

Role of plasmapheresis in the treatment of severe pruritus in pregnant patients with primary biliary cirrhosis: Case reports

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BACKGROUND: Primary biliary cirrhosis (PBC) may be associated with pruritus and, when present, may be accentuated during pregnancy. Several therapeutic modalities have been used to control itching caused by cholestasis, with variable responses. Drug therapies are ill-advised, particularly in early pregnancy. Plasmapheresis has been successful in controlling pruritus in patients with cholestasis. The use of plasmapheresis to alleviate severe life-threatening pruritus during pregnancy is reported in two patients with PBC.

CASE PRESENTATIONS: Two patients with PBC presented during their second trimester of pregnancy with severe pruritus that did not respond to the anion exchange resin cholestyramine. Their symptoms were disabling to the point that one patient had suicidal ideation. Given the severity of their symptoms, multiple sessions of plasmapheresis were instituted with good control of pruritus. Both patients tolerated the procedure well and delivered healthy babies.

CONCLUSION: Plasmapheresis is a relatively safe and rapidly effective treatment for severe pruritus during pregnancy in patients with PBC.

Key Words: PBC; Plasmapheresis; Pregnancy; Primary biliary cirrhosis; Pruritus

Primary biliary cirrhosis (PBC) is a variably progressive autoimmune disease of the liver that primarily affects women (1). Pruritus is the second most common symptom (after fatigue) of PBC, occurring in 19% of patients (2). It may be quite severe and occasionally is refractory to medical treatment. Pruritus occurring de novo during pregnancy may be the first presenting symptom of PBC, brought to the fore by the cholestatic effect of estrogen. But unless a diagnosis of PBC is made before the patient becomes pregnant, it may be mistaken for pruritus related to idiopathic cholestasis of pregnancy (3). However, the pattern of liver enzymes in the latter is typically hepatic (ie, aspartate aminotransferase [AST], alanine aminotransferase [ALT]) and gamma-glutamyl transferase [GGT] levels are often normal, with minimal elevation in alkaline phosphatase [ALP] levels). The pathogenesis of pruritus secondary to cholestasis remains uncertain, but the role of bile acid accumulation in tissues may be a factor (4). Others

Rôle de la plasmaphérèse dans le traitement du prurit intense chez des patientes enceintes souffrant de cirrhose biliaire primaire : Rapports de cas

HISTORIQUE : La cirrhose biliaire primaire (CBP) peut être associée au prurit qui, le cas échéant, se trouve accentué durant la grossesse. Plusieurs modalités thérapeutiques ont été utilisées pour maîtriser les démangeaisons causées par la cholestase avec des résultats variables. Les traitements médicamenteux sont à déconseiller, surtout en début de grossesse. La plasmaphérèse a permis de corriger le prurit chez les patientes présentant une cholestase. Les auteurs présentent ici deux rapports de cas de patientes atteintes de CBP chez qui la plasmaphérèse a été utilisée avec succès pour soulager un prurit gravissime durant la grossesse.

PRÉSENTATION DE CAS : Deux patientes atteintes de CBP ont consulté au cours de leur second trimestre de grossesse pour un prurit intense qui ne répondait pas à la cholestyramine, une résine échangeuse d'anions. Leurs symptômes étaient invalidants au point où une patiente a songé au suicide. Compte tenu de la gravité de leurs symptômes, plusieurs séances de plasmaphérèse ont été instaurées et ont permis de corriger le prurit. Les deux patientes ont bien toléré l'intervention et ont donné naissance à des bébés en bonne santé.

CONCLUSION : La plasmaphérèse est une intervention relativement sûre et rapidement efficace pour le prurit sévère durant la grossesse chez des patientes atteintes de CBP.

have suggested that the high level of endogenous opioids that can be detected in patients with PBC may also be responsible for pruritus (5).

