Liver disorders during pregnancy

The liver function test abnormalities most often seen in pregnancy are those which are pre-existing, particularly those associated with chronic hepatitis C and nonalcoholic fatty liver disease.

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Liver function tests (LFTs) normally change during pregnancy. The mother's blood volume increases by 40% and her total body water increases by 20%; this is reflected in a 10 to 60% fall in serum albumin and a fall in haemoglobin. Because of the increased circulating oestrogen, up to 50% of women develop spider naevi and palmar erythema during pregnancy, which reverses quickly after delivery. Serum alkaline phosphatase increases two to fourfold in the third trimester (placental) and gamma glutamyltranspeptidase may decrease slightly (Table 1). No change is normally observed in the aminotransferases or the prothrombin time, and a rise in aminotransferase levels should prompt further investigation.

The best guide in determining the cause of abnormal LFTs is the timing of the problem during pregnancy (see the flowchart on page 40). The differential diagnoses include:

- liver diseases unique to pregnancy – generally occur in the third trimester (Table 2)
- liver diseases occurring concomitantly – can occur any time during pregnancy (Table 3)
- pre-existing chronic liver problems (Table 4).

During pregnancy, the bile becomes more lithogenic, with the result that cholecystitis and cholelithiasis are more common in pregnant than nonpregnant women. These conditions can present with right upper quadrant pain, nausea and abnormal LFTs, and should be included in any differential diagnosis. Gallstone pancreatitis may also occur, and can happen any time during pregnancy and in the early postpartum period.

Liver diseases unique to pregnancy

Hyperemesis gravidarum (morning sickness) is not a liver disease but an affected patient may have elevated aminotransferase levels. The condition classically occurs in the first trimester and resolves by about week 20, and is usually worse in twin and first pregnancies. The LFT abnormalities improve on fluid and electrolyte management.

Cholestasis of pregnancy

Cholestasis of pregnancy is the most common liver disease unique to pregnancy. The incidence is about one in 500 pregnancies (0.2%) in Australia but is much higher in Scandinavia and South

IN SUMMARY

- **During pregnancy a woman's albumin level normally decreases and her alkaline phosphatase level normally increases.**
- **Abnormal transaminase levels and prothrombin time indicate liver pathology.**
- **Think of cholestasis in pregnancy in women with an itch in late pregnancy; check the bile acids.**
- **Development of nausea and abdominal pain in late pregnancy could indicate serious liver problems.**
- **Pregnant and postpartum women have an increased risk of cholelithiasis.**

America (a 14% risk in Chile). It is characterised by pruritus and an increase in the serum bile acids.

The condition is usually seen in the third trimester, and women present with an itch without any skin lesions, although there may be scratch marks (Figure 1). There may be a history of mothers or sisters with the same problem, and it may have occurred in previous pregnancies. The itch normally goes within days after delivery.

Investigations

Itch is the only symptom. If there is a history of pain, cholelithiasis should be excluded. Check to see if there are any skin lesions and order fasting bile acids, LFTs and upper abdominal ultrasound. Also check that the woman is not taking any drugs or herbs that could cause hepatotoxicity. Rarely, thyrotoxicosis or primary biliary cirrhosis can present with an itch during pregnancy; these can be excluded by thyroid function tests and antimitochondrial antibodies, respectively, especially if the problem does not resolve postpartum.

A liver biopsy is not necessary for the diagnosis, but liver histology would show intracanalicular cholestasis, without inflammation or liver damage (Figures 2a and b). The hepatocyte and the bile canalicular membranes become slightly leaky during a normal pregnancy; this is more pronounced in women with a genetic predisposition.

Table 1. Normal changes in LFTs during pregnancy

Blood test	Normal change during pregnancy
Alkaline phosphatase	Twofold to fourfold increase
Gamma glutamyltranspeptidase	No change or slight decrease
Aspartate aminotransferase	No change
Alanine aminotransferase	No change
Bilirubin	No change or slight increase
Bile salts	No change
Albumin	10 to 60% decrease
Globulin	Increase
Ceruloplasmin	Increase
Prothrombin time	No change
Cholesterol	Twofold increase
Triglycerides	Threefold increase

