Abnormal liver function tests in pregnancy

Ian Walker,1 Lucy C Chappell,2 Catherine Williamson2

A 34 year old South Asian nursery worker presented to her general practitioner at 32 weeks’ gestation in her first pregnancy complaining of increasingly severe itching. There was no relevant medical or family history, and she was not taking regular medication. Physical examination was normal with no evident rash. Her blood pressure was 115/65 mm Hg, and there was no proteinuria. The liver function tests were: total bilirubin 6 μmol/L, alkaline phosphatase 178 IU/L, alanine transaminase 42 IU/L, and albumin 34 g/L.

What is the next investigation?
Alkaline phosphatase normally increases during pregnancy because of production of the placental isoenzyme and, by term, may reach three times the normal adult upper reference value. The value of 178 IU/L is therefore likely to be normal (table 1). Pregnant women with isolated raised alkaline phosphatase in this range do not need any further investigation. Likewise, albumin is often decreased in normal pregnancy (table 1) as a consequence of haemodilution. In contrast, the concentrations of the transaminases (alanine and aspartate) and γ-glutamyltransferase normally decrease during pregnancy, and it is important to compare values to an appropriate reference range (table 1). The alanine transaminase result of 42 IU/L is therefore not normal and, because liver disease in pregnancy can have serious consequences, should be followed up within a week.

Table 1 | Typical reference ranges for liver enzymes by pregnancy and trimester

<table>
<thead>
<tr>
<th>Liver enzyme</th>
<th>Not pregnant</th>
<th>Pregnant</th>
<th>1st trimester</th>
<th>2nd trimester</th>
<th>3rd trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine transaminase (IU/L)</td>
<td>0–60</td>
<td>—</td>
<td>6–32</td>
<td>6–32</td>
<td>6–32</td>
</tr>
<tr>
<td>Aspartate transaminase (IU/L)</td>
<td>7–40</td>
<td>—</td>
<td>10–28</td>
<td>11–29</td>
<td>11–30</td>
</tr>
<tr>
<td>Bilirubin (μmol/L)</td>
<td>0–17</td>
<td>—</td>
<td>4–16</td>
<td>3–13</td>
<td>3–14</td>
</tr>
<tr>
<td>γ-glutamyltransferase (IU/L)</td>
<td>11–50</td>
<td>—</td>
<td>5–37</td>
<td>5–43</td>
<td>3–41</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>30–130</td>
<td>—</td>
<td>32–100</td>
<td>43–135</td>
<td>133–418</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>35–46</td>
<td>28–37</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bile acids (μmol/L)</td>
<td>0–14</td>
<td>0–14</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Adapted from Grigil et al 1997,1 Walker et al 2002,2 and Nelson-Penry 2010.3 (Non-pregnant reference ranges will be specified locally and may differ from those quoted here.)

When should liver function testing be considered in pregnancy?
Liver disease may present with non-specific symptoms and signs during pregnancy, as shown in table 2. A careful history will establish whether the woman has any infectious contacts or risk factors for bloodborne infections. Any of these features would justify an initial check of liver function tests. Testing may also be indicated in women known to be at high risk (such as those with previously affected pregnancies, a family history of liver disease in pregnancy, or known pre-existing liver disease). In contrast, palmar erythema and spider naevi may occur in uncomplicated pregnancy and are not a reason for concern (or liver function tests) when present in isolation. Transient mild abnormalities of liver function tests are common whether pregnant or not. Because liver abnormalities presenting for the first time during pregnancy may represent a pregnancy specific liver disease or may reveal a pre-existing undiagnosed liver condition that has been exacerbated by the physiological and metabolic stresses of the pregnancy, it is important to follow these up promptly. If there is concern about hepatic decompensation, additional tests that should be performed are prothrombin time (a sensitive indicator of hepatic synthetic function) and plasma glucose level (to...
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When to order an antinuclear antibody test

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Investigating hypocalcaemia

Investigating microcytic anaemia

exclude hypoglycaemia). The normal ranges for these tests do not change in pregnancy.

How are the commonest liver diseases differentiated?

Most liver diseases present with a characteristic constellation of symptoms in pregnant women (table 2). The typical changes in liver function tests for the pregnancy-specific diseases are summarised in table 3. A liver ultrasound scan can be useful if biliary obstruction if suspected.

