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Liver disease in pregnancy

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Liver dysfunction discovered during pregnancy causes great anxiety to the patient, her family and sometimes her medical attendants. Liver disease is foreign territory to most obstetricians, while the duty physician whose opinion is sought out of hours may have only hazy knowledge of obstetric liver problems. The first on the scene is usually the on-call medical team. This review is designed to provide a guide in diagnosis and management of this relatively common problem.

Liver dysfunction can appear at any point in pregnancy and the timing is often helpful in diagnosis. There are three broad categories to consider:

- liver dysfunction specific to pregnancy
- hepatobiliary problems which occur more frequently in pregnancy (eg gallstones) or run a more serious course (eg acute hepatitis E)
- coincident liver disease which may affect management or have implications after delivery (eg chronic hepatitis B and C).

Most cases are in the first category and this review concentrates on those. The relative frequency of each of these pregnancy-specific conditions depends slightly on geography and ethnicity but is similar in most parts of the UK. The conditions in order of frequency reported in a recent prospective study from South Wales are:[1]

- liver dysfunction related to pre-eclampsia
- haemolysis, elevated liver enzymes, and low platelet count (HELLP syndrome)
- acute fatty liver of pregnancy
- obstetric cholestasis (OC)
- hyperemesis gravidarum.

Recent epidemiological data from the UK,[1,2] Northern Europe[3,4] and USA[5,6] show that OC and acute fatty liver of pregnancy (AFLP) are commoner than previously believed. This apparent increase in frequency is likely to be explained by less severe cases coming to light with improved ascertainment. Many cases of liver disease in pregnancy still remain unnoticed and undiagnosed because liver function tests (LFT) are not part of routine antenatal blood testing[1] and the symptoms may not directly suggest liver dysfunction.

Key Points

- **Liver dysfunction is seen in at least 3% of pregnancies and is under-diagnosed**
- **Pregnancy-specific conditions are usually responsible**
- **Pre-eclampsia and obstetric cholestasis are common and impact on fetal mortality**
- **HELLP syndrome and acute fatty liver of pregnancy may rarely cause liver haemorrhage, liver failure and maternal death**
- **Acute fatty liver of pregnancy is more common though less catastrophic than generally perceived**
- **Boundaries between pregnancy specific liver conditions are sometimes blurred**
- **Mechanisms are poorly defined but becoming clearer; genetic defects are only detected in a minority**

KEY WORDS: acute fatty liver of pregnancy, clinical management, HELLP syndrome, hyperemesis gravidarum, incidence, intrahepatic cholestasis of pregnancy, liver disease, pre-eclampsia, pregnancy, obstetric cholestasis

Liver dysfunction in pre-eclampsia

Pre-eclampsia is defined as the triad of hypertension, proteinuria and oedema occurring after 20 weeks gestation. It affects 5–10% of pregnancies, especially primiparae, and is characterised by defective placentation, endothelial dysfunction, activation of the coagulation system and microvascular impairment. The liver, though affected, does not usually bear the brunt of the damage.[7] The kidneys, lungs and brain are the most vulnerable organs. The more severe the pre-eclampsia, the greater the likelihood of abnormal LFT, usually a modest elevation of serum transaminases and occasionally bilirubin.[1,7] This does not generally herald major hepatic problems but indicates the severity of pre-eclampsia and is a warning to monitor other affected organs.

HELLP syndrome

The acronym HELLP was devised by Weinstein in 1982[8] to define the syndrome of haemolysis, elevated liver enzymes and low platelets on a background of pre-eclampsia or eclampsia. An association with poor maternal and neonatal outcome was noted. Case definition is imprecise, which can be confusing. Two American classifications[9] are shown in Table 1.

Table 1. HELLP syndrome: classification systems to predict outcome.

