Viral A Hepatitis In Pregnancy During Kathmandu Epidemic

—report of high incidence of Fulminant Hepatic Failure.

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Introduction:

Infectious hepatitis was endemic in Kathmandu valley. However a situation of an epidemic of this disease occurred in the valley in 1973 from January to October with a peak period in June, July and August. It was estimated that about 10,000 mostly young people were affected (11). As it was noticed during this epidemic that the disease had a more deleterious effect on the pregnant women, many of whom were admitted in Fulminant hepatic failure (FHF) with its accompanying high mortality a special unit to take care of the affected pregnant women was delineated from April to September 1973 at Bir Hospital. This paper discusses our experience of Viral A hepatitis in pregnant women admitted to this unit.

Summary:

Out of 118 affected women admitted to this unit 41 were in fulminant hepatic failure. The foetal loss was 62%. The maternal loss in FHF group was 75.6%. In this group an increased bleeding tendency especially from the gastro-intestinal tract was observed in 75.6%. though bleeding itself was responsible for death only in 38.7%. Hypoglycaemia was noted in 17 (41%), and hyperventilation in 7 (17%). The mortality however was more directly correlated with the grade of encephalopathy.

The course of the severe hepatitis was not influenced by termination of pregnancy. Besides, 7 out of 10 patients in full term pregnancy went into coma after normal delivery. Corticosteroid was used in 21 in FHF of whom 19 died. L-dopa was used in three patients in grade IV encephalopathy, one of whom survived to leave the hospital.

Significant findings of this study were the correlation of the occurrence of FHF to the physical activity during the pre and early icteric phase of the hepatitis in the second and third trimester of pregnancy, and its high incidence in women of poor socio-economic class.

Epidemiological note:

During the early period of epidemic when an increasing number of young adults were seen with symptoms of malaise, fever, loss of appetite and jaundice with raised serum bilirubin and GPT a comprehension of an epidemic most probably of Viral A hepatitis was made. But to exclude the possibility of an epidemic of an Arbo virus causing hepatic damage – a screening CF test was done (at Yale Arbovirus Research unit through the kind courtesy of Dr. Robert E. Shope), using the following antigens: Chikungunya, Ross River, Dengue-2, yellow fever, Omsk haemorrhagic fever, Junin and Lassa. Results were negative in dilutions from 1:4 to 1:32.

Australia Antigen: The sera of a total of 101 patients during the acute phase was tested for HB Ag by immunodiffusion method. HB Ag was detected in none.

These serological tests and the subsequent epidemiological study (11) confirmed our earlier impression of this disease being a Viral A hepatitis.

Report:

From April to September 1973 a total of 118 patients were admitted in this unit. Five of these were in 1st trimester, 42 in 2nd trimester, 61 in 3rd trimester and 10 immediate postpartum. (Fig 1.)

Foetal loss: The foetal loss in this series was very high. Four had abortion. Thirteen had stillbirth. And there was 14 neonatal death (11 in hospital and 3 outside the hospital). Twelve mothers died pregnant. The total number of deliveries in this series was 61. The foetal loss among this group including 4 abortions and 12 maternal deaths comes to about 62%.

This hospital has an active obstetric service unit. The incidence of foetal loss for all deliveries in this hospital taken for six months covering this same period was found to be only 4.2% for a total of 893 women without hepatitis.

Fulminant Hepatic Failure (FHF): 38% of our patients i.e. 41 out of 118 were in FHF. Whereas only 1 out of 5 in 1st trimester developed coma, 11 out of 42 in 2nd trimester, 21 out of 61 in 3rd trimester and 7 out of 10 in immediate post-partum period developed FHF. The incidence of FHF thus increased with increase in period of gestation. And this complication occurred mainly in 2nd and 3rd trimester and following delivery. (Fig 1)

(Duration of pregnancy in months)
CASES OF VIRAL A HEPATITIS IN PREGNANCY-ADMITTED TO
BIR HOSPITAL FROM APRIL-SEPTEMBER 1973.

