STUDIES IN TOXAEMIA OF PREGNANCY

LIVER BIOPSY STUDY IN NORMAL AND TOXAEMIC PREGNANCY

by

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Despite long drawn out research the aetiology of the hypertensive toxaemias of pregnancy has defied elucidation. Pathogenesis being vague, therapy is empirical and symptomatic. It is thus not surprising that the toxaemias of pregnancy still account for 20 per cent of maternal and about 15 per cent of foetal deaths.

The histopathological changes in various organs in normal and toxaemic pregnancy have been studied from time to time. Assessment of changes in the liver is but one aspect of this complex problem. Earlier descriptions of liver pathology were distorted by postmortem changes. Sheehan (1950) was able to minimise this error by taking material immediately after the death of the patient. Autopsy, however, was a poor substitute for biopsy. An accurate evaluation of the hepatic lesions associated with toxaemia of pregnancy can be made only by the histopathological examination of tissue obtained during the acute stage of the disease.

Needle biopsy of the liver covers more than one hepatic lobule and reflects any generalised change in the liver. Hepatic pathological changes in pregnancy are fortunately diffuse and the lesions are virtually uniform throughout the liver. Needle biopsy is a fairly representative sample of the whole liver. It spares the need for laparotomy and surgical biopsy.

Only a few isolated reports are available on liver blopsy studies in normal and toxaemic pregnancy.

The present study was undertaken in pre-eclampsia and eclampsia in order to elucidate whether such morbid conditions are accompanied by histological changes of the liver and if so, how early these changes make their appearance and whether there be any demonstrable relation between the clinical features and the development of typical histological changes. In order to provide a yardstick with which to compare the results and to determine the changes in structure and function concurrent to normal pregnancy, this group has also been studied.

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Material & Method

The present study has been conducted in the department of Obstetrics and the department of Pathology of Medical College, Amritsar. Needle biopsies of the liver have been studied in 66 cases. These cases belonged to the following groups:

Group I.

Twenty-five healthy women with normal pregnancy of 24-40 weeks' duration were studied to serve as controls. It was considered important, in the selection of these patients, that they should be in good general health. Patients with malnutrition, anaemia, vitamin deficiency and other metabolic disturbances were excluded because these have an important bearing on the hepatic structure. The chronic changes in the hepatic morphology due to long-standing illness are liable to viciate the results. Women with previous history of pregnancy toxaemias and unaccountable still-births were likewise excluded from the present study.

Group II.

Fifteen women with pre-eclampsia complicating pregnancy.

Mild pre-eclampsia	..	5
Severe pre-eclampsia	..	10

(blood pressure 160/100 m.m. Hg or above. Albumin in a catheter specimen of urine, oliguria and toxic manifestations).

Group III.

Twenty-six women with eclampsia complicating pregnancy.

Antepartum	..	22
Intra-partum	..	2
Post-partum	..	2

Postmortem liver biopsies have been studied in 4 cases of eclampsia.

Age: In the present series there was no significant difference between the three groups so far as the age distribution was concerned. The age of the patients varied from 16-40 years.

Parity: Pre-eclampsia occurred in 5 cases out of 15 in the primigravidae. Out of the 10 multigravidae, 5 had a previous history of premature or full-time still-births, which may or may not have been due to pre-eclampsia complicating those pregnancies. These were thus probably cases of recurrent toxaemia. One case had triplets with hydramnios which might have been the precipitating factor for the occurrence of pre-eclampsia.

Eclampsia was predominantly more common in the primigravidae than in multigravidae; out of 26 cases of eclampsia, 20 were primigravidae and only 6 were multigravidae.

Duration of Pregnancy

Pre-eclampsia was commonest between 29 to 36 weeks of pregnancy; 2 cases with a past history of pre-eclampsia in the previous pregnancy, developed the disease at 24 weeks in the present pregnancy. Eclampsia was commonest between 33 and 36 weeks of pregnancy. The shortest duration of pregnancy associated with eclampsia was 24 weeks in a primigravida without any past or family history of hypertension.

