Pregnancy in active chronic hepatitis on immunosuppressive therapy

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PREGNANCY occurring in women with chronic liver disease is very rare. Deliveries in cirrhotics have, however, been reported (Slater, 1954; Moore & Hughes, 1960; Dreifus & McKinney, 1966; McArthur & Flax, 1968), and cases of active chronic hepatitis, treated with steroids, have also come to term successfully (Bearn, Kunkel & Slater, 1956; Jackson, 1962; Seedat & Raine, 1965). Recently azathioprine, an immunosuppressive agent, has been used with good effect in the treatment of active chronic hepatitis (Mackay, Weiden & Ungar, 1964; Corley, 1966). Azathioprine is teratogenic in animals (Githens, Rosenkrantz & Tunnock, 1965; Rosenkrantz *et al.*, 1967), but its effects on human pregnancy are not fully known. However, pregnancy in a woman on azathioprine and steroid therapy following renal transplantation has occurred (Board *et al.*, 1967). This paper describes a successful pregnancy in a patient with active chronic hepatitis who was on both azathioprine and steroid therapy.

Case report

A Jamaican girl aged 17, who had been in England for 15 months, presented at Kings College Hospital in early 1965, complaining of recurrent epistaxis for 3 months. There was no significant past history, and she had never drunk toxic bush teas.

Clinical examination revealed hepatomegaly and telangiectasia on the nasal mucosa.

Investigations showed a total serum bilirubin of 11.6 g/100 ml, serum alkaline phosphatase 16 KA units, serum glutamic oxaloacetic transaminase (SGOT) 105 units/ml, and total serum proteins of 11 g/100 ml, with an albumin of 2.8 g/100 ml and γ -globulin of 6.6 g/100 ml. LE cell test was negative, and barium swallow showed no oesophageal varices. Liver histology (Dr D. M. Ansell) showed fibrosis and nodule formation. There were hydropic hepa-

tocytes with rosette formation and marked piecemeal necrosis, indicative of active chronic hepatitis.

Shortly after admission, she became febrile. Her haemoglobin fell to 8 g/100 ml, and she developed a pancytopenia. Ascites accumulated. She was treated by transfusion, diuretics and prednisone 40 mg daily, with gradual clinical and biochemical improvement. She was discharged well after 6 weeks, on prednisone 10 mg daily.

In January 1967, she was admitted for re-assessment. She had no complaints, but was anxious to know if she could have children.

Clinical examination was negative apart from hepatomegaly 5 cm below the costal margin. In addition to liver function tests shown in Fig. 1, a bromsulphthalein test showed 45% retention at 45 min, and prothrombin time was prolonged at 20 sec (control 14 sec). LE cell tests were again negative.

She was advised against pregnancy, and since serum enzymes were raised, it was decided to add azathioprine to her therapy.

In March 1967, she was re-admitted with an acute arthritis of her right knee. Rose-Waaler and latex tests were at first negative, but later became positive in a titre of 1:16. Synovial biopsy showed no diagnostic features. Her prednisone was increased to 40 mg daily and the arthritis subsided.

When she re-attended out-patients in June, she was clearly pregnant, at about 22 weeks' gestation. Since the first admission in 1965, her periods had been irregular, occurring every few months, and in retrospect, she had been about 3 weeks pregnant at the time the azathioprine was commenced. Prednisone and azathioprine were continued, and the pregnancy proceeded uneventfully. She delivered at term in early November of a normal female child weighing 5½ lb.

Despite advice to the contrary, she again became pregnant in early December. She has been continued on azathioprine, but her steroids were reduced in January 1968 and finally stopped in March. At the

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FIG. 1. Liver function tests.

time of writing (early June), she remains clinically very well.

Discussion

This patient showed the characteristic clinical biochemical and histological features of active chronic hepatitis. Like many others with this condition, she also showed marked symptomatic improvement once steroids were commenced. Liver function tests improved, although the serum transaminase level never fell completely to normal. The episodes of arthritis probably indicated that her disease was still active. Whether survival is prolonged on steroid therapy is uncertain (Harvald, 1967) and the results of controlled trials currently in progress are awaited. It is noteworthy that the patient has not yet shown signs of irreversible cirrhosis such as portal hypertension. Azathioprine led to a further improvement in biochemical tests. This has been described with a number of recent cases, although benefits over steroids have not yet been established on a controlled trial. The dose of azathioprine used must be low, for although doses of 50–75 mg daily over prolonged periods have led to symptomatic and biochemical improvement, doses of 100 mg daily and over, have caused toxic reactions such as further liver damage and leukopenia, within a few weeks (Mistilis & Blackburn, 1967).

Cirrhotic patients usually have amenorrhoea and are sterile. Moore & Hughes (1960), in a review of the literature, found twenty-three pregnancies recorded in twenty patients. There were five maternal and three foetal deaths. In their own three cases, liver function tests deteriorated during pregnancy, but re-improved following delivery, and the overall course of the disease was unaffected by pregnancy.

Both corticosteroids and azathioprine are teratogenic in animals. Corticosteroids decrease foetal viability in large doses, but in pharmacological doses cause only minor anomalies such as cleft palate. Bongiovanni & McPadden (1960) reviewed 260 pregnant women treated with steroids, and found two cleft palates as the only teratogenic result. Azathioprine, in mice, causes skeletal anomalies when given in the embryonic period and haematopoietic depression given in the foetal period (Rosenkrantz *et al.*, 1967). It is also teratogenic in rabbits and dogs. Fertility of the adult mouse, however, is unaffected. In humans, the number of cases in which pregnancy has occurred whilst on azathioprine is so low that the effects on the foetus at present cannot be assessed.

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Paroxysmal nocturnal haemoglobinuria with fatal puerperal stroke due to sagittal sinus thrombosis*

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PAROXYSMAL nocturnal haemoglobinuria (PNH) is an uncommon disorder with an approximate incidence of two per million population (Crosby, 1953). Pregnancy is a rather rare event in PNH, and although until the time of delivery no especial risk has been reported, the puerperium is generally stormy. In a comprehensive review based on fifty-six cases of PNH, Dacie (1967) records three cases who became pregnant after its onset, one of whom developed thrombo-embolic disease.

In the present case, PNH was diagnosed at the time of delivery. Early in the puerperium a severe haemolytic episode developed which was followed by a slowly progressive and eventually fatal stroke

due to sagittal sinus thrombosis. Although venous thrombosis is common in PNH, sagittal sinus thrombosis is a rare event and its occurrence in a young post-partum woman with PNH has not previously been reported. Of particular interest in this case was evidence suggestive of reduced fibrinolytic activity during an episode of venous thrombosis.

Case report

A 34-year-old woman developed a transient right hemiparesis in October 1967 during the 28th week of her second pregnancy. An air encephalogram at that time showed an expanding lesion in the left cerebral hemisphere. She made a full spontaneous recovery over a period of 7 days. A macrocytic anaemia was noted and oral iron and folic acid were given for the rest of the pregnancy but without

* This case has been presented to the Caledonian Branch of the Association of Clinical Pathologists and the British Neuropathological Society.