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Primary sclerosing cholangitis: A new case of cirrhosis in pregnancy

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Abstract

Cirrhosis is a multisystemic condition in which pregnancy is uncommon; however, the combination may lead to a higher incidence of spontaneous fetal loss and complications such as progressive jaundice, ascites and variceal bleeding. Here we present a 21-year-old woman who presented at 14 weeks' gestation with new jaundice and a two-month history of melena consistent with pre-existing cirrhosis of unclear aetiology. She delivered a healthy male infant at 34 weeks and five days of gestation vaginally with good haemostasis. In the literature, maternal mortality rates have been reported in up to 61% of these women, however, this risk is likely lower now with modern endoscopic therapies and improved access to blood products. There is limited information about labour and delivery in cirrhosis, although the best outcomes to date have been described in well-compensated women.

Keywords

Pregnancy complications, haematologic, cirrhosis, primary sclerosing cholangitis

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Introduction

Cirrhosis is a multisystem condition associated with irreversible fibrosis and architectural distortion of the hepatic parenchyma.[1] It has an estimated prevalence of 45 per 100,000 women of reproductive age.[2] Pregnancy is uncommon in women with cirrhosis, although the exact incidence is unknown. The reasons for this are two-fold. Cirrhosis typically takes many years to develop, and women may be beyond reproductive age by the time this happens. Second, cirrhosis is commonly accompanied by hormonal changes that induce anovulation and infertility.[3]

Although cirrhosis still carries significant morbidity, advances in medical care have led to an increase in successful pregnancies.[2] Nevertheless, cirrhosis still carries its own unique challenges. Maternal mortality for women with cirrhosis was once documented as high as 10–60% in the postpartum period, due to complications of haemorrhage and decompensated liver failure.[2]

History

A 21-year-old woman in her second pregnancy was admitted at 14 weeks' gestation with new jaundice. Her past medical history was unremarkable and she was on no medications. She consumed no alcohol and had no relevant family history. Her first pregnancy ended in miscarriage at 11 weeks and six days of gestation, at which point she was noted to have elevated liver enzymes and thrombocytopenia. Five months later, she presented to her local emergency room at 14 weeks of gestation with jaundice and a two-month history of melaena. She had laboratory indices that showed the following: platelet count of 65×10^9/L, alanine aminotransferase of 161 U/L (normal range < 33 U/L), bilirubin of 44.4 μmoL/L (0–5 μmoL/L), international normalised ratio of 1.0, albumin of 32 g/L (35–52 g/L), alkaline phosphatase (ALP) of 173 U/L (35–104 U/L), and gamma-glutamyl transferase of 33 U/L (<31 U/L). Renal function remained normal with a creatinine of 48 μmoL/L. Calculated Model of End-Stage Liver Disease (MELD) score at the time of presentation was 10. An ultrasound showed splenomegaly (17.1 cm) and mild hepatomegaly (liver span of 15 cm), but normal portal and hepatic veins. Endoscopy demonstrated three columns of varices, requiring placement of four bands. She was diagnosed with Child-Pugh class B cirrhosis.

Her work up for autoimmune, viral and metabolic causes of her liver dysfunction did not show any abnormality. She had negative immunoglobulins, anti-liver kidney antibody, antimitochondrial antibody, anti-smooth muscle antibody, cytomegalovirus, Epstein–Barr virus and hepatitis B and C serologies. Alpha-1-antitrypsin and ceruloplasmin levels were elevated. Iron studies were not suggestive of haemochromatosis. Fibroscan results were consistent with cirrhosis. On review of her laboratory results and clinical picture, she was felt to have possible autoimmune hepatitis resulting in cirrhosis despite negative antibodies. Biopsy during the second trimester was initially discussed but was deferred given that she had already developed

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cirrhosis at the time of presentation, and it was unlikely to change management in the short term.