Table 2. Liver diseases unique to pregnancy

Disease	Incidence	Pathology	Maternal mortality	Fetal mortality	Postpartum recovery	Recurrence in subsequent pregnancies
Cholestasis of pregnancy	1 in 500 pregnancies in Australia; higher in Scandinavia and South America	Centrilobular cholestasis, canalicular bile plugs	Unaffected	About fivefold increase	Complete	70%
Pre-eclampsia	10% of cases (5 to 10% of all pregnancies) will have LFT abnormalities	Sinusoidal fibrin deposition, periportal haemorrhage and necrosis	Variable	Variable	Complete	Sometimes
HELLP*	0.2 to 0.6% of all pregnancies; about 20% of severe eclampsia cases	Sinusoidal fibrin deposition, periportal haemorrhage and necrosis	3 to 5%	35%	Complete	3 to 19%
Acute fatty liver of pregnancy	Rare (1 in 13,000 pregnancies)	Microvesicular fatty infiltration in zones 2 and 3	15%	36%	Complete	Very rare

* HELLP = Haemolysis, elevated liver enzymes and low platelet syndrome.

continued

Table 3. Liver diseases occurring concomitantly during pregnancy

Disease	Change during pregnancy	Conception rates	Management	Effects on fetus
Acute hepatitis A, B and C	Acute hepatitis B may be severe in third trimester	No change	Supportive	Depends on mother's health
Acute hepatitis E	Increase in fulminant cases in third trimester	No change	As for fulminant liver failure	Depends on maternal status
Herpes simplex virus	High fetal mortality	No change	Viral swabs, intravenous aciclovir	Vertical transmission may occur
Focal nodular hyperplasia/hepatic adenomas	Increase in size, may rupture	No change	If large, consider surgical removal before pregnancy	Relates to maternal health
Alcoholic liver disease	Probably none	Decreased fertility	Stop alcohol consumption	Fetal alcohol syndrome, liver dysfunction in some cases

Table 4. Liver diseases existing before pregnancy

Disease	Change during pregnancy	Conception rates	Management	Effects on fetus
Cirrhosis and portal hypertension	0 to 20% maternal mortality from liver failure, variceal haemorrhage	Decreased fertility	Close monitoring required	Increased prematurity and miscarriage
Extrahepatic portal hypertension	Probably increased risk of variceal haemorrhage in third trimester and labour	No change	May need oesophageal banding or beta blockers	Fetal risk related to maternal risk of haemorrhage
Chronic hepatitis B	None	Normal fertility	Hyperimmune gamma globulin plus hepatitis B vaccine at birth	Very low chance of hepatitis B virus transmission *in utero*
Chronic hepatitis C	Decrease in aminotransferases	Normal fertility	No change	5% vertical transmission (15% vertical transmission if HIV plus hepatitis C virus coinfection)
Autoimmune chronic active hepatitis	None, unless cirrhotic	Decreased fertility	Continue corticosteroids +/- azathioprine Close monitoring required	Azathioprine: slightly increased miscarriage and perinatal death
Wilson's disease	None, unless cirrhotic	Decreased fertility	Continue chelating agent (penicillamine) Close monitoring required	Some congenital defects on penicillamine
Nonalcoholic fatty liver	None	No change	No change	Nil

Figure 1. Cholestasis of pregnancy causes a severe itch in the mother and an increased risk of preterm labour and stillbirth.

A guide to diagnosing liver disorders in pregnancy

Pregnant patient has abnormal LFTs*

- Abnormal LFTs present before pregnancy
  - Patient has pre-existing liver disease:
    - chronic hepatitis B
    - chronic hepatitis C
    - autoimmune chronic active hepatitis
    - Wilson's disease
    - nonalcoholic fatty liver disease
- Abnormal LFTs commenced in third trimester
  - Patient probably has a liver disorder unique to pregnancy:
    - cholestasis of pregnancy
    - pre-eclampsia with liver involvement (HELLP)†
    - acute fatty liver of pregnancy
- Abnormal LFTs commenced anytime during pregnancy
  - Patient has a concomitant liver disorder:
    - acute viral hepatitis
    - cholelithiasis
    - hepatic adenomas and focal nodular hyperplasia
    - Budd–Chiari syndrome
    - alcohol problems

*LFTs = liver function tests; †HELLP = haemolysis, elevated liver enzymes and low platelet syndrome.

