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Non-alcoholic fatty liver disease in pregnancy

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is now the commonest liver pathology in the UK; however, relatively little is known about its course in pregnancy or the effect it has on maternal or fetal outcomes. Described here is a 24-year-old woman in her first pregnancy who presented with non-specific symptoms and raised alanine aminotransferase with ultrasonography of her liver showing changes of steatosis and suspicious for cirrhosis, leading to a diagnosis of NAFLD. The case illustrates the need for the clinician to have awareness of this increasingly prevalent condition and for multidisciplinary management.

Keywords

Non-alcoholic fatty liver disease, pregnancy, steatohepatitis, fibrosis, cirrhosis, elevated liver enzymes

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is now the commonest cause of abnormal liver function tests (LFTs) in the UK;[1] however, relatively little is known about its course in pregnancy or the effect it has on maternal or fetal outcomes. Preliminary associations have previously been made between NAFLD and adverse pregnancy outcomes,[2] including gestational diabetes, pre-eclampsia, caesarean section, preterm birth and low birthweight; however, the current literature is not robust enough for any links to be drawn regarding causation or the effects of pregnancy on the condition. Co-existent obesity is likely to be a significant confounder. NAFLD is estimated to affect approximately 10% of women of child-bearing age,[3] but fatty liver is reported in 90% of individuals undergoing bariatric surgery.

The vast majority may remain undiagnosed due to lack of symptoms warranting investigation. Here, we describe a 24-year-old female in her first pregnancy who presented with non-specific symptoms and incidental proteinuria, who was found to have an abnormally raised alanine aminotransferase (ALT) and ultrasonography of her liver showing changes consistent with steatosis, which led to a diagnosis of NAFLD.

Case

A woman was referred by her GP at 30 weeks' gestation to her local maternity assessment unit with a history of malaise and significant proteinuria. She had a medical history notable for a body mass index (BMI) of 52 kg/m^2, for which she had been referred for consideration of bariatric surgery but this had been postponed when she became pregnant. She also had a history of obstructive sleep apnoea for which she was using a Continuous Positive Airway Pressure (CPAP) machine at night. A recent urine culture had grown Group B streptococcus, so antibiotic treatment was started. Blood tests taken at this presentation showed a raised ALT (73 U/L). An oral glucose tolerance test was normal at 28 weeks.

At 32 weeks' gestation the woman was referred again to the assessment unit with ongoing malaise and nausea. She also reported right upper quadrant pain, unrelated to oral intake, and frontal headaches. Repeated blood tests showed an increasing ALT (119 U/L). Examination revealed right upper quadrant tenderness with no guarding. There was no peripheral oedema. She was haemodynamically stable and serum glucose was normal. She was admitted to hospital for further investigations and bloods continued to show a rising ALT. Blood tests for autoimmune and infective causes of liver pathology were normal, including screening for viral hepatitides and liver autoantibodies. Liver ultrasound demonstrated an enlarged liver with a coarse and hyperechoic echotexture indicative of hepatic steatosis but also raising the possibility of cirrhosis. Reassuringly, there was normal spleen size, hepatopetal portal blood flow and no evidence of ascites.

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The woman was given analgesia and discharged. The diagnosis of NAFLD was made on subsequent outpatient review, considering the findings of fatty liver on ultrasound scan in conjunction with risk factors for metabolic dysfunction, lack of excessive alcohol and a negative chronic liver disease screen. No further diagnostic investigations or treatment was required in pregnancy. A plan was made for regular outpatient review and repeat LFTs.

Subsequently, persistent glycosuria was noted at 36 weeks' gestation. A diagnosis of gestational diabetes mellitus was made after serial measurements of her capillary blood glucose were abnormal. She was started on 500 mg metformin twice a day. At this point an USS of the fetus showed a sharp increase in growth velocity, with the abdominal circumference measuring greater than the 97th centile. Liquor volume remained normal.

Induction of labour was offered at 36 weeks and 5 days' gestation in view of the new diagnosis of hyperglycaemia and accelerated fetal growth. Her ALT had now risen to 161 U/L and her weight had increased to 137 kg, an increase of 17 kg from booking. Induction was commenced but abandoned in the early stages due to presumed fetal compromise. A category 2 lower segment caesarean section was performed under spinal anaesthesia and a live male infant weighing 2625 g was born in good condition.