Procedure

It must be stressed at the very outset that needle biopsy of the liver

should be undertaken only by those well trained in its execution. The frequency of serious complications is high in inexperienced hands, and although simple to perform, it should never be undertaken casually.

In the present study, before taking the biopsy, it was ensured that the patient's blood haemoglobin content was 10 grams per cent or over and the bleeding, coagulation and prothrombin times were well within the normal limits. Blood was grouped and cross-matched. Each patient was given 10 mgs. Vitamin K one day before the biopsy and 10 mgs. on the day of biopsy. Two grains of phenobarbitone sodium were given orally thirty minutes prior to biopsy to all the cases who were not already receiving sedatives as a part of the treatment regime. As the patient's cooperation was required, stronger narcosis was not used. The patient was made to lie on her left side as near the edge of the bed as possible, with a firm pillow placed underneath the lower part of the chest. Liver dullness was percussed and a site was chosen in the intercostal space corresponding to the point of maximal hepatic dullness in the posterior axillary line. This was generally in the ninth intercostal space.

Observing all aseptic and antiseptic precautions, the skin was anaesthetised with 2% novocaine solution. A long fine bore needle was used to infiltrate the pleura and was then passed through the diaphragm to anaesthetise the peritoneum and capsule of the liver. Liver biopsy was then taken with the Vim Silvermann needle as follows:

The short outer needle fitted with the stylet was passed through the skin but not through the diaphragm and the patient was instructed to take a deep breath, let it out, and then hold her breath. This helped to displace the lung upwards and ensured apposition of the diaphragmatic and costal pleurae. The needle and stylet were now pushed through the diaphragm into the right lobe of the liver for about 1 to 1.5 cms. The stylet was next withdrawn and the longer biflanged needle inserted into the outer carrier needle advancing 2 cms. further into the substance of the liver. A fragment of liver tissue was thereby trapped between the two prongs of the inner needle. Then with the inner needle immobile, the outer carrier needle was advanced to cover the prongs of the inner needle for 2 cms. i.e. until the tips of the outer and inner needle were level. The instrument was then rapidly withdrawn. The puncture wound in the skin was sealed with tincture benzoin co.

Immediately after the biopsy a tight binder was applied over the lower chest and upper abdomen. The patient was then made to lie on her right side so that all of her body weight rested on her right arm pressing it against the side of the wound. This simple device facilitated and hastened haemostasis of the deep tissues more effectively than the manual compression method, recommended by Terry (1962). Since rigid asepsis was observed routine administration of antibiotics was not required.

Difficulties and Complications

Failure to Obtain Biopsy

Failure to obtain a sample occurred

in 3 instances out of 66 cases (4.3%). In the first patient a piece of skin was obtained. In the second the lung was accidently punctured. Just as the trocar was withdrawn, air came out of the carrier needle and the needle was immediately withdrawn. Liver biopsy was not repeated on this patient. In the third case no tissue was obtained.

Failure to obtain a sample may occur if the trocar is not sufficiently sharp to penetrate the liver capsule. Secondly the trocar may be withdrawn before the instrument has pierced the liver capsule, and the relatively blunt cannula has great difficulty in penetrating even the normal hepatic capsule.

Pain

The procedure was attended with very little discomfort to the patients. The degree of post-operative pain could not be assessed in the 26 cases of eclampsia because these patients were not fully conscious. In the remaining 40 there was no pain in 6, trivial pain in 26, and severe pain in 8 cases for which an injection of morphia had to be given. All patients were free of pain after 24 hours.

Pleurisy and perihepatitis

A brief friction rub was heard over the wound in the case in whom the lung was accidentally punctured. It was of little consequence and the pain subsided with analgesics. No pneumothorax was seen in an X-Ray chest taken on the third day after biopsy.