Risks to the mother

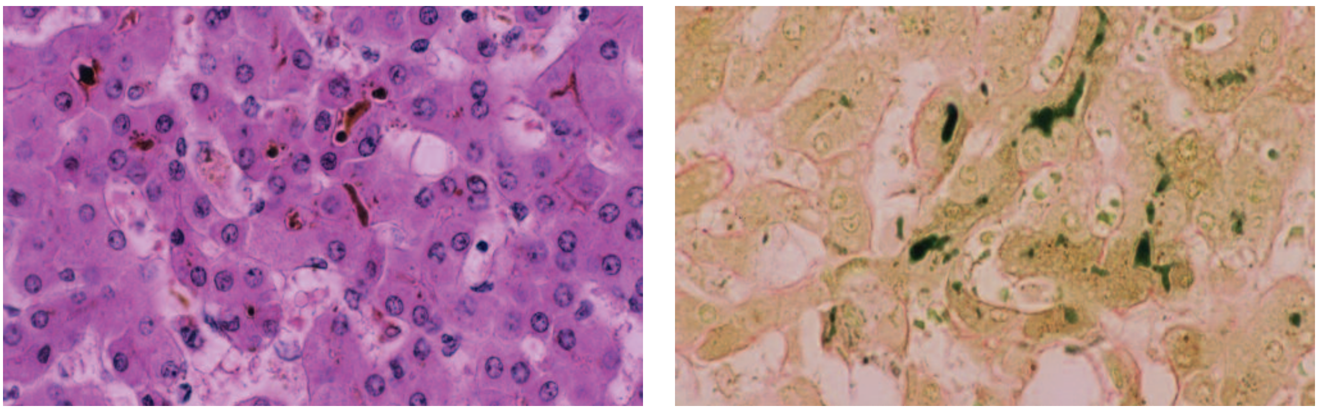
Apart from a severe itch, cholestasis of pregnancy does not affect the mother. Some women may develop LFT abnormalities – the bilirubin may rise to 100 μmol/L and serum aminotransferases increase to two to 10 times the upper limit of normal – but there is not an associated increased risk of liver failure. There is, however, an increased risk of a postpartum haemorrhage, and a 70% chance of recurrence during a subsequent pregnancy.

Risks to the baby

Overall cholestasis of pregnancy increases fivefold the risk of preterm labour and stillbirth. Fetal monitoring does not predict babies at risk. When the total bile acids are 40 μmol/L or greater, fetal complications can occur. Women with this condition are normally delivered at 38 weeks, to decrease the fetal risk.

Treatment

Women in whom cholestasis of pregnancy occurs earlier than week 36 of pregnancy or those with high levels of bile acids should be offered treatment. Early studies have shown that ursodeoxycholic acid (Urso - falk) used at a dose of 15 to 25 mg/kg/day in divided doses can improve both the mother's itch and the fetal outcome. Other



Figures 2a and b. Liver histology, cholestasis of pregnancy. a (left). H and E stain. b (right). Fouchet's stain.

treatments, such as antihistamines, are not effective.

Pre-eclampsia and the HELLP syndrome

About 10% of women with pre-eclampsia (which occurs in 5 to 10% of all pregnancies) have minor LFT abnormalities. Pre-eclampsia is characterised by hypertension and proteinuria, usually during the third trimester of the first pregnancy.

The haemolysis, elevated liver enzymes and low platelet syndrome (HELLP) occurs in 0.2 to 0.6% of all pregnancies, and in about 20% of women with severe pre-eclampsia. One-fifth of cases occur postpartum. Usually women present after week 32 with anorexia, nausea, right upper quadrant pain and/or bleeding from gums and intravenous access sites. The platelet count is 100,000/mm^3 or less, and the blood film is consistent with haemolysis. Aminotransferases are elevated and the prothrombin time may be normal unless complicated by disseminated intravascular coagulation (DIC). The symptoms can be nonspecific, and the condition may not be diagnosed until blood tests are done for pre-eclampsia.

The liver problem in pre-eclampsia and HELLP relates to microvascular blood changes. These changes lead to vasospasm and endothelial damage, which can cause hepatic infarcts, which in turn can precipitate thrombosis from DIC, worsening the problem. The histology shown in Figures 3a and b demonstrates small vessel thrombosis and areas of haemorrhage and ischaemia.