Mississippi
Class I: Platelets <50 × 10^9/l
Class II: Platelets 50–100 × 10^9/l
Class III: Platelets 100–150 × 10^9/l
and:
LDH >600 u/l
AST >40 u/l
Tennessee
Complete:
Platelets <100 ×10^9/l
LDH >600 u/l
AST >70 u/l
Incomplete:
Only one or two of above

AST = aspartate aminotransferase; LDH = lactate dehydrogenase

Many reports of HELLP omit diagnostic criteria, making it hard to compare incidence and outcomes in different centres. There is agreement that nadir platelet counts and peak transaminase levels reflect disease severity and that incomplete forms of HELLP syndrome are commoner and less dangerous than the full syndrome.[8–10]

Clinical presentation

HELLP syndrome can occur from 20 weeks gestation but usually at 27–36 weeks. Patients complain of right upper quadrant or epigastric pain with nausea, vomiting and sometimes headache. General malaise is prominent and often precedes pain by a few days. The condition may be misdiagnosed as gastritis, gastro-oesophageal reflux, peptic ulcer or gall bladder disease. Such symptoms in a patient with pre-eclampsia should trigger an urgent blood count and full biochemical profile.

HELLP syndrome may also appear postpartum (ca 25% in many large series) but is probably initiated before parturition.

Laboratory findings

Thrombocytopenia is the earliest laboratory feature and the *sine qua non* of HELLP syndrome. Its appearance is sudden and precipitous. Haemoglobin is often normal initially but then falls and anaemia may be profound. Signs of haemolysis can be seen on the blood film (deformed red cells of micro-angiopathy). It is important to request clotting tests and full biochemical profile as obstetric teams tend to monitor only blood count, urea and electrolytes. LFT will show a moderately raised transaminase, usually less than 100 u/l, and bilirubin may be slightly elevated. Renal function is often impaired as the disease advances and hyperuricaemia is the rule. The clotting screen will be normal except in advanced cases where disseminated intravascular coagulation has supervened.

Management

The mainstay of treatment is delivery as the syndrome usually resolves thereafter. However, this is not always straightforward.[8–10] The decision is easiest with uncomplicated HELLP syndrome occurring after 34 weeks gestation when the fetus is almost mature and the risks of prematurity are slight. Urgent delivery by caesarean section is safest unless the patient is already in labour. Balancing maternal against fetal outcome when HELLP syndrome develops earlier in pregnancy is difficult. Medical treatments designed to gain gestational time or ameliorate the disease process have been advocated by some authors but with little trial-based evidence. Such regimens include plasma volume expansion, vasodilatation, low-dose aspirin and corticosteroids have been advocated but with little trial based evidence.

When HELLP syndrome is advanced or complicated by organ failure, urgent delivery is hazardous. The principles of management are rapid correction of fluid imbalance, hypertension, hypoxia, seizures and coagulopathy, with intensive care facilities. The aim is delivery as soon as the patient is stable. Dexamethasone is usually given to promote maturity of fetal lungs and in an attempt to alleviate the HELLP syndrome. There is no randomised controlled trial evidence to support this but it is the practice of many experienced departments based on observation.[11]

Complications

HELLP syndrome is not primarily a liver disease but a form of severe pre-eclampsia, which can lead to many serious complications (Table 2).[10] In a small proportion of cases the liver is critically involved, with subcapsular haematoma leading to liver rupture which is often fatal. Subcapsular haematoma should be managed conservatively if unruptured, but by urgent laparotomy with surgical packing if rupture ensues. The delay and dangers inherent in transfer to a hepatobiliary unit may outweigh any surgical advantage but advice from a liver unit should

always be sought at the earliest opportunity. Prodigious quantities of blood, platelets and clotting factors are required.

Outcome

Recent large series found that maternal mortality has fallen below 1% but perinatal mortality is still 10–20%.[9,10]

Acute fatty liver of pregnancy

The most feared and rarest of the pregnancy-specific liver diseases, and the one most likely to progress rapidly to hepatic failure, is AFLP. It was not widely recognised until the 1980s when there were reports from liver units in America[12] and Europe[13] of advanced liver failure and its terrible consequences in pregnancy (maternal and fetal mortality of 30–70%). Since then several groups have stressed that the disease is commoner, less severe and associated with a better outcome than portrayed in those early reports.[1,6,14] Maternal and fetal mortality has improved markedly in recent years; it is higher in reports from tertiary liver centres than obstetric or medical departments of general hospitals, reflecting referral bias (Table 3). There is no clear geographical or racial predisposition to AFLP and incidence figures are generally unreliable. The commonly quoted estimates of one in 6,600–15,000 deliveries are epidemiologically unsound as they are derived from retrospective analysis of referrals to specialist centres in North and South America. The only published prospective studies[1,14] are small but suggest an incidence of one in 1,000 in the UK.

One of the major problems with AFLP is the lack of diagnostic criteria. Early reports relied on biopsy or post-mortem liver histology. Nowadays, liver biopsy is rarely carried out and diagnosis is usually based on clinical and laboratory evidence of acute impairment of hepatic metabolic function in late pregnancy. If liver biopsy is deemed necessary, it should be done in the postpartum period when the condition is settling and the coagulopathy has resolved. The histological findings are characteristic. Architecture is not disturbed; neither inflammation nor necrosis is prominent though some cholestasis is common. Hepatocytes are swollen and foamy because of microvesicular fat, which may not be obvious without specific stains (oil red O). Microvesicular fat is dissolved by normal tissue fixing processes so frozen or non-defatted sections must be requested.

Aetiology and pathogenesis

AFLP is one of several microvesicular fat diseases affecting the liver with similarities to Reye's syndrome, certain drug toxicities and mitochondrial beta-oxidation defects. In the 1990s, several important studies showed a link between AFLP, HELLP syndrome and inherited defects of fatty acid oxidation.[18] Notably, mothers of infants born with homozygous E474Q mutations conferring long chain 3-hydroxyacyl co-A dehydrogenase (LCHAD) deficiency suffered AFLP or HELLP syndrome during pregnancy. These studies clearly demonstrated a cause for AFLP in some cases, but most subsequent work in sporadic AFLP shows maternal heterozygosity for the E474Q mutation to be infrequent and that most offspring of mothers suffering AFLP do not have LCHAD deficiency.[19,20]

The cause of AFLP remains a mystery in all but a few cases, though identified risk factors include older maternal age, primiparity, multiple pregnancy, pre-eclampsia, male fetus and previous AFLP.

Clinical features

Presentation is usually at 32–36 weeks with malaise, nausea, vomiting and upper abdominal pain. Polyuria and polydipsia are common, sometimes amounting to diabetes insipidus. In earlier reports[12,13] jaundice and encephalopathy were nearly always present but these are late features and may be avoided with prompt diagnosis and urgent delivery. Pancreatitis is probably a frequent complication of AFLP but, as its symptoms are similar to the underlying condition, it has to be tested for specifically. Examination is usually unhelpful although advanced cases may show jaundice, asterixis or ascites.

Laboratory features

Simple laboratory tests are essential to diagnosis. Almost all cases show neutrophilic leucocytosis. Platelet count is normal at the onset of AFLP but may fall as the disease progresses. Haemoglobin levels are usually normal. Hypoglycaemia, rising bilirubin, hyperammonaemia and coagulopathy are early and important features of failing liver metabolic function. Transaminase levels

Table 2. Complications of the HELLP syndrome.

Complications	Patients affected (%)
DIC	20
Placental abruption	16
Pulmonary oedema/effusion	12
Renal failure	8
Ascites	8
Other, severe	5
Liver haematoma	1
Death	1

DIC = disseminated intravascular coagulation.

Table 3. Mortality from acute fatty liver of pregnancy.

Author	Year	Ref.	Location	Maternal (%)	Fetal (%)
Kunelis[15]	1965	15	Los Angeles	75	63
Burroughs	1982	13	London	33	67
Pockros[16]	1984	16	Los Angeles	11	25
Rolfes	1985	12	Washington	6	14
Riely[17]	1987	17	New Haven	0	10
Castro	1999	6	Los Angeles	0	6
Ch'ng	2002	14	Swansea	0	0

are raised, usually modestly (2-10 times normal), which tallies with the scant inflammation and necrosis seen histologically. Renal function is often impaired and uric acid levels high.

Imaging

Ultrasound scanning and computed tomography (CT) are not especially helpful. Microvesicular steatosis is not easy to detect on CT and may not render the liver bright on ultrasound, but ascites and pancreatitis can be readily identified.

Diagnostic criteria

The previous gold standard for diagnosis, liver biopsy, has lost its pre-eminence. Microvesicular fat is not as specific for AFLP as originally believed, having been described in both pre-eclampsia and HELLP syndrome, and liver biopsy is not often clinically justifiable.[6] Table 4 shows the criteria used to diagnose AFLP in prospective studies from South Wales.[1,14] It may sometimes be difficult to differentiate AFLP from HELLP syndrome. Table 5 shows shared features and those which help to discriminate, particularly early on.

