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Intrahepatic cholestasis of pregnancy: Recent advances☆

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Abstract Intrahepatic cholestasis of pregnancy, also known as obstetric cholestasis, is a pruritic condition of pregnancy characterized by an underlying elevation in circulating bile acids and liver derangement, and associated with adverse fetal outcomes, such as preterm labor and stillbirth. Limited understanding of the underlying pathophysiology and mechanisms involved in adverse outcomes has previously restricted treatment options and pregnancy management. Recent advances in these research fields provide tantalizing targets to improve the care of pregnant women affected by this condition.

Introduction

Intrahepatic cholestasis of pregnancy (ICP), also called obstetric cholestasis, is a liver condition of pregnancy characterized by pruritus and the biochemical finding of elevated serum bile acids, often in the presence of other signs of liver dysfunction. By definition, ICP is confined to pregnancy and the peripartum period and is diagnosed after exclusion of other causes of cholestasis. In addition to the maternal symptomatology, ICP can be associated with adverse fetal outcomes, such as spontaneous preterm birth, meconium staining of the amniotic fluid, and stillbirth[1]; hence, appropriate recognition and management are significant.

The incidence of ICP varies and is dependent on geographic location and ethnicity. For example, the incidence is 4% in Chile[2]; in the United Kingdom it is 0.7%, but is higher in women of Indian or Pakistani origin,[3] whereas the incidence in China has recently been estimated at 1.2%, based on more than 100,000 hospital births.[4] Within the Californian population, genetic ancestry mapping has indicated higher levels of ICP in women of Native American ethnicity.[5]

ICP is more common in women with preexisting hepatitis C and gallstone disease; hence, the benefit of serum screening and liver ultrasound in all women diagnosed with the condition.[6] Its incidence is also higher in women with multiple gestation pregnancies[7] and in those who conceived using assisted reproduction.[8]

Symptoms

The hallmark symptom of ICP is pruritus—that is, "itching in the absence of an eruption;" yet, scratching can often lead to secondary skin changes. Traditionally, pruritus is described on the palms and soles, but ICP-associated pruritus can be generalized.[9] Itching ranges from mild to debilitating and intense, and it is typically worse at night. Excoriated lesions

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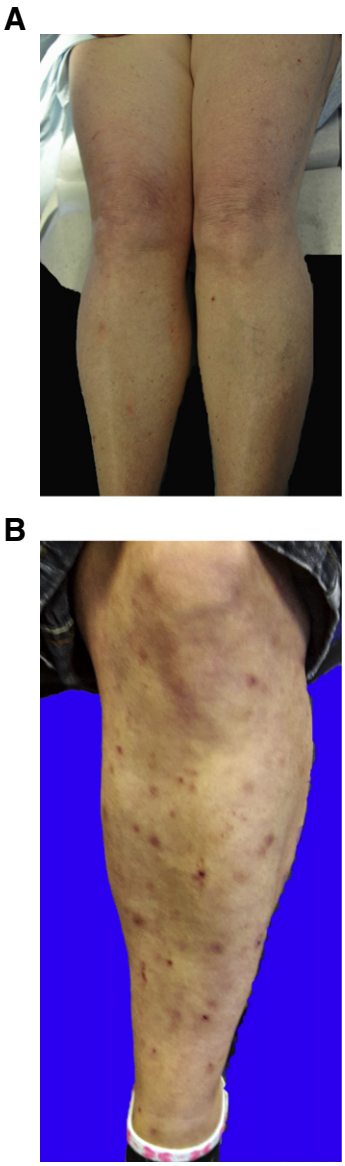

Fig. 1 Excoriated skin lesions in patients with intrahepatic cholestasis of pregnancy. A, Mild, early skin changes (Courtesy Dr. George Kroumpouzos). B, Appearance of skin lesions after prolonged scratching. (Used with permission of Jenny Chambers, ICP Support, Sutton Coldfield, England.)

(Figure 1) can become complicated by secondary infection. The onset of pruritus often precedes biochemical derangement,[10] making the diagnosis one to be considered in any woman with the characteristic itch in pregnancy.

Further symptoms relate to the effects of liver impairment. Bilirubin is elevated in approximately 10% of cases, and in this group jaundice can be detected (the condition was initially recognized as recurrent jaundice in pregnancy), and symptoms suggestive of malabsorption of fats (eg, steatorrhea) can occur.[11] If there is evidence of malabsorption, impaired coagulation can occur secondary to reduced vitamin K absorption, although this is not common, and a recent study into the coagulation parameters of 319 women with ICP did not find any women with abnormal coagulation.[12]

Pruritus in pregnancy and ICP

The cause of pruritus in ICP is not fully understood, although a number of possible pruritogens have been identified. It has long been established that bile acids can elicit itch when applied to the skin,[13] and the lowering of serum bile acids with the use of ursodeoxycholic acid (UDCA) treatment for ICP is mirrored by a reduction in itch intensity.[14] There is some experimental evidence for a role of bile acids in pruritus because the secondary bile acid deoxycholic acid has been found to activate the G-protein coupled receptor, TGR5, on cutaneous afferent neurons, thereby eliciting a scratch response. However, the concentrations of deoxycholic acid used for these experiments were much higher than are observed in women with ICP.[15] Also, the clinical relevance of this observation is not clear because the pattern of bile acid levels and subjective itch intensity do not correlate well in ICP,[10] so bile acids alone are unlikely to explain pruritus in the disorder.

Lysophosphatidic acid (LPA) is a potent pruritogen[16] that is produced from lysophosphatidyl choline by the action of the enzyme autotaxin. Autotaxin activity is elevated in the serum of patients with pruritic cholestatic conditions,[17] and it is higher in women with ICP than with other liver-associated disorders of pregnancy.[18] Genetic variants of the enzyme adiponutrin (PNPLA3) have been found in women with ICP; this enzyme is expressed in the liver and skin and catalyzes the breakdown of LPA.[19]

Progesterone, which rises during pregnancy, is destined for excretion in part by conjugation with a sulfate group, which renders the hormone more soluble. Sulfated metabolites of progesterone are elevated in ICP compared with normal pregnancy,[20] and of these, 5β-pregnan-3α-20α-diol-sulfate (PM3S) is directly associated with the level of pruritus experienced by the patient.[21] PM3S has been found to signal via TGR5 in a cell line when exposed to PM3S at the physiologic concentrations found in the serum of women with ICP, and it triggered a scratch response when administered to mice intradermally.[21] LPA and PM3S are thus likely candidates to be the pruritogens in ICP.

Etiology

Maternal disease

The etiology of ICP is influenced by a combination of genetic, endocrine, and environmental factors. Evidence for a genetic etiology includes an increased risk in first-degree relatives,[22] the presence of mutations in biliary transporters, such as the bile salt export pump (BSEP/ABCB11) and multi-drug resistance protein 3 (MDR3/ABCB4),[23,24] and polymorphisms that confer susceptibility in these genes and the principal nuclear receptor influencing bile acid homeostasis, farnesoid X receptor (FXR).[25] By definition, women with ICP are not typically cholestatic outside of pregnancy. As