The management is expedient delivery. If the condition occurs before 34 weeks' gestation, the mother needs to be monitored in an intensive care setting with intravenous dexamethasone (Dexamethasone Sodium Phosphate Injection USP) for fetal lung maturity, and delivery as soon as practicable. A fetal mortality rate as high as 35% has been reported.

The differential diagnoses include viral hepatitis, autoimmune thrombocytopenia and systemic lupus erythematosus, as well as acute fatty liver of pregnancy.

Acute fatty liver of pregnancy

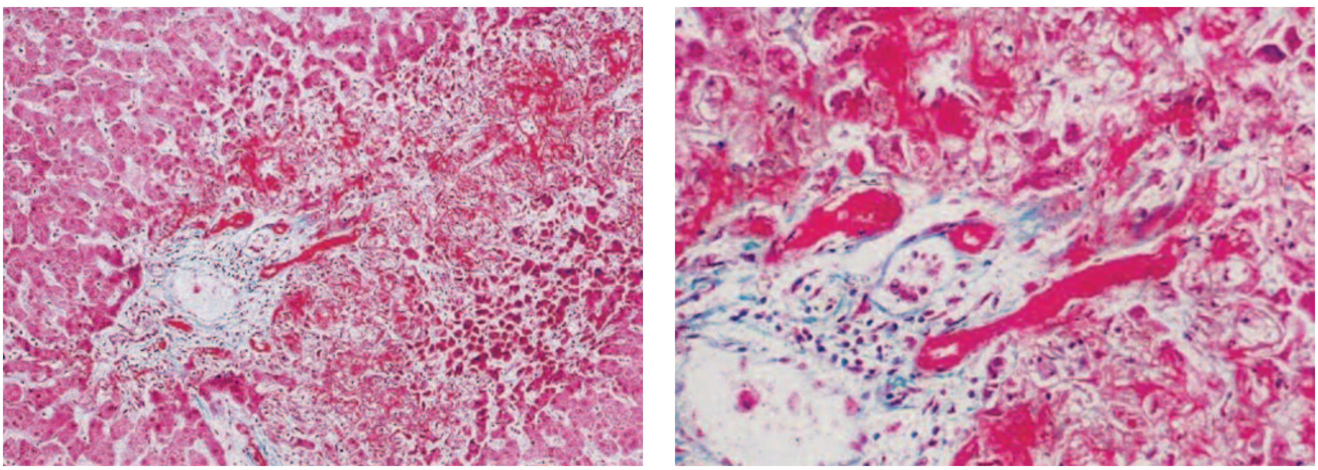
Acute fatty liver of pregnancy (AFLP) occurs in one in 13,000 pregnancies, typically in late pregnancy. Symptoms include malaise, vomiting and abdominal pain, and jaundice may be evident. Coagulopathy, moderately elevated aminotransferases (500 U/L or below) and renal dysfunction are common, and uric acid is increased. There will be severe hepatic dysfunction manifested by profound hypoglycaemia and high ammonia levels. DIC is almost universal, and the condition may progress to fulminate liver failure with death of the mother and baby.

Women with AFLP should be managed in a specialty obstetric unit. Expedient delivery is the usual course of action. Although the pathogenesis is unclear, the oxidative stress of pregnancy may cause defective mitochondrial fatty acid oxidation. Liver histology shows microvesicular steatosis; this is seen more obviously using the fat stain Oil Red O (Figures 4a and b).

After the delivery, the mother should make a full recovery without any long term sequelae, although this may take up to a month. The condition was thought not to recur, but there are occasional reports of an associated mitochondrial fatty acid oxidation enzyme deficiency in both mother and baby that would make these women at risk of recurrence (see below).

Fatty acid oxidation enzyme deficiency and severe maternal liver disease

About 20% of babies born to mothers with acute fatty liver of pregnancy have a homozygous deficiency of long chain 3-hydroxyacyl-CoA dehydrogenase. This enzyme is needed for fatty acid oxidation at the mitochondria to produce glucose during periods of fasting. These babies are at risk of sudden death from hypoglycaemia, and develop severe microvesicular



Figures 3a and b. Liver histology, HELLP (H and E stain). a (left). Low power. b (right) Higher power.

