Acute fatty liver of pregnancy

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Acute fatty liver of pregnancy was established as an entity by Sheehan (1940) under the name 'obstetric acute yellow atrophy'. He reviewed the earlier literature and distinguished three types of acute hepatic failure in pregnancy.

The first of these was 'true acute yellow atrophy', and corresponds to the disease now called massive hepatic necrosis. It may occur in pregnant or non-pregnant patients, and is characterized pathologically by massive parenchymal cell necrosis without fatty change in liver cells. It is generally ascribed, although without proof, to a fulminating acute virus hepatitis.

Sheehan's second entity was delayed chloroform poisoning. The pathological change in this was of liver cell necrosis occurring in isolated cells, or as mid-zonal or centrilobular necrosis. Affected cells had a swollen, non-fatty cytoplasm and pyknotic nucleus, and fatty change was slight or absent. However, this lesion is now of historic rather than clinical interest.

The third type of liver change Sheehan termed 'obstetric acute yellow atrophy'. This was clinically similar to massive hepatic necrosis but occurred only late in pregnancy at 36 to 40 weeks and was frequently associated with toxaemic manifestations such as hypertension and proteinuria. It progressed rapidly, leading to maternal death within two weeks. The histological appearances were characteristic. There was 'an entire absence of necrobiosis', but an intense fatty change affecting all cells of the lobule, except for a sharply defined rim of normal cells adjacent to the portal tracts. This fatty change occurred diffusely throughout the cytoplasm, giving it a ballooned, vacuolated appearance. The distribution of the affected cells and the diffuse fatty change throughout the cytoplasm clearly distinguished the condition from the occasional fat droplets seen in centrilobular cells following hyperemesis of late pregnancy (Sheehan, 1939). Portal tracts were normal and bile thrombi rare or absent. This obstetric acute yellow atrophy is now generally called acute fatty liver of pregnancy. It remains probably the gravest form of liver disease in pregnancy.

In recent years, some authors have included fatty liver associated with tetracycline therapy during pregnancy in the general group of acute fatty liver of pregnancy (Kunelis, Peters, and Edmondson, 1965). It does, however, occur in non-pregnant patients, and may be associated with other drugs of the tetracycline series (Saint and Joske, 1953; Klatskin, 1963). Despite its clinical and pathological similarities to acute fatty liver of pregnancy, it should, therefore, be regarded as a separate entity with a different aetiology and pathogenesis.

True acute fatty liver of pregnancy is a rare condition. Ober and LeCompte (1955) reported 14 cases including three of their own in 1955, and in 1966 Haemmerli extended the collective experience to 40 cases. The clinical picture is of a rapidly progressive parenchymal cell failure which is clinically indistinguishable from that of acute massive necrosis. It has been reported in patients ranging in age from 16 to 42 years, and in 37 of the 40 cases it occurred during the first pregnancy. The prognosis is grave: of the 40 cases collected by Haemmerli, only six mothers and five children have survived.

The pathological appearances in all cases correspond to those described by Sheehan (1940). They are potentially reversible, for in one survivor followed up by serial liver biopsies, normal histological appearances were ultimately restored (Whitacre and Fang, 1942).

The present paper reports a further case of acute fatty liver of pregnancy, which is of interest because of some unusual features, in particular steady progression of the lesion despite delivery of a living child, haemolytic anaemia, and the finding at necropsy of massive mid-zonal hepatic necrosis.

CASE REPORT

A primipara aged 21 years had a normal pregnancy until the thirty-seventh week, when she developed oedema of both legs to the knees and was noted by her husband to be jaundiced. There was no history of jaundice or of exposure to hepatitis or hepatotoxic drugs or chemicals. Two days later (day 3) she was admitted to hospital, where she was found to have a blood pressure of 150/100 mm Hg (previously 135/50 mm Hg), and protein-
The patient was admitted to the Royal Perth Hospital on day 9. At this time, she was disorientated in time and place. Pulse was 120 per minute and blood pressure 140/85 mm Hg. There was moderate jaundice and pitting oedema of all extremities. The cerebral venous pressure was not raised, and the heart and chest showed no abnormal signs. Neither liver nor spleen was palpable. Neurological examination showed that the limbs were hypotonic with some muscular twitching. The reflexes were symmetrical and brisk and the plantar responses were flexor. The genitalia showed the usual signs of a recent delivery. There were no signs of chronic liver disease such as spider naevi or palmar erythema.

Serial haematological studies and liver function tests are shown in Table 1. A chest radiograph and vaginal swab were normal. The urine contained protein and culture grew coliform organisms. The blood film showed anisocytosis, burr cells, and fragmented cells, with normoblasts and occasional macronormoblasts with Howell-Jolly bodies; there was toxic granulation of neutrophils. Direct and indirect Coombs tests were negative. Blood cultures and a cervical smear grew no pathogens. 

Treatment was begun with kanamycin 3.0 g daily and ampicillin 2.0 g daily by intragastric tube and methicillin 4.0 g daily by injection. A transfusion of 1 pint of blood was given followed by dextrose and saline solution. On day 10 she was stuporous, with neck retraction, hyperpyrexia, and augmented tendon reflexes. Spider naevi appeared over the arms and chest. The liver remained impalpable. The following day she developed clonic movements of the limbs which were controlled only by the use of phenobarbital, paraldehyde, and magnesium sulphate by injection. Hydrocortisone was also given by injection, 400 mg daily. Other treatment, including further blood transfusion, was continued.

Her progress was steadily downhill and chest infection required tracheostomy on day 12. Her urinary output was maintained and exceeded 1,800 ml daily. The blood ammonia nitrogen level continued to rise, and she developed hyperpyrexia (40-5°C) and died on the following day.

Necropsy was performed nine-and-a-half hours after death. The body was that of a well-nourished, deeply jaundiced, young female (weighing 49 kg and measuring 160 cm in length). The face, hands and legs were oedematous. Bilateral pale yellow pleural effusions were present measuring 350 ml and 100 ml. The right and left lungs weighed 480 g and 360 g respectively; both showed basal collapse and minimal oedema. The state of the genital organs was consistent with the post-partum state. The
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The diagnosis of acute fatty liver of pregnancy in this patient is based on clinical and pathological findings. The clinical picture of a rapidly progressive parenchymal failure accompanied by manifestations of toxaemia in the last month of pregnancy in a primipara is characteristic of the disease. The laboratory findings are also typical: hyperbilirubinaemia with an increase in serum alkaline phosphatase but no increase in γ-globulin and negative flocculation tests. Azotaemia is present in about half the cases and is generally ascribed to oligoamia. The terminal decrease in plasma urea is also a usual finding and is probably the result of decreased hepatic synthesis of urea. The intense leucocytosis is also common, recorded figures varying from 19,200 to 32,000 per cubic millimetre (Haemmerli, 1966). However, a haemolytic anaemia of the degree seen in this patient is unusual and does not appear to have been recorded previously. Its explanation is unknown.

The pathological findings in the present case are also unusual. The diagnosis of acute fatty liver of pregnancy is supported by the diffuse cytoplasmic fatty change in hepatocytes, the rim of normal cells adjacent to portal tracts, and the minimal inflammatory infiltrate in the liver. The massive midzonal necrosis seen here has not, however, been reported previously, and its explanation is uncertain. The patient received no hepatotoxic drugs before the onset of her illness, and there was no known exposure to hepatitis A virus. Lesions such as those produced by tetracycline toxicity are thus excluded. It may reflect the relatively long survival period of seven days after delivery, which is the longest re-
FIG. 2. Section of liver. Some of the hepatocytes are shrunken with densely staining eosinophilic cytoplasm, whilst others are swollen with a vacuolated cytoplasm. Oil Red O confirms the lipid nature of the vacuoles. A few lymphocytes are present. Haematoxylin and eosin × 475.

FIG. 3. Section of liver. The hepatocytes in the centrilocular zone contain many small cytoplasmic vacuoles. Haematoxylin and eosin × 475.

FIG. 4. Section of liver showing surviving hepatocytes in the periportal region and early regeneration. Haematoxylin and eosin × 475.
A further case of acute fatty liver of pregnancy is reported, making the 41st acceptable case in the literature. Unusual features were steady progression of the disease after natural delivery of a living child, severe haemolytic anaemia, and the finding at necropsy of massive midzonal hepatic necrosis.

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REFERENCES


—- (1940). The pathology of acute yellow atrophy and delayed chloroform poisoning. Ibid., 47, 49-62.