Generalised pruritus without a rash

Around 25% of pregnant women report pruritus, and it is benign in most cases. However, in combination with abnormal liver function tests, a diagnosis of intrahepatic cholestasis of pregnancy (affecting about 0.7% of pregnant women in the UK) should be considered. It is associated with increased rates of preterm labour, fetal hypoxia, and intrauterine death.Raised bile acid concentrations, but not alanine transaminase, are predictive of adverse pregnancy outcome.5 If intrahepatic cholestasis of pregnancy is diagnosed, referral for hospital review is necessary.

Headache, malaise, epigastric pain, nausea, and vomiting in the second half of pregnancy

For a woman with some of these symptoms (not all need to be present), a disease within the pre-eclampsia spectrum should be excluded. Pre-eclampsia may be complicated by increased transaminase concentrations in 11% of cases, but these liver abnormalities are rarely the presenting feature and are not strongly predictive of maternal or fetal outcome. Checking for hypertension (≥140/90 mm Hg) and dipstick proteinuria should be a routine part of every antenatal visit.

Healthcare professionals should follow the NICE guidelines for management of hypertension in pregnancy to determine thresholds for referral and need for further investigations.

At the severe end of the pre-eclampsia spectrum there is overlap with HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome. HELLP syndrome also usually emerges during the third trimester, typically presenting with symptoms of epigastric pain, nausea, vomiting, headache, and visual disturbance. The diagnosis is made on detecting haemolysis (on a peripheral blood film or with elevated serum lactate dehydrogenase levels and unconjugated bilirubin) with elevated liver enzymes (typically increased alanine transaminase) and a low platelet count (<100×109/L) and is not usually made in primary care. It is associated with high maternal and perinatal mortality. Haematological and biochemical indices are useful for monitoring ongoing severity of disease but are not independent predictors of adverse outcome. However, any woman with hypertension and symptoms, signs, or investigations consistent with liver involvement requires immediate referral to an obstetric centre.

Acute fatty liver of pregnancy is rare, with an estimated incidence between 1:1000 and 1:20 000 pregnancies. The presentation is similar to that for HELLP syndrome, but affected women may also complain of polydipsia, polyuria, or jaundice. Women with acute fatty liver of pregnancy may deteriorate rapidly, developing fulminant hepatic failure and encephalopathy. Historical reviews have reported maternal mortality of 12-18%, but in a recent large series from the UK, with modern management, deaths were rare. Acute fatty liver of pregnancy is therefore a medical emergency that requires immediate referral if suspected. Typical blood test abnormalities are shown in table 3.

Severe nausea and vomiting in the first trimester

Women with severe nausea and vomiting may have hyperemesis gravidarum (intractable vomiting in pregnancy which prevents a woman from maintaining normal hydration or nutrition). This occurs in less than 1% of pregnancies; abnormal liver tests, likely a consequence of starvation, are found in up to 60% of such cases, more commonly in women who require re-admission to hospital. The alanine transaminase concentration will generally improve as the condition resolves. Persistent liver function test abnormalities may reflect a pre-existing underlying liver disease, and referral to a hepatologist is recommended.

Drug induced abnormal liver function tests

There are many drugs that can cause hepatocellular or cholestatic liver injury, but only a few are used during pregnancy (box 1). Affected women are usually asymptomatic, and the abnormal liver function tests are noted when a blood test is performed for another reason (such as a screen for a hypertensive woman treated with methyldopa). First line management should be to stop the drug, switching to an alternative if needed. If the cause is not obvious, it is important to be alert to the possibility of non-prescribed drugs and agents, including some drugs of misuse (such as ecstasy), herbal remedies (which can be hepatotoxic), or even mushroom poisoning (such as Amanita and Gyromitra species).

Liver disease not specific to pregnancy

If a pregnancy specific liver disease is not diagnosed, it is important to consider disorders incidental to pregnancy (box 2), which may require referral to a hepatologist. In the UK probably the commonest cause of abnormal liver function tests (usually an isolated stable raised alanine transaminase concentration) is fatty infiltration with or without chronic low grade inflammation (non-alcoholic steatohepatitis), which does not routinely require referral. Comparison of test results with any previous investigations before pregnancy is necessary.