Postnatally, she made a good recovery and lifestyle advice regarding diet and exercise was given. Blood glucose readings were normal after delivery and her ALT improved rapidly after delivery and had normalised within 6 weeks. She was discharged on dalteparin for thromboprophylaxis. She subsequently underwent a liver biopsy which showed moderate steatosis affecting approximately 60% of hepatocytes with a macro:microvesicular ratio of 1:4. There was no evidence of inflammation, ballooning of hepatocytes or any other features consistent with steatohepatitis. There was also no evidence of advanced fibrosis or cirrhosis, reflective of the low sensitivity and specificity of ultrasound in the diagnosis of early changes of cirrhosis.[4]

Discussion

What is NAFLD?

NAFLD encompasses a spectrum of conditions ranging progressively from fatty liver to non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis.[5,6] Non-alcoholic fatty liver is defined by an excess of fat in the liver, otherwise known as steatosis. The condition is becoming increasingly known by its new description as metabolic (dysfunction) associated fatty liver disease, more accurately representing the pathogenesis of the condition.[7] It is important to distinguish this condition from acute fatty liver of pregnancy, an entirely different entity, where microvesicular steatosis is the key histological feature, and which results in acute and potentially life-threatening liver dysfunction.

It has been estimated that around a quarter of the general population have this largely asymptomatic condition.[5,6] In obese individuals or those with type 2 diabetes, the prevalence is 70%–90%.[8] Between 10% and 30% of people with NAFLD will have the progressive form of the disease, NASH, which features hepatocellular injury and inflammation with potential progression to fibrosis and cirrhosis in 20%–30%.[1] Liver biopsies in individuals undergoing bariatric surgery have shown the incidence of fatty liver to be around 90%, with 37% showing features of NASH and 1.7% having unexpected cirrhosis.[9] With the BMI of pregnant women ever increasing,[10] clinicians should expect to encounter more cases of NAFLD in pregnancy in the future.

Diagnosis of NAFLD in pregnancy

Diagnosing NAFLD during pregnancy is challenging.[11] The vast majority of cases will go undiagnosed due to the presence of vague (or lack of) symptoms which inevitably results in no formal biochemical or radiological testing. Even if LFTs are measured, these may remain normal.[11] A diagnosis of NAFLD is typically made from the results of either liver biopsy or imaging,[1] although the latter lacks sensitivity for milder cases and is unreliable in detecting steatosis of lesser than 20%.[6] Features of established cirrhosis such as an irregular liver contour may be seen on ultrasound scanning to allow a clinical diagnosis of cirrhosis to be made with good diagnostic accuracy,[12] which may explain why such an inference was made on the initial ultrasound scan in this case; however, ultrasound scanning is not sensitive to detect early cirrhosis reliably (particularly in the absence of portal hypertension) and such appearances may not, as in this case, be specific for cirrhosis. Other pathology such as heterogeneous fat distribution or the presence of nodular regenerative hyperplasia may cause similar appearances on ultrasound scanning. While biopsy has the benefit of histological confirmation, there are reservations about performing this in pregnancy. Transient Elastography, most commonly known as 'FibroScan', can also be useful in determining both the diagnosis and extent of liver fibrosis and cirrhosis. It is, however, contraindicated in pregnancy on advice of the manufacturer. Other tools used to categorise the degree of fibrosis, such as the FIB-4 score, are not validated in pregnancy due to the effects of pregnancy-related conditions on relevant blood parameters, e.g. pre-eclampsia affecting liver enzymes and gestational thrombocytopenia affecting platelet count.

One case series consisting of five pregnant women has previously reported abnormal LFTs resulting in a diagnosis of NAFLD.[13] Similar to our case, they also noted a presence of vague, non-specific symptoms and elevated LFTs. In addition, all women had a raised BMI. However, specific details on peripartum management of these cases were not provided.

The case described here adds to the growing body of literature that suggests that NAFLD should be considered as an important differential diagnosis in pregnant women with deranged LFTs. The index of suspicion should be particularly high in those with features of metabolic syndrome such as a high BMI, a diagnosis of polycystic ovarian syndrome or diabetes mellitus. A multi-disciplinary approach is strongly recommended during pregnancy to optimise the outcome for both mother and baby, but also importantly postnatally to prevent further progression of NAFLD.

