Idiopathic acute fatty liver of pregnancy

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SUMMARY A maternal survivor of idiopathic fatty liver, with the characteristic histological appearance on liver biopsy, is reported. Profound hypoglycaemia was the major complication in this patient and it is suggested that more attention should be given to the blood glucose in this disease. The consideration of future pregnancy in this patient is discussed.

Idiopathic acute fatty liver of pregnancy is a rare and usually fatal condition with characteristic liver histology. In this case report a further survivor is described emphasizing the major problem encountered in management, namely, severe hypoglycaemia and the question of future pregnancies.

Case Report

The patient, a 23-year-old woman, was admitted to hospital in the thirty-seventh week of pregnancy, complaining of nausea, vomiting, and drowsiness for four days. Spontaneous labour commenced the next day and stillborn twins were delivered 12 hours later. Thirteen hours after delivery the

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patient had a generalized convulsion. Jaundice was then noticed. Initial investigations taken six days after the onset of symptoms are recorded in the Table. The patient remained mildly jaundiced and semicomatose for the next three days when she was transferred to the authors' hospital.

There had been one normal pregnancy two years previously and the present pregnancy had been observed regularly and had progressed normally until the thirty-seventh week. There was no history of drug ingestion or contact with hepatitis. Physical examination revealed a well nourished, jaundiced, unconscious female. The temperature and pulse were normal and blood pressure was 170/100 mm mercury. The liver edge was palpable 3 cm below the costal margin. Minimal peripheral oedema was present. The level of serum bilirubin was 7.4 mg/100 ml and serum alkaline phosphatase was 70 King Armstrong units/100 ml. Serum glutamic oxaloacetic transaminase was 67 Sigma Frankel units/100 ml, the blood urea was 52 mg/100 ml, haemoglobin was 12.2 g/100 ml, leucocyte count 30,400 per mm³ (73% neutrophils), and the blood film showed vacuolated neutrophils, target cells, and burr cells.

The prothrombin index was 50% of normal and rose to 70% of normal in 12 hours following parenteral vitamin K. A percutaneous liver biopsy was performed without complication and showed the typical appearances of acute fatty liver of pregnancy (Fig.). Blood glucose concentration on admission was 10 mg/100 ml. Intravenous administration of dextrose (75 g) was followed by marked improvement in mental state, such that the

Day	Serum Bilirubin (mg/100 ml)	Serum Alkaline Phosphatase (KA units/ 100 ml)	Serum Glutamic Oxaloacetic Transaminase (Sigma Frankel units/100 ml)	Concentration of Blood Glucose (mg/100 ml)	Total Leucocyte Count (mm ³)
7	7.9	—	42	—	34,000
10	7.4	70	67	10	30,400
11	5.9	50	104	75	26,100
12	5.0	50	75	76	21,000
16	3.5	12	55	106	—
23	1.3	27	45	100	9,800
90	0.7	—	20	—	7,500

Table Serial biochemistry and leucocyte counts commencing on the seventh day after the onset of symptoms

Fig. The hepatocytes are distended by multiple small vacuoles containing fat which stains with Sudan III. The nuclei are central. (Haematoxylin and eosin, $\times 800$.)

patient was able to converse. She became drowsy twice in the next 24 hours but improved with increased dextrose administration. Clinical improvement continued and intravenous dextrose was ceased after 154 hours. No further complications ensued and the biochemical abnormalities gradually returned to normal (Table). A liver biopsy at three weeks showed considerable improvement and a further biopsy at three months was normal. After 10 months the patient was physically well and had normal liver function tests.

Discussion

Although first described by Stander and Cadden in 1934, it was Sheehan in 1940 who recognized and first defined the typical histology of this condition which he called 'obstetrical acute yellow atrophy'. Subsequently terminology has varied (Ober and le Compte, 1955) but the term 'acute fatty liver of pregnancy' (Moore, 1956) is favoured by the authors. The occurrence of an identical clinical picture following the intravenous administration of tetracycline to pregnant women is well documented (Kunelis, Peters, and Edmonson,

1965). Whether the histological changes after tetracycline are identical to those of acute fatty liver of pregnancy has been questioned (Schultz, Adamson, Workman, and Norman, 1963; Iber, 1965); hence the diagnosis should be qualified as 'idiopathic' or 'tetracycline associated', as first suggested by Kunelis *et al* (1965).

The first documented survivor of idiopathic fatty liver was reported in 1942 (Whiteacre and Fang). The total number of cases and maternal survivors recorded in the literature varies with the diagnostic criteria applied. Thus, Kunelis *et al* (1965) who included tetracycline-associated cases, listed 54 patients of whom 10 survived. Iber (1965) found 46 cases and seven survivors and Haemmerli (1966) found 40 cases with six survivors; both these authors excluded patients given tetracycline. Only six infants have survived (Joske, McCully, and Mastaglia, 1968). Acute fatty liver is one of the least common entities in the major series of jaundice in pregnancy (Sheehan, 1961; Siegler and Keyser, 1963; Haemmerli, 1966).

Reported cases have strikingly similar clinical features, occurring in mothers of widely varying ages, commonly in the first or second pregnancy. The illness usually commences after the thirty-sixth week with the relatively sudden onset of nausea, vomiting, and epigastric pain, followed by jaundice and drowsiness. In most cases, spontaneous labour ensues with delivery of a stillborn infant and subsequent deterioration of the mother with death from hypoglycaemia, shock, metabolic acidosis, hepatic failure, or renal failure.