Haemorrhage

No case of haemorrhage was encountered in the present series.

Results

Hepatic Histology in Normal Pregnancy (25 Cases)

The histological examination of liver tissue obtained by needle biopsy did not reveal any significant deviation from normal. The liver architecture was normal in all the cases. The polyhedral hepatic cells had a finely granular or reticulated cytoplasm. Fine vacuolation was seen only on one occasion. The nuclei were prominent, vesicular and often contained well-defined nucleoli. In 2 cases the sinusoids were slightly congested. The Kupffer cells were normal in all the cases. A mild round cell infiltration was seen in the portal space in one case. In no instance could any increase be demonstrated in the amount of connective tissue.

Hepatic Histology in Pre-eclampsia (15 cases)

In the present study in all the 5 cases of mild pre-eclampsia the hepatic histology revealed no deviation from normal. Out of the 10 cases of severe pre-eclampsia 5 had a normal hepatic histology. In one case there was an increase in the number of binucleated cells. Apart from this the rest of the liver morphology revealed no abnormality. In 2 cases the hepatic cells showed marked fatty change. (Fig. 1). The hepatic architecture was normal; liver cells were markedly vacuolated at places, so much so that in some cells the nuclei had completely disappeared. There was a mild round cell infiltration of portal tract. One case showed perisinusoidal oedema with compression of the sinusoids and prominent Kupffer cells. (Fig. 2). The hepatic

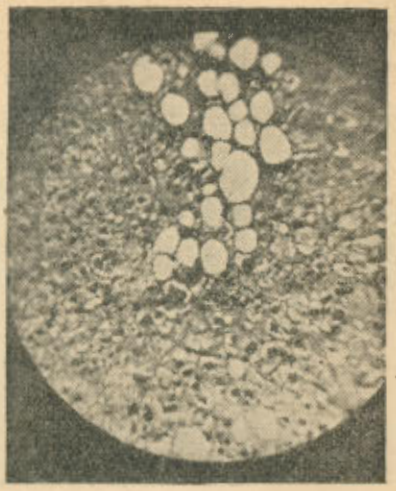

Fig. 1
Shows cords of hepatic cells with vacuolated cytoplasm. In the field are also seen several large fat cysts, sinusoids appear to be collapsed x 20.

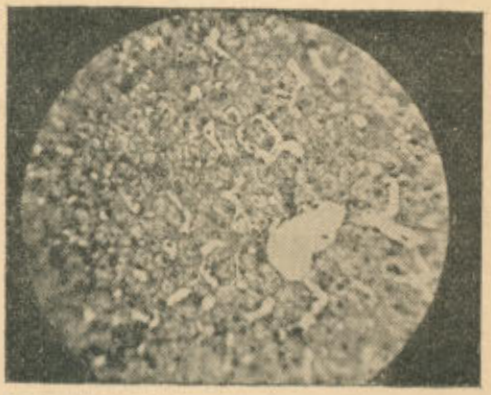

Fig. 2
Liver section shows prominent Kupffer cells with peri-sinusoidal oedema and compression of sinusoids x 240.

cell cytoplasm was granular and at places the nuclei were pyknotic. In one case the liver cells were of variable size and shape. The cytoplasm of the hepatic cells was granular, nuclei were pyknotic and absent at places. Some of the cells were joined together to form granular areas with disappearance of intervening septa. Sinusoids were dilated and congested.

Hepatic Histology in Eclampsia

In the cases under study normal liver tissue was seen in 5 instances. Perisinusoidal oedema due to exudation of plasma leading on to compression of the sinusoids without necrosis was observed in 9 cases. (Fig. 3).