Management and outcome

There is universal agreement that AFLP resolves only after delivery. Emergency caesarean section is the quickest and most effective course of action. Intensive care is usually needed, with correction of coagulopathy, management of renal dysfunction, acidosis and sepsis, and avoidance of cerebral oedema. Maternal death is now uncommon and perinatal death should be below 10%. It is unusual, but well recorded, for AFLP to recur in subsequent pregnancies.

The possibility of inherited fatty acid beta-oxidation defects in the infant must be borne in mind. However, as discussed at the beginning of this section, the majority of cases of AFLP are obscure in origin and not associated with heritable mutations of the mitochondrial trifunctional protein.

Table 4. Diagnostic criteria for acute fatty liver of pregnancy.

Six or more of the following in absence of other cause in third trimester:

- Vomiting
- Abdominal pain
- Polyuria/polydipsia
- Encephalopathy
- Leucocytosis
- Coagulopathy
- Ascites (USS)
- Elevated bilirubin
- Hypoglycaemia
- Elevated transaminase
- Elevated ammonia
- Renal impairment
- Elevated urate
- Microvesicular fat (liver biopsy)

USS = ultrasound scan.

Table 5. HELLP versus acute fatty liver of pregnancy (AFLP).

Features in common	Discriminant features	
abdominal pain and vomiting	**HELLP:**	**AFLP:**
↑ AST ± bilirubin	platelets ↓↓	polyuria and polydipsia
↑ creatinine and uric acid	normal PT	leucocytosis
	Hb ↓	PT ↑
	abnormal blood film	glucose ↓
		ammonia ↑

AST = aspartate aminotransferase; HB = haemoglobin; PT = prothrombin.

Obstetric cholestasis

Once considered rare outside Scandinavia and Chile, OC is now increasingly recognised. There is little to suggest that its true incidence is rising – in fact, it is becoming less frequent in some high incidence areas such as Chile, possibly as a consequence of improved antenatal care and nutrition. Its emergence as a common obstetric problem is largely down to increased awareness and appropriate investigation of pruritus. Unfortunately, this new awareness is by no means universal and pruritus is still often regarded as a natural consequence of pregnancy.[21] Furthermore, the misapprehension that jaundice is a prerequisite for the diagnosis of OC persists in obstetric and medical circles. Its importance lies not in its effects on the mother but on the fetus. The prime concerns are prematurity, fetal distress and stillbirth.

OC was first described in Scandinavia in the 1950s and is apparently commoner there than in the rest of Europe and North America, though this may be partly explained by better case ascertainment. Recent publications from other parts of Europe[1-3,22] suggest similar incidences when the disease is sought with enthusiasm (Table 6). Ethnicity is a major factor, particularly in South America, but also in the UK.

Pathophysiology

OC is a condition of pure cholestasis without hepatic inflammation or

Table 6. Prevalence of obstetric cholestasis: geographic, ethnic and temporal variations.

Country	Ethnicity	Time of survey	Prevalence (%)
Sweden & Finland	White	1980s	1
Chile	Indian	1970s	27
Chile	White	1970s	15
Chile	White	1990s	1.5
France	White	1980s	0.7
UK	White	1990s	0.6
UK	Asian	1990s	1.5
Wales	White	2000s	0.6

necrosis. In most cases no single cause can be found, but there are many probable influences. There are clear ethnic variations, environmental factors, hormonal effects and a striking familial tendency (Table 7).[3]

Hormonal factors

Oestrogens and progestogens play a primary role in OC. The disease is commonest late in pregnancy and with multiple pregnancy when hormone levels are highest, resolving rapidly with falling hormone levels after delivery. It is associated with administration of exogenous progestogens. Oestrogens have been shown to be cholestatic in animal models.

Genetic factors

Much recent research has centred on gene analysis of bile transporters.[5,23,24] There are many similarities between OC and the rare inherited benign recurrent intrahepatic cholestasis (BRIC) and progressive familial intrahepatic cholestasis (PFIC) types I, II and III, caused by mutations in the FIC1, bile salt export pump (BSEP) and multidrug resistant (MDR3) genes, respectively. There was early hope that mutations of one of these genes would explain OC, but unfortunately it is only an occasional finding. There have been scattered reports of FIC1 mutations in OC patients with normal gamma-glutamyl transpeptidase (GGT) levels (like PFIC type I and BRIC) and MDR3 mutations in those with raised GGT (like PFIC type III). So far there are no reports of BSEP mutations. Recent large studies from Finland[23] and London[24] found very few mutations of the FIC1 or MDR3 genes.