Fig. 1

Age group and socio-economic class: The age group of those that went into FHF were comparable to the rest. Following were the age group of the patients in FHF group:

- below 20 yrs : 5
- 20 - 25 yrs : 17.
- 26 - 30 yrs : 10.
- above 31 yrs : 9.

Most of our patients in this group (FHF) came from the adjoining rural areas of the valley. Only 8 were from Kathmandu urban area. All these were housewives and, except all of them were engaged in heavy manual work as farming. Three belonged to the socio-economic class II and the rest 38 to class III.

Twenty six were brought in coma. They gave history of jaundice of short duration of 2 to 7 days, but were still working till they suddenly became drowsy and comatose and

brought to hospital. Of these 3 were not aware of the disease and were still working in the field till they were suddenly struck by hepatic encephalopathy.

Grade of hepatic encephalopathy: The grading is done according to Trey and Davidson (5). Of these 41 patients in FHF 8 were in grade II encephalopathy, 4 in grade III and 29 in grade IV.

Complications: Haemorrhage was noted in 31 (75.6%). Sixteen developed bleeding from gastro-intestinal tract, 12 from oral mucosa, 6 had heavy postpartum haemorrhage, 4 had pulmonary bleeding, 3 had hematuria and 3 developed echymosis and petichiae. Increased tendency to bleed from the venipuncture site was noted in all 41 patients. Bleeding was directly responsible for death in 12 (38.7%).

Hypoglycaemia was found in 17 (41%). Four hourly estimation of the blood sugar by Dextrostic method proved very helpful in the detection and management of this condition. Seven developed hyperventillation. Acid-base status could not be assessed in these because of the lack of facility. Four had convulsion and was in a state of decerebrate rigidity. Oedema of leg, and hands were noted in 9. Four complained of sudden impairment of vision at the outset of the encephalopathy. Fundi were normal in all of them. One who survived regained normal vision.

Investigations and result: Estimations of serum bilirubin, GPT, alkaline phosphatase, blood urea, glucose, and total serum protein was done. Haematological study included estimation of one stage prothrombine time, platelet count, total and differential white cell count. As bleeding was the complications of FHF a detailed coagulation study was done in 55 patients with hepatitis including 12 in FHF. This study included beside estimation of prothrombine time, and platelet count, estimation of fibrinogen level, thrombine time, partial thrombine time estimation and screening test for disseminated intravascular coagulation. Estimation of the fibrin degradation product and ^{125}I fibrin turn over study could not be done.

The results of the biochemical and haematological study and the comparison of the findings in the FHF group and the rest is shown in the charts. The level of serum bilirubin, GPT and total serum protein in two groups are comparable. So is the platelet count, TT and PTT. Fibrinogen level was on the low side in FHF group. However, the only significant point was the finding of prolonged prothrombine time in patients with FHF compared to the rest. PT was above 1 minute in 13, between 30 sec to 1 min in 25 and less than 27 sec in this group. PT correlated with the severity of the hepatitis and the prognosis but not directly with the incidence of bleeding. Some evidence of disseminated intravascular coagulation was seen in 12 patients with hepatitis including 7 in FHF. But it did not seem to be related to the incidence of bleeding except in two. Other coagulation study were also not distinctive of any group or the incidence of bleeding. (Chart I&II)

Chart I

Chart II

White blood cell count of 12 thousand per cu. mm. was seen only in 17 patients not in FHF, whereas out of 34 patients in FHF it was above 12 thousand per cu. mm. in 17, in 13 of which it was higher than 20 thousand per cu. mm. Blood urea was either normal or low. Renal failure was not seen in any of our patients.

