Progress report

Pregnancy and liver disease

The concurrence of pregnancy and liver disease is uncommon, and in most cases no alteration in the management of either condition is required. Occasionally, liver disease specific to pregnancy occurs or a patient known to have liver disease becomes pregnant and special consideration must be given to the fetus and the maternal liver disease. The diagnosis and management of liver disease in the pregnant patient has not been considered unless it is specifically altered on account of the pregnancy, and in these cases reference to standard textbooks will be found useful.1-3 The changes in liver function which occur during normal pregnancy have been well reviewed4-6 and are summarised in the Table. Hepatic blood flow is not increased during pregnancy, and a smaller proportion of the cardiac output, which is increased during pregnancy, passes to the liver. Histological examination of liver biopsy specimens from normal pregnant patients show no significant abnormalities.6 7

Table  Liver function tests in pregnancy5 6 182 192 193

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal range</th>
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<tbody>
<tr>
<td>Bilirubin</td>
<td></td>
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<tr>
<td>Transaminases (AST, ALT)</td>
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<tr>
<td>Transpeptidase (GGT)</td>
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<td>5 Nucleotidase (5 NT)</td>
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<tr>
<td>Prothrombin time</td>
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<tr>
<td>Alkaline phosphatase</td>
<td>Increased. Up to double non-pregnant values</td>
</tr>
<tr>
<td>Total protein</td>
<td>Decreased. Falls in 1st trimester to 85% of non-pregnant values and changes little thereafter</td>
</tr>
<tr>
<td>Albumin</td>
<td>Decreased. Maximal fall in 1st trimester reaching 66% of non-pregnant values at term</td>
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<tr>
<td>Globulins</td>
<td>Increased. Rise in α and β fractions, small fall in γ</td>
</tr>
<tr>
<td>Bromsulphthalein dye test</td>
<td>Increased. Dye retention at 45 min up to five times non-pregnant values. Values increase towards term</td>
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In considering liver disease in pregnancy, it is useful to use Sherlock’s classification4 and consider
(1) liver disease peculiar to pregnancy;
(2) intercurrent liver disease occurring during pregnancy;
(3) pregnancy complicating liver disease.

Previous authors have considered jaundice during pregnancy,4-6 but, as jaundice may be absent or subclinical, we have elected not to use this classification. There have been several studies of the incidence of jaundice, clinical and biochemical, occurring in pregnancy, and figures quoted for the incidence
vary widely. These may reflect different disease patterns, as infectious hepatitis, one of the commonest causes, varies widely, geographically and temporally, in incidence. In his comprehensive review, Haemmerli\(^5\) found infectious hepatitis to be the commonest cause of jaundice and responsible for 41 % of 456 cases from several countries. Cholestasis of pregnancy caused over 20 % of cases and a variety of other conditions made up the remainder. In smaller series different proportions were seen.\(^8–11\) In a South African series no case of jaundice due to intrahepatic cholestasis of pregnancy was seen, while, in an Australian series, this diagnosis was four times commoner than infectious hepatitis. No cases of infectious hepatitis were considered to be responsible for jaundice in a series from Poland.

**Liver disease peculiar to pregnancy**

**INTRAHEPATIC CHOLESTASIS OF PREGNANCY (ICP)**

This condition has also been known as hepatitis of pregnancy, benign recurrent cholestasis of pregnancy, idiopathic jaundice of pregnancy, and pruritus gravidarum. The condition probably represents a spectrum of cholestatic disease which may manifest itself solely as pruritus or in more severe form as clinical jaundice. It is often but not always recurrent, and may not always be totally benign. For these reasons the above name is preferred. Ahlfeld has been credited\(^12\) with the first description of the condition in 1883, but the syndrome was first defined in Scandinavia.\(^5,13\) Continued interest in the condition in Scandinavia\(^14–16\) and reports from Chile\(^17,18\) led to the belief that it was more common in those countries and that heredity might be a factor. Ethnic variations within Chile\(^19\) and other countries\(^20,21\) supported this view. The incidence of ICP varies widely, but diagnostic criteria may be partly responsible, as some authors did not consider cases without jaundice and others did not include non-recurrent cases. Figures for the incidence of between 1 in 750\(^11\) and 1 in 7000\(^5\) pregnancies have been recorded. Surprisingly, no cases were seen in 17 cases of jaundice in pregnancy from over 4000 deliveries in a mainly white South African population,\(^9\) but 85 % of a Polish series,\(^11\) 77 % of a Danish series,\(^22\) and 65 % of an Australian series\(^10\) were attributed to this cause.

The characteristic clinical picture, amply described by Haemmerli,\(^5\) begins with increasingly severe pruritus in the third trimester of pregnancy, although cases have been reported earlier. Scratch marks and secondary infection are common as the result of severe pruritus. Some cases progress to clinical jaundice, which occurs two to 22 weeks after the onset of pruritus. Typical features of obstructive jaundice, including pale stools and dark urine, accompany the jaundice but, in contrast with infectious hepatitis, which may present in a similar fashion, the patient feels generally well. The liver and spleen are rarely palpable, and jaundice or pruritus persists till delivery, when rapid remission of symptoms occurs in every case. Liver function tests show an obstructive pattern with rises in alkaline phosphatase and bilirubin. Transaminases may be raised, but, if levels are high, hepatitis should be suspected. Bilirubin levels are moderately raised and levels above 85 \(\mu\)mol/l (5 mg/100 ml) are unusual. Raised 5-nucleotidase levels\(^23\) and the presence of lipoprotein X\(^14\) confirm the obstructive nature of the jaundice. Bile acids are raised\(^24,25\) and considered to be responsible for the pruritus. Bilirubin and bile salts may be found in the urine and urobilinogen is reduced but not
absent. BSP dye retention is always prolonged and may remain abnormal months after pregnancy, in contrast with the other liver function tests, which quickly return to normal.

Liver biopsy of patients with pruritus or jaundice shows bile plugs in normal or slightly enlarged cannaliculi. Hepatocellular necrosis and inflammation are absent or minimal and readily distinguish ICP from hepatitis if the clinical picture or liver function tests do not. An association between ICP and the presence of gallstones has been noted, but duct obstruction by gallstones is seldom seen. The condition may recur in subsequent pregnancies or with oral contraceptives. Nulligravid patients may experience a similar syndrome with the oral contraceptive and are at risk of subsequent ICP.

This association and also a case recurrent with menstruation suggests a role for oestrogens and progestagens. Several authors have noted abnormal liver function tests in patients with ICP, subsequently challenged with a variety of oestrogens accompanied in some cases by typical symptoms. Diminished biliary excretion of oestrogen metabolites has been shown, but could be a secondary phenomenon. Abnormal levels of serum lipids have also been noted, along with abnormal metabolism of lecithin. This would reduce the solubility of cholesterol in bile, resulting in crystallisation with an increase in the incidence of gallstones. No long-term sequelae have been reported for the mother, even when the condition is recurrent. Although it was previously considered to be benign, an increased incidence of premature labour has been noted, and a role for bile salts which cross the placental barrier has been suggested. Although many authors consider this to be the only effect on the fetus, one author noted six fetal deaths in 56 pregnancies and found a high incidence of post-partum haemorrhage which has been confirmed by others. Termination of the pregnancy is not recommended unless fetal distress occurs.

Cholestyramine is effective for severe pruritus and barbiturates may reduce the level of bilirubin, presumably by enzyme induction, although symptoms may not be relieved. Prophylactic vitamin K has been recommended in view of the malabsorption occasioned by cholestasis and the increased incidence of post-partum haemorrhage.

The condition is easily diagnosed if it is recurrent in a multiparous patient, but may be confused with familial jaundice, drug-induced cholestasis, cholelithiasis, chronic liver disease, or viral hepatitis in de novo cases. The prominent pruritus and absent constitutional symptoms favour cholestasis and liver function tests are helpful. Liver biopsy is definitive if hepatitis serology is not available. Demonstration of the biliary tree by ultrasound examination will differentiate biliary obstruction due to calculi or other obstructing lesions. Treatment may be required for symptomatic relief of pruritus, and vitamin K should be given prophylactically to the mother and child to prevent bleeding. Special care facilities for the baby should be available in view of the increased incidence of prematurity.

**ACUTE FATTY LIVER OF PREGNANCY**

This severe form of liver disease occurring in pregnancy was first reported by Sheehan in 1940. The syndrome is held to be a rare cause of jaundice in pregnancy, but more than 50 cases have been reported and a maternal
mortality of more than 80% noted with fetal loss in 70% of cases. Fetal loss was only 40% in mothers who survived. The typical clinical presentation includes the onset in the third trimester of nausea, vomiting, abdominal pain, and headache, progressing to jaundice, oliguria, and gastrointestinal bleeding. Laboratory examinations confirm the presence of fulminant hepatic and acute renal failure, and in severe cases evidence of disseminated intravascular coagulation may be seen.45-44 Histology of the liver typically shows panlobular fatty change with periportal sparing39 45 and the absence of hepatocellular necrosis or significant inflammatory infiltrate serves to distinguish acute fatty liver of pregnancy from fulminant viral hepatitis with which it may be confused. Clinical and pathological evidence of pancreatic involvement may be found.41 45

The aetiology is unknown, but one series40 reported an association with the use of high dose intravenous tetracycline, and toxins, viruses, nutritional factors, and pre-eclampsia have all been considered as possible causes.41 46 Treatment is essentially supportive,4 as for other cases of hepatic and renal failure,41 but the importance of correcting hypoglycaemia with adequate intravenous dextrose has been emphasised.39 Fresh coagulation factors have been used and heparin has been recommended in the presence of disseminated intravascular coagulation, although both the mother and infant so treated died.44 It has been stated that early delivery by Caesarean section is advisable47 and may improve the fetal prognosis, but whether this benefits the mother is disputed.46 The surviving infants do not appear to be affected and the maternal liver recovers completely45 46 in the survivors. It is agreed that further pregnancies are possible and safe and that recurrence of the maternal acute fatty liver does not occur.39 46

HYPEREMESIS GRAVIDARUM
This disabling condition may be associated with liver dysfunction. In a series of 103 cases,48 liver function tests, apart from the BSP dye test, were normal in 57 patients, who were managed as outpatients. In 46 who needed to be admitted to hospital, biochemical abnormalities were frequent. Mild rises in bilirubin were seen in one third and modest rises in transaminases in one quarter. Using the sensitive BSP dye test, 60% had increased dye retention. This retention, when studied in detail, was found to be due to reduced excretion of the dye. Histological examination of liver biopsies in four cases revealed no abnormalities and would help to distinguish the condition from viral hepatitis in cases with similar clinical or biochemical features. Hyperemesis makes up a small percentage of all cases of jaundice of pregnancy, and Haemmerli4 found only 27 in his review of 456 cases. Two of 16 cases of jaundice from one centre were attributed to hyperemesis and resulted in one premature labour with perinatal death of the infant.8 In a necropsy series38 of obstetric deaths, six of 19 cases of hyperemesis had slight jaundice. As with pre-eclampsia, no specific treatment is necessary for jaundice attributed to hyperemesis if other conditions are excluded.

PRE-ECLAMPSIA, ECLAMPSIA, AND SPONTANEOUS RUPTURE OF THE LIVER
The liver is not primarily involved in pre-eclampsia and eclampsia,6 but severe cases may be associated with liver dysfunction. In a series of fatal cases
of eclampsia,³⁸ 11% had haemolytic jaundice, and histological liver changes were considered a preterminal event. One survey of jaundice in pregnancy⁸ attributed four of 17 cases to pre-eclampsia, and one mother died and two others had three stillbirths, including a set of twins. In his large review, Haemmerli⁹ attributed 21 of 456 cases of jaundice in pregnancy to eclampsia. Histology of the liver in these cases showed periportal haemorrhage and fibrin deposition without an inflammatory reaction, similar to the picture seen in disseminated intravascular coagulation. These changes are not characteristic and only five of 15 eclamptic patients had significant histological changes in one series.⁷ The other eclamptic patients and pre-eclamptic patients did not have significant changes on liver biopsy.

A rare association of pre-eclampsia and eclampsia is spontaneous rupture of the liver.⁴⁹ While rupture of the liver is most commonly associated with trauma in the non-pregnant, it is associated with pre-eclampsia or eclampsia in 80% of pregnant cases. The remainder of cases are associated with rupture of an underlying amoebic abscess,⁵⁰ haemangioma,⁶¹ adenoma⁵²–⁵⁴ or hepatocellular carcinoma.⁵⁵ Disordered blood coagulation and trauma have not been shown to be important in pregnant patients.

Occasional cases of spontaneous hepatic rupture in the absence of any known predisposing factor are seen. Spontaneous rupture of the liver during pregnancy was first recorded in 1844 by Abercrombie,⁶⁶ and more than 50 cases have been reported since. The majority of cases are seen in the last trimester,⁵⁷ but occasional cases occur earlier and 14% of one series were found post-partum, mostly within 24 hours of delivery.⁶¹ The majority of cases occur in multiparous patients,⁵⁸ ⁶⁹ but primigravida are also at risk.⁶⁰–⁶³ The clinical features include the sudden onset of epigastric or right upper quadrant pain, nausea, and vomiting.⁶³ Occasionally a diagnosis has been made at this stage, when a Caesarean section performed on account of the eclampsia has revealed petechial haemorrhages of the liver capsule. Deranged liver function tests of a hepatic nature and features of disseminated intravascular coagulation may also be found. More infrequently, the onset of hypotension, shock, and abdominal swelling occurs with the presumptive diagnosis of a ruptured abdominal viscus. Often an obstetric cause is assumed,⁶⁰ ⁶⁴ and only on laparotomy is the characteristic subcapsular hepatic haematoma with rupture of Glisson's capsule found.⁶³ The tear nearly always involves the right lobe and varies from a haemorrhagic ooze to a split several centimetres long. The time from onset of symptoms until rupture of the capsule varies from minutes to days. In cases with a longer time course, investigation by radionuclide scanning, ultrasound, or hepatic angiography⁵⁹ ⁶⁵ have helped make the diagnosis. More often, a sudden collapse with hypotension and abdominal swelling only allows time for fluid replacement before proceeding to laparotomy.

A variety of measures, including direct pressure on the tear, oversewing, packing, hepatic artery ligation, and partial hepatectomy, have been used, depending on the extent of the tear.⁶³ Several authors have stressed the need to deliver the fetus by Caesarean section in addition to repairing the tear,⁶¹ ⁶² ⁶³ ⁶⁶ and cases not so treated have resulted in maternal and fetal death.⁵⁶ ⁵⁷ Postoperative complications are frequent and include rebleeding, necessitating a second laparotomy,⁶⁰ ⁶⁶ hepatic⁶⁷ and renal⁶⁸ failure, and pulmonary complications.⁵⁸ ⁶² Right lower lobe collapse and
effusion are frequent and infection, embolism, or subdiaphragmatic abscess may be suspected. A case of hepatic haematoma which penetrated the diaphragm leading to haemothorax has been reported.\(^6\) Despite treatment, a high maternal mortality is noted. Occasional cases have recovered without definitive surgery,\(^53\) \(^58\) but most authors found no survivors in patients treated non-surgically.\(^60\) \(^51\) \(^59\) It must, however, be stated that those dying quickest would not have the option of surgery, and that cases with subcapsular haematomas without rupture may recover without surgery. The maternal mortality is approximately 50\%.\(^51\) \(^57\) \(^66\) but all seven puerperal cases treated surgically in one series survived.

The fetal mortality is also high and only 38\% of 53 fetuses survived in one series.\(^51\) Most infants survive if puerperal rupture occurs,\(^62\) but only 14\% if rupture occurs antenatally. Intrauterine deaths, stillbirths, and neonatal deaths of prematurely delivered infants are most often responsible for the fetal wastage.

The cause of this condition may be disseminated intravascular coagulation,\(^61\) \(^67\) which accompanies pre-eclampsia and eclampsia in some cases. As a result, a haemorrhagic necrosis with sinusoidal dilatation, capillary, and sinus thrombosis and fibrin deposition are seen histologically, which presumably leads to intrahepatic haemorrhage, subcapsular haematoma, and, in severe cases, hepatic rupture. Occasionally other features have been seen.\(^61\) \(^65\) The sudden onset of severe abdominal pain in the last trimester of pregnancy or post-partum should alert the obstetrician to the possibility of hepatic rupture, particularly in a multiparous patient with pre-eclampsia or eclampsia. Paracentesis which reveals fresh blood indicates the necessity for laparotomy,\(^63\) \(^64\) \(^66\) although obstetric emergencies, including tubal pregnancy or ruptured uterus, and other intra-abdominal conditions should be considered. The treatment of jaundice associated with eclampsia is directed towards the toxaemia, and only supportive measures are available for hepatic failure.

**Intercurrent liver disease occurring during pregnancy**

Viral hepatitis is the commonest cause of jaundice during pregnancy.\(^6\) \(^69\) Early work, however, does not distinguish between the two main agents involved, hepatitis A virus and hepatitis B virus (HBV). The majority of European cases reviewed by Haemmerli would be expected to be due to hepatitis A virus, and a recent Australian series describes pregnancies in patients with a positive serological diagnosis of hepatitis A.\(^70\) Pregnancy in patients carrying or suffering clinically from hepatitis due to hepatitis B virus have been more widely discussed recently because specific serological diagnosis has been possible for a longer period. There are no reports of pregnancy occurring in patients suffering from the newly described non-A non-B variant, although it is likely that earlier series have contained some cases.

**HEPATITIS A**

In an extensive review of the world literature,\(^6\) 449 cases of hepatitis occurring during pregnancy are described from European centres. The mortality of 1.8\% is similar to that in non-pregnant patients. One report included describes an epidemic in Hamburg, most probably due to hepatitis A virus,
where the mortality of pregnant females was lower than that for non-pregnant females of child-bearing age. Contrary to smaller series, it was felt that hepatitis was neither more frequent nor more severe in pregnancy. From these European cases, it was found that prematurity occurred in 20% of 229 deliveries, an increase from normal, and there was a significant mortality in these cases. One report suggests an association with stillbirth but, apart from this, obstetric complications and congenital malformations were not increased, and there were no cases of neonatal hepatitis in 528 children. American studies confirm these findings.

A more recent study of 30 cases of hepatitis with negative serology for hepatitis B virus found no effect of pregnancy on the maternal hepatitis and no effect on the fetus, apart from an increased incidence of prematurity. Approximately half of 49 cases of hepatitis during pregnancy were positively diagnosed as being due to hepatitis A virus in an Australian series. In the first 22 weeks of pregnancy, 93% of jaundiced patients with a suspected diagnosis of hepatitis were confirmed, but only 34% were confirmed thereafter. The major cause of jaundice in the later stages was intrahepatic cholestasis, which was more frequent in immigrants. It has been suggested that neonatal hepatitis can occur if the mother has hepatitis A during the last trimester of pregnancy, but this appears to be uncommon. Although pregnancy and hepatitis do not appear to be mutually deleterious in European cases, this may not be true for other parts of the world. Fulminant hepatitis is more common in third world countries, and maternal and fetal deaths are frequent. Hepatitis is the third commonest cause of maternal mortality in India, and 29 of 61 cases of hepatitis in pregnancy were fulminant, with 21 deaths, in an Iranian study. By comparison, 14 fulminant cases with 12 deaths occurred in 68 non-pregnant women of child-bearing age. In addition, hepatitis in the third trimester had a worse prognosis and there was an apparent effect of maternal malnutrition. In the same study there was a fetal mortality of 69% in fulminant and 21% in non-fulminant hepatitis. Similar reports have come from Libya and other countries, but it does not appear that a higher proportion of HBV cases is responsible, as none of 33 fatal cases in one series and only one of 10 severe cases in another had serological evidence of hepatitis B virus infection. It must therefore be concluded that hepatitis A virus infection is particularly severe in these patients, or that a different and presently undiscovered agent is responsible.

**Hepatitis B**

There are many reports of pregnancy occurring in mothers with hepatitis due to hepatitis B virus. These and other reports consider the more common case of pregnancy occurring in the asymptomatic chronic carrier of hepatitis B virus, as measured by the presence of hepatitis B virus surface antigen (HBsAg) in maternal serum. The course of hepatitis B infection does not appear to be altered by pregnancy, although, like hepatitis A, this may not be true for underdeveloped countries. As in hepatitis A infection, obstetric problems other than prematurity are not increased, although one small series showed high perinatal mortality rates. Nearly one-third of the patients in one series had a premature labour, and in under-developed countries prematurity in hepatitis has a very high mortality. Earlier reports
that maternal hepatitis B infection was associated with an increased incidence of congenital malformations and Down's syndrome have not been confirmed.\textsuperscript{5 69 90 98 99} Of great interest has been the transmission of hepatitis B from mother to infant; so-called 'vertical transmission'. Cases of neonatal hepatitis have been reported in the offspring of mothers carrying the HBV, whether transiently during an acute infection\textsuperscript{85 86} or as chronic carriers,\textsuperscript{100–103} but this is an uncommon occurrence. The development of chronic liver disease in these children\textsuperscript{104} is also rare. More frequently, the presence of HBV in the mother leads to subclinical hepatitis and persistent carriage of the virus by the infant.\textsuperscript{69 75 83 85 95} This is more frequent in infants of mothers with clinical attacks\textsuperscript{87 89–92 100 105 106} of hepatitis due to hepatitis B virus than in chronic asymptomatic carriers\textsuperscript{100 105 106 107} and is more common in mothers with hepatitis later rather than earlier in pregnancy.\textsuperscript{69 85 100 106 107}

Infants of mothers with clinical hepatitis early in pregnancy are usually unaffected.\textsuperscript{85 100} Asymptomatic chronic carriage of hepatitis B virus varies widely with geographical area, as does the transmission rate to children. Similarly, within ethnic groups there is variation; in one British series only 28\% of patients screened antenatally for hepatitis B virus and found positive were of European origin and none of 17 infants who became carriers were of European origin.\textsuperscript{105} Factors which correlate with transmission of the disease were previously said to be the maternal HBsAg titre and the serology of the cord blood at delivery. However, because contamination of the cord by maternal blood may occur, a positive test cannot be taken as definite evidence of hepatitis B virus production in the infant.

More recently, the discovery of the 'e' antigen and its association with infectivity led to the important finding that vertical transmission of hepatitis B virus correlated closely with maternal 'e' antigen status. In the original report,\textsuperscript{108} all 10 infants of 'e' Ag-positive mothers become carriers and no offspring of seven 'e' antibody-carrying mothers became carriers. Two of six offspring of mothers with neither 'e' Ag nor 'e' Ab became carriers.\textsuperscript{108} Additional reports confirmed the findings with respect to the 'e' Ag, but there was some discord concerning 'e' Ab findings.\textsuperscript{105 109–114} Variable results with the group carrying neither 'e' Ag nor 'e' Ab probably reflect inconsistency in the testing procedure.\textsuperscript{108 112} The discovery of the importance of 'e' Ag in vertical transmission explains many of the puzzling variations in transmission, including the geographical and ethnic variations.

The route and timing of transmission have been the source of much debate. The presence of HBsAg in cord blood has suggested transplacental transmission,\textsuperscript{115} but there are reasons for suspecting this data, including the possibility of cord blood contamination by maternal blood,\textsuperscript{80 109 116} although in one case cord blood after a Caesarean section was used. Moreover, serial studies on infants have shown that most infants become positive for HBsAg at six weeks, suggesting infection intra- or post-partum.\textsuperscript{75 90 92 109 117 120} In one interesting study, 95\% of infants had HBsAg present in the gastric aspirate in high titre, a possible portal of infection.\textsuperscript{109} Infection during passage through the birth canal has been suggested, but Caesarean section does not prevent infection.\textsuperscript{86 121} Although breast milk contains HBsAg in carrier mothers,\textsuperscript{122} no difference in infant HBsAg carriage rates could be shown between breast and bottle-fed children.\textsuperscript{123}

The long-term sequelae of the carriage of hepatitis B by children are
unknown, but the association with chronic liver disease and hepatoma, as well as infectivity in adults, has led several workers to treat children by passive immunisation. Several studies have shown no effect of immune gammaglobulin from donors, but others, using high titre anti-HBs gammaglobulin soon after delivery, have had impressive results. A recent study used monthly injections of high titre immunoglobulin for six months and was very effective. Treatment within 48 hours of birth would seem to be important, as two of three children treated four or five days after birth became positive for HBsAg. One treated child also showed evidence of continued HBsAb after the period of passive immunisation, suggesting that active immunisation had occurred. This is of obvious importance, as these children all continue to be exposed to maternal hepatitis B virus. Further trials of vaccination are in progress. It has recently been shown that an excess of males are born to HBV-carrying mothers. The reason for this is not clear, but may represent a selective increase in spontaneous abortion of female embryos. Additional work is required to elaborate the findings.

The dangers to staff and patients of contact with patients suffering from hepatitis or carrying hepatitis B virus are best met by having the mother and baby in a single room and by handling infected material with care.

In summary, hepatitis during pregnancy is similar in frequency and severity to that in non-pregnant females, and treatment is the same. Apart from an increased incidence of prematurity, no obstetric complications are likely. The vertical transmission of hepatitis correlates with the presence of the 'e' antigen, as does the maternal infectivity. Children of mothers with 'e' antigen should be treated with high titre anti-HBsAg gammaglobulin within 48 hours of birth and possibly with additional monthly injections for six months. Breast feeding can be permitted. The long term sequelae of chronic carriage of HBV by the infant are unclear.

AMOEBIASIS
Infestation with the parasite Entamoeba histolytica is often asymptomatic, but may cause diarrhoeal illness. Occasionally hepatic cysts lead to presentation with symptoms or signs suggesting primary liver disease. Several cases have presented during pregnancy. It has been stated that pregnancy renders a woman more susceptible to hepatic amoebiasis and that the mortality is higher, perhaps because of the altered immunological or hormonal state, but this has not been proven. Only one case was reported from a centre where 20,000 deliveries per year were conducted, and where amoebiasis is not infrequent. Six cases were reviewed by Cowan, and rupture of the abscess during birth occurred once and after the birth in two cases. Successful treatment involves drainage of the abscess and the peritoneum if rupture has occurred, and combined treatment with emetine and metronidazole. A spontaneous abortion followed an exploratory laparotomy in one case presenting antenatally and stillbirth in another. The prognosis for the mother is good if the disorder is successfully treated.

OTHER INFECTIOUS DISEASES
Pregnancies have been recorded in several other infectious diseases. Herpes hepatitis resulted in maternal death in one of two cases reported, and both fetuses died. Four cases of leptospirosis during pregnancy resulted in
three live infants, and all four mothers survived. One mother, seriously ill with leptospiral meningoencephalitis, had a stillbirth. The method of diagnosis was not stated. Definitive diagnosis can be made by culturing the organism from the blood during the first phase of the illness or from the urine during the second phase. Immunofluorescent staining of the organism in the blood or urine can also be used, and rising titres of antibodies concurrent with the clinical illness are diagnostic. Organisms may be cultured from the urine for months after the illness and serological tests remain positive for years, so care is needed in interpreting the results of these tests. Many people living in agricultural communities will show evidence of past infection, and antisera commonly used in diagnostic practice will cross-react with the various leptospiral subtypes.

**DRUGS AND JAUNDICE**

Hepatotoxic drugs may cause jaundice in both the pregnant and the non-pregnant. A severe condition, similar to acute fatty liver of pregnancy, has been reported after the use of high doses of intravenous tetracycline, particularly in patients with pyelonephritis in the third trimester of pregnancy. As in the idiopathic cases, high maternal mortality and fetal losses are reported, and, in addition to the fatty liver, pathological changes were also noted in the kidney and pancreas. In the reported cases, the doses of tetracycline were above the recommended maximum. Smaller doses used in a study of the effect of tetracycline on 18 pregnant women had no effect on liver function tests, but increased amounts of fat were apparent on liver biopsies after the tetracycline. The dangers of diuretics have been discussed with reference to compensated cirrhotics. A patient with cirrhosis treated with chlorothiazide for mild pre-eclampsia developed hepatic failure and the hepatorenal syndrome, but recovered after treatment with the drug was ended, although premature labour and stillbirth occurred. Anaesthetic drugs may be responsible for acute liver dysfunction in pregnant patients. One case associated with the use of halothane and another after methoxyflurane have been reported. In contrast with similar cases in non-pregnant patients, a cholestatic phase followed the acute hepatitis, but the mother recovered soon afterwards. Cholestatic jaundice associated with the use of chlorpromazine may be prolonged and severe in pregnancy.

The effect of alcohol on the fetal liver is unclear, as is its effect on maternal fertility. The increasing numbers of younger women with alcohol-related disease will probably elucidate these problems in future. The newly described fetal alcohol syndrome did not originally encompass hepatic manifestations, but several case reports have now appeared. Hepatomegaly and raised transaminases and alkaline phosphatases were noted, but histology was variable. One case had bile duct proliferation, two had central vein sclerosis, and another case who had been on immunosuppressives after kidney transplantation for renal agenesis developed hepatoblastoma. Until more reports are available, the existence of a specific fetal liver condition in this syndrome remains conjectural.

**BUDD-CHIARI SYNDROME**

There are several reports of hepatic vein obstruction related to pregnancy. Patients have presented with painful swollen legs and distension
of veins, and venous thrombosis may be suspected.150 The development of ascites, dilated abdominal veins, hepatospleno- megaly, or oesophageal haemorrhage makes the diagnosis clear. Liver function tests are minimally upset,147 152 153 and the ascitic fluid, in contrast with malignancy or infection, seldom contains more than a few lymphocytes or macrophages.149 150 Catheterisation of the inferior vena cava may reveal increased venous pressure147 and allows contrast venography which may reveal obstruction of the hepatic veins or inferior vena cava.148 151 This technique requires considerable expertise, and direct percutaneous injection of contrast material into the hepatic parenchyma has been recommended.153 Hepatic angiography is diagnostic of the condition and liver biopsy shows thrombosis in the dilated sinusoids and central veins.147 148 150 151 153 High quality ultrasonography or CAT scanning if available will offer effective non-invasive ways of delineating the obstruction to the hepatic venous outflow.

The aetiology of the condition is not clear, but in Japan membranous obstruction of the inferior vena cava at the level of the hepatic vein is commonly found147 and may have a better prognosis than those cases with hepatic vein thrombosis.153 An increased incidence of the Budd-Chiari syndrome has been noted in users of the contraceptive pill, and it has been suggested that hypercoagulability due to the higher levels of oestrogen may be responsible in both pill-users and pregnant women.148 151 153 The prognosis of the condition is poor, and, although surgical removal of the obstructing membrane was possible in one Japanese case, three others died after surgery. Eight of 16 patients who developed Budd-Chiari syndrome after pregnancy died within a year of the onset in another series.153 Portacaval shunt surgery was unavailing and ascitic fluid infusion for resistant ascites showed only temporary benefit, but one early case improved dramatically with anticoagulants. Most cases occur post-partum and do not affect the fetus, but in one case occurring in pregnancy intrauterine death occurred.150

Hepatic tumours

Increasing numbers of hepatic adenomas occurring in young women have been reported,154 -158 and an association with the use of oral contraceptives suggested. Cases occurring during pregnancy and in the puerperium have been noted.52 -55 159-163 Patients presenting with an acute abdomen due to rupture of the tumour have a high mortality,53 54 157 160 and high fetal losses.54 Bleeding and rupture seem more frequent in pregnant women,157 but pregnancy has continued successfully in the presence of a known adenoma.54 An uneventful pregnancy has occurred one and a half years after resection of an adenoma164 and fears that the increased maternal oestrogens during pregnancy might promote a recurrence have not been confirmed.54

The suggestion that another hepatic lesion, focal nodular hyperplasia, may be associated with oral contraception has been made,165 and cases occurring during pregnancy have also been reported.156 161 166 167 These tumours are highly vascular, and attempts to remove them after successful completion of pregnancy resulted in operative death in two cases.166 167 The natural history of focal nodular hyperplasia is unclear, and it can be difficult to distinguish this lesion from hepatic adenoma.158 The concurrence of focal nodular hyperplasia and hepatic adenoma in a single lesion suggests an inter-relationship and the concurrence of hepatic adenoma and carcinoma158 raises
the possibility that focal nodular hyperplasia, hepatic adenoma, and hepatocellular carcinoma may represent a continuum of evolving malignancy. Focal nodular hyperplasia and hepatic adenoma associated with oral contraceptive use may regress when the drug is discontinued, so attempts at radical surgery might not be justified, and additional studies are required.

Carcinomatous lesions of the liver during pregnancy have been reported. One patient successfully treated 11 years previously for hepatocellular carcinoma died in the last trimester of pregnancy with recurrent carcinoma, and another patient with cirrhosis who died of variceal haemorrhage despite a shunt operation had hepatocellular carcinoma in a cirrhotic liver at necropsy. The fetus died in both instances. In another case, maternal death occurred because of rupture of the liver and at laparotomy a cirrhotic liver containing hepatocellular carcinoma was found. A live infant was delivered by Caesarean section at laparotomy. Two cases of cholangiocarcinoma of the intrahepatic ducts have also been reported. In one, a premature stillbirth was followed by maternal death from sepsis and cholangiocarcinoma was diagnosed at necropsy. Another patient with disseminated malignancy discovered five months post-partum had cholangiocarcinoma at necropsy. A patient with hepatocellular carcinoma associated with oral contraceptive use underwent an uneventful pregnancy without evidence of liver dysfunction 18 months after a successful surgical removal of the tumour (Wright, R. Personal communication).

Biliary disease

Gallstones are commoner in women than men and commoner in menstruating than post-menopausal women. Similarly an increased incidence has been noted in women using the oral contraceptive pill. Reduced biliary chenodeoxycholic acid with subsequent reduction in cholesterol solubility has been held responsible, and recent studies showed decrease in the rate of gallbladder emptying and percentage emptied. The larger residual volume of the gallbladder would tend to increase the formation of gallstones, and there is an impression that biliary disease is more common in pregnant women. Whether new stones are formed or whether pre-existing ones become symptomatic has not been proved. Biliary obstruction by gallstones during pregnancy is considered rare and accounted for only 27 of 456 cases of jaundice in a large series. A higher incidence was seen in several smaller series, and gallstones accounted for three of 49 cases of jaundice in a Polish series. Treatment is unaltered by pregnancy and surgery is recommended only in cases with common bile-duct obstruction. A few cases with carcinoma of the bile-duct presenting during pregnancy have been recorded, but treatment is similar to that of the non-pregnant.

Pregnancy and pre-existing liver dysfunction

Familial hyperbilirubinaemia

The effect of pregnancy on the familial hyperbilirubinaemias is variable. An increase in jaundice without pruritus has been noted in the Dubin-Johnson form of conjugated hyperbilirubinaemia, which reaches a maximum in the third trimester. This increased jaundice was not seen in a patient with the Rotor syndrome, another form of conjugated hyperbilirubinaemia. The increased jaundice in the Dubin-Johnson syndrome has been confirmed and
an association with abortion and stillbirth noted. The effect of pregnancy on patients with Gilbert’s unconjugated hyperbilirubinaemia is not known.

**Porphyria**

A high maternal mortality has been reported in patients with hereditary porphyria. A more recent detailed study of the hereditary hepatic porphyrias showed frequent attacks of acute intermittent porphyria and hereditary coproporphyria during pregnancy and in the puerperium; the perinatal mortality was increased to 8% in acute intermittent porphyria and 15% in hereditary coproporphyria, but the spontaneous abortion rate was probably not increased and there was only one maternal death. One patient with variegate porphyria had three uneventful, successful pregnancies. The outlook for a successful pregnancy in porphyria is therefore better than previously reported.

**Wilson’s Disease**

Patients with untreated Wilson’s disease are reportedly subfertile, but pregnancies have been reported, mainly in patients with a long presymptomatic course. Amenorrhoea and spontaneous abortions are frequent, particularly in patients with cirrhosis, and high intrauterine levels of copper have been noted and may produce an effect similar to that which has promoted the use of copper-coated intrauterine devices as effective contraceptives. Successful treatment of Wilson’s disease with chelating agents seems to correct the subfertility, and successful pregnancies have been reported. Many of the patients had a predominantly neurological illness, and the number with histologically evident cirrhosis who became pregnant is not apparent. It has been stated that pregnancy of itself produces a beneficial effect on the neurological state, which may persist for weeks or months, perhaps because of the fetal requirement for copper. Small increases in maternal serum caeruloplasmin levels have been noted during pregnancy. Patients with advanced liver disease may tolerate pregnancy poorly, and those with hepatic insufficiency or who had previously bled from oesophageal varices were advised against pregnancy by one author. The fetus seems to be unaffected by the maternal disease, apart from the increase in the spontaneous abortion rate, and a normal term delivery may be expected. Caeruloplasmin levels in the neonate are normal, and Wilson’s disease is only apparent in the rare cases where both parents carry the defective gene.

Penicillamine treatment of maternal Wilson’s disease should be continued throughout pregnancy, and fears of teratogenicity have not been substantiated. Pyridoxine supplements are recommended, as D penicillamine may deplete maternal stores, and discontinuation of the chelating agent should be considered if a Caesarean section is planned, as it may impair wound healing. In general, however, pregnancy is well tolerated, as evidenced by over 60 successful cases reported, and one patient who had a relapse of Wilson’s disease during pregnancy was considered to be inadequately ‘decoppered’.

**Chronic hepatitis**

**Chronic Persistent Hepatitis**

This chronic liver dysfunction, which follows viral hepatitis, is generally
regarded as benign and rarely progresses to cirrhosis. Ten pregnancies occurring in seven women have been reported. Apart from four abortions for non-medical reasons, all pregnancies proceeded normally and resulted in live spontaneous term deliveries. The women were unaffected clinically and biochemically by pregnancy, and the neonates were normal and healthy. In contrast with chronic active hepatitis, the menstrual patterns of four women were normal. Pregnancy in chronic persistent hepatitis can therefore be assumed to be safe, but the extension of this conclusion to patients with chronic active hepatitis does not seem warranted.

**CHRONIC ACTIVE HEPATITIS**

This chronic relapsing liver disease with a characteristic histological appearance, chronic aggressive hepatitis, is being increasingly recognised. It has the propensity to progress to cirrhosis, portal hypertension, and hepatic failure, and is attended by a decreased life expectancy. In some populations it is most commonly seen in chronic carriers of HBsAg, but in the West it is usually associated with autoimmune features. The nomenclature of chronic liver disease has recently been clarified and earlier reports of patients with cirrhosis who become pregnant may have included some cases of chronic active hepatitis.

Amenorrhoea and infertility are frequent in young women with chronic active hepatitis, and the fertility has recently been estimated to be half that of a control population. The reason for the infertility has not been ascertained, but the introduction of corticosteroid and immunosuppressant treatment has led to increased fertility as well as survival in young women with autoimmune chronic active hepatitis. In comparison with 36 reported pregnancies in the literature, where five maternal deaths and six perinatal deaths occurred, a recent series reported no maternal deaths and four perinatal deaths from 30 pregnancies at a single centre. There was no evidence of deterioration in the maternal chronic active hepatitis during or after pregnancy, but the fetus was at risk from prematurity and low birth weight. These results suggested that a safe and successful pregnancy was possible in chronic active hepatitis of the autoimmune type and that treatment with prednisolone with or without azathioprine should be continued throughout the pregnancy.

There has been no confirmation in humans of teratogenesis with corticosteroids and, although neither oncogenesis nor teratogenesis has been noted in the children of parents treated for CAH with azathioprine, it should be discontinued if pregnancy occurs.

Earlier work recommending termination of any pregnancy or sterilisation of young women with chronic active hepatitis could not be supported. It should be noted that detailed information on pregnancy in patients with CAH associated with HBsAg carriage is not available, and in one report two such patients died. Oestriol measurement as an index of feto-placental function is valueless in patients taking prednisolone, as the production of the oestriol precursor by the fetus is suppressed by prednisolone.

**PRIMARY BILIARY CIRRHOSIS**

Pregnancies have rarely been reported in this progressive severe liver disease, possibly because the disease commonly presents clinically in women at the end of and after the reproductive age. Five women in one report had
six pregnancies, but only two live children resulted. Jaundice, without pruritus, increased in all patients towards term and bilirubin remained raised after delivery. Although there were no severe maternal complications, three of the five women died a few years after the pregnancy, which would present problems of family management. Another report concerns three patients, two of whom were diagnosed during pregnancy. One patient had a successful pregnancy with delivery by Caesarean section, but one aborted spontaneously and the third underwent therapeutic abortion on medical advice. In the one patient studied biochemically, there was a paradoxical fall in bilirubin during pregnancy. Menstrual function was abnormal in nearly all the patients studied, and this fact, combined with the age at onset of the disease, would explain the small number of pregnancies. Increasing numbers of patients with primary biliary cirrhosis are being diagnosed at a pre-symptomatic stage and more pregnancies may be expected. Cases of cholestatic jaundice of pregnancy may later turn out to have primary biliary cirrhosis.

CIRRHOSIS

There is a large literature on the concurrence of pregnancy and cirrhosis. Changes in histological classification and terminology have led to difficulties in comparing reports from different centres and different periods. It is likely that a heterogeneous group of conditions is encompassed and the outcome of pregnancy in the individual diseases may be different. In addition, the severity of the disease, including the incidence of complications, may vary between reports and would prejudice the results presented. The earliest report is attributed to Scaglione in 1923 and resulted in maternal death from haemorrhage. The outcome for the fetus is not stated, but necropsy on the mother revealed Laennec’s cirrhosis. Other reports vary in detail, and some cases were diagnosed without liver biopsy. Two early reviews together encompass 34 reported pregnancies in which there were six maternal deaths. Twenty-four live children resulted from the 29 pregnancies in which the outcome for the fetus was recorded. Four patients were considered to have post-necrotic cirrhosis, one Laennec’s cirrhosis, and one patient who was reported to be a heavy drinker had ‘fatty’ cirrhosis. One patient had cirrhosis and severe ulcerative colitis and one other had cirrhosis after repeated biliary infections, but all others were only classified as cirrhotic. Another large review included 74 reported and 21 personally supervised pregnancies, and found 15 maternal deaths, mainly in the last trimester and puerperium. Many deaths were associated with hepatic failure precipitated by variceal haemorrhage, which was found to be frequent in patients known to have varices, although the documentation of the presence of varices was incomplete. Variceal haemorrhage was unusual in patients who had undergone a shunt operation. There was no consistent alteration in biochemical tests of liver function, and the maternal prognosis was not thought to be altered by pregnancy. Ten of 71 pregnancies proceeding to the third trimester resulted in perinatal death, confirming the findings of earlier work.

A more recent series from Iran reports on nine cirrhotics achieving pregnancy. Six had postnecrotic cirrhosis, one underlying chronic active hepatitis and one of two with post-hepatitic cirrhosis also had multifocal hepatoma. Two mothers died of variceal bleeding, and only half the completed pregnancies resulted in live children. Another review considered
patients according to the presence of a surgically created portacaval shunt. Although the groups were otherwise unmatched, there were no maternal deaths from 23 pregnancies in patients who had previously undergone shunt surgery, nor were there any maternal deaths in seven pregnancies where shunt surgery was required for variceal bleeding during the pregnancy. Two maternal deaths occurred in 87 pregnancies in patients without a shunt, but the perinatal mortality was similarly increased in all three groups. Perinatal death was commonly associated with prematurity, and, although laparotomy is generally hazardous in cirrhotics, judiciously performed Caesarean section has been safely used in the case of a threatened intrauterine death.

In cirrhosis, therefore, pregnancy is uncommon, although the reason for the apparent infertility has not been demonstrated. In those who become pregnant, the maternal mortality has not been shown to be higher than for a matched, non-pregnant control group. Variceal bleeding, the major maternal hazard, can be safely treated medically and surgically notwithstanding the pregnancy. High fetal losses may be expected, commonly associated with prematurity. The greatest contraindication to pregnancy is the long-term maternal prognosis. Pregnancy is most often seen in patients with post-necrotic cirrhosis or underlying chronic active hepatitis, and is rare in Laennec’s and alcoholic cirrhosis.

EXTRAHEPATIC PORTAL VEIN OBSTRUCTION (EHPVO)
Patients with portal vein obstruction are liable to the hazards of variceal haemorrhage, but as the hepatic parenchyma is usually intact the patients usually have normal fertility and escape the possible danger of hepatic failure. In a review of 32 pregnancies in patients with EHPVO, it was found that one post-partum maternal death after surgery for bleeding varices and three perinatal deaths from the 26 pregnancies with known outcome and prematurity was frequent. Variceal bleeding was common, but could be successfully managed medically or surgically during pregnancy. Unlike cirrhosis, post-partum haemorrhage was not more frequent than normal.

Conclusions
The occurrence of pregnancy in a patient with liver disease is seldom severely detrimental to the mother. The potential threat to the fetus in this situation or when liver disease arises in a previously healthy pregnant patient should prompt close co-operation between physician, obstetrician, and paediatrician to ensure a safe and successful outcome to the pregnancy.

I would like to thank Professor Ralph Wright for helpful criticism in the preparation of this paper, and Mrs Isabella Strachan for typing the manuscript.

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Received for publication 3 February 1981
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