<table>
<thead>
<tr>
<th>Box 1</th>
<th>Drugs that can cause liver injury and commonly used by women of childbearing age</th>
</tr>
</thead>
</table>
| Hepatocellular damage (typically greatly increased alanine and aspartate transaminase levels, and variably increased total bilirubin) | • Paracetamol  
• Methyldopa  
• Antibacterial drugs (amoxicillin, co-amoxiclav)  
• Propylthiouracil  
• Nevirapine  
• Highly active antiretroviral therapy |
| Cholestatic damage (typically increased alanine and aspartate transaminase levels, increased total bile acids, variably increased total bilirubin and y-glutamyltransferase) | • Antibacterial drugs (amoxicillin, co-amoxiclav, fluoxacinil)  
• Progestogens and oestrogens  
• First and second generation antipsychotics  
• Proton pump inhibitors |
important, and the absence of symptoms or other abnormalities on liver function tests may be helpful in distinguishing non-alcoholic steatohepatitis from other liver disease.

Outcome
A repeat blood sample taken from the patient one week later showed total bilirubin concentration 6 μmol/L, alkaline phosphatase 170 IU/L, alanine transaminase 65 IU/L, γ-glutamyltransferase 32 IU/L, and serum total bile acids 30 μmol/L (reference ranges given in table 1). The prothrombin time was normal. A provisional diagnosis of intrahepatic cholestasis of pregnancy was made, and the woman was referred to the obstetric unit for review the next day. Further investigations (table 3) did not show any other cause for this woman's abnormal liver function tests, and a diagnosis of intrahepatic cholestasis of pregnancy was made.

Liver function tests and total bile acids were monitored weekly, following the Royal College of Obstetricians and Gynaecologists guidelines. Monitoring is undertaken with the aim of detecting a rapid rise in total bile acids (to >40 μmol/L), known to be associated with adverse perinatal outcomes in intrahepatic cholestasis of pregnancy. A marked deterioration in maternal liver function should also alert the clinician to the possibility of other underlying hepatic disorders that might cause maternal decompensation.

By 36 weeks' gestation, the patient's alanine transaminase concentration had increased to 160 IU/L and total bile acids to 86 μmol/L. The woman went into spontaneous labour at 36 weeks, delivering a healthy male infant. 

Table 3 | Typical pattern of liver function tests, and additional investigations, in women with liver diseases specific to pregnancy

<table>
<thead>
<tr>
<th>Pattern of liver function test changes</th>
<th>Likely diagnosis</th>
<th>Estimated proportion of pregnant women with abnormal liver function tests who have the diagnosis (%)</th>
<th>Recommended additional investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine transaminase increased (1.5 to 6-fold) Total serum bile acids increased (1.5 to 15-fold) Total bilirubin usually normal</td>
<td>Intrahepatic cholestasis of pregnancy (also known as obstetric cholestasis)</td>
<td>17</td>
<td>Hepatitis C etiology</td>
</tr>
<tr>
<td>Alanine transaminase increased (2 to 5-fold) Total serum bile acids usually normal Total bilirubin usually normal</td>
<td>Pre-eclampsia with hepatic impairment</td>
<td>49</td>
<td>Blood pressure (increased in most)</td>
</tr>
<tr>
<td>Alanine transaminase increased (2 to 30-fold) Total serum bile acids usually normal Total bilirubin increased (1.5 to 10-fold)</td>
<td>HELLP syndrome</td>
<td>22</td>
<td>Blood pressure (increased in most)</td>
</tr>
<tr>
<td>Alanine transaminase increased (3 to 15-fold) Total serum bile acids usually normal Total bilirubin increased (4 to 15-fold)</td>
<td>Acute fatty liver of pregnancy</td>
<td>4</td>
<td>Blood pressure (increased in most)</td>
</tr>
<tr>
<td>Alanine transaminase increased (2 to 5-fold) Total serum bile acids usually normal Total bilirubin usually normal</td>
<td>Hyperemesis gravidum (severe intractable vomiting)</td>
<td>8</td>
<td>Serum Na⁺ (decreased) Serum K⁺ (decreased) Thymol (increased), TSH (greatly decreased)</td>
</tr>
</tbody>
</table>

TRELP: thrombosis, elevated liver enzymes, and low platelets, TSH: thyroid-stimulating hormone.
*During a 15 month study of a total of 4 377 deliveries, 142 women (3%) with 206 diagnoses were found to have abnormal liver function tests: of these, 138 diagnoses were pregnancy-specific liver disease (Ch'ng et al 2002). One other woman had hepatic infarct or haematoma 15 symptoms of thyrotoxicosis rarely seen. TSH is normally suppressed during first trimester but is detectable in uncomplicated pregnancy. Thyroid function tests do not need to be checked in cases of non-severe nausea and vomiting in early pregnancy.
A PATIENT’S JOURNEY

From haemochromatosis to liver transplant

Mike Davis,1 Phaedra Maria Tachtatzis2

This patient describes the limitations of being on a waiting list for transplant and his experiences after surgery

My journey began in 2003 when my doctor spotted a slight abnormality in routine blood tests during monitoring of my type 2 diabetes. I was referred to a gastroenterologist who, after further investigations, diagnosed haemochromatosis. Over the next few months I had venesection on a weekly basis and my condition stabilised, with ferritin levels slightly below normal. I subsequently had the occasional review and in 2009 I experienced a gastrointestinal bleed caused by portal hypertension. Investigations indicated that I had cirrhosis and this would be monitored.

