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PRACTICE

RATIONAL TESTING

Abnormal liver function tests in pregnancy

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This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor, head of department of academic endocrinology, diabetes, and metabolism, Hull York Medical School; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. To suggest a topic for this series, please email us at practice@bmj.com.

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.

Other follow-up tests should include initial investigations directed toward the symptoms, as detailed below and in tables 2⇓ and 3⇓. In the present case these may include:

- Serum total bile acids (measured in a random blood sample)—Normally present at low concentrations in the peripheral circulation because of efficient hepatic first-pass clearance. The reference range usually quoted (<14 μmol/L) allows for the modest increase seen postprandially, so any increase above this is a sensitive marker of hepatic or post-hepatic cholestasis.
- γ-glutamyltransferase—Derived principally from the bile ducts, it is a sensitive test of liver dysfunction, and so a normal value helps to reassure that any increase in alkaline phosphatase concentration is physiological and not pathological.

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 exclude

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Learning points

- Symptoms and signs associated with the commonest pregnancy-specific liver diseases are pruritus, upper abdominal pain, and jaundice
- Reference ranges for liver function tests for alanine and aspartate transaminases, bilirubin, and alkaline phosphatase are different in pregnancy
- Abnormal liver function tests in conjunction with relevant symptoms or signs should result in referral to secondary care, as should raised serum bile acids or coexistent hypertension or proteinuria
- Palmar erythema, spider naevae, and isolated raised alkaline phosphatase in the third trimester can occur in uncomplicated pregnancy and do not usually require further investigation

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.[5 6] Raised bile acid concentrations, but not alanine transaminase, are predictive of adverse pregnancy outcome.[5 6] 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,[7] but these liver abnormalities are rarely the presenting feature and are not strongly predictive of maternal or fetal outcome.[8] 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[9] 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 ($<100\times10^9$/L) and is not usually made in primary care. It is associated with high maternal and perinatal mortality.[10] Haematological and biochemical indices are useful for monitoring ongoing severity of disease but are not independent predictors of adverse outcome.[11] 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.[12] 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.[12] 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.[13] 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),[14] 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 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.

Box 1: Drugs that can cause liver injury and commonly used by women of childbearing age

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 γ-glutamyltransferase)

- Antibacterial drugs (amoxicillin, co-amoxiclav, flucloxacillin)
- Progestogens and oestrogens
- First and second generation antipsychotics
- Proton pump inhibitors

Box 2: Incidental liver disease that may present during pregnancy

- Non-alcoholic steatohepatitis
- Gallbladder disease; cholangitis
- Viral hepatitis (hepatitis A, B, C, or E)
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Budd-Chiari syndrome
- Autoimmune hepatitis

Note that other multisystem conditions (such as sepsis or cardiac failure) may also present with abnormal liver function tests

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.[15] 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.[5 6] 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. The woman's symptoms resolved rapidly postpartum. Her liver function tests and total bile acids were re-checked six weeks postnatally and were normal. This remains an important final check: liver diseases specific to pregnancy should resolve after delivery. Persistence of abnormal liver function tests in the postnatal period should prompt a further search for other liver disease not related to pregnancy.

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Tables

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

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

Adapted from Girling et al 1997,[1] Walker et al 2002,[2] and Nelson-Piercy 2010.[3] (Non-pregnant reference ranges will be specified locally and may differ from those quoted here).

Table 2| Typical symptoms associated with abnormal liver function tests in pregnancy and likely associated diagnosis

Symptom	Likely diagnosis	Other possible diagnoses
Pruritus	ICP	Pre-eclampsia, AFLP, biliary obstruction, pre-existing hepatobiliary disease (PBC, PSC), DILI
Epigastric pain Nausea and vomiting (2nd and 3rd trimesters) Headache Visual disturbance	Pre-eclampsia, HELLP syndrome, AFLP	Gallbladder disease, cholangitis, viral hepatitis
Nausea and vomiting (1st trimester)	Hyperemesis gravidarum	Viral hepatitis
Jaundice	Viral hepatitis	HELLP syndrome, gallbladder disease, cholangitis, DILI Rarely ICP, AFLP, pre-eclampsia
Pale stools and dark urine	Biliary obstruction secondary to gallstone disease	ICP, cholangitis, viral hepatitis, other rare causes of biliary obstruction

ICP=intrahepatic cholestasis of pregnancy, AFLP=acute fatty liver of pregnancy, PBC=primary biliary cirrhosis, PSC=primary sclerosing cholangitis, DILI=drug induced liver injury, HELLP=haemolysis, elevated liver enzymes, and low platelets.

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

Pattern of liver function test changes	Likely diagnosis	Estimated proportion of pregnant women with abnormal liver function tests who have the diagnosis (%)*	Recommended additional investigations
Alanine transaminase increased (1.5–8-fold) Total serum bile acids increased (1.5–15-fold) Total bilirubin usually normal	Intrahepatic cholestasis of pregnancy (also known as obstetric cholestasis)	17	Hepatitis C serology Antimitochondrial and anti-smooth muscle antibodies Abdominal ultrasonography
Alanine transaminase increased (2–5-fold) Total serum bile acids usually normal Total bilirubin usually normal	Pre-eclampsia with hepatic impairment	49	Blood pressure (increased in most) Urine analysis for protein Creatinine (increased) Platelets (decreased)
Alanine transaminase increased (2–30-fold) Total serum bile acids usually normal Total bilirubin increased (1.5–10-fold)	HELLP syndrome	22	Blood pressure (increased in most) Urine analysis for protein (positive in most) Creatinine (increased) Platelets (decreased in all) Lactate dehydrogenase (increased) Haemoglobin (decreased)
Alanine transaminase increased (3–15-fold) Total serum bile acids usually normal Total bilirubin increased (4–15-fold)	Acute fatty liver of pregnancy	4	Blood pressure (increased in most) Urine analysis for protein (positive in most) Creatinine (increased) Platelets (decreased) White blood cell count (increased) Plasma glucose (decreased)
Alanine transaminase increased (2–5-fold) Total serum bile acids usually normal Total bilirubin usually normal	Hyperemesis gravidarum (severe intractable vomiting)	8	Serum Na^+ (decreased) Serum K^+ (decreased) Thyroxine (increased), TSH (greatly decreased)†

HELLP=haemolysis, elevated liver enzymes, and low platelets, TSH=thyroid stimulating hormone.

*During a 15 month study of a total of 4377 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[4]). One other woman had hepatic infarct or haematoma.

†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.