She was subsequently started on ursodeoxycholic acid at 500 mg orally three times a day at 16 weeks given her high bile acid level of 130 μmoL/L (upper limit of normal 6.6 μmoL/L). This was started due to intense pruritus and with consideration of possible superimposed intrahepatic cholestasis of pregnancy(reference range 0-5 μmoL/L). Her direct bilirubin level also peaked at 16 weeks at 62.5 μmoL/L. Her fasting bile acids never normalised and remained elevated at 151.5 μmoL/L when measured shortly before delivery. Her liver enzymes remained normal with initiation of ursodeoxycholic acid except her ALP, which was 368 U/L and her bilirubin. Her direct bilirubin gradually decreased to 30 μmoL/L shortly before her delivery, but did not normalise, which was consistent with cirrhosis. She presented to hospital at 34 weeks and five days of gestation in preterm labour, with spontaneous rupture of membranes. She gave birth to a healthy male infant weighing 2.49 kg via spontaneous vaginal delivery. She suffered no peripartum haemorrhage and was discharged from hospital two days later. The work up for cirrhosis continued postpartum. Five months postpartum she required further banding of oesophageal varices. Magnetic resonance cholangiopancreatography demonstrated intra- and extrahepatic duct stricturing and dilated peripheral intrahepatic ducts consistent with primary sclerosing cholangitis (PSC). She also underwent liver biopsy eight-months following delivery which showed a chronic cholestatic disorder but no evidence of concurrent autoimmune hepatitis. It also showed septal fibrosis, severe ductopenia and marked ductular reaction with proliferation. This biopsy did not confirm cirrhosis, but a repeat biopsy three months later did show developing cirrhosis. She also underwent genetic testing for progressive familial intrahepatic cholestasis and Alagille syndrome which revealed a heterozygous variant of the *ABCB4* gene with uncertain significance. Colonoscopy was also done following delivery as she developed chronic diarrhoea, with random biopsies showing focal active colitis. She is currently under consideration for liver transplant.

Discussion

There are many important physiological and hormonal changes occurring in pregnancy which can impact underlying cirrhosis, for example, an increase in plasma volume by 30–50% and spleen size.[4,5] A hyper-oestrogenic state can also lead to increased palmar erythema and spider angiomata in 70% of women.[4] Biochemically, transaminases and bilirubin generally remain unchanged, although ALP typically rises due to production of the placental isoenzyme.[6] Clinically insignificant varices can occur in up to 50% of women due to the compression of the inferior vena cava by the uterus and a decrease in systemic vascular resistance.[6]

Pregnancy complications

Pregnancy is rare in women with cirrhosis. When pregnancy does happen, it carries significant fetal risks including an increased risk of spontaneous pregnancy loss, preterm labour and perinatal death.[6] Maternal morbidity and mortality is also increased with higher rates of hepatic decompensation, ascites and encephalopathy.[6] In a recent published retrospective study of 11 cases, all three women with decompensated cirrhosis developed gastrointestinal bleeding and premature delivery before 30 weeks.[7] A study of 62 pregnancies in 29 women with cirrhosis described an overall hepatic decompensation rate of 10%.[8] A MELD score of 10 was thought to confer an 83% sensitivity and specificity for predicting hepatic decompensation.[8] The only therapy for fulminant hepatic failure during pregnancy is liver transplantation, which has been described in a small number of case reports.[9] Otherwise, many aspects of management are similar to the non-pregnant population.[4] The incidence of variceal bleeding with hepatic decompensation ranges between 25 and 64% of pregnant women with cirrhosis.[10] Variceal bleeding commonly occurs during the second and third trimesters when the increasing blood volume and decreasing systemic vascular resistance result in increased portal venous pressures.[6] Overall, the peripartum mortality rate in women with pre-existing varices can reach approximately 50%.[10] The frequency of hepatic decompensation after variceal bleeding is approximately 24%, postpartum haemorrhage following delivery is 10% and splenic artery rupture occurs in 2–3%.[3] Upper endoscopy is generally safe in pregnancy. No cases of premature labour or fetal malformations have been reported as a result of this procedure.[3]

