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REVIEW

Liver disease in pregnancy

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The diseases which affect the liver in pregnancy can be subdivided into those which occur simultaneously with gestation and those which occur in the context of and exclusively during pregnancy. This review deals with the latter group and describes the histopathological features of acute fatty liver of pregnancy and liver disease in toxaemia of pregnancy, hyperemesis gravidarum and intrahepatic cholestasis of pregnancy.

Keywords: pregnancy, liver disease, acute fatty liver of pregnancy, toxaemia of pregnancy, intrahepatic cholestasis of pregnancy, hyperemesis gravidarum

Introduction

Liver disease is uncommon in pregnancy. The most frequent clinical manifestation is jaundice and this is seen in only one of 1500 pregnancies (Haemmerli 1966). The disorders which affect the liver can be divided into two groups; those which simply occur simultaneously with gestation but are aetiologically unrelated to it, and those which develop only in the context of pregnancy. The former category includes acute viral hepatitis, which is reputed to be the most common cause of jaundice during pregnancy. It is no more severe in the pregnant patient (provided she is well nourished) than in the non-pregnant female. However, the entire spectrum of liver disease can occur in the gravid patient. As a rule the clinical course of concurrent liver disease remains unaffected by gestation, with the exception of a few diseases,

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such as cirrhosis with portal hypertension, chronic active hepatitis and the Dubin–Johnson syndrome (Gitlin 1985). This review examines those diseases which develop exclusively during pregnancy. They include acute fatty liver of pregnancy, liver disease in toxaemia of pregnancy, intrahepatic cholestasis of pregnancy and liver disease in hyperemesis gravidarum. Diseases not specific to pregnancy are considered in other reviews (Steven 1981, Kregs 1983, Snydman 1985).

The liver during normal pregnancy

The light microscopic appearance of the liver is normal during gestation. No histological changes accompany the mild increases in total and direct serum bilirubin found in 20% of pregnant women, which reflect physiological cholestasis related to increased circulating oestrogens. However, minor subcellular alterations, including some involving bile canaliculi, have been reported in pregnancy (Ishak 1981).

Acute fatty liver of pregnancy

Acute fatty liver of pregnancy is a disease of the third trimester and occurs any time from the 30th to the 40th week of gestation. Both primigravidae and multiparae may be affected. An increased incidence is observed with twin gestations and in pregnancies with male offspring. The illness typically has a rapid clinical course lasting about 3 weeks. It begins with a prodrome of malaise, nausea and vomiting. The patient subsequently becomes jaundiced and shortly afterwards develops hepatic encephalopathy. Liver function tests reflect a predominantly cholestatic disorder with serum bilirubins of 170–250 μmol/l and a moderate rise of alkaline phosphatase. The serum aminotransferases are usually below 300 U/l and almost always less than 500 U/l. Hypoglycaemia, a correctable manifestation of the liver failure, and hyperuricaemia are commonly observed. Extrahepatic complications frequently accompany the disease and include azotaemia and renal failure, disseminated intravascular coagulation, peptic ulceration with gastrointestinal bleeding and acute pancreatitis. Signs and symptoms of mild toxaemia, i.e. hypertension and proteinuria, develop in 20–40% of cases (Pockros, Peters & Reynolds 1984). Their presence should not dissuade the clinician from considering a diagnosis of acute fatty liver or lead to delay as prompt treatment is essential.

Acute fatty liver is the most serious of the pregnancy associated diseases. A review of cases reported in the literature up to 1980 found maternal and fetal mortalities of 75% and 85%, respectively (Varner & Rinderknecht 1980). Recent series, with one exception (Hague *et al.* 1983), have shown a dramatic improvement in the prognosis associated with this disorder. Maternal mortality rates have fallen to 8–33% and fetal deaths to 14–66% of cases (Davies *et al.* 1980, Riely 1980, Burroughs *et al.* 1982, Bernuau *et al.* 1983, Pockros *et al.* 1984, Rolfes &

Ishak 1985). The explanation for this vastly improved outlook is two-fold (Sherlock 1983, Riely 1984, Kaplan 1985). One is prompt termination of the pregnancy upon diagnosis of the disorder and better supportive care for the hepatic encephalopathy and extrahepatic complications which develop. The other is the recognition that milder cases exist. Older series were based largely on autopsies while more recent series have been clinical studies that better document the natural course of this disease. It is now evident that some mothers do not develop hepatic encephalopathy, while others manifest early stages of it but do not inevitably progress to coma. In fact, acute fatty liver should be considered in the differential diagnosis of any woman in the third trimester of pregnancy with evidence of liver dysfunction, even in the absence of jaundice (Hague *et al.* 1983). It has been suggested that the newer imaging techniques, such as computed tomography, ultrasonography and magnetic resonance imaging, could be helpful in early diagnosis (Bova & Schenker 1985).

Thirteen women are now known to have had normal pregnancies following one complicated by acute fatty liver and no recurrence has been reported to date (Breen *et al.* 1972, MacKenna *et al.* 1977, Davies *et al.* 1980, Jenkins & Darling 1980, Burroughs *et al.* 1982, Ebert *et al.* 1984, Pockros *et al.* 1984). Therefore, an attitude of guarded optimism can be expressed to patients who wish to become pregnant again.

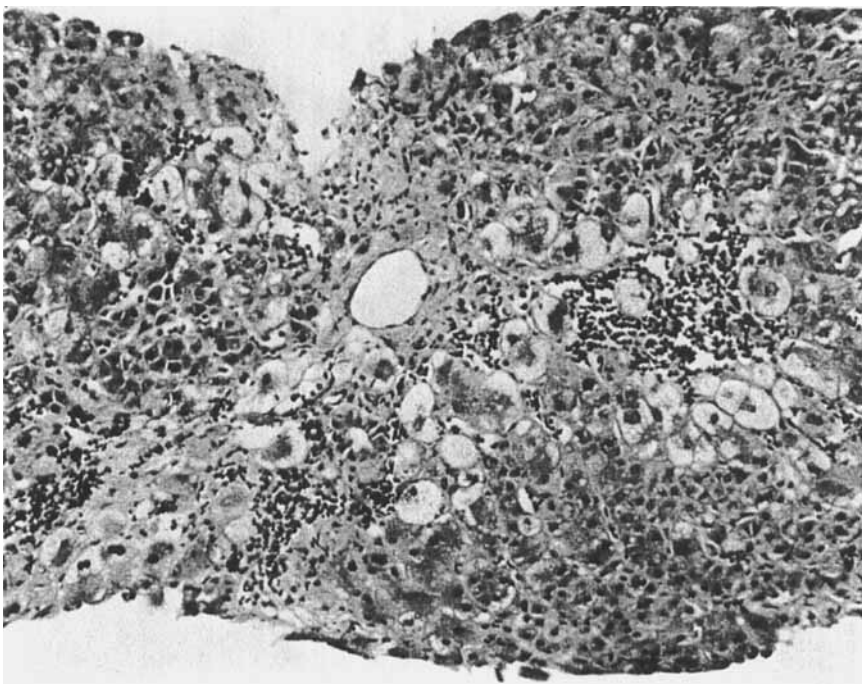

Figure 1. Fatty change may be pan-acinar to zonal in distribution. In this liver biopsy the lipid is confined to acinar zone 3. Lysed groups of liver cells have been replaced by haemorrhage. H & E. ×160.

Affected livers are grossly yellow and frequently small, a reflection of substantial loss of parenchyma. Microscopically, the most characteristic feature is microvesicular steatosis. This is also typical of tetracycline toxicity (Kunelis, Peters & Edmondson 1965, Peters *et al.* 1967, Robinson & Rywlin 1970), Reye's syndrome (Bove *et al.* 1975), alcoholic foamy degeneration (Uchida *et al.* 1983), valproic acid injury (Zimmerman & Ishak 1982), salicylate intoxication (Starko & Mullick 1983), cholesterol ester storage disease (Dincsoy *et al.* 1984) and Wolman's disease (Miller *et al.* 1982). The clinical setting should readily distinguish acute fatty liver of pregnancy from these conditions. Fatty change may involve the liver in a pan-acinar distribution or zonally, affecting both acinar zones 2 and 3, or may be restricted to the latter (Figure 1). In most instances the small fat droplets produce discrete vacuoles in the hepatocyte and the fatty change is readily recognized (Figure 2A). However, liver cells containing fine fat droplets (less than 1 μm in diameter) do not exhibit distinct vacuolation but have an appearance of diffuse cytoplasmic ballooning (Figure 2B). In some biopsy samples this is the predominant or only change. This mimics the hydropic swelling of liver cells in acute viral hepatitis and it is particularly confusing when accompanied by a lympho-plasmacytic infiltrate and acidophil bodies which are present in 10–20% of the cases (Burroughs *et al.* 1982, Rolfes & Ishak 1985). In such instances, viral hepatitis and acute fatty liver may not be reliably distinguished in routinely

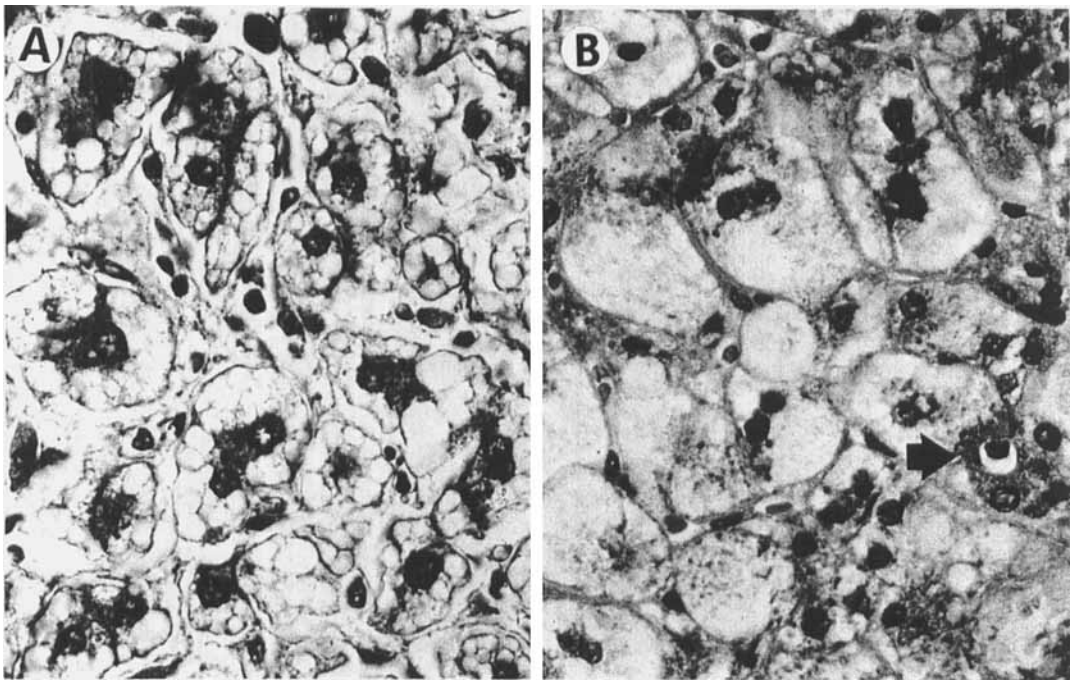

Figure 2. Microvesicular steatosis in the liver is characterized by vacuoles of variable size (**A**) or by diffuse cytoplasmic ballooning (**B**). In the latter, the presence of lipid is 'masked'. A canalicular bile plug is indicated by an arrow. H & E. ×504.

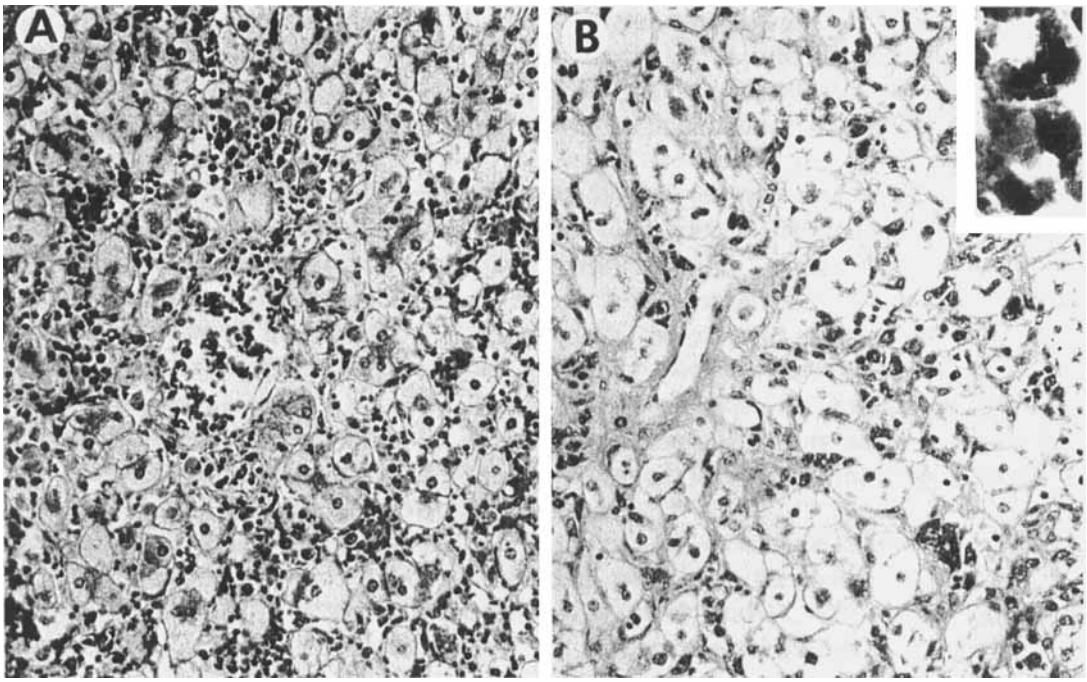

Figure 3. A case of acute fatty liver of pregnancy histopathologically mimicking acute viral hepatitis is illustrated. **A** Liver cells are diffusely swollen without discrete vacuoles. A moderate lymphocytic infiltrate is present and haemorrhage is evident in areas of hepatocytolysis. H & E. ×200. **B** Hyperplastic aggregates of Kupffer cells containing lipofuscin represent 'tombstones' for necrotic liver cells whose debris they have engulfed and degraded. DPAS. ×200. *Inset:* A frozen section stained with oil red-O demonstrates the presence of lipid in hepatocytes and allows a confident diagnosis of acute fatty liver.

processed material (Figure 3). This is unfortunate because these biopsies are most often performed in cases which are clinically confusing. Termination of pregnancy has not been shown to improve the outcome in acute viral hepatitis and the additional stress placed on the liver, particularly if a general anaesthetic is used for Caesarean section, may cause further harm. Therefore, whenever acute fatty liver is in the differential diagnosis, a small piece of the specimen should not be processed but kept fresh frozen for the potential need to demonstrate the lipid with an oil red-O stain. While acute viral hepatitis may on occasion lead to mild fatty change, it does not approach in degree that seen in acute fatty liver of pregnancy nor is it zonal in distribution.

The lipid is rapidly mobilized in patients who survive, receding towards the terminal hepatic venule. It may be undetectable after 1 month of convalescence (Duma *et al.* 1965). A normal hepatic architecture is reconstituted and scarring or other chronic sequelae do not develop.

Microvesicular steatosis is commonly accompanied by other changes. Intrahepatic cholestasis is an almost regular finding, including bile in canaliculi (Figure 2B) and hepatocytes as well as an acute cholangiolitis. Liver cell necrosis occurs and is

predominantly due to hepatocytolysis. Single hepatocytes (Figure 3A) and small groups of them (Figure 1) disappear, leaving behind hyperplastic aggregates of Kupffer cells as 'tombstones' (Figure 3B). Finally, extramedullary haemopoiesis including erythroid islands, myeloid groups and megakaryocytes may be present in sinusoids.

The cause of this disorder is unknown but speculation on the pathogenesis has included mitochondrial injury and the free fatty acid content of these livers. Deficiencies of several mitochondrial urea cycle enzymes has been reported (Weber *et al.* 1979). Enlarged, often needle-shaped mitochondria may be observed by light and electron microscopy (Weber *et al.* 1979, Burroughs *et al.* 1982, Rolfes & Ishak 1985). Ultrastructurally, crystalline inclusions can be found in their matrix. However, unlike the specific mitochondrial changes associated with Reye's syndrome, these morphological alterations can be observed in a wide variety of circumstances and along with the urea cycle enzyme deficiencies, are not invariably present (Maier *et al.* 1982). They probably represent secondary degenerative or adaptive phenomena in an altered metabolic environment. There is one case, however, in which ultrastructural studies revealed swollen mitochondria and damaged cristae (Aburatani *et al.* 1984). Biochemical analysis of plasma lipoproteins suggested defective removal and decreased synthesis. Biochemical analysis of the lipid from a fatal case showed it to be predominantly free fatty acid, which is known to be injurious to cells and tissues (Eisele, Barker & Smuckler 1975). In contrast, the lipid is principally neutral triglyceride in other disorders associated with fat accumulation such as alcoholism, obesity, diabetes mellitus, and starvation (Hoyumpa *et al.* 1975). While the fat in these latter disorders is a result and not the cause of liver cell injury, free fatty acid may contribute to hepatocellular dysfunction in acute fatty liver of pregnancy.

Liver disease in toxaemia of pregnancy

Pre-eclampsia is characterized by hypertension induced or aggravated by pregnancy in association with proteinuria and peripheral oedema. Convulsions and coma may follow and this stage is termed eclampsia. Pre-eclampsia develops in 5% of pregnancies, usually during the third trimester, and principally affects primigravidae. Antecedent factors have not been clearly identified but patients with systemic lupus erythematosus with lupus anticoagulant have high rates of pre-eclampsia and fetal growth retardation (Branch *et al.* 1985). Comprehensive reviews of the history and epidemiology (Chesley 1984), clinical and laboratory manifestations (DeVoe & O'Shaughnessy 1984), and the pathophysiology (Gant & Worley 1980, Worley 1984) of toxaemia are recommended for further reading.

The liver is not manifestly involved in early toxaemia, but it is a target organ that is damaged in severe pre-eclampsia and eclampsia. This is usually characterized by upper abdominal pain, nausea and vomiting, and occasionally by jaundice. Hepatocellular dysfunction is reflected by elevation of the serum aminotransferases, which can be in the hepatitic range. Bilirubin increases are typically mild,

usually below 100 μmol/l, and are largely related to an accompanying microangiopathic haemolytic anaemia. Occasionally, when deep jaundice develops, hepatocellular dysfunction contributes to the hyperbilirubinaemia (Long, Scheuer & Sherlock 1977). Liver disease most often occurs in women with advanced toxaemia due to poor pre-natal care. It is usually accompanied by other manifestations of severe disease including a high diastolic blood pressure (greater than 110 mm Hg), marked proteinuria, oliguria, elevated serum creatinine, cerebral and visual disturbances, thrombocytopenia and fetal growth retardation. With this constellation of findings the cause of the liver disease is usually readily apparent. On the other hand, some patients with pre-eclampsia may present principally with hepatic dysfunction, and show laboratory evidence of *h*aemolytic anaemia, *e*levated *l*iver enzymes, and *l*ow *p*latelets (Killam *et al.* 1975, Goodlin 1976, Goodlin & Holdt 1981, MacKenna, Doven & Brame 1983, Ogle & Sanders 1984, Worley 1984, Lindheimer & Katz 1985). This atypical presentation of advanced toxaemia has been termed the HELLP syndrome (Weinstein 1982). Affected patients often have only mild elevations of blood pressure and slight proteinuria and symptoms may be mistaken for those of acute viral hepatitis or other abdominal complications.

Macroscopically the liver in toxaemia shows diffuse fine or blotchy haemorrhages over the capsule and on the cut surface (Figure 4). Histopathologically, periportal regions reveal variable combinations of fibrin deposition, haemorrhage and hepatocellular necrosis (Figure 5). In some areas there is pure fibrin deposition in sinusoids with replacement of periportal liver cells. Thrombi can also be detected in portal tract capillaries, occasionally in hepatic arteries, and rarely in

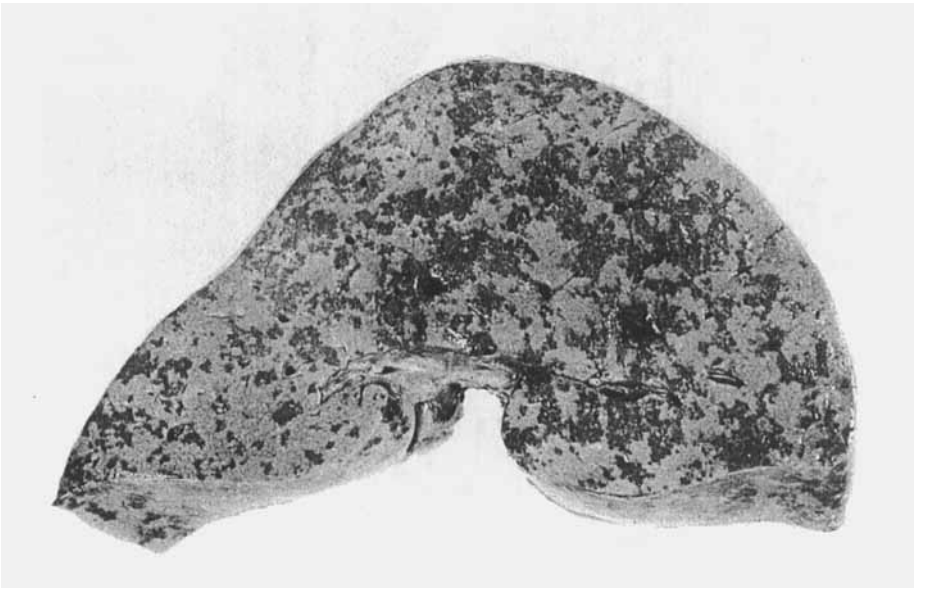

Figure 4. Cut section of a liver from a fatal case of toxaemia reveals darkly-stained areas of haemorrhage and necrosis scattered in both lobes.

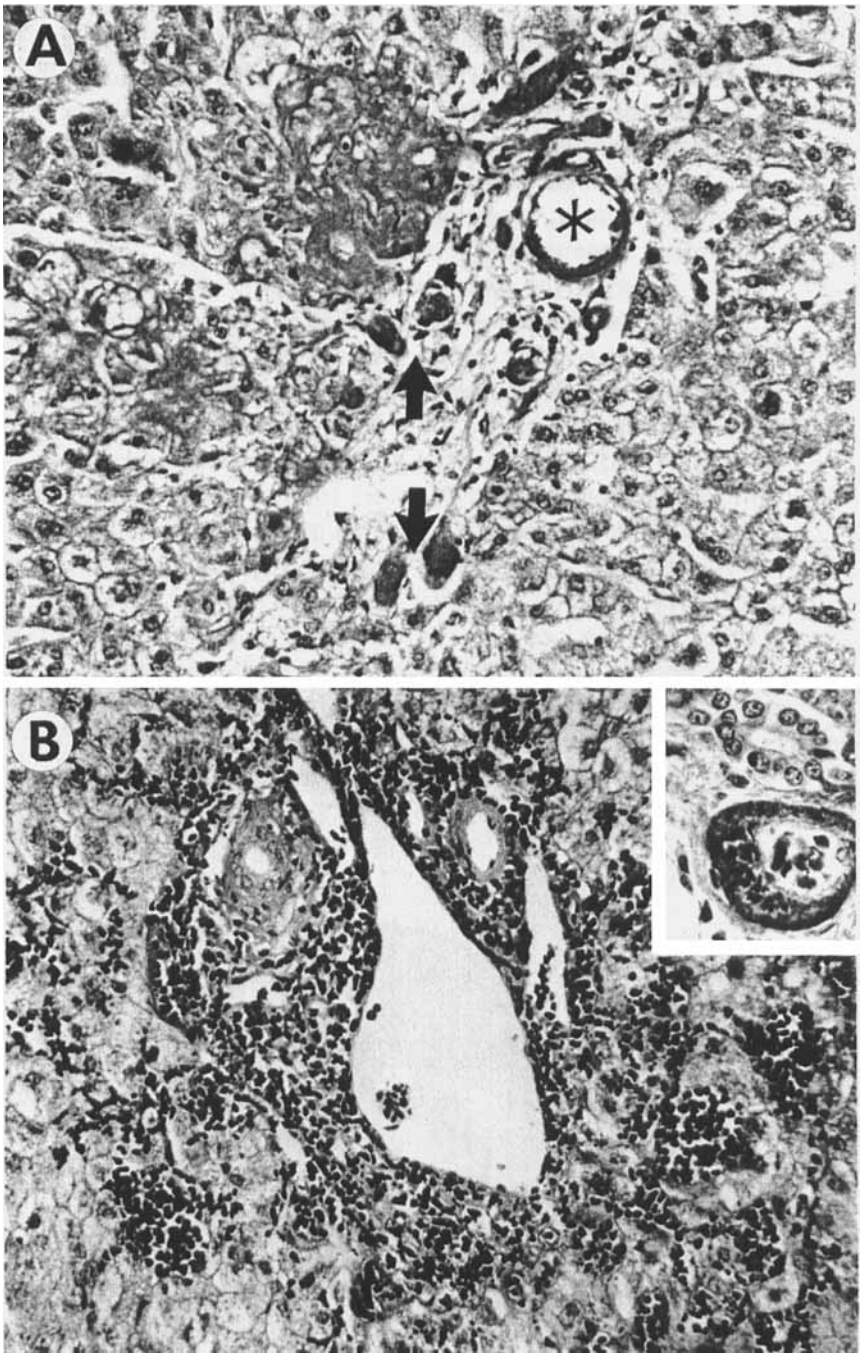

Figure 5. Different histopathological patterns of injury in portal and periportal areas in toxaemia are illustrated in this composite figure. **A** Pure fibrin deposition is seen in the sinusoids and replacing liver cells within the acinus. Thrombi occlude portal tract capillaries (arrows) and line the wall of a hepatic artery (*). H & E. ×150. **B** Haemorrhage floods the portal connective tissue and the adjacent acinus. H & E. ×250. *Inset:* Red blood cells pass through the wall of a hepatic artery. **C** A mixture of fibrin and haemorrhage is present around a portal area (*). PTAH. ×250.

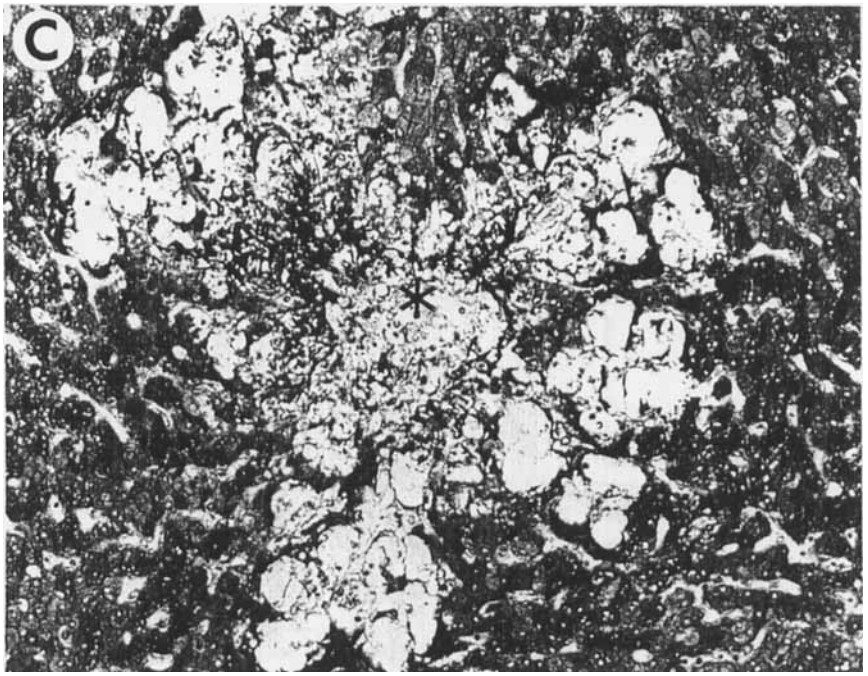

Figure 5—*continued*

portal vein branches. In other areas there is haemorrhage in the portal tracts and the periportal regions but no fibrin is present. In still other areas variable admixtures of fibrin and haemorrhage are observed.

The characteristic periportal lesions are detected at autopsy in more than 75% of women dying with eclampsia (McKay 1964). They are observed less often in needle biopsy specimens due to sampling artifact and the presence of generally milder disease (Ingerslev & Teilum 1945, Sheehan 1950, McKay *et al.* 1953, Anita *et al.* 1958, Arias & Mancilla-Jimenez 1976). They are seen in only 25% of such specimens from women with eclampsia and rarely in women in pre-eclampsia.

Opinions have differed on the sequence and cause of the changes in toxaemia. Some investigators have suggested that liver cell necrosis or haemorrhage (Sheehan & Lynch 1973) are the primary events, but these views are not supported by histological observations. Most have considered periportal sinusoidal fibrin deposition as primary, and have attributed it to disseminated intravascular coagulation (McKay *et al.* 1953, Page 1972). However, only a minority of patients with eclampsia have such coagulation abnormalities (Naish *et al.* 1973, Arias & Mancilla-Jimenez 1976, Condie 1976, Pritchard, Cunningham & Mason 1976, Gant & Worley 1980, Sibai, Anderson & McCubbin 1982, DeVoe & Shaughnessy 1984). Segmental vasospasm is important in the pathogenesis of toxaemia and a vasculopathy related to this phenomenon could be responsible for the hepatic changes (Arias & Mancilla-Jimenez 1976, Pritchard, Cunningham & Mason 1976) (Figure 6). Endothelial cells are injured in constricted segments and in dilated segments they are separated. As a consequence, subendothelial collagen is exposed

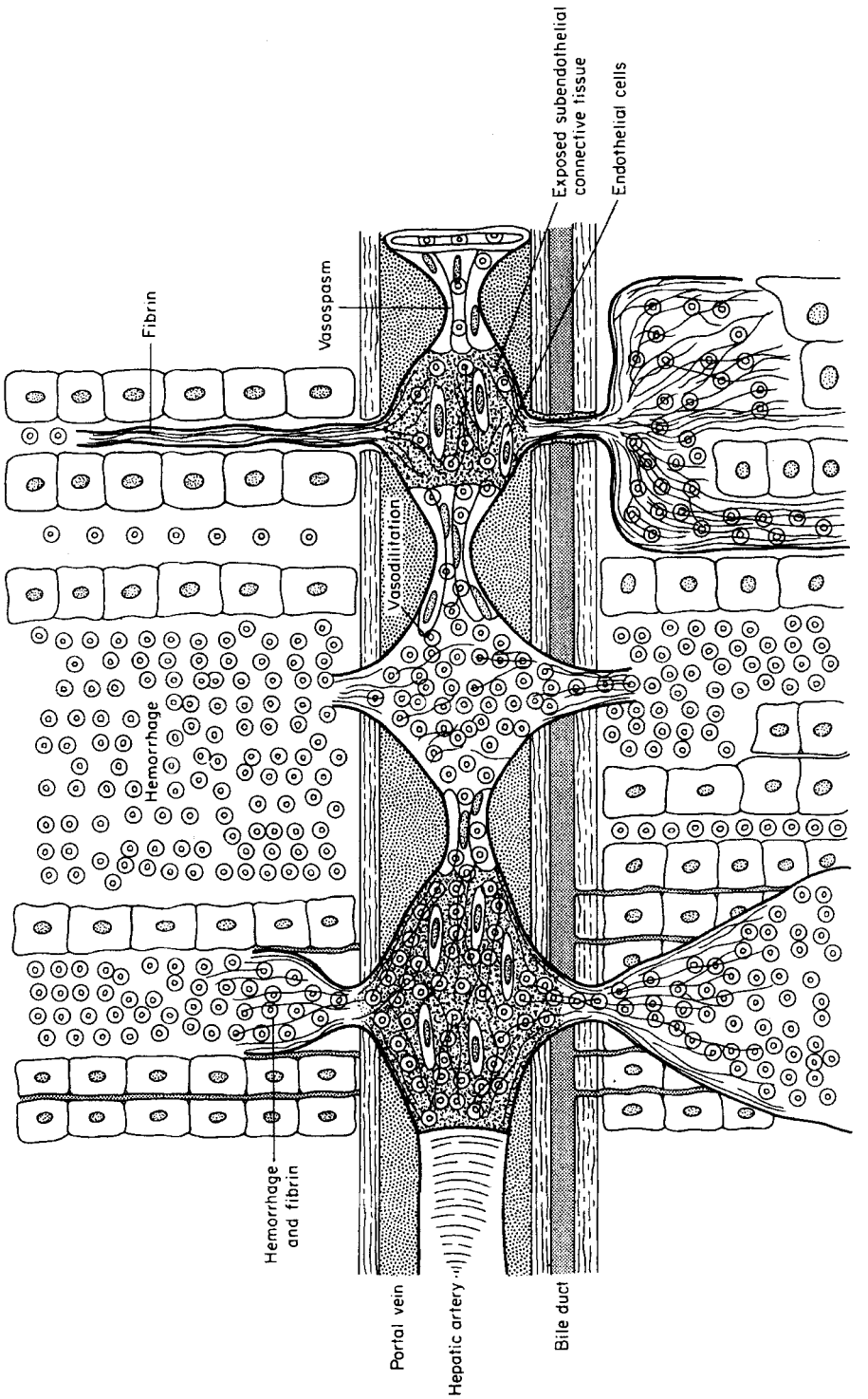

Figure 6. An exaggeration of toxaemic vasospasm at the level of small hepatic arteries is probably responsible for the changes in the liver, as illustrated in this diagram. Injury and disruption of the endothelium produce a localized consumptive coagulopathy (right). Increased pressure in the dilated segments produces tears in the arterial wall and rupture of vascular anastomoses (middle). In still other regions both fibrin deposition and haemorrhage develop (left).

leading to platelet adherence and aggregation as well as fibrin precipitation. Haemorrhage could be secondary to liver cell necrosis related to this phenomenon. Alternatively, the haemorrhage could be related to increased lumenal pressure in the dilated segments producing mural arterial haemorrhage and tears, as well as rupture of anastomoses with the portal vein and sinusoids.

Central nervous system catastrophies are the usual cause of death in toxaemia; however, liver involvement may also be responsible. Extensive periportal lesions may lead to liver failure, and two rare complications, rupture and infarction, often prove fatal.

Eighty per cent of women who develop spontaneous hepatic rupture during pregnancy are toxaemic (Bis & Waxman 1976, Steven 1981, Stalter & Sterling 1985). The patients are usually in the older reproductive age group and are multiparous. They present with the sudden onset of right upper quadrant pain and shock late in the third trimester, or during the early post-partum period. Pre-operative diagnosis is infrequent, being based on radioisotope liver scans, and more recently on the use of ultrasonography (Greca *et al.* 1984). The rupture is preceded by a parenchymal haematoma which almost always develops in the right lobe. The haematoma detaches the capsule from the underlying liver and, if bleeding continues, the capsule is stretched and eventually torn. The intact hepatic haematoma can probably be managed by blood product replacement, so long as the patient remains haemodynamically stable (Manas *et al.* 1985). However, when rupture occurs, surgery to control haemostasis is usually considered the only chance for survival of the patient (Stalter & Sterling 1985). One recent report described successful treatment of this complication by transcatheteric embolization (Loevinger *et al.* 1985).

Hepatic infarction may occur in toxaemia. This can involve localized areas or as much as 50–90% of the parenchyma. Intense arterial vasospasm may be responsible in some instances. Women with massive hepatic infarction have often had profound episodes of shock. The poor perfusion of the liver during these periods, superimposed on the obstruction to sinusoidal blood flow created by the fibrin deposition, probably accounts for the severe ischaemia that leads to such widespread necrosis.

Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy is second only to viral hepatitis as a cause of jaundice during gestation and accounts for 20% of cases. Though referred to as jaundice of late pregnancy by some, it can occur at any time during the first to the third trimesters. It begins with a prodrome of pruritus and in some instances no further symptoms will develop, a forme fruste referred to as pruritus gravidarum. In most cases, the pruritus is followed in 2 weeks by the onset of mild jaundice, often with dark urine and light stools. Both pruritus and jaundice persist for the duration of the pregnancy. Laboratory studies typically reveal mild elevations of the serum bilirubin (less than 85 μmol/l, predominantly direct reacting) and alkaline

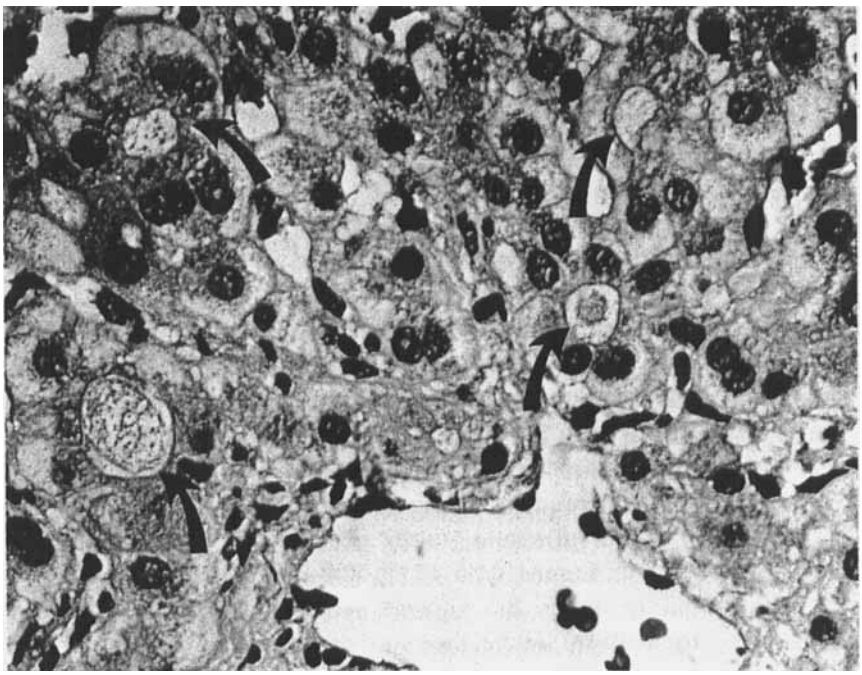

Figure 7. Canalicular bile plugs (arrows) in section of liver biopsy specimen from a patient with intrahepatic cholestasis of pregnancy. A terminal hepatic venule is present at bottom of field. H & E. ×630.

phosphatase activity. Rarely, higher serum bilibrubins are observed and a record level of 600 μmol/l has been reported (Misra *et al.* 1980). Serum bile acids are increased 10–100 times. The serum aminotransferase values may be increased but are usually less than 250 U/l.

This disorder is benign for the mother and all signs and symptoms resolve, usually within 2 weeks following delivery. Mild pruritus during pregnancy may respond to the use of antihistamines and more severe symptoms sometimes improve with cholestyramine. Preliminary trials using *S*-adenosyl-L-methionine have been encouraging (Frezza *et al.* 1984). A subsequent risk of developing cholelithiasis and gallbladder disease is observed in these women (Samsioe *et al.* 1975, Misra *et al.* 1980). The fetus, however, is at risk in these pregnancies (Steven 1981, Kregs 1983). Fetal distress, fetal death and premature deliveries can occur. A role for maternal bile salts which cross the placenta has been postulated (Laatikainen 1975, Laatikainen & Tulenheimo 1984). The overall foetal perinatal mortality is four times that of controls and close perinatal monitoring is necessary.

The histopathology is characterized by acinar cholestasis (Figure 7). Bile is seen in canaliculi and hepatocytes, predominantly in zone 3. These changes are often subtle. Inflammation and necrosis are typically not observed and portal tracts are unaffected.

Intrahepatic cholestasis of pregnancy is due to maternal hypersensitivity to the

cholestatic effects of oestrogens. Symptoms often recur in subsequent pregnancies and during administration of oral contraceptives or synthetic oestrogens (Kreek *et al.* 1967). This tendency appears to be inherited since close family members may be affected. Genetic transmission is also implicated because of the variable expression in certain ethnic and geographically segregated groups. Intrahepatic cholestasis of pregnancy occurs with a very high incidence in Chile, where it develops in 10% of pregnant women and it is also quite common in Scandinavian countries (Reyes 1982).

Liver disease in hyperemesis gravidarum

Nausea and vomiting are common accompaniments of pregnancy and, when severe, can be associated with liver dysfunction (Adams, Gordon & Combes 1968). Such patients are usually diagnosed in the hospital after being admitted for the treatment of dehydration and malnutrition. Occasionally, jaundice develops, but asymptomatic abnormalities of liver function tests are observed more frequently. The level of bilirubin is usually below 68 μmol/l, the aminotransferases may be increased up to 200 U/l and the alkaline phosphatase activity may be mildly raised. Liver biopsies are only rarely performed on these patients. They usually show a normal parenchyma or mild fatty change, but a recent report recorded cholestasis and scarce necrotic hepatocytes (Larrey *et al.* 1984). Liver dysfunction responds to the control of vomiting and the correction of dehydration and malnutrition.

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