In early 2011 I combined a working visit to Mexico with a holiday and before going I had routine scans. I was told that I would hear if there were any problems.

On my return in the early hours of 14 April I listened to increasingly urgent recorded messages for me to contact Blackpool Victoria Hospital. Eventually, consultations with the gastroenterologist confirmed that I had a small liver tumour and that I would need an urgent referral to the liver unit at St James’s University Hospital in Leeds. My appointment was on 3 May.

The diagnosis was a shock and I spent the following nine months somewhat emotionally numb. Consultations came and went over the next few weeks, confirming that I needed a transplant and that I would be recommended to go on the transplant list. Waiting for the results of the meeting was tense—the decision was delayed twice—and there was no clear indication of how decisions were made. The possibility that I was close to the top of the list made my family and I rethink about travel. Although there had been apparent openness in discussions with consultants, there had been no clear explanation of how decisions were made about transplant: the UKELD (United Kingdom end stage liver disease) score was never referred to, for example. Clearly I met the criteria.

My family and I decided to restrict our travel to the United Kingdom, within three hours’ travel time of Leeds. We booked to spend three days in Chester in December and were on our second day when the phone rang at about 10 30 pm and I was told that there was a good chance of a
The overall experience, however, was not pleasant and I mentioned it to my consultant on ward rounds later that day. She decided to give me a sleeping tablet along with my other medications. The impact of this was remarkable. At the time of the operation I had not had an alcoholic drink for almost 12 months. The sleeping tablet had the same effect as two large glasses of red wine and very quickly. My contemporary recollection was that I did not sleep very much, but this is probably not the case. I did, however, have a distinct series of full blown hallucinations. Professionally, I am a medical educator and have an interest in simulation. My hallucination, which I acted out, had me running a real time simulation in the liver ward: all the patients, doctors, and nurses were participants and were following the outline of, but an unspecified, script which seemed to require them to do what they normally did. However, my recollection is that I observed (unspecified) suboptimal performance and decided to cut the simulation short, telling participants that we were going to resume at 6:13 am (this time was quite specific). After a period of sleep (my bed had been moved to a new location), I awoke to find that the deadline had passed and nobody had restarted the simulation. I could not understand this and spent time watching someone construct a bar chart using tiny pieces of coloured paper and putting the end product in a window of the nurses’ station. This experience had a profound and vivid effect on me and it represents the beginning of a major transition in my recovery. As with the earlier hallucinations, I was aware that there were competing realities. Willingly “suspending disbelief,” I was acting out the simulation and having conversations with the nursing staff, but with a realisation that there was another, more real, reality in the background, and occasionally I would occupy this mental space as I watched my invented reality unfold. In other words, part of me was observing the hallucination.

Following this, I became increasingly alert and engaged with an active process of recovery. I walked around the ward, did chair bound exercises, and took an active interest in ward life. I wrote a letter to the Guardian (which was published) about the need for more people to join the donor register.

I was discharged 10 days after my operation and continued a relatively quick recovery. I work from home for much of the time and I tentatively returned to my computer. I attended my first work related course in Manchester in mid-January and gave two lectures. By the end of the month I had my first full day course and by the end of February a three day course.

The diagnosis of a major illness is an important life event, particularly when the illness is symptom free. Throughout the nine months from my diagnosis to the transplant I never felt ill and this made it easier to push the condition to one side and get on with normal life. In marked contrast, I was now someone with an illness, some minor symptoms, a significant drug regimen, and a long list of injunctions against what I could do and eat. Some of these made sense; others (sparkling bottled water but not still) made no sense at all.

I am, of course, still a transplantee and will be overseen by the liver transplant team at St James’s hospital for the rest of my life. This is not a problem and I welcome its support and encouragement. The team’s positive outlook and active engagement in my case feels incredibly supportive and mitigates any of the minor failings I experienced during my stay on the ward.

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