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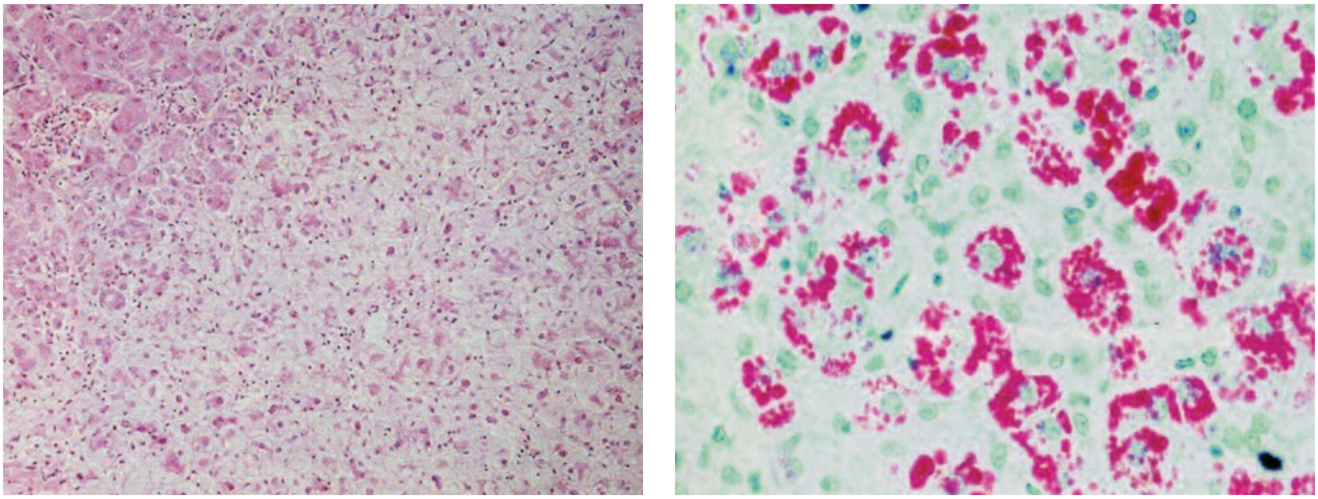

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Figures 4a and b. Liver histology, acute fatty liver of pregnancy. a (left). H and E stain. b (right). Oil red O stain.

steatosis in the liver, heart and skeletal muscles, dying within months.

The mother is heterozygous for this enzyme deficiency. The stress of pregnancy and carrying a baby homozygous for the enzyme deficiency puts her at risk of severe liver disease, AFLP and HELLP.

Women and babies from these complicated pregnancies should be screened and genetic counselling should be offered.

Liver diseases occurring concomitantly

Liver disorders that occur concomitantly with pregnancy are the hepatic problems associated with pregnancy most likely to be seen in general practice.

Women of childbearing age who are alcohol dependent do not usually have liver problems. They should, however, be counselled about the risks to a pregnancy of drinking alcohol as continued drinking puts the baby at risk of the fetal alcohol syndrome.

Acute viral hepatitis

Acute viral hepatitis can occur any time during pregnancy. Most cases are due to hepatitis A virus infection, but occasionally hepatitis B or C viruses will be the cause. Epstein–Barr virus and cytomegalovirus can be associated with a mild hepatitis. Rarely, hepatitis is seen with the conditions herpes simplex and herpes zoster. Herpes simplex hepatitis can be severe in pregnancy; a rash will be seen and treatment with intravenous aciclovir (Acihexal Intravenous Infusion, Zovirax Intravenous Infusion) is recommended. A history of intravenous drug use, recent travel or illnesses in other family members supports a diagnosis of viral hepatitis. Skin lesions (such as herpes) and stigmata of chronic liver disease may be apparent on examination.

Hepatitis E has a high association with fulminant hepatitis in the third trimester of pregnancy. This should be considered in women returning from regions where hepatitis E is seen, such as the Indian subcontinent.

Hepatic adenomas and focal nodular hyperplasia

Hepatic adenomas and focal nodular hyperplasia are rare, occurring in one in one million women. They are usually asymptomatic and may be picked up on a routine ultrasound. If diagnosed before conception, it is recommended that they are removed if they are greater than 6 cm in diameter, as they may increase in size during pregnancy and then spontaneously rupture.