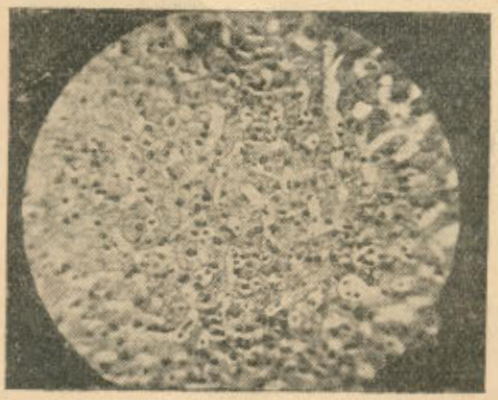

Fig. 3
Shows widening of the perisinusoidal spaces, Kupffer cells are prominent. Liver cells show reticulated cytoplasm.

Early necrosis of the hepatic cells consequent to compression of the sinusoids was seen in 3 cases, mild in 2 cases and severe in 1 case (Fig. 4).

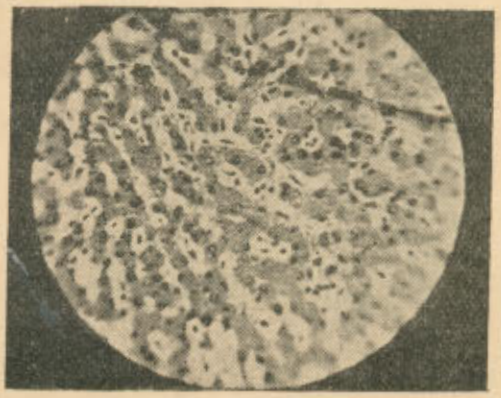

Fig. 4
Shows cords of hepatic cells with markedly dilated spaces of Disse containing light and pinkish oedema fluid. At places there is complete obliteration of sinusoids and adjoining cells show atrophy x 240.

Round cell infiltration was present in 2 cases (Fig. 5). Periportal haemorrhagic necrosis of the focal type was seen only in 3 cases. (Fig. 6).

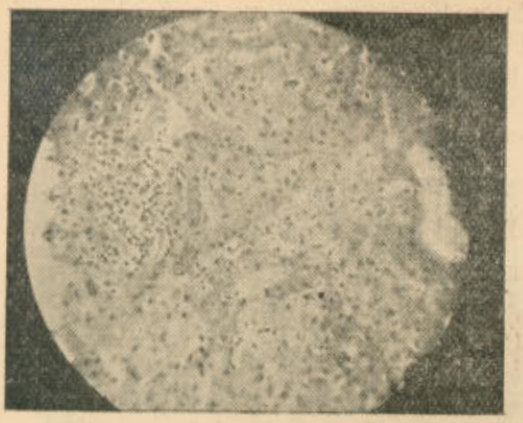

Fig. 5
Shows prominent persinusoidal oedema. At one place there is round cell infiltration giving the appearance of focal necrosis with disappearance of the liver cells x 240.

Fig. 6
Shows an area of periportal haemorrhage with fragmentation of hepatic cells x 240.

Diffuse haemorrhagic necrosis of the liver was not seen in any of the antemortem liver biopsies but was seen in two of the four postmortem biopsies (50%) (Fig. 7).

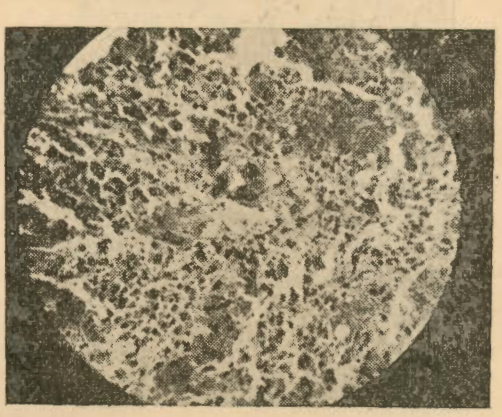

Fig. 7
Liver biopsy shows extensive area of haemorrhage near the peripheral region of the section with complete destruction of hepatic cords. A few fragments of liver cells with pyknotic nuclei are present mixed with red cells. No, Kupffer cell seen x 240.