Clinical presentation

OC typically presents at 30–36 weeks gestation with generalised pruritus, especially of the palms and soles and at night, but it can start as early as the first trimester. Jaundice is uncommon (<10%) and reflects more severe cholestasis. Close questioning of mothers and parous sisters often reveals a family history (30%). It may be associated with, or precipitated by, urinary infection. The pruritus and biochemical abnormalities resolve rapidly after delivery, usually within a few days.

Laboratory findings

It is important for physicians and obstetricians to be aware that the abnormalities on routine LFT characteristic of OC are not those generally expected with cholestasis. The main abnormality is transaminase elevation, seen in almost all patients, though not necessarily at the onset of pruritus. Such elevation, sometimes exceeding 10 times normal,[3,25] is surprising in the absence of hepatic inflammation or necrosis and may reflect increased membrane permeability. Transaminase elevation in an otherwise well woman with pruritus in pregnancy is virtually diagnostic of OC.

Elevations of alkaline phosphatase (AP) and GGT, as seen in primary biliary cirrhosis, drug cholestasis or biliary obstruction, are not usual. Mild elevation of AP (placental and bone origin) is expected in late pregnancy so is unhelpful in diagnosis of liver disease. GGT is raised in only 30% of OC cases, but to a modest degree.[1,3,25]

Serum bile acids are a more specific, but not more sensitive, marker of OC. Many laboratories lack facilities for rapid measurement which may result in delays or failure of diagnosis. Bile acid levels correlate poorly with transaminases both in timing and degree and transaminase elevation may precede that of bile acids.[4,25] Bilirubin levels are slightly raised in about 10% of cases but rarely exceed 100 umol/l. Renal function and full blood count remain normal. Prothrombin time may increase in the rare cases with prolonged jaundice or in those treated with cholestyramine.

Maternal and fetal outcome

Even though OC is distressing and tiring for the woman, it does not cause significant liver damage and always resolves after delivery. If abnormal liver tests persist, an alternative or additional diagnosis must be sought.

The fetus is undoubtedly at risk from prematurity (10–60%), fetal distress (15–25%), meconium staining (20–30%), stillbirth (<1–10%), and perinatal death (up to 10%). The reported incidence of these outcomes varies widely depending when and from where the report originated as well as how the pregnancy was managed. Earlier reports, which predate the principle of early delivery, show perinatal mortality around 10%, but in recent studies of actively managed OC this has fallen below 1%.[22] These encouraging figures reflecting best practice mask the fact that active diagnosis and management are still not widely adopted as shown by an alarming 7% intrauterine death rate

Table 7. Factors influencing prevalence of obstetric cholestasis.

Ethnic
Native Indians > whites in Chile and Bolivia
Asians > whites in Birmingham UK
Environmental
Incidence decreased 10-fold in 20 years in Chile
Association with low selenium levels
Hormonal
Effects of oestrogen and progesterone
Commoner in late pregnancy and with multiple pregnancy
Relationship to contraceptive pill jaundice
Precipitated by exogenous progestogens
Genetic
Strong familial tendency
Specific gene mutations in a few (MDR3, FIC1)

identified from a patient's support group in London in 2004.[26]

Peak bile acid levels may predict fetal outcome. A Scandinavian study[4] recommended early delivery only when bile acid levels were above 40 μmol/l with expectant management for lower levels. Confirmation is needed before wide adoption of this policy.

Management

Antihistamines and cholestyramine are conventionally offered to relieve itching but have limited benefit. Ursodeoxycholic acid (UDCA) is used increasingly as it reduces maternal bile acid levels and may help pruritus. Small trials suggest it to be safe, but such treatment has yet to be shown to improve fetal outcome, even though it ameliorates surrogate markers.[3] With a policy of planned early delivery and attentive supporting care, perinatal mortality is below 1% in North-West Europe so a very large trial would be required to prove outcome benefit with UDCA. It is not currently licensed for use in OC.

