Editorial

Don't Hold the Salt When Working Up Dermatoses of Pregnancy

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What is the role of the dermatologist in the diagnosis and treatment of intrahepatic cholestasis of pregnancy (ICP)? Intrahepatic cholestasis of pregnancy is a known pregnancy-related disorder impacting the liver, which results from an interaction of genetic, hormonal, and immunologic factors during pregnancy.[1] Being a medical condition without primary skin lesions, it was not originally considered a skin condition in the domain of the dermatologist. However, Shornick[2] clearly reconfirmed that ICP belongs as a distinctive dermatosis of pregnancy when he restructured the classification scheme in 1998 to include only 4 conditions, with ICP being one of them. Its proper inclusion as a dermatosis of pregnancy is important for 2 reasons: the presenting symptom is pruritus, and cutaneous manifestations, albeit secondary in nature, are best interpreted by a skin specialist. Prior to the Shornick[2] study, in 1994 Roger et al[3] highlighted the importance of ICP in the old classification when his study provided strong evidence for a high correlation of ICP with fetal risk.

The skin changes of ICP are due to excoriations from intense pruritus, which is brought on by the accumulation of excess bile acids in the skin.[4] Pruritus is an important sign of disease and it is in the dermatologist's domain and expertise to assess the cause. Is the pruritus due to skin inflammation directly from a primary skin disorder or is it due to an underlying systemic disease state as in ICP? For this condition of severe pruritus in pregnancy, the dermatologist and the obstetrician must work closely because of the potential severe health implications for the mother and fetus. Adverse fetal effects can include premature labor, fetal distress, and fetal death.[2] The symptoms of ICP typically begin with nocturnal pruritus at 25 to 32 weeks of gestation, or late in the second trimester to early third trimester.[3] As the pruritus and scratching intensify, resultant cutaneous manifestations include linear excoriations, or in longer-standing disease, prurigo nodules. The dermatologist is at an ideal vantage point to assess the cutaneous manifestations, determine if they are arising from a primary cutaneous process, and initiate workup to elucidate the etiology of the pruritus. Due to the increased physiologic and metabolic stress of pregnancy, subclinical liver disorders may present during pregnancy, and this situation must be distinguished from pregnancy-specific ICP, which resolves after delivery.

Liver function tests should be performed in every pregnant woman with pruritus, but mild elevations or even normal results may be found in ICP. The most specific and earliest laboratory abnormality in ICP is the elevation of serum bile acids, which is considered a hallmark for the diagnosis.[5] There is value in knowing the exact level of the serum bile acids because early delivery has been shown to be warranted at a threshold of 40 μmol/L (reference range, 0.73–5.63 μmol/L) to prevent fetal complications, as increased exposure time for the fetus to the increased maternal bile acid levels predicts fetal complication rates.[6]

What is the status of the bile acid laboratory testing? There are improved methods for the testing of serum bile acids using high-performance liquid chromatography mass spectrometry with an electrospray interface. New, more accessible, and accurate testing for serum bile acids will make it an important tool in the diagnosis and management of ICP. Detecting elevations of bile acids early on in the disorder and understanding how these levels correlate with the disease process is important. In a 2010 study, Sinakos and Lindor[5] detected an elevation of bile levels approximately 4 weeks after the onset of pruritus. In light of this lag time between symptom onset and laboratory evidence of ICP, serial evaluation of the patient and repeat laboratory testing is indicated so as not to discount the diagnosis after a single normal bile acid level. After confirmation

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of the diagnosis of ICP, the dermatologist can work with the obstetrician to initiate treatment. The goal of treatment is to provide symptomatic relief to the mother and to decrease the level of maternal serum bile acids to diminish fetal risk.

Ursodeoxycholic acid, a tertiary bile acid, is first-line treatment. It currently is the only treatment that has been proven to achieve both reduction in the level of maternal serum bile acids and relief of pruritus.[7] An early study proved the efficacy of ursodeoxycholic acid at a dosage of 1 g daily[8] with no adverse effects to the mother or fetus. It should be clarified that it is used off label, as it is not approved for use in pregnancy.[9] Close obstetric follow-up is important because it is recommended that labor be induced at 36 weeks in severe cases of ICP and 38 weeks in mild cases of ICP to reduce the risks to the fetus.[10] The dermatologist also may recommend antihistamines, UV phototherapy, or topical corticosteroids to provide relief of symptoms. With the improvement and simplification of bile acid testing, it represents a critical component in the evaluation of ICP and for other cholestatic disorders.[11]

The strides that are being made in relation to the genetics of ICP are exciting because there is potential for new targeted therapy. In a study of 50 genetically unrelated women with ICP, 16% (8/50) were shown to demonstrate ATP-binding cassette, sub-family B (MDR/TAP), member 4, *ABCB4*, mutations in this disorder.[12] The *ABCB4* gene encodes the multidrug-resistant protein 3 (*MDR3*) P-glycoprotein, which is located on chromosome arm 17q21.1. At least 10 different *MDR3* mutations have been found under the umbrella of progressive familial intrahepatic cholestasis for which ICP is classified.[13] An understanding of genetic commonalities between ICP and other cholestatic disorders will help define the pathogenesis and future treatments. In addition, the strong genetic predisposition (20-fold increased risk in first-degree relatives of an affected woman) and high likelihood of recurrence with subsequent pregnancy further emphasize the importance of accurate diagnosis for counseling purposes.[14]

Medical dermatology is a critical realm in the domain of the clinical dermatologist, particularly in this era of shift toward cosmetic and procedural dermatology.[15] Understanding medical disorders as they relate to skin disease such as ICP and having an expertise in treating them is essential for optimal patient care. The expertise of the clinical dermatologist in evaluating pruritus in a pregnant woman should not be minimized. Few other providers will have the training and experience to order the appropriate studies and initiate the appropriate therapy. Moreover, by working closely with the obstetrician, the dermatologist can not only provide the patient symptomatic relief but also ensure the treatment is safe for the mother and her unborn child. The process of diagnosing and treating ICP requires multiple specialists and speaks to the importance of collaboration between specialists to optimize patient care.

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