduce medical care costs. This proposal has been debated and further studies are needed before making recommendations.[5,43]

Conclusion

ICP continues to be a puzzling pregnancy-associated disorder of obscure etiology. Functional and molecular data gathered from rodents and humans suggest that pregnancy itself is a cholestatic-prone condition and that ICP results from an exaggerated response to high levels of estrogen and progesterone metabolites present in the last third of pregnancy, likely associated to a genetic predisposition modulated by some environmental factor(s). Further research on the regulation and genetics of hepatic transport systems and detoxifying pathways of the hepatocyte may help to delineate the events involved in the pathogenesis of ICP. In addition, a detailed study of the consequences of maternal cholestasis on both placental transport function and fetal hepatic transport capacity may help to prevent fetal distress and intrauterine death in the clinical setting of ICP. The changing epidemiology of ICP is one of the most intriguing aspects of the disease. This past and present riddle[44] deserves an answer because of its scientific and clinical relevance and to avoid an eventual increase in the prevalence of the disease in high-risk populations.

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