Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific disorder 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 the disease is unknown but likely involves a genetic hypersensitivity to estrogens 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. Though 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. The present article summarizes current concepts of the disease.

Epidemiology

ICP has been diagnosed in almost all ethnic groups. 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. 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. Reported figures reached up to 14% of pregnant women in Chile. Interestingly, in the following years the prevalence of the disease has markedly decreased in both regions. The estimated current prevalence in Chile ranges from 1.5 to 4% of all pregnancies. 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.

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 variation in the intensity of the disease in subsequent pregnancies and in a random fashion.

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. 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. 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...
twin pregnancies which are characterized by higher levels of estrogens than single pregnancies. Second, ICP closely resembles the cholestatic picture developed in some women using oral contraceptives with a high estrogen content. 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). These transporters, among others, are critical for the generation of bile flow as well as for the excreto...
Management

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%. 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

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 intrapartum 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 riddle44 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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References