Cholestyramine has been recommended as the first-line therapy for pruritus of cholestasis (6). Rifampin is also effective in controlling pruritus in 77% of patients, at least over the short term, according to a recent meta-analysis (7). The opioid antagonists, naloxone (8) and naltrexone (9), have also been shown to alleviate pruritus of cholestasis. However, their use may be accompanied by symptoms typical of opioid 'withdrawal' and, when given over the long term, may be associated with chronic pain syndrome (10). Sertraline has been shown, in a small, randomized, placebo-controlled trial (11), to reduce the pruritus of cholestasis. Ursodeoxycholic acid, which is the standard of care for PBC (6), has not brought relief of pruritus in patients with PBC (12), in contrast to the benefits seen when using this agent to treat intrahepatic cholestasis of

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pregnancy (13). Clinical experience suggests that the pruritogen of cholestasis is present in bile and in blood, because biliary diversion (14,15), extracorporeal albumin dialysis (16,17) and plasmapheresis (18,19) effectively alleviate pruritus of cholestasis.

We report our experience of safely treating severe pruritus with plasmapheresis in two pregnant women with PBC. To our knowledge, the present paper is the first to report the use of plasmapheresis to treat severe pruritus during pregnancy in patients with PBC.

CASE PRESENTATIONS

Patient 1

A 33-year-old pregnant woman with biopsy-proven PBC is described. She first presented at 28 years of age with pruritus and was found to have elevated serum bilirubin and ALP levels, and tested antimitochondrial antibody-positive. Her liver profile was: ALT 143 U/L (normal level less than 40 U/L); AST 98 U/L (normal level less than 40 U/L); ALP 690 U/L (normal level less than 112 U/L); total bilirubin 36 μ mol/L (normal level less than 23 μ mol/L); albumin 47 g/L (normal level greater than 35 g/L); and an international normalized ratio (INR) of 0.97. An ultrasound of her liver was normal. Her liver biopsy showed stage I-II PBC. She was noted to have unconjugated hyperbilirubinemia (Gilbert's syndrome). She was started on ursodeoxycholic acid (UDCA) 1 g/day with dinner, and cholestyramine was prescribed to be taken before and after breakfast to treat her pruritus. The latter treatment had no significant effect. Her prescription was changed to rifampin 150 mg twice per day, which led to better control of her pruritus. One year later, the patient planned to get pregnant; UDCA and rifampin were stopped per patient's request to avoid any potential drug effects on the fetus. Over the following four years, she took UDCA twice for intermittent periods when she was not planning to conceive. Her pruritus was manageable without medication. She succeeded in becoming pregnant at 33 years of age. The patient developed significant pruritus at 12 weeks gestation. The only medication she was taking was a multivitamin. At that time, her liver profile was: ALT 137 U/L; AST 81 U/L; ALP 301 U/L; GGT 151 U/L (normal level less than 60 U/L); total bilirubin 12 μ mol/L; albumin 36 g/L; and an INR of 0.92. She was restarted on cholestyramine 4 g before and after breakfast. The patient was reassessed on an urgent basis at 22 weeks gestation for severe pruritus. She had been unable to sleep for days and when she presented to the liver clinic at Toronto Western Hospital (Toronto, Ontario), she had suicidal ideation. Given the severity of her symptoms, she was immediately treated with plasmapheresis for her pruritus; this was repeated the following day, and twice the following week. Each exchange consisted of one plasma volume with 5% albumin as replacement fluid. The patient had significant relief of her pruritus after the second plasmapheresis session. No complications were reported during the plasma exchange. Once good control of her pruritus was achieved, she was started on rifampin, as well as ultraviolet B light therapy twice per week for the duration of her pregnancy; good control of her pruritus was maintained. She delivered a 1.75 kg baby girl prematurely at 31 weeks gestation, following spontaneous rupture of membranes. The baby continues to do well. Three months after delivery, the patient resumed taking rifampin and UDCA, and had no pruritus.

Patient 2

A 31-year-old G4 P3 woman is described. She was referred for the first time to the liver clinic at Toronto Western Hospital with severe pruritus at her 31st week of pregnancy. She had mild pruritus for the previous three years, which she attributed to dry skin. She also reported mild pruritus during her previous three pregnancies, but this was never investigated further. During the current pregnancy, she started to complain of significant pruritus at 12 weeks gestation. She was found to have an elevated ALP level and tested antimitochondrial antibody-positive. Her liver profile results included: ALT 99 U/L; AST 62 U/L; ALP 713 U/L; GGT 160 U/L; total bilirubin 28 μ mol/L; albumin 35 g/L; and an INR of 0.93. An ultrasound of her liver was normal. A clinical diagnosis of PBC was made and she was started on cholestyramine 4 g twice per day before and after breakfast, and UDCA 1 g daily with dinner. However, by the 31st week of gestation, the patient's pruritus was so severe that it interfered with her sleep and ability to care for her family. Her cholestyramine was increased to 4 g three times per day but this was unhelpful. Once referred to the liver clinic at Toronto Western Hospital, other oral agents usually used in the treatment of pruritus due to cholestasis (ie, rifampin and opioid antagonists) were declined by the patient, who was concerned about any potential effect on the fetus. The patient underwent plasmapheresis to manage her pruritus. This was performed on two consecutive days that week, with significant alleviation of her pruritus. Thereafter, plasmapheresis was repeated every 10 days until delivery, with a total of six exchanges. Each exchange consisted of one plasma volume with 5% albumin as replacement fluid. No complications were reported during the exchanges. The patient delivered a 3.2 kg boy after induction of labour at 38 weeks gestation. The patient continued to have pruritus after delivery, which supported the diagnosis of PBC. Five months later, a liver biopsy showed stage I-II PBC with 90% loss of bile ducts. The baby continues to do well.

DISCUSSION

Plasmapheresis is a rapid-acting, effective rescue procedure that may be used to gain immediate control of pruritus due to cholestasis. Plasmapheresis is an extracorporeal procedure that can remove large molecular weight substances from the plasma. It is generally safe and well tolerated, and can be used safely in pregnant women, although rare complications of hypotension and citrate reaction may occur. The exact mechanism of how plasmapheresis decreases pruritus is unknown.

To our knowledge, the present report describes the first time that plasmapheresis has been used to treat pruritus in patients with PBC during pregnancy. In the first case, the severity of pruritus was life-threatening. Plasmapheresis was a very useful emergency tool, which controlled the patient's symptoms almost immediately until other therapies (ie, rifampin and ultraviolet B light) were introduced and given time to exert their beneficial effect. The second patient, who had been given cholestyramine without benefit, had pruritus that was sufficiently severe to interfere with her daily life and her ability to look after her three children. Plasmapheresis was performed because she declined trying other oral agents, and it controlled her symptoms quickly. This benefit was maintained by repeated plasmapheresis throughout the rest of her pregnancy. No deterioration in liver or fetal function was noted in either case after the introduction of plasmapheresis

treatment. The first patient experienced premature labour at 31 weeks gestation. It is unlikely that this was due to the plasmapheresis procedure, because it occurred eight weeks after her last session. However, it may have been prompted by her chronic cholestasis. The second patient had a term delivery despite receiving plasma exchange on an intermittent basis until the end of her pregnancy. Both patients had babies who have thrived.

Estrogens are known to provoke cholestasis. Exogenous estrogens (eg, oral contraceptives) are associated with pruritus and jaundice in women who are prone to cholestasis of pregnancy (20,21). However, Poupon et al (22) reported a follow-up study of nine pregnancies in six patients with PBC. These patients were all taking UDCA and none had pruritus before becoming pregnant. All patients remained without

pruritus during their entire pregnancy. The present paper reports two patients with PBC (both of whom had experienced pruritus before their pregnancy) whose pruritus worsened during pregnancy. It is possible that severe pruritus during pregnancy in women with PBC is more likely to happen in those who have pruritus before pregnancy. Their symptoms presumably are aggravated by the high estrogen levels present during pregnancy.

Plasmapheresis is an expensive and limited resource. It should be reserved for cases of pruritus that are incapacitating and/or when oral agents have failed.

CONCLUSION

Plasmapheresis is a relatively safe and rapidly effective treatment for severe pruritus during pregnancy in patients with PBC.

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