Management of uncomplicated NAFLD in pregnancy

In the non-pregnant individual, weight loss appears to reduce the progression of this condition and may reverse the histological changes seen.[14] In overweight pregnant women, dietary modification and restriction of weight gain are advocated but the evidence that this influences pregnancy outcome is lacking.

The woman described here had a progressive rise in ALT throughout pregnancy, with a significant improvement postdelivery. This is in contrast to the results of another case series[13] where four out of five women studied showed deterioration in liver function postnatally. There was no clinical evidence of an additional pathology explaining the deterioration in LFTs during pregnancy, but this should always be considered in any woman with liver disease as it cannot simply be assumed that deterioration in function is purely due to the underlying liver disorder. Evidently, not enough is known about the natural course of ALT in pregnancy with or without a diagnosis of NAFLD for this alone to guide management.

Management of cirrhosis in pregnancy

Pregnancy in women with liver cirrhosis is rare, due to both the low prevalence in women of reproductive age and its associated reduction in fertility.[15] This woman had changes suggestive of cirrhosis on ultrasound but reassuringly had normal hepatic and portal blood flow at that time, as well as a later biopsy which did not show cirrhotic changes. If cirrhosis is present, then other complications in pregnancy are more common and vigilance is required for their development. It has been reported that up to one-third of pregnant women with cirrhosis have oesophageal varices, of which 78% will experience gastrointestinal haemorrhage during pregnancy. Other complications include prematurity, miscarriage, acute hepatic decompensation, splenic artery aneurysm rupture and postpartum haemorrhage.[15]

Delivery timing

In the acute setting, there is no evidence of a threshold of ALT where complications arise and where delivery should be advocated. If clinically well, a conservative approach is appropriate. Early delivery is not routinely indicated unless other maternal or fetal pathology co-exists or is at high risk of evolving. Association between NAFLD and raised BMI[16] inherently raises the risk of the woman developing other conditions such as gestational diabetes and pre-eclampsia,[17] with the presence of either condition potentially warranting early delivery. Decision regarding mode of birth should be based on the individual, taking into account co-morbidities and fetal well-being.

Postnatal management

Postnatal management should focus on lifestyle advice, weight loss and planning for any future pregnancies (i.e. contraception, pregnancy spacing). Education about lifestyle measures that can be undertaken to slow the progression or even contribute to partial reversal of the condition is imperative. A healthy diet, exercise and any other appropriate weight loss measures (in this case, consideration of bariatric surgery) are crucial to halting the progression of the disease to more severe presentations such as NASH or cirrhosis.[18] All women with suspected NAFLD should undergo risk stratification using a non-invasive test according to local protocols[6] with referral to a hepatologist if the woman has clinical signs of advanced liver disease, is at high risk of advanced liver fibrosis on the basis of non-invasive tests or if there is uncertainty regarding the diagnosis.[19] A multidisciplinary approach to management, with the involvement of diabetologists, metabolic physicians and hepatologists alongside allied health professionals with expertise in diet and lifestyle, has been shown to improve markers of both liver and cardio-metabolic disease.[20]

Interestingly, this woman also suffered from obstructive sleep apnoea (OSA) which has been associated with the development of NAFLD independent of BMI.[21] The mechanism of this association has not been proven; however, inflammatory insult alongside raised levels of hypoxia are purported theories.[21] While treatments for OSA, such as CPAP, have not been shown to improve LFTs in these individuals,[21] weight loss will contribute to reducing the severity of symptoms.

When consulting with the woman in the postnatal period, it is also prudent to discuss contraception and pregnancy spacing, as any of the above measures that can be taken postnatally can significantly reduce the risks for a future pregnancy.[22]

Conclusion

With NAFLD becoming increasingly prevalent worldwide, the average BMI of pregnant women increasing, and the increasing incidence of gestational diabetes mellitus, clinicians should expect to encounter the condition more frequently in pregnancy and be vigilant about considering this diagnosis in women at high risk. With little currently known about the course of the disease in pregnancy or its effect on mother or baby, a multidisciplinary approach is crucial. Appropriate postnatal management, focusing on weight loss and lifestyle modification, is imperative to ensure improved longer term health of the woman and minimise risk for future pregnancies.

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CJF is the guarantor of the present work.

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CF conceived the idea of the manuscript. CB drafted the manuscript and all authors approved the final draft.

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