Treatment: Patients in FHF were treated with supportive measures which include infusion of 12% Dextrose, Inj. Vit K and B complex, Neomycin by Ryles' tube and restriction of protein ingestion and rectae wash. Those who developed bleeding received fresh blood transfusion. Three also received fresh frozen plasma. Four with gastro-intestinal bleed received antacids. In two with evidence of intravascular coagulation as low platelet count, progressive decrease in level of fibrinogen and positive screening test, and gastro-intestinal bleeding along with blood heparin was given. Both of the patients died. L-dopa was given orally in three patients in grade IV coma, of whom one survived to leave the hospital. I.V. infusion of 8.4% Sodium bicarbonate was given to those thought to be acidotic clinically, especially those with hyperventillation. Corticosteroid was used in 21, 19 of whom died. It was considered that the presence of foetus may be contributory to the fatal outcome. So in the early stage termination of pregnancy was carried out in three. All of whom died. Moreover 7 out of our 10 patients in full term pregnancy went into FHF after normal delivery. Termination of pregnancy thus by adding strain upon an already failing liver proved more harmful.

Mortality: Thirty out of 41 in FHF died. The overall mortality in this group being 75.6%. The relationship of mortality to the period of gestation is shown in the chart. There is no death in the 1st trimester. Seven out of 11 in the 2nd trimester, 16 out of 21 in the 3rd trimester and 7 out of 8 in immediate post-partum period died. Thus mortality increased with the increase in the period of gestation, and was highest in the immediate post-partum period. (Fig. 2)

Fig. 2

Mortality also correlated well with the degree of encephalopathy rather than to any other biochemical or haematological parameters. There was no death in grade II encephalopathy, whereas the mortality were 50% and 97% in grade III and IV respectively.

Postmortum could be done in only two and limited postmortum in four. Liver was found to be considerably shrunk in all and the histological showed massive necrosis of the liver cells. Lung in one showed pneumonic changes with microthrombi and haemorrhage. The kidney, supraenals, heart and brain showed normal histology. Fodtal liver showed only autolytic changes, (Photomikes)

1. Case 5: Lung Showing pneumonic changes (175X)

2. Cases 5: Lung Showing pneumonic changes, haemorrhage & microthrombi (75X)

3. Case 5: Liver Showing widespread necrosis (75X)

4. Case 5: Liver Showing detail of surviving but injured --looking liver cells (480X)

Discussion:

In the Boston study FHF was defined as the clinical syndrome associated with massive necrosis of liver cells or with sudden severe impairment of hepatic function. It is characterised by an acute onset of progressive and severe mental changes starting with confusion and rapidly advancing to stupor and coma. Jaundice appear and rapidly increases in depth. Serum enzyme levels are markedly raised and the prothrombine time considerably prolonged. The Fulminant Hepatic Failure Surveillance study included within their definition all those patients in whom the signs described appear within 8 weeks of the onset and in whom there had been no evidence of liver disease previously (5, 22).

The significant increase of the incidence of FHF in pregnancy is indicative of greater severity of hepatitis during pregnancy, especially in 2nd and 3rd trimester. Similar high incidence of FHF in viral hepatitis during pregnancy had also been reported from India (Naidu et al, 1957), Ghana (Morrow et al, 1968), Saudi Arabia (Gelpi, 1970) and Iran (Barhanmunash et al, 1973). However such higher susceptibility to FHF in hepatitis was not noted in Europe and the United States (Cahill, 1962; Adams and Combes, 1965; and Hammerli, 1966).

Undernutrition of the pregnant women in Asia and Africa, and the metabolic and hormonal changes during the later period of gestation may be responsible for this phenomena. Occurrence of FHF in 42 belonging mainly to poor economic class during their 2nd and 3rd trimester in this series seems to substantiate this assumption.