Discussion

The concept of "Insuffisance Hepatique" in normal pregnancy was originally introduced by Tarnier, Laennec and Blot (1856) who carried out post-mortem studies in women, strongly supported by Hofbauer who in 1908 described fatty infiltration, dilatation of bile channels, central vein and afferant capillaries as characteristic features in the liver of the normal pregnant woman. This evidence however could not be confirmed by later workers.

Ingerslev and Teilum (1945) carried out an extensive study of liver biopsies in non-pregnant and pregnant women. Routine biopsies from pregnant women gave the impression of normal liver structure, to which sometimes were added minor histological deviations such as a difference in shape of the liver cells with in-

TABLE I

Showing the Frequency of Hepatic Lesions in Normal Pregnancy, Pre-eclampsia and Eclampsia

	Total No.	Normal Liver	Perisinusoidal oedema without necrosis	Perisinusoidal oedema with focal necrosis	Periportal focal haemorrhagic necrosis	Diffuse haemmorrhgic necrosis	Binucleation and anisocytosis	Fatty change	Congestion
	1	2	3	4	5	6	7	8	9
Normal pregnancy	25	25 (100%)	—	—	—	—	—	—	—
Mild preeclampsia	5	5 (100%)	—	—	—	—	—	—	—
Severe preeclampsia ..	10	5 (50%)	1 (10%)	—	—	—	2 (20%)	2 (20%)	—
Eclampsia	26	5 (19.3%)	9 (34.6%)	3 (11.5%)	3 (11.5%)	—	—	6 (23.1%)	—
						—	—		—
Postmortem biopsy	4	—	—	—	1 (25%)	2 (50%)	—	—	1 (25%)

crease in the number of large nuclei, irregularity of nuclei, and increased glycogen load of the cytoplasm. All these were an expression of the labile state of the liver and served to demonstrate what might be termed hepatic resilience. Deitel (1947) observed an increased number of binucleated cells in normal pregnancy. Nixon (1947) and Antia et Bhardwaj (1958) were unable to demonstrate any uniform morphological changes in the liver of normal pregnant women.

In the present study no histopathological changes have been found in the liver of normal pregnancy. In a few cases there were areas of light and dark liver cells which have been shown to be fixation artefacts (Ingerslev and Teilum 1945). There was no evidence of increase in the number of binucleated cells as reported by Dietel (1947), nor any hyperplasia of the reticulo-endothelial cells. It seems therefore that there is no justification for the assumption of the so called "pregnancy liver".

As far as the toxaemias of pregnancy are concerned, the basic pathologic process in pre-eclampsia and eclampsia is vasospasm. The essential lesion exists in the pre-capilary arterioles, the nature of the change being a fibrinoid degeneration of the media of the arterioles. This vascular process is initiated by wide-spread vasospasm. This vasospasm imposes a resistance to blood flow and may produce focal areas of hypoxia.

Vasospasm probably has a noxious effect on the circulation in the vasa-vasorum, thus leading to damage to the vascular walls. These vascular changes, together with local tissue hypoxia, are presumably the cause of haemorrhagic necrosis and most of the other disturbances observed in this disease.

Vasospasm looms large in the mechanism of the whole disease process of acute toxaemia. The concept was first advanced by Volhard in 1918 and has been widely accepted.

In the present cases of pre-eclampsia, exudation of plasma into the perisinusoidal spaces of Disse due to the generalised vascular disorder, was seen only in one instance.

Anisocytosis, increased binucleation, and fatty change in the hepatic cells which have been observed in one case, could also have been the result of interference with the normal blood supply of these cells.

Increased binucleation and anisocytosis in pre-eclampsia observed in this study are in conformity with the findings of Antia (1958).

These observations, however, could not be substantiated by later investigators. In the present cases of pre-eclampsia fatty changes in the liver cells were seen on one occasion.

Occurrence of eclampsia being a late event in the course of the disease, the frequency of histological lesions was much higher than in the pre-eclampsia group.