The risk of stillbirth increases after 36 weeks gestation (earlier in twin pregnancies) so delivery is recommended at 36–38 weeks, striking a balance between the risks of prematurity and intrauterine death. Mothers should be warned of the high likelihood of recurrence of OC in subsequent pregnancies (50–75%).

Hyperemesis gravidarum

Nausea and vomiting are common in normal early pregnancy. Hyperemesis, a severe form with intractable symptoms requiring hospital admission, affects less than 1% of pregnancies. It is commoner in younger, obese multiparae and with twins. Onset is usually at 4–10 weeks gestation. LFT are deranged in up to 50% of cases.[27] The characteristic pattern is transaminase elevation between two and 10 times normal, but it is occasionally above 1,000 U/l. Jaundice is uncommon. Viral hepatitis and paracetamol toxicity have to be considered in differential diagnosis. Invasive tests are not warranted; liver histology is unremarkable. Most cases settle with rehydration, electrolyte replacement and glucose. If improvement is slow, parenteral hydrocortisone sometimes leads to rapid resolution.

Despite its apparent severity and effect on maternal weight early in pregnancy, maternal and fetal outcomes are not influenced.

Conclusions

Liver dysfunction in pregnancy is commoner than generally perceived, often passing unnoticed, but when identified prospectively affects at least 3% of pregnancies.[1] The cause is not always evident but usually one of the specific pregnancy related diseases is responsible. Although these are presented here as separate entities, they share common ground with blurring of boundaries or evolution of one condition to another. No single mechanism is pinpointed in most cases though genetic mutations are occasionally found. Lessons can be taken from clinical observations of rare disorders. For example, in a study of 63 pregnancies with an LCHAD-deficient fetus, AFLP, HELLP, pre-eclampsia, OC and hyperemesis gravidarum all occurred more frequently than would be expected in mothers bearing healthy fetuses.[28] With early diagnosis and appropriate management of urgent delivery (for HELLP, AFLP) or planned early delivery (for OC), maternal and foetal loss can be minimised.

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An update in acute liver failure: when to transplant and the role of liver support devices

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Definition

Acute liver failure (ALF) is a syndrome manifest by the rapid cessation of normal function in individuals with previously normal livers. The rate of decline dictates the manner in which the syndrome manifests and influences the outcome. The aetiology is the main influence on the rate of deterioration in function and the likelihood of spontaneous recovery.[1] The rate of decline in function is usually described from the onset of jaundice to the first signs of hepatic encephalopathy; this represents the defining point in the diagnosis of ALF. Classification of ALF has been refined over the years since the original classification at the beginning of the 1970s.[2] The most recent and widely accepted iteration splits ALF into three groups according to the rate of onset (Table 1).[1]

Changing pattern of aetiology in the UK and USA

Within the UK, and as recently reported in the USA, paracetamol hepatotoxicity is the leading cause of ALF, followed by liver failure of unknown aetiology or seronegative hepatitis.[3,4] Viral hepatitis remains the most prevalent form within the developing world.[5] Over the last 30 years the pattern of ALF within the UK and USA has changed.[3,4] In the UK, paracetamol overdose (POD) is almost invariably due to deliberate self-harm. In contrast, the USA data suggest that over half the cases of ALF due to POD are caused by therapeutic misadventure. Some doubts have been expressed regarding this interpretation, suggesting that some patients in the misadventure group may in fact be occult suicide attempts.[4,6]

Until the late 1990s the rate of hospital admission due to paracetamol ingestion had risen year on year. In 1998, legislation was introduced in the UK in which over-the-counter sales of paracetamol were restricted to tablets in blister packs (16 tablets from most retail outlets and 32 from pharmacies). Since then the rates of admission to hospital, severe liver toxicity and transplantation for POD have fallen.[7]

These changes have occurred on a background of a reducing incidence of acute viral hepatitis, especially hepatitis A. In our unit, however, there has been

Table 1. Classification of acute liver failure.

	Time from onset of symptoms to encephalopathy	Common aetiologies
Hyperacute liver failure	<7 days	Paracetamol hepatotoxicity Hepatitis A, B
Acute liver failure	28–7 days	Hepatitis A, B, E Idiosyncratic drug reaction NANB hepatitis
Subacute liver failure	28–5 weeks	NANB hepatitis

NANB = non-A non-B hepatitis.