Deranged liver function tests in pregnancy: the importance of postnatal follow-up

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Summary: We report an asymptomatic 40-year-old woman with persistently deranged liver function tests found incidentally in the first trimester of her second pregnancy. No cause was apparent clinically, serologically or with imaging studies until a new finding of hepatomegaly led to a repeat ultrasound scan six weeks following delivery. A mass in the region of the common hepatic duct was confirmed to be a cholangiocarcinoma, with vascular invasion precluding curative surgical resection. This case highlights the need for close vigilance of patients with unexplained and persistently abnormal liver function tests, antenatally and postdelivery.

Keywords: liver function tests, cholangiocarcinoma, pregnancy

CASE

A 40-year-old woman was found to have abnormal liver function tests when baseline levels were established in the first trimester of a second pregnancy.

Her first pregnancy, three years previously, was complicated by mild pregnancy-induced hypertension; her liver function tests were normal at that time. She had no other past medical history, was a non-smoker, of normal body mass index with minimal alcohol intake and had she used non-hormonal contraception.

At five weeks gestation in this pregnancy, her booking blood pressure was elevated (148/96 mmHg). She was referred to an obstetric medicine clinic where her history and examination were unremarkable; she neither had hyperemesis gravidarum nor ongoing hypertension. In view of an increased risk of developing preeclampsia, liver function assays were performed as part of a baseline assessment. Unexpectedly, these were highly abnormal (Figure 1; γ -glutamyl transferase [GGT] 318 IU/L, alanine transaminase [ALT] 61 IU/L, aspartate transaminase [AST] 41 IU/L, alkaline phosphatase [ALP] 267 IU/L and bilirubin 12 μ mol/L). A screening for hepatitis was performed and liver function tests were repeated.

She was reviewed with the results of these investigations in the obstetric medicine clinic at 23 weeks gestation. Preeclampsia and obstetric cholestasis were excluded clinically and serologically, and no other risk factors for liver dysfunction were identified in the history. She was asymptomatic, with no stigmata of chronic liver disease. Hepatitis A, B and C, Epstein-Barr virus and cytomegalovirus antibody assays were negative. A screening for autoimmune hepatitis was negative. An ultrasound scan reported the liver to be of uniform reflectivity with no focal lesions and no evidence of intra- or

extrahepatic biliary duct dilation. Thus, a diagnosis was not reached. As the assays seemed to be returning towards normal (Figure 1), further causes were not looked for. She was seen regularly for liver function and blood pressure monitoring.

She remained asymptomatic. At 38 weeks gestation, she developed non-proteinuric hypertension and methyldopa therapy was commenced. Shortly after, she presented with spontaneous rupture of membranes. Labour was induced and she had an assisted delivery of a healthy boy weighing 3740 g. Her blood pressure normalized and the methyldopa therapy was stopped immediately postpartum.

Her liver function tests rose rapidly following delivery (Figure 1): at six weeks postpartum, the GGT was >800 IU/L, ALT >250 IU/L, AST 150 IU/L and ALP 750 IU/L. She was reviewed in the obstetric medicine clinic. She remained well, but abdominal examination revealed a palpable liver edge, prompting a repeat ultrasound scan and referral to gastroenterology. This second scan, five months after the first, reported intrahepatic duct dilation with a small tissue mass in the region of the common hepatic duct; the bile duct was not dilated. The impression of a high biliary obstruction indicative of a cholangiocarcinoma was subsequently confirmed on computed tomography scan, magnetic resonance imaging and endoscopic retrograde cholangiopancreatography with brush cytology. Four months postpartum, Doppler of the portal vein demonstrated vascular invasion with tumour involvement of the common trunk of the portal vein, thus excluding the possibility of curative surgical resection. She commenced chemotherapy soon after.

DISCUSSION

Cholangiocarcinoma is a rare primary malignancy of biliary epithelium. Risk factors include conditions that cause local chronic inflammation such as primary sclerosing cholangitis.¹

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Figure 1 Graph demonstrating the fluctuating concentrations of γ -glutamyl transferase (GGT), aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP) and bilirubin (bili) from first measurement at 12 weeks gestation to diagnosis postpartum (pregnancy-specific reference ranges were used: GGT <40 IU/L, ALT <30 IU/L, AST <30 IU/L, ALP <450 IU/L and bili <15 μ mol/L)

The diagnosis can be elusive and is often reached when curative surgical resection is no longer feasible. Current diagnostic modalities include serum and bile tumour markers, radiological and endoscopic imaging, and histology.¹ Cholangiocarcinoma is strongly resistant to most chemotherapy and there is no non-surgical treatment that slows disease progression; median five years survival from diagnosis is 7–8%, with a median survival time of only seven months.²

Only three other cases of cholangiocarcinoma have been reported in pregnancy,^{3–5} of which two were initially given pregnancy-specific diagnoses – HELLP (haemolysis, elevated liver enzymes and low platelet count) syndrome³ and obstetric cholestasis;⁴ the third was diagnosed prior to conception.⁵ In the present case, the liver function tests were abnormal in the first trimester of pregnancy but a diagnosis was not reached. The tumour was not visible on the first ultrasound scan, despite retrospective review of the images.

It is not known whether pregnancy influences growth of cholangiocarcinoma. Long-term use of combined oral contraceptives has been implicated as a possible factor in the development of hepatocellular carcinoma, but there is less evidence that they stimulate cholangiocarcinoma.⁶ *In vitro* studies suggest that oestrogen plays a role in the development and progression of pathologies involving the biliary tree, including cholangiocarcinoma.⁷ Oestrogens activate intracellular signalling cascades of certain growth factors, which can modulate cholangiocyte proliferation, and, in one study, liver biopsies from patients with intrahepatic cholangiocarcinoma were positive for oestrogen receptor α - and β -subtypes, while cholangiocytes of the normal liver were negative.⁸ It is interesting that this patient's liver function appeared to show improvement during the pregnancy and that enzyme levels accelerated in the first six weeks postnatally, at which time the liver edge

became palpable and the tumour was large enough to be detected by ultrasound imaging. While it is feasible that this reflects usual tumour behaviour, it is certainly not typical of a stimulatory effect of oestrogen and introduces the intriguing concept that in some way the pregnancy exerted an inhibitory effect.

Liver dysfunction in pregnancy is common, occurring in over 3% of pregnancies in one series, with the majority of causes being due to pregnancy-specific conditions such as hyperemesis gravidarum, obstetric cholestasis, preeclampsia and its variants.⁹ However, out of 46 women referred to a Liver Failure Unit with presumed acute fatty liver of pregnancy or HELLP syndrome, six had liver disease unrelated to pregnancy, one with hepatic infiltration by an adenocarcinoma of unknown primary and one with lymphoma.¹⁰ The authors emphasized the need to exclude other causes of liver impairment in patients with clinical features of pregnancy-related liver disease. Although alcohol intake was said to be minimal in this patient's case, measurement of serum carbohydrate-deficient transferrin would have excluded alcohol-related liver disease.

In conclusion, this case highlights the importance of following patients with unexplained laboratory abnormalities and serially repeating the physical examination and/or investigations. It is good practice to see women with pregnancy-related abnormalities of liver function postnatally, to ensure that the diagnosis remains valid, that abnormalities have resolved and that advice regarding recurrence and contraception is given. Minor and non-specific abnormalities of liver function seem to be common and often resolve without a clear diagnosis or significant impact on the patient, but this must not be assumed.

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