The safety of octreotide as a therapy for acute variceal bleeding, is not well established in pregnancy, but could be used in an emergency.[10] There are a few case reports of trans-intrahepatic portosystemic shunt procedures being performed, with the main risk being radiation exposure to the fetus.[10,11] Non-selective beta blockers such as propranolol and nadolol can be considered in a woman at a significantly increased risk of an acute bleed. Due to its long half-life, nadolol may be less preferable in this setting, and if used, the fetus must be monitored for bradycardia and intrauterine growth restriction.[4]

Interestingly, a retrospective study of 33 women showed an association of cirrhosis with preeclampsia.[2] Another population-based study was conducted based on the US Nationwide Inpatient Sample database of patients admitted between 1993 and 2005 and demonstrated pregnant women with cirrhosis were more likely to develop hypertensive disorders of pregnancy (odds ratio 1.63 (1.19–2.23, $p < 0.003$)) and preeclampsia (odds ratio 1.78 (1.15–2.78, $p < 0.02$)).[12] There is no standard guideline for treatment and prophylaxis in such cases. Though small doses of aspirin are used to prevent preeclampsia in women at elevated risk, women with cirrhosis may also have contraindications to receiving such therapy, such as an increased risk of gastrointestinal bleeding.[13] A woman with Child-Pugh Class A cirrhosis may benefit from low dose aspirin, if there is no synthetic dysfunction and no history of bleeding or gastritis.

Mode of delivery

There is no guideline consensus on an approach to vaginal versus caesarean section for cirrhotic women with portal hypertension.[6] Some experts early on recommended elective caesarean section, as repetitive Valsalva manoeuvres during vaginal delivery can increase intraabdominal pressure and potentially increase the risk of variceal bleeding.[3] Others more recently recommend caesarean section only for obstetric indications, with an attempted short second stage of labour, avoidance of Valsalva straining and use of forceps and vacuum assistance as necessary.[6] If a caesarean section is performed, a vascular surgeon is recommended to be available, in case there is bleeding from pelvic or abdominal wall collateral vessels.[3] Postpartum haemorrhage should be managed by administration of blood and other coagulation products, alongside the standard treatment of oxytocin and other agents.[3]

PSC in pregnancy

PSC is a disease more often affecting men, although 30% of cases are in women. One 1996 review identified 10 women who had PSC during pregnancy, the majority of whom had inflammatory bowel disease.[14] Two of these women developed jaundice and pruritus in pregnancy and were found to have PSC, confirmed after pregnancy.[14] The study authors did not find any adverse outcome with respect to worsening of hepatic function, and outcomes for mother and baby were generally favourable. The only significant complication was intense pruritus that developed in five of these women, which was so intense that two of these pregnancies had to be terminated.[14] Another study

examined pregnancies in 25 women with PSC.[15] Again, in this study, fetal loss was estimated at around 16%, less than autoimmune hepatitis which reported at 30%, and pruritus was a major problem. Preterm birth also occurred in 10% of cases.[15] In this study, ursodeoxycholic acid was used for symptomatic relief of pruritus and was associated with reduced elevation of liver enzymes than in the women who were not prescribed it.[15] In the case described here, urodeoxycholic acid was started at 16 weeks for possible intrahepatic cholestasis of pregnancy, after the fasting bile acid levels were found to be elevated in the context of severe pruritus. Other cases of women with PSC have similarly demonstrated elevated fasting bile acid levels in pregnancy, with some also postulating concomitant intrahepatic cholestasis.[15,16] However, the presence of elevated fasting bile acids is worth noting, as endogenous bile acids have been hypothesised to play a role in the progression of PSC.[17] Further studies will therefore need to be done to determine if fasting bile acids levels during pregnancy change long-term outcomes in women with PSC.

Conclusions

Through multidisciplinary care and close follow-up, the woman described here had a good outcome. Women with cirrhosis have an increased risk of decompensation and variceal bleeding in pregnancy. There is limited information available in the literature on how to best manage labour and delivery in this population. The safety information on commonly used drugs in cirrhosis is limited, and the treatment strategy is extrapolated from the non-pregnant population. Although rare, PSC needs to be included in the consideration for aetiology of cirrhosis in women of child-bearing age.

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Guarantor

VSK is the guarantor of the present work.

Contributorship

All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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