Kirkler and Zilberg (1966) from Rhodesia reported FHF in 5 healthy Europeans following hepatitis. All of them had undertaken vigorous physical activity like playing tennis during the early stage of the infection. In Dec, 1974 one of us (SMS) saw a case of fatal Viral B hepatitis in a doctor at the Kings College Hospital, London who suddenly became comatose followed a fairly heavy game of tennis. Strenuous physical activity during preicteric and early icteric stage of hepatitis may be very harmful. In spite of some report contrary to it (18). And it seems to have been the precipitating factor in the development of FHF in at least 26 out of our 41 patients.

Bleeding was noted in 31 patients in this series. It proved fatal in 12 (38.7%). Ritt et al (1969) noted gastrointestinal tract bleeding in 24 out of 31 patients. In the King's College Hospital series of 132 patients bleeding disorder was related to mortality

in 31% (8). In FHF there is general reduction of protein synthesis by the liver. It leads to fall in the plasma concentration of many clotting factors such as factor II, V, VII, IX and X, which is often sufficient to cause spontaneous bleeding (6). But the workers at the Liver Unit, King's College Hospital, London found that the replacement of these clotting factors in the form of fresh frozen plasma made no difference to the mortality. And often the prothrombine time had returned to near normal level at the time of bleeding (8).

Rake et al (1971) had reported occurrence of intravascular coagulation in acute hepatic necrosis. Williams (1971) thinks it presumably due to release of tissue thromboplastin into the circulation from the necrotic hepatocytes. There is some evidence of occurrence of intravascular coagulation in 12 of our patients with hepatitis including 7 in FHF. Rake et al (1971) recommended use of heparin to correct intravascular coagulation and fresh frozen plasma for the synthesis defect. We found that occurrence of disseminated intravascular coagulation did not correlate well with the occurrence of bleeding in this series and treatment with heparin and fresh frozen plasma did not make any difference to the mortality. Gazzard (1974) noted occurrence of local lesions either in stomach, esophagus or duodenum as erosive esophagitis or haemorrhagic gastritis in 23 out of 26 major bleeding in their series. Similar local gastrointestinal lesions were common in portocaval shunts and responds to treatment with antacids (8).

Corticosteroids have been used extensively since the work of Ducci and Katz (1952). It was found to be of no help to our patients. Benhamon, Ruff and Sicot (1972) in a critical review of the treatment of severe hepatic failure found no support to its use. As 19 out of 21 patients who received steroid died, and because of the possibility of the occurrence of local lesions in the gastrointestinal tract we wonder steroid may be more harmful.

Haemodialysis, Peritoneal dialysis, Exchange transfusion, pig, calf, baboon and cadaver liver perfusion and even cross circulation with human volunteers, which might endanger the donor have been tried in the management of FHF (2, 24). Redekar et al (1973) found in a control trial that exchange transfusion did not improve the survival. Benhamon, Ruff and Sicot (1972) in the review of the literature found that none of these procedure contributed to any significant improvement in survival.

The mortality of FHF remains very high despite all measures. The mortality is 82% in the first 318 patients reported from centres through out the world to the Fulminant

Hepatic Failure Surveillance study (5). The mortality of 75.6% in this series inspite of just simple supportive but intensive measures was comparable to the available figures.

The aim of treatment was to sustain life untill such time as the liver regenerates. Recently, treatment, with charcoal haemoperfusion have shown some improvement in survival rate (7). But yet we do not know of any method which will help to accelerate the rate of liver regeneration.

The extent of foetal loss of 62% compared to 4.2% in normal population was very high. This high incidence of foetal loss in viral A hepatitis in this series is due to high incidence of FHF. Borhanmanesh et al (1973) have reported 69% and 21% in FHF group respectively. This another indication of the harmful effect of hepatitis on pregnancy. However, others have not observed an increased foetal wastage in pregnancies complicated by hepatitis (1,4). No congenital defects were noted in babies delivered during illness. Of course a better idea of the affect of hepatitis on this aspect will yield only from follow up of the babies whose mothers developed hepatitis during an early period of pregnancy. Neonatal hepatitis was not observed in this series.

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