Normal liver histology was present in 5 cases out of 26 cases of eclampsia. Depending upon the severity of the vascular disorder various grades of lesions were produced. The earliest manifestation was exudation of plasma into the perisinusoidal spaces of Disse. This exuded plasma compressed the hepatic sinusoids thus in-

terfering with the nutrition of the liver cells leading to their necrosis. In addition the perisinusoidal oedema pushed the liver cells away from the periportal area.

Fatty change in the liver cells due to toxaemia of pregnancy has not been previously described in antemortem biopsies. The high frequency with which this change has been observed in the present series is too significant to be overlooked. It might be suggested that this fatty change could have been present even before the occurrence of toxaemia due to poor nutritional status of the patient. If this was so then the frequency of fatty change should have been the same in normal pregnancy and toxaemia groups, this, however, was not so. There was no evidence of fatty change in any case of normal pregnancy. In the pre-eclampsia group it was observed only in 2 cases whereas in the eclampsia group it was seen in 6 cases. It may be theorised that this fatty change in the liver cells may be the result of interference with the blood supply of the hepatic cells due to the vascular changes of pre-eclampsia and eclampsia.

In cases where the vascular disorder was more pronounced the exudation of plasma was replaced by exudation of blood and even frank haemorrhage. This resulted in the production of focal and diffuse haemorrhagic necrosis described by Sheehan (1950). In the present series diffuse haemorrhagic necrosis was not seen in any of the liver biopsies taken from the living patients. It was observed only in 2 postmortem liver biopsies. In one of these sections the liver cell columns were completely fragmented and broken up. In the diffuse lesions described by Sheehan (1950) although the sinusoidal lining was stripped away from the parenchymal cells the continuity of the liver cells themselves was maintained. Such fragmentation of the liver cell plates in diffuse haemorrhagic necrosis has been reported by Antia and Bhardwaj (1958). The intensity of the hepatic histologic changes is related to the severity of the disease process. Liver biopsy can thus serve as an aid in establishing the prognosis in a case of texaemia of pregnancy.

Summary and Conclusions

In order to assess and evaluate the hepatic structure in normal and toxaemia pregnancy, needle biopsies of the liver have been studied in the following groups of cases.

Group I. 25 women with normal pregnancy.

Group II. 15 women with pre-eclampsia complicating pregnancy.

Group III. 26 women with eclampsia.

In addition postmortem liver biopsies have been studied in 4 cases.

Liver biopsy was taken by the Vim-Silvermann technique.

In normal pregnancy and mild pre-eclampsia there was no abnormality in the hepatic histology.

In severe pre-eclampsia 5 cases (50%) showed no histopathological lesions in the liver biopsy. In one case (10%) perisinusoidal oedema was observed. In the remaining cases 2 (20%) showed fatty change in the liver cells, anisocytosis was seen in the third (10%) and increased binucleation of the liver cells in the fourth (10%) case. These may

have been the result of interference with the vascular supply of these cells as a consequence of vasospastic changes.

The frequency of histological lesions was much higher in the eclampsia group. Normal liver tissue was seen only in 5 (19.3%) cases. In 12 (46.1%) cases perisinusoidal oedema with compression of the sinusoids was observed; 3 out of these revealed necrosis of the liver cells due to interference with their blood supply. Periportal focal haemorrhagic necrosis was seen in 3 (11.5%) cases. Diffuse haemorrhagic necrosis was not manifest in any of the antemortem liver biopsies though it was seen in 2 postmortem liver biopsies out of the 4 i.e. 50%.

Fatty change in the liver cells due to toxaemia has not been previously described. It was seen in 6(23.1%) cases of eclampsia in the present series. This was not an incidental finding due to poor nutrition because it was not seen in any case of normal pregnancy and in only one of pre-eclampsia. The frequency and severity of hepatic lesions have been found to be directly proportionate to the severity of the disease process.

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