Cholestasis during pregnancy: Rare hepatic diseases unmasked by pregnancy

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Abstract

The occurrence of cholestasis during pregnancy may be due to several disorders. These include pregnancy-specific diseases, like intrahepatic cholestasis of pregnancy (ICP), as well as to other causes such as oligosymptomatic choleodolithiasis, viral hepatitis and other underlying liver disorders like primary biliary cirrhosis. In recent years, the discovery of mutations in hepatobiliary transporters genes responsible of some rare forms of genetic cholestasis have led to the study of this mutations in pregnant women with cholestasis. 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. However, patients included in these studies belong to a heterogeneous population, which may not represent true cases of ICP since some reports include patients diagnosed in the first trimester of pregnancy, with elevated serum levels of gamma-glutamyl transpeptidase and clear evidence of chronic liver disease. Thus, consideration must be given to the possibility of other rare underlying hepatic disorders may be unmasked during pregnancy with cholestasis as its first manifestation.

Differential diagnosis of cholestasis during pregnancy

The occurrence of cholestasis during pregnancy may be due to several disorders. These include pregnancy-specific diseases, like intrahepatic cholestasis of pregnancy (ICP), as well as to other causes coincidental with pregnancy such as oligosymptomatic choleodolithiasis, viral hepatitis and other underlying liver disorders like primary biliary cirrhosis. Drug-induced cholestasis is also a diagnosis to keep in mind when facing these patients. A careful interpretation of liver functions test, performance of abdominal ultrasound and, when indicated, serum markers of viral infection or autoimmune diseases are helpful in identifying the precise diagnosis.

ICP is regarded as the most frequent cause of cholestasis during pregnancy. Diagnosis of ICP is made on the following grounds:

a) cholestasis appears during the third trimester of pregnancy (80% after week 30). A careful history may reveal itching during a previous pregnancy or itching whilst on the oral contraceptive pill. Familial cases of cholestasis during pregnancy are frequently reported.
b) Serum levels of aminotransferases are frequently from 2 to 10 times the upper normal value rarely exceeding this threshold. A minority of patients (about 20%) presents with conjugated hyperbilirubinemia seldom revealing a mild jaundice. Serum levels of alkaline phosphatase are not contributory since they are raised in normal pregnancy as the placenta produces this enzyme. Lastly, elevated levels of gamma-glutamyl transpeptidase (GGT) are infrequent. Owing to unknown reasons GGT remain unchanged in several hepatobiliary disorders during pregnancy.7

c) Other causes of liver diseases are excluded.

d) A complete recovery is seen after delivery. Patients with ICP do not have signs of liver disease and display normal standard liver function test when examined outside of pregnancy. Persistence of pruritus or laboratory alterations for more than a week after delivery raises doubt about the diagnosis of ICP.

As mentioned, making the correct diagnosis is important since implies a benign prognosis for the mother. Care must be taken to exclude other underlying liver disorders especially in the presence of markedly raised liver function tests or jaundice.8 Since pregnant women are more prone to cholestasis other disorders may be disclosed by pregnancy. Among them chronic cholestatic diseases like primary biliary cirrhosis or fibrotic autoimmune liver diseases may be seen. In addition, some forms of genetic cholestasis related to mutations in hepatic transporters have been reported as first diagnosed during pregnancy.

Mutations of transporter genes and cholestasis during pregnancy

In recent years, the identification of several genes, the disruption of which results in cholestasis have shed light on the molecular basis of progressive familial intrahepatic cholestasis (PFIC). Thus, ATP8B1 (FIC1) a protein thought to act as an aminophospholipid transporter in hepatocytes and cholangiocytes plasma membrane, ABCB11 (BSEP) the canalicular bile salt export pump, and ABCB4 (MDR3) the canalicular phospholipid transporter are considered responsible for distinct PFIC phenotypes [for review see refs. 9 and 10] and references herein]. The observation by Jacquemin et al in 199911 that an heterozygous non-sense mutation of the ABCB4/MDR3 gene was present in some patients that suffered from cholestasis during pregnancy prompted to investigators to search for mutations of this transporters in pregnant women diagnosed in the first trimester of pregnancy, with elevated serum levels of gamma-glutamyl transpeptidase and clear evidence of chronic liver disease. Larger studies have failed to find a strong association between mutations in the ABCB4/MDR3 gene and ICP.14,15 Rather, variants of ABCB4/MDR3 may represent genetic risk factors for the severe form of intrahepatic cholestasis of pregnancy as shown recently in a study from Sweden.16 The same may be valid for ATP8B1 (FIC1)17 and ABCB11/BSEP genes.13 Although the later gene has been regarded as less important for the development of pregnancy-associated cholestasis, a recent report suggest that a combinations of mutations may determine severe cholestasis during pregnancy.18

Thus, in our view, cholestasis seen during pregnancy in patients harboring mutations that determine severe dysfunction of critical hepatobiliary transporters must be interpreted with caution. They may represent a hitherto underlying genetic defect that is unmasked by pregnancy rather than true ICP, which is a well-defined benign clinical entity. Women with suspected ICP and elevated gamma-glutamyl transpeptidase might represent a subgroup of patients that may indeed have a disorder related to ABCB4/MDR3 deficiency and should be offered genetic testing for ABCB4/MDR3 mutations and eventually tested for mutations in other transporters. This is also valid for patients that do not resolve their symptoms or laboratory alterations after delivery. Finally, it seems clear that the nomenclature of pregnancy-related cholestasis should be clarified. Distinction should be made between classic ICP with low GGT and benign course and high GGT ICP, which may includes a variety of conditions, including those associated to ABCB4/MDR3 dysfunction. This condition deserves careful follow-up because these patients may develop biliary cirrhosis later in life. They are also prone to intrahepatic and gallbladder cholesterol stones19 and they would eventually benefit from long-term bile acid therapy including ursodeoxycholic acid.

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References