Budd–Chiari syndrome

Pregnancy heightens a procoagulant status. Pregnant women with a thrombophilic condition are at risk of hepatic vein thrombosis (Budd–Chiari syndrome), and will present with an enlarged, tender liver and ascites. Budd–Chiari syndrome has a poor outcome and affected women need to be managed in a specialty unit. Fortunately, the condition is rare.

Pre-existing chronic liver disease

While most women with chronic liver disease are not of childbearing age, those that are usually have a lower fertility rate due to the liver disease.

Of women with chronic liver disease who do become pregnant, those with liver cirrhosis have an increased risk of hepatic decompensation and preterm delivery, and need to be closely monitored during pregnancy. If the mother has portal hypertension, a gastroscopy is recommended to see if she has oesophageal varices. If oesophageal varices are present, depending on their size and the risk of haemorrhage, prophylactic banding and/or nonselective beta blockers may be recommended. Women with noncirrhotic portal hypertension have normal fertility but are at risk of a complicated pregnancy, and should be counselled.

continued

Chronic hepatitis B

Hepatitis B serology (hepatitis B virus [HBV] surface antigen) is usually part of routine antenatal screening in Australia. If chronic hepatitis B is diagnosed at screening, the patient should be referred if necessary and other family members checked.

In previously diagnosed patients, LFTs and markers of viral replication (that is, HBV e antigen and/or DNA) should be checked. The baby will receive vaccination and hyperimmune gamma globulin (Hepatitis B Immunoglobulin) at birth, and then follow up vaccinations. The risk of vertical transmission drops to 5% in vaccinated babies.

Chronic hepatitis C virus

Women with chronic hepatitis C usually give a history of previous intravenous drug use. Routine antenatal screening in Australia generally includes hepatitis C serology (hepatitis C virus [HCV] antibody test).

LFTs and HCV-RNA status should be checked in women who are positive for HCV antibody (that is, anti-HCV positive). There is a 5% risk of vertical transmission in women who are HCV-RNA positive. This rate is possibly influenced by the mode of delivery but as yet there are no recommendations for preferred mode of delivery. Breastfeeding, however, appears to be safe.

The liver enzymes in patients with hepatitis C decrease during pregnancy. These women need to be tested after delivery to get a more representative picture of how hepatitis C affects their liver.

The usual treatments for hepatitis C, pegylated interferon and ribavirin, are contraindicated in pregnancy, and a hepatitis C vaccine has not yet been developed.

Autoimmune chronic active hepatitis and Wilson's disease

Both autoimmune chronic active hepatitis and Wilson's disease (also called hepatolenticular degeneration) can occur in young women. Pregnancy should be timed and the severity of liver disease assessed. Immunosuppressive drugs should be maintained in those with autoimmune chronic active hepatitis, and chelating agents (penicillamine [D-Penamine]) in those with Wilson's disease.

Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis

Nonalcoholic fatty liver disease (NAFLD) and its more severe form, nonalcoholic steatohepatitis (NASH), are the most common causes of LFT abnormalities in the general community – as obesity rates rise, so does the incidence of the associated liver problems. Liver histology in NAFLD and NASH shows macrovesicular fat, with or without an inflammatory reaction and increased fibrosis (fibrosis is the characteristic histological feature seen in NASH). These histological changes are similar to the histology seen with alcohol damage. In contrast, the histological features seen with AFLP are distinct (microvesicular steatosis).

NAFLD and NASH remain stable throughout pregnancy and postpartum. The aminotransferases and gamma glutamyltranspeptidase are minimally elevated, and an ultrasound may show a hyperechoic liver consistent with fatty infiltration. Cirrhosis is unlikely to be seen in this age group. Affected women may give a family history of maturity onset diabetes, and have a higher body mass index and increased risk of hypertension, diabetes and cholelithiasis.

Conclusion

General practitioners should be aware that pregnant women with serious liver problems might present with nonspecific symptoms of nausea and abdominal discomfort in late pregnancy. The diagnosis is guided by the timing of the symptoms during the pregnancy and associated features. A liver problem may occur coincidentally with the pregnancy, or be specifically related to the pregnancy.

Interpreting LFTs during pregnancy can be difficult. The normal physiological changes during pregnancy (such as decrease in albumin, increase in alkaline phosphatase and slight decrease in gamma glutamyltranspeptidase) need to be considered. However, changes are not normally seen in aminotransferase levels, so a rise in these enzymes should prompt searching for a cause. MT

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