Acute Fatty Liver in Pregnancy

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Abstract : **We report a woman with a 36 week twin pregnancy who presented with labor pains 8 hours prior to hospitalization. Jaundice was found on clinical examination in the out patient department. After admission for investigation, laboratory tests which demonstrated abnormal bleeding, rapidly worsened and the condition of the fetuses worsened. Emergency caesarian section was performed while resuscitating the patient. The twins were delivered with a good outcome but their mother's condition worsened and she expired from sepsis on the 32nd day after admission. The differential diagnosis of jaundice in the third trimester, treatment, optimization for operation and outcome of acute fatty liver of pregnancy are discussed. Acute fatty liver in pregnancy is a rare but usually fatal disease in pregnant woman.**

เรื่องย่อ : ภาวะ Acute Fatty Liver ในผู้ป่วยตั้งครรภ์

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สารศิริราช 2545; 54: 33-38.

รายงานผู้ป่วยตั้งครรภ์ 36 สัปดาห์ มาพบแพทย์ด้วยอาการเจ็บครรภ์และตรวจพบอาการดีซ่าน ต่อมาผู้ป่วยเกิดภาวะเลือดออกผิดปกติอย่างรวดเร็วและรุนแรง ขณะที่เด็กในครรภ์อยู่ในสภาวะที่ไม่เหมาะสม มีการตัดสินการผ่าตัดคลอดเด็กทางหน้าท้องอย่างฉุกเฉิน การผ่าตัดประสบความสำเร็จได้ทารกแฝด แต่ผู้ป่วยเสียชีวิตด้วยภาวะติดเชื้อใน 32 วันหลังรับเข้ารักษาในโรงพยาบาล คณะผู้รายงานเสนอขั้นตอนการวินิจฉัยแยกโรคในภาวะดีซ่านของผู้ป่วยตั้งครรภ์ไตรมาสที่ 3 และวิธีการดูแลรักษาผู้ป่วยเพื่อการผ่าตัดในภาวะ acute fatty liver ในผู้ป่วยตั้งครรภ์ภาวะ acute fatty liver เป็นภาวะที่พบได้น้อย แต่มีความรุนแรงถึงชีวิตได้ การให้การวินิจฉัยและรักษาอย่างรวดเร็วจะให้ผลลัพธ์ที่ดีกว่าแก่ผู้ป่วย

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From Interdepartmental Conference, June 18, 2001.

INTRODUCTION

Severe hepatocellular diseases in late pregnancy is an interesting subject for physicians. Acute fatty liver in pregnancy is a rare but fatal disease. The outcome can be changed by proper and timely treatment. The following case illustrates the perioperative management of this disorder by a team approach.

CASE REPORT

A 22-year-old, gradvida 2, para 1, abortion 0 pregnant woman with a 36 week twin pregnancy and who had had a previous caesarian section presented with labor pains for 8 hours prior to arrival at Siriraj Hospital. Two weeks previously she had had symptoms of fever, rhinorrhea and white turbid sputum. The tertiary care hospital which she attended for antenatal care, had gave an antipyretic and anticough medication that had made the symptoms better. Three days prior to admission, she had had malaise, nausea and vomiting and dark yellow urine without itching and pale stool.

When she came to Siriraj Hospital, the doctor admitted her for moderate jaundice with uterine contractions. Her vital signs were stable. Ultrasonography revealed viable twins, vertex/breech, with a gestational age of 36 weeks. A non-stress test showed regular spontaneous contractions with late deceleration in all contractions. Other investigations showed a normal hemoglobin (12 g/dl), normal hematocrit (37.5%) and normal platelet count (167,000/ mm^3) respectively. There was prolonged coagulation (venous clotting time 25 minutes, prothrombin time (PT) 52sec., partial thromboplastin time (aPTT) 106.3 sec., D-dimer level 1,396 ug/ml). Her blood urea nitrogen and creatinine were elevated (BUN 19, creatinine 3.4 mg/dl). Her serum electrolytes were normal (sodium 139 mEq/l, potassium 5 mEq/l, chloride 106 mEql/l, bicarbonate 12 mmol/l). She had severe hypoglycemia (serum glucose 22 mg/dl). Liver function was impaired (aspartate aminotransa-minase 501 U/L, alanine aminotransaminase 251U/L, γ-glutamyl transferase 55 U/L, and alkaline phosphatase 668 U/L). The cholesterol level was 116 mg/dl. The total bilirubin level was 13.8 mg/dl with 10.7 mg/dl of direct bilirubin. Urine protein was negative.

A clinical diagnosis of a 36 week twin pregnancy with late decelerations with jaundice of unknown cause was made. Emergency termination of the pregnancy was planned because of the late decelerations of the fetuses but the severe coagulopathy delayed the cesarian section for 6 hours while it was corrected.

Hepatologists and Anesthesiologists were consulted for preoperative evaluation and preparation. Two thousand mls of fresh frozen plasma with cryoprecipitate and 30 mg vitamin K were administrated IV. After administering the first 1000 ml, the prothrombin time (PT) decreased to 30 sec. and the partial thromboplastin time (aPTT) was 77 sec. Blood serology for HBs Ag, anti-HAV IgM, anti HBc IgM was done. While waiting for correction of the coagulopathy the patient was kept NPO, glucose was given for treatment of her hypoglycemia, she was placed on her left side and oxygen was given to maximise the uteroplacental circulation. Four units of whole blood, 10 units of platelets and 1,000 ml of fresh frozen plasma were prepared for the procedure in the operating room. The clinical picture deteriorated with bleeding from her gums, bleeding per vagina and hematemesis. A decision to proceed with the operation was made. Her blood pressure was 120/80 mmHg, pulse rate was 120/min and she was mildly drowsy. Rapid sequence induction of general anesthesia was achieved with thiopental plus ketamine and rocuronium IV and the trachea was intubated. Anesthesia was maintained with 50% nitrous oxide and oxygen, vecuronium as a muscle relaxant and isoflurane (not exceeding 0.6%) were used until delivery. Fentanyl (75 microgram) and midazolam (4 mg) were administered after delivery of two female infants with Apgar scores of 4 at one minute to 8 at 5 minute for both infants. FFP 1,320 ml, 10 units of cryoprecipitate, 3 units of whole blood and 1,150 ml of crystalloid were administered. Urine output was 180ml; and the estimated blood loss was 2,500 ml over the 2 and a half hour operative period. This blood came from the surgical field, nasal bleeding and severe gastrointestinal tract bleeding via the orogastric tube. Gastric lavage, H2 blockers and nasal packing were performed during the operation.

Uterine contractions was increased by syntocinon, methergin and nalodor in successive sequence. Adequate hemostasis and uterine contraction were achieved by the end of surgery. The patient was transferred to the intensive care unit without extubation. Immediate postoperative vital signs were quite good with a blood pressure of 100/80 mmHg, pulse rate 100/min and urine output 1-2 ml/kg/hr. The coagulopathy continued. After10 hours replacement in ICU with 4 units of whole blood and 850 ml of fresh frozen plasma, the hematocrit was 29%. PT decreased to 17 sec., aPTT 34 sec and platelet 136,000 /mm^3. During the 1st week in ICU she was given 7,000 ml of fresh frozen plasma, 20 units of cryoprecipitate, 8 units of whole blood and 3 units of packed red cells in order to correct her coagulopathy. Fluid resuscitation was performed to correct her acute renal failure. The results of Cytomegalo virus (CMV) antigen, CMV IgM antibody and Herpes simplex virus (HSV) IgM antibody were all negative. CMV IgG antibody and HSV IgG antibody were positive. Her symptoms seemed to improve after the 2nd week. Her liver function tests improved except for her bilirubin level. However, she had a fever from day 1 until the 21st day of admission when she went into septic shock. There was a clinical improvement after aggressive antibiotic administration during the first week but this worsened again a week later. The source of infection was considered to be from the uterus. Suction curettage was performed on the 29th day of admission but she worsened and expired on the 32nd day.

DISCUSSION

Obstetric patients with jaundice are interesting for both the obstetrician and the anesthesiologist. There are many differential diagnoses and methods of approach. Particular consideration must be paid to survival and well being at the same time. The risks and benefits of termination of pregnancy versus the period of gestation must be weighed up. The time needed for stabilization and correction of the coagulopathy and optimization of liver function should be as short as possible. Early diagnosis, awareness of the condition, timely and proper management can change the outcome for the patