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Maternal Deaths Due To Liver Disease In Malaysia

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Summary

Liver disease is an important and serious condition in pregnancy. The Confidential Enquiries Into Maternal Deaths in Malaysia showed that there were 23 maternal deaths attributed to liver disease between 1991 - 1994. Over the same period, there were 1066 reported maternal deaths with 929 of them being due to direct and indirect causes. Thus 2.15% of such deaths were due to liver disease in Malaysia. The three main causes of maternal deaths due to liver disease in pregnancy were hepatitis (6 cases), acute fatty liver in pregnancy (6 cases) and septicaemia (4 cases). Liver disease is common at a mean of thirty weeks of gestation with a preponderance to women of low parity. Only two patients in this series had no antenatal care. The majority of cases (45.8%) presented between 28 - 37 weeks of gestation. All cases delivered by spontaneous vaginal delivery. Remediable factors that were identified included failure to appreciate the severity of disease. Case summaries of all the cases of maternal deaths due to liver disease are discussed and a guideline to management of liver disease in pregnancy presented.

Key Words: Liver disease, Maternal deaths

Introduction

Liver disease in pregnancy is an important and serious complication[1]. It has been noted to complicate approximately 1 in 1000 pregnancies. When liver disease supervenes, it may do so in a dramatic and tragic fashion for both the mother and the infant. Diseases such as acute fatty liver of pregnancy may begin with mild symptoms and liver enzyme abnormalities but can rapidly progress to jaundice, liver failure and death. Prompt management with hepatologists results in a better outcome. Liver disease may not present with jaundice and it is no longer acceptable to recognise this disorder only when jaundice manifests clinically. An awareness of the varied presentations of hepatic disorders and a high index of suspicion will provide more rapid diagnosis. Specific therapy is available for both mother and infant in many instances. There will certainly be important management steps and precautions to be undertaken in future pregnancies.

Since 1991, there has been a confidential enquiry system to review all maternal deaths in Malaysia. This was established by the obstetricians and gynaecologists in Malaysia with the secretarial support from the Family Health Development Division of the Ministry of Health Malaysia. Maternal deaths occurring in all sectors of health care, including the private sector, are included in this enquiry system. With this improved enquiry system in place, there has been a paradoxical rise in maternal death rates.

Liver disease in pregnancy or its complications have been responsible for a proportion of maternal deaths. The aim of this audit is to review the deaths occurring between 1991 and 1994. We hope to increase the awareness of the caregivers who look after pregnant mothers about the presentations of liver disease, therefore avoiding some of the shortfalls in care identified during the management of these mothers who died.

Materials and Methods

A process of confidential enquiry into maternal deaths was established by the Family Health Development division of the Ministry of Health, Malaysia since 1991. In public hospitals, the system requires a named maternal death coordinator to review every instance of maternal mortality. Maternal mortality was defined as any death of a woman during pregnancy or within 42 days of termination of pregnancy irrespective of duration or site of pregnancy, or from any causes related to or aggravated by the pregnancy or its management. Maternal deaths were sub-classified into 'direct' deaths resulting from obstetric complications of pregnancy, labour and puerperium, 'indirect' deaths resulting from either a previous existing disease or from a disease which developed during pregnancy or was aggravated by pregnancy and 'fortuitous' deaths resulting from causes not related to or influenced by pregnancy.

Instances of death at home were reviewed by the community health coordinator in the district concerned; this process included interviewing family members. The coordinators present their findings to the obstetricians in the hospitals that provided care for the patients or to the district health officers concerned. The regional maternal and child health officer, who is initially contacted by telephone and subsequently in writing, passes the information to a state review committee which then sends a confidential report outlining the cause of death, suggestions for future improvement and actions taken to the National Technical Committee.

The questionnaires were completed in a narrative form and gave details about the course of events that lead to maternal death, the category of personnel involved, the results of any investigation, and postmortem report, if this was performed. Due to cultural and religious reasons, postmortem examinations are not usually performed in Malaysia.

The data was then analysed, minus personal identification details, at the national level by a committee comprising of six obstetricians and gynaecologists, a senior physician, a senior anaesthetist, health administrative personnel and a nursing matron. It is a unique characteristic of the Confidential Enquiries that it is an anonymous audit where all names of persons involved in the care and the places where the cases occurred are not known to the committee. It is also non-punitive in nature. The original case notes were not available for study and this article is based on the investigation formats returned to the National Technical Committee. The national committee reached a consensus on the causes of death and coded them according to the International Classification of Diseases 9th Edition. At present the reports of the confidential enquiries from 1991 to 1994 have been released.

Notification of deaths in private hospitals were given by the police and an investigation conducted by the district health officer. Although participation in the enquiry process was not compulsory for private hospitals, there was almost complete feedback from them.

Utilising the data obtained from the Confidential Enquiry into Maternal Deaths 1991 - 1994, deaths that were related to liver disease were identified and analysed. The parameters used to analyse the deaths included parity, ethnicity, educational status of the mother, number of antenatal visits during pregnancy, the period of gestation at the time of admission and at delivery, the place and mode of delivery, whether combined management with other specialties was carried out and if this was done, the timing of these referrals. Recommendations and commentaries at all levels of the investigation were assessed. The causes of death related to liver disease in Malaysia were then tabulated.

Results

In Malaysia, there were 23 maternal deaths attributed to liver disease between 1991 - 1994. Over the same period, there were 1066 reported maternal deaths, 808

of them direct, 121 indirect and the rest fortuitous. There were thus 2.15% of maternal deaths due to liver disease among those mothers dying from direct and indirect causes.

Age

The highest number of deaths from liver disease, 62.5% or 15 cases, were in the age group 21 - 30 years. This can be attributed to the fact that the highest number of deliveries were from women who fall in that age group. In the range of 31 - 40 years there were 7 cases. The extreme ends of the range consisted of a woman who was 18 years of age while at the other end was a 40 year old mother.

Parity

Ten of the mothers who died were primigravida (41.6%). Seven of the mothers were para 2 to para 5 (29.1%). This group accounted for 65% of the deliveries from 1991 to 1994.

Ethnicity

The majority of deaths were amongst the Malays (15 out of 23 or 65.2%). The Malays accounted for 65% of the deliveries in the country during the review period. The Chinese accounted for 4 cases while the Indians accounted for 2 cases. Three cases occurred among the immigrant population in East Malaysia.

Antenatal care

The majority or 45.8 percent of the women had received at least more than 5 antenatal check-ups. Five of the cases had more than 10 antenatal visits while 5 cases had between 1 - 4 antenatal visits. Only 2 patients had no antenatal check up.

Period of gestation at admission for liver disease

The majority or 45.8% of the cases presented between 28 - 37 weeks of gestation. The mean period of gestation was 30.1 weeks. This is identical to western data. Only 9 cases presented at gestation period of under 28 weeks.

Place of delivery

Seventy five percent of the cases or 18 patients were delivered at the general hospitals. Except for home deliveries, the remaining cases were delivered in districts that had specialists.

Type Of delivery

All deliveries occurred by spontaneous vaginal delivery. No operative deliveries were recorded third stage complications most often noted was post partum haemorrhage.

Referral to medical specialties

58% of the cases had an early referral to the other specialists within two days of admission to the hospital once the diagnosis was established.

Illustrative case summaries

Case 1

A 25-year-old primigravida booked in at 30 weeks of gestation with 5 previous antenatal visits including a hospital visit at 36 weeks of gestation. Five days after the hospital visit, she was seen by the doctor at the health clinic with a history of jaundice and fever for five days. She was admitted to the hospital where her blood pressure was noted to be 130/90 with a proteinuria of 2+ on dipstick. An ultrasound examination showed an intrauterine death. She was diagnosed to have viral hepatitis based on the liver function tests which showed a marked elevation of liver enzymes. Two days after admission, she had a spontaneous vaginal delivery complicated by postpartum haemorrhage and hypotension requiring four units of blood transfusion. After she was stabilised, she was referred to the medical ward where she was treated as acute liver failure with early encephalopathy. She died three days later with acute fulminant hepatitis with hepatorenal failure. Investigations for leptospirosis and malaria were negative. Hepatitis screening was also negative. It was suggested by the national committee that a liver biopsy would have been useful in this case.

Case 2

This was a 36 year old G6P5 with heart disease from 1979. The exact nature of the cardiac lesion was not documented. She was noted to be jaundiced at 24 weeks of gestation and was referred to hospital. Her jaundice rapidly worsened and she developed repeated episodes of hypoglycemia. Her liver function tests showed marked hyoalbuminemia and marked elevation of the liver enzymes. She died two weeks after admission with the cause of death being listed as fulminant hepatitis with septicemic shock. Her hepatitis B serum antigen was negative.

Case 3

A 34 year old G4P3 was noted to be jaundiced at the 36th week of pregnancy. She had a normal delivery five days after admission with jaundice. The patient then developed aggressive behaviour two days later and was noted to be even more deeply jaundiced. Her prothrombin time was prolonged. Her liver enzymes were elevated. Ultrasound examination did not show dilated bile ducts. Her hepatitis B Ag was positive. She died 18 days later from fulminant viral hepatitis.

Case 4

The patient was a 22 year old pseudoprimigravida. She was booked in at 22 weeks but refused to be examined by a male doctor and frequently did not attend antenatal clinics. At 38 weeks she was referred by a general practitioner with a two week history of fever, vomiting, headache and jaundice. She was diagnosed to have acute hepatitis by the medical officer. She had a spontaneous vaginal delivery the next day to a live fetus. On the first day after admission, her condition deteriorated with abdominal pain, drowsiness and restlessness. On day two, she developed behaviour attributed to metabolic causes. Later the same day, she became hypotensive and pale with abdominal distension. A peritoneal tap confirmed the presence of peritonitis and she was commenced on cefoperazone, metronidazole and penicillin. The next day, she was seen by the gastroenterologist who diagnosed hepatic failure. Ceftazidime was added to the antibiotic regime and the patient transferred to intensive care. Ultrasound examination showed hepatomegaly with patent portal and hepatic ducts. She improved and was transferred to the general ward after four days. Two days after transfer, she developed a massive gastrointestinal bleed and died. No postmortem liver biopsy was done. She was diagnosed to have had gastrointestinal bleed secondary to fulminant hepatic failure. Liver function test results were not stated in the case summary.

Case 5

A 26 year old G5P4 was referred to the hospital for pallor at the 34th week after being booked at 26 weeks. The liver was grossly enlarged at 9cm below the costal margin. The liver function tests showed hepatocellular dysfunction with low albumin levels. The hepatitis B Ag was positive. She was then referred to another hospital for delivery. She had a normal delivery four days later to a live baby. She was referred to the medical unit the next day. Both the liver and spleen were enlarged. Ultrasound examination showed a coarse liver parenchyma with no focal lesion. Ascitic fluid tap showed haemorrhagic fluid with increased proteins suggesting an exudate. Serum alpha fetoprotein was grossly elevated (7100mg/ml). A liver biopsy was planned but never done because of the altered coagulation profile. She sought discharge at her own risk six days later. Two weeks after this, she was readmitted to the original referring hospital with deep jaundice. The liver was hard and knobbly. She died soon after. Liver biopsy consent was refused. The cause of death was listed as cirrhosis of liver due to hepatitis B with hepatoma.

Case 6

A 18 year old primigravida was admitted after having ingested 20 grams of paracetamol tablets. She was admitted 12 hours after having ingested the tablets. She was at 12 weeks of gestation with no previous antenatal booking recorded. She developed vaginal bleeding. She was managed in the intensive care unit for acute hepatic failure and developed disseminated intravascular coagulation and respiratory failure. She succumbed three days later. Her case summary prepared by the medical unit made no mention of any attempt to give her an antidote.

Case 7

A 28 year old G4P3 had an intrauterine death at 32 weeks of gestation. No antenatal cause for the death could be discerned. She became febrile on admission. The dead fetus was induced with prostaglandins successfully and concurrently she was also started on ampicillin, gentamicin and metronidazole. However, she continued to remain febrile and the antibiotics were changed to cefuroxime and netromycin. An ultrasound scan showed an empty uterus. She developed a macular rash four days after delivery. She was then referred to the medical unit. A drug reaction was diagnosed by the dermatologist. The previous antibiotics were stopped and she was started on doxycycline. She developed disseminated intravascular coagulation seven days after delivery. At this juncture, chloromycetin was commenced. Two days later, she developed jaundice and agranulocytosis. The antibiotic was changed to

ceftazidine and she was commenced on steroids. Twelve days after delivery, she was discharged at her own request. Three days later, she was readmitted with fever and jaundice. There was an abscess on the hand which cultured methicillin resistant staphylococcus aureus. The vaginal culture grew *E.coli*. She was started on ceftriaxone, gentamicin, metronidazole and hydrocortisone. Fucidic acid was added later. Ultrasound revealed retained products but a evacuation was not carried out due to thrombocytopenia. She continued to develop multiple abscesses and bed sores. She passed out septic products of conception 22 days after delivery and succumbed to hepatic encephalopathy seven days later. The committee attributed the death to septicaemia with hepatic failure. The liver scan and liver function results were not stated in the case summary.

Case 8

The patient gave birth to a premature infant at 28 weeks of gestation. No antenatal risk factors or complications had been noted prior to the premature delivery. The delivery took place in a district hospital where no O & G specialist care was available. The infant died 15 minutes later. Soon after delivery the patient became tachypnoiec. She had bilateral basal crepitations. The chest X-ray showed evidence of congestive cardiac failure. She was then referred to a general hospital with specialist care. On arrival, she was noted to be jaundiced. The physician made a diagnosis of obstructive jaundice with septicemia and bronchopneumonia. She was also dialysed for acute renal failure. She died the next day attributed to septicemia with hepatorenal failure. There is no mention by the physician who managed the case of any cardiac abnormalities or echocardiogram being done. No liver scan was performed before the patient died.

Case 9

A 27 year old primigravida was admitted to hospital after having tried to self induce an abortion with grass stalks. The 16-week pregnancy was successfully evacuated with oxytocin infusion. The next day she deteriorated and died in intensive care. The blood culture grew E.coli and the liver biopsy showed periportal infiltrate of lymphocytes and polymorphs within the sinusoids. She was diagnosed to have died of hepatorenal syndrome with septicemia.

Case 10

A 36 year old G6P5 lady was diagnosed with pre-eclampsia at 22 weeks of gestation. She was treated with labetolol tablets by the medical officer at the health centre. She went into spontaneous labour at 37 weeks of gestation. She was a case of undiagnosed twin pregnancy. The first twin was a fresh still birth but the second twin was retained. She was referred to another district hospital where she had a breech delivery to a fresh still birth. She developed dark coloured stools, pallor and jaundice on the first postpartum day. She was referred to the surgical unit where a medical officer who saw her treated her conservatively for an upper gastrointestinal bleed. Her condition deteriorated further and she was transferred to a General Hospital. She required 2 pints of blood before the transfer. On arrival at the general hospital 11/2 hours later, the patient collapsed at the emergency ward. She was actively resuscitated and given blood and blood products. She was nursed in the intensive care unit. An ultrasound showed a shrunken liver with ascitis. She was too ill to have any surgical intervention done and she succumbed the next day. No postmortem was done. She was diagnosed to have died of HELLP syndrome.

Case 11

A 28-year-old primigravida was admitted with a history of jaundice, diarrhea and vomiting for 3 days. Three days later she developed fever and subsequently went into spontaneous labour. She had a normal vaginal delivery followed by persistent vaginal bleeding. No local source of bleeding was identified. She then went into hepatic coma, later developing septicemia & disseminated intravascular coagulation. Tests were negative for leptospirosis. There was no history of drug ingestion. She died after one week. Her diagnosis at death was cholestatic jaundice in pregnancy.

Case 12

32 year old lady who was a G2P1 had uneventful antenatal check ups until 37 weeks of gestation. She complained of epigastric discomfort and backache for which she was treated with antacids. A week later, she was admitted with complaints of fever, jaundice and tea coloured urine and reduced fetal movement. She subsequently went into spontaneous labour and delivered a baby boy. Following delivery she was anuric

and was nursed in the intensive care unit. She had features of disseminated intravascular coagulation and was managed accordingly. The medical team treated her for impending hepatic coma. She was on antibiotics (ceftazidime and metronidazole). She was HbS Ag positive and Hbe antigen negative. The ultrasound showed features of fatty infiltration/hepatitis with subdiaphragmatic free fluid. Despite treatment, she developed septicemia and multi-organ failure. She died two weeks after her delivery. The cause of death was acute hepatic failure.

Case 13

A 23 year old G6P5 lady had a normal delivery at home at 39 weeks of gestation. After delivery she complained of breathlessness and epigastric pain. She was sent to the hospital and there was noted to be pale and jaundiced. She had a large palpable nodular liver, splenomegaly and ascites. She was allowed home leave after 3 days of admission. There were no reports of any further investigation. At home, she developed massive haematemesis and died after 3 hours. The cause of death was listed as hepatoma. The national committee listed it as unspecified liver disease with evidence of portal hypertension and hepatomegaly.

Case 14

A 24-year-old primigravida was admitted to the hospital at the 30th week of pregnancy for breathlessness, vomiting, chest pain and fever. She was noted to be jaundiced and her liver function showed a raised liver enzyme and bilirubin. She was then referred to another hospital where she was diagnosed to have an intrauterine death. She later delivered a macerated still birth. Her bleeding profile was normal. Postpartum, she developed a gastrointestinal bleed. There was no postpartum haemorrhage. She was treated as a case of hepatic encephalopathy and failure. Her HBs Ag screening was negative. She developed progressive abdominal distention, ascites and hypoglycemia. She was ventilated. However she died after 8 days. She was diagnosed to have died from acute fatty liver of pregnancy.

Case 15

A 36-year-old lady was admitted at 35 weeks in labour with history of jaundice and gray coloured stool of three days duration. She was diagnosed to have hypertension and an impaired glucose tolerance test at 33 weeks. She needed a vacuum aided delivery in view of poor maternal effort and manual removal of placenta for retained placenta. She collapsed an hour after delivery. She was resuscitated and sent to the general hospital. She was diagnosed to be in hepatic failure with disseminated intravascular coagulation, hypocalcemia and cerebral oedema. She was ventilated. She later had a subtotal hysterectomy for postpartum haemorrhage one day after being ventilated. She died four days later. She was diagnosed to have died of fulminant hepatic failure, disseminated intravascular coagulation and septicemia.

Case 16

A 25 year primigravida was booked at 35 weeks of gestation with signs and symptoms of viral hepatitis that progressed to liver failure. She died 3 days later in the intensive care unit undelivered. She was diagnosed to have acute fatty liver of pregnancy based on a postmortem liver biopsy.

Case 17

A 25 year old G2P0 was noted to be jaundiced at 31 weeks. She was managed conservatively by the medical officer at the health centre who noted clinical improvement. No mention was made of the liver function test results. She was admitted 3 weeks later for a urinary tract infection. She was treated with bacampicillin orally and discharged the next day. There was no mention of jaundice. She was admitted 4 days later with jaundice. Her liver function tests showed a raised bilirubin with a prolonged prothrombin time. She had fetal distress and an emergency lower segment caesarian section was done. Post operatively she was nursed in the labour ward. Pethidine was given and 3 hours later she suddenly screamed of pain and collapsed. She was diagnosed to have died from hepatic encephalopathy.

Case 18

A 28 year old G8P6 lady was admitted at 34 weeks of gestation to the medical unit for fever, vomiting and diarrhea for 3 days. She gave a history of alcoholic consumption and was diagnosed as hepatitis in pregnancy. Three days later she was referred to the obstetrics unit for reduced fetal movements. She had a prolonged bleeding profile, which was corrected, and she delivered a macerated stillbirth. There was no post partum

haemorrhage. On the first postpartum day, the patient became comatose and was treated for hepatic failure. She died the next day. Post mortem liver biopsy showed massive centrizonal necrosis. She was diagnosed as a case of acute fatty liver by the team that attended to her.

Case 19

A 40 year old lady was admitted to the hospital at her due date with history of fall in the toilet and abdominal pain. Her blood pressure was 169/90. She was diagnosed as abruptio placenta. An lower segment caesarian section was done. Four hours later she became hypotensive and pale with abdominal distention. A relaparotomy was done There was no bleeding from the uterus. However there was bleeding from the liver. Post operatively the patient was managed by the obstetrician, surgeon and the anesthetist. The patient died 15 days later from methicillin-resistant staphylococcos aureus septicemia and severe pre-eclampsia. She was diagnosed to have died from severe pre-eclampsia with liver haemorrhage.

Case 20

A 34 year lady was under follow up at a private centre. She was subfertile for 10 years. She presented at 37 weeks of gestation for painless vaginal bleeding. She gave a one week history of jaundice. She also gave a history of ingestion of Chinese traditional medication. There was history of a jungle visit to where her husband had a fish rearing pond. She was then admitted to a private hospital. She was later referred to a general hospital with a differential diagnosis of drug-induced hepatitis, leptospirosis or acute fatty liver in pregnancy. On arrival at the general hospital she was deeply jaundiced, in early labour with disseminated intravascular coagulation and anuric. The physician and obstetrician jointly managed her. Her disseminated intravascular coagulation was corrected. She was treated with antibiotics and she had an assisted vaginal delivery. Postpartum, she developed hemorrhage, hypotension and haematuria despite treatment. She required intensive care nursing with ventilation. She developed adult respiratory distress syndrome, persistent metabolic acidosis and anuria. She died 12 hours post delivery. A post mortem liver biopsy was done and confirmed an acute fatty liver of pregnancy.

Case 21

A 24 year old G6P5 had complaints of giddiness and fever for two weeks before being seen at a health clinic. She was noted to be jaundiced and gave a history of ingestion of Chinese herbal medication. She also gave a history of leaking liquor for one week. She delivered at home. On day one postpartum, her jaundice worsened and she became ill. She was referred to a hospital where her liver enzymes and bilirubin were noted to be elevated. Urine analysis confirmed haematuria and positive urobilinogen. She was initially treated as a case of acute ascending cholangitis. She then became even more ill becoming drowsy, hypertonic with bilateral clonus and a positive Babinsky sign on the left. The diagnosis was then revised to hepatic encephalopathy. She developed disseminated intravascular coagulation. Her HbS Ag was positive. A septic work out was negative. She was ventilated in the intensive care unit. An ultrasound showed cirrhosis of the liver with gross ascites. Four days later, she was transferred out of intensive care unit as the bed was needed by another patient. She was nursed in the high dependency unit in the labour ward and expired on the same day. She succumbed to decompensated liver disease with hepatic encephalopathy secondary to underlying chronic hepatits B.

Case 22

A 29 year old primigravida was admitted at 30 weeks of gestation to a private hospital's intensive care unit for severe jaundice, septicemia and respiratory failure secondary to bronchopneumonia. She was ventilated and started on antibiotics. Four days later she delivered a stillbirth. Her hepatitis and HIV screening was negative. She later developed a coagulopathy with suspected bacterial peritonitis, renal dysfunction, hypotension requiring inotrophic support, hypernatremia, hypoalbunemia and upper gastrointestinal bleed. She was then transferred to a general hospital due to financial constraints. On arrival she was comatose, deeply jaundiced and febrile. She also had basal crepitations, hepatomegaly, ascites and hyporeflexia. Ultrasound revealed gross ascitis with no focal lesions. An echo cardiography showed a mildly dilated right ventricle. Other parameters were normal. A chest X-ray revealed haziness of the right lung. A post

mortem liver biopsy showed fatty changes. A lung biopsy showed features of shock lung. Ascitic fluid culture and sensitivity showed no growth. Her diagnosis at death was acute liver failure secondary to septicemia and bronchopneumonia.

Case 23

A 27 year old primigravida with twin pregnancy presented at 33 weeks with pre-eclampsia and a history of fever of 2 weeks. She developed jaundice 3 days before coming to the hospital. A lower segment caeserian section was done for fetal distress. The first twin survived but the second twin died of disseminated intravascular coagulation and pulmonary complications. The patient's condition worsened and she went into hepatic and renal failure. She developed acute respiratory distress syndrome and haemoperitoneum. She died 26 days post caesarian section. Her blood culture done on the fifth day after surgery grew pseudomonas aeroginosa. An ultrasound of the biliary system was normal. Leptospirosis, viral hepatitis and connective tissue screening were negative. She was diagnosed to have died of acute fatty liver with hepatic coma.

The causes of maternal deaths from liver disease for the period 1991 to 1994 are listed in Table I.

Discussion

Liver disease complicates approximately 1 in 1000 pregnancies and can affect both the mother and fetus.

Table I
Causes of Maternal Deaths from Liver Disease 1991 - 1994

Causes of Death	
Acute fulminant hepatitis	6
Acute fatty liver	6
Septicaemia	4
Hepatic enchalopathy	1
HELLP Syndrome	1
Hepatoma	2
Liver failure-Drug induced	1
Cholestatic jaundice	1
Severe pre-eclampsia	1

Between 1991 and 1994 there were a total of 1066 maternal deaths in Malaysia. Liver disease alone accounts for 23 (2.15%) of these deaths.

The three main of causes of maternal deaths from liver disease during this review period were hepatitis, acute fatty liver in pregnancy and sepsis with multiorgan failure. From the case histories above, it is quite apparent that the diagnosis of the disease at the early stage is quite difficult. Some of the normal physiological changes in pregnancy can mimic abnormalities associated with liver disease in pregnancy[1]. In normal pregnancy, the liver is pushed postero-superiorly[1]. A palpable liver is thus an indication of pathology. The appearance of palmar erythema, spider nevi, engorged oesophageal varices and abdominal wall veins (caput medusa) are common in normal pregnancy and do not necessary reflect hepatic pathology[2]. A dilutional fall in serum albumin is seen in pregnancy, 35 - 50g/dl outside pregnancy to 22 - 33g/dl in pregnancy[3]. There is an estrogen dependent increase in production of most coagulation factors, globulin, fibrinogen and hormone binding proteins such as thyroxin binding globulin and cortisol binding globulin. The level of bilirubin, ALT, AST and GGT are relatively unchanged in pregnancy. The level of alkaline phosphatase is three times higher due to placental alkaline phosphatase.

The highest number of deaths due to liver disease in pregnancy was due to fulminant hepatitis. There were 6 cases in all. Of these cases, only two cases were confirmed as hepatitis B positive. There was no mention of other viral screening done nor were there any results available of other causes of hepatitis. The most common presentation was fever with jaundice. The majority of patients progressively became worse after delivery and developed hepatic encephalopathy or hepatic failure. There were varied presentations including hypoglycemia and deranged coagulation profiles. Some patients developed post partum haermorrhage as a result of this. The range of gestation at which the patients presented was 24 - 38 weeks. Viral hepatitis can occur at any time[1]. It is actually the most common cause of jaundice in women of childbearing age, whether pregnant or not pregnant[5]. Viral hepatitis, except for hepatitis E does not occur more frequently or with greater severity in pregnancy[5]. Hepatitis due to herpes simplex virus has

also been reported in pregnancy with a mortality rate of 43%[6]. However there were no mention of these diseases being looked for in the case reviews.

The limitation in diagnosis has been the lack of viral serological evidence (in some cases) and the tendency to classify the diagnosis as hepatitis based on increased liver enzyme levels. Acute fatty liver causes the same type of changes and can lead to death whereas hepatitis rarely ever causes death. For instance, the mortality rate of acute Hepatitis A is 0.2% to 2.0% and the top end is only seen in the elderly. Increased mortality in cases with acute hepatitis in pregnancy is seen in hepatitis E infection but this affliction remains largely confined to South Asia and has not been reported in South East Asia as yet.

The next commonest cause of death was acute fatty liver in pregnancy. This is a potentially fatal but uncommon disorder that may occur in the third trimester[7]. The incidence of this disease is between 1 in 9000 to 1 in 13000 pregnancies[8]. Until the 1970's, the disease had a dismal prognosis with the fetal as well as maternal mortality approaching 85%[9]. With the early recognition and rapid termination of pregnancy, the rates have fallen to 18 - 23%[5]. Only 3 cases were confirmed by a post mortem liver biopsy. Typically these biopsies would show hepatocytes in the swollen and pale pericentral areas[7]. The other 3 cases were diagnosed clinically. The most common presentation was between 30 - 37 weeks of gestation. All the cases had deranged coagulation profiles with complications such as DIVC and PPH. Most of the patients died from hepatic failure.

The third commonest cause of death was liver failure due to septicemia. There were four cases reported. The source of infection was from varied places i.e.: septic abortion, septic retained products of conception and bronchopneumonia. In one case, the name of the organism was not mentioned. The antibiotic used to treat the patients covered both gram positive and negative organisms as well as anaerobes. Steroid therapy was used in some cases. The majority of the patients succumb to hepatic failure. The organism was E.coli in two cases of abortion. We were unable to ascertain the organism involved in the case of bronchopneumonia and the case with peritonitis.

There were two cases of hepatoma. Both the cases were clinically diagnosed and there was no confirmatory biopsy as consent was refused. In one case, the liver was noted to be 9cm below the costal margin only after the second visit. She was noted to be hepatitis B serum Ag positive. The diagnosis was made when alpha-fetoprotein was markedly elevated. The second case was only diagnosed when the patient was referred to the hospital after a home delivery. Only then was a nodular liver with splenomegaly and ascitis noted. The patient requested for discharge and died at home.

There was one case of HELLP syndrome. This syndrome complicates 0.2 - 0.6% of all pregnancies and 4 - 10% of women with pre-eclampsia[10]. Jaundice is only evident in 5% of the cases[11]. This patient developed severe gastrointestinal haemorrhage and by the time she was sent to a tertiary center, she was too ill to have any procedure performed. The mortality rate for women with HELLP syndrome is 1 - 3% although rates as high as 25% have been noted[10].

Another patient died from severe pre eclampsia. She initially had an LSCS and later required a laparotomy due to intra-abdominal bleeding. The source of the bleeding was noted to be from the liver. Hepatic complications, including subcapsular hematoma and rupture, infarction and fulminant liver failure accounts for 20% of the maternal deaths occurring from pre-eclampsia[12,13,14].

One case died due to an overdose of drug ingestion. This patient died from liver failure, DIVC and respiratory failure. The patient had ingested 20gms of paracetamol. High dose of paracetamol produces liver cell necrosis. The toxic metabolite binds irreversibly to the liver cell membrane[16]. Marked liver necrosis can occur with as little as 10gms and death can occur with 15gms[17].

There was one case of cholestatic disease in pregnancy. In this case the patient had jaundice, diarrhea and vomiting. There was no mention of jaundice or pruritis but the patient had developed postpartum haemorrhage. The cause of intrahepatic cholestasis of pregnancy is unknown[18]. Post partum bleeding may result from decreased absorption of vitamin K[18,19,20].

To reduce the overall incidence of deaths due to liver disease, our review also looked at the standard of care that

was provided. This is so as to be able to formulate remedial measures to further improve the standard of care. Remediable factors identified included failure to appreciate the severity of disease by health personnel who saw the patient first. There were conditions where the patient was not admitted for jaundice until three weeks later. There were also delays in referring to other specialties when such services were available. There were cases where the patient themselves refused to be examined by a male doctor. Patients were not properly examined to look for source of infection. There is a lack of appreciation of the seriousness of the disease process. This was evidenced by a case where a patient, who came with complaints of epigastric pain and nausea in late pregnancy was summarily dismissed as having gastritis and not called back for review until the patient came back with jaundice.

This study is based on a retrospective review of the case summaries prepared by the doctors who cared for the patient. The summaries were prepared for the purposes of national Confidential Enquiries into Maternal Deaths. It was noted that in many instances the physicians who managed the cases did not give a detailed report with summaries of the investigations performed. The task was often delegated to the medical officers. There are obvious limitations in terms of the study being reported here. However, all diagnoses were arrived at by consensus by a group of specialists who judged their peers taking into consideration the facilities and the human resources available.

There is a need to address these problems. It is recommended that patients who are at risk e.g.: pre-eclamptic patients, patients with history of jaundice in their previous pregnancy, patients who are exposed to people who are jaundiced be seen early in the ante-natal clinics. This is so as to be able to identify the patients who are at high risk and therefore would need close follow up. Pregnant women who are jaundiced should be referred early to the obstetrician and the physicians for combined care Deliveries should be in a hospital equipped to handle such cases. Cases should be thoroughly examined to look for the cause of jaundice. The usefulness of liver biopsy should be considered more carefully.

Heightened awareness is of foremost importance, as we know that in acute fatty liver, termination of pregnancy can save the life of the mother and maybe the baby as well (in view of improved neonatal management facilities). Ultimately clinical detection is extremely important in the primary care setting and will play a significant role in improving outcome.

Guidelines for the management of liver disease in pregnancy should include the following:

1. Baseline and serial liver function tests and prothrombin time in addition to a full blood count, serum urea and electrolytes, blood glucose, serum alpha feto-protein and urine for bile.
2. Ultrasound of the hepatobiliary system is essential and should include liver architecture, focal lesions, splenic size, patency of the portal veins and arteries and if doppler is available, the direction of flow of the blood in the portal vein.
3. Viral serology - IgM antiHAV, IgM antiHBc, IgG anti HBc, HBs Ag, Anti HCV, Anti HDV, IgM anti HEV and Herpes Simplex antibodies in imunocompromised patients.
4. Liver biopsy may not be needed unless a diagnostic doubt exists.

Conclusion

Liver disease in pregnancy is a serious and potentially fatal condition that can affect both mother and fetus. Our review shows that the condition is common at a mean of 30 weeks of gestation with a preponderance to women of low parity. Nausea, vomiting and epigastric pain in late pregnancy should not be dismissed lightly. Early referral to a center equipped for diagnosis and management should be advocated.

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