Severe hypoglycaemia has been overlooked as a major complication of acute fatty liver. Early reports (Stander and Cadden, 1934; Whitacre and Fang, 1942) mention this risk but blood glucose concentrations have rarely been mentioned by recent reviewers (Schultz *et al*, 1963; Duma, Dowling, Alexander, Sibrans, and Dempsey, 1965; Kunelis *et al*, 1965; Giles, 1967; Morrin, Handa, Valberg, Benscosme, Kipkie, and Wyllie, 1967; Joske *et al*, 1968). Coma has been the most common mode of death in reported cases and is usually attributed to hepatic failure, or less commonly to renal failure or shock (Ober and le Compte, 1955; Sheehan, 1961). In a few cases coma has followed progressive severe hyperbilirubinaemia, bleeding, and a clinical picture typical of massive liver necrosis. However in most cases the bilirubin level remains less than 10 mg/100 ml (Haemmerli, 1969) and coma has occurred without a clinical course typical of severe hepatic failure (Haemmerli, 1966). Azotaemia is usually moderate and related to dehydration or shock, although fatty vacuolation of renal tubular cells has been reported (Ober and le Compte, 1955). In many cases coma has appeared extremely rapidly, before the onset of hypotension or renal failure, and in the majority of patients has not been adequately explained. It is suggested that

coma in these cases is the result of hypoglycaemia. Experience in the present case indicates that the blood glucose concentration requires frequent monitoring and that large quantities of dextrose are needed to maintain normal levels.

Other complications have included haemorrhage of the upper gastrointestinal tract and acute pancreatitis, the latter clinically unsuspected and found at necropsy. The clinical status of the six surviving infants has not been reported in depth and few details are available regarding the state of the liver in the stillborn infants. On two occasions the foetal liver has not shown marked fatty change (Lewis, Takeda, and Warren, 1963; Giles, 1967).

The histological appearances in acute fatty liver of pregnancy are distinctive and diagnostic. The features shown in the Figure are representative. The hepatocytes are distended and have a foamy appearance, which on staining can be shown to be due to fat distributed in multiple vacuoles about a central nucleus. Periportal hepatocytes are often spared this process, a feature thought by some authors to distinguish the idiopathic condition from tetracycline-associated fatty liver (Iber, 1965; Kunelis *et al*, 1965; Giles, 1967).

There is no disturbance of hepatic architecture, and cell necrosis and inflammation are unusual. In most reported cases this histology has been reported only at necropsy. The serial liver biopsies in the present case confirm the previously published observations on the rate and degree of histological recovery, showing return to normal within three months (Duma *et al*, 1965).

The pathogenesis is unknown and many theories have been advanced to explain the aetiology of this condition. Administration of ethionine (a methionine antagonist) or deficiency of choline can each cause a similar appearance in experimental animals (Goldberg and Chaikoff, 1951; Hutterer, Fitschen, and Popper, 1961; Kunelis *et al*, 1965) but there is no convincing evidence that nutritional deficiency has been a factor in reported cases of acute fatty liver of pregnancy. The role of tetracycline has been mentioned above and is discussed in detail by Schultz *et al* (1962) and Kunelis *et al* (1965). No other drugs have been implicated. It has been suggested that a usually fatal childhood illness resembling acute fatty liver of pregnancy in many of its clinical features and in its histological appearances may be secondary to viral infection (Reye, Morgan, and Boral, 1963; Barr, Glass, and Chawla, 1968). The possibility that an undetected virus or toxin may cause acute fatty liver has also been mentioned by other workers (Whitacre and Fang, 1942; Iber, 1965; Joske *et al*, 1968). There is no evidence that acute fatty liver of pregnancy is in any way related to acute yellow atrophy, acute infectious hepatitis, or cholestasis of pregnancy (Sheehan, 1961; Haemmerli, 1966). Preeclamptic toxæmia has been present in a minority of cases, insufficient to suggest that it is a

predisposing condition (Iber, 1965).

On the basis of a small number of maternal survivors in whom Caesarean section or induction of labour appeared to bring about improvement, several writers have suggested that immediate termination of pregnancy is advisable (Ober and le Compte, 1955; Iber, 1965). However others have expressed doubt that termination improves maternal survival rates (Kunelis *et al*, 1965; Giles, 1967). Foetal survival figures may be improved by immediate termination as the condition usually presents after 36 weeks of gestation when the foetus is viable. The majority of maternal survivors have been treated with symptomatic measures alone (Sheehan, 1961; Peters, Edmonson, and Kunelis, 1962; Siegler and Keyser, 1963). Specific therapeutic agents, including choline chloride (Moore, 1956), steroids (Recant and Lacy, 1963; Woolf, Johnston, Stokes, and Robertson, 1964), and methionine (Faloon, 1954), have been used without convincing evidence of benefit. The supportive measures to be employed are well reviewed by Iber (1965) but the anticipation and treatment of hypoglycaemia warrants reemphasis.

The question of further pregnancy in survivors of acute fatty liver was not discussed in previous case reports or reviews and there is no recorded recurrence of acute fatty liver in subsequent pregnancies. On the other hand, Moore (personal communication) has recorded one survivor followed through a subsequent uncomplicated pregnancy. This information indicates that the risk of recurrence is a relative rather than an absolute contraindication to subsequent pregnancy. The patient reported here is anxious to have further children, and, should pregnancy ensue, it is intended to monitor liver function closely and to consider elective termination of pregnancy at 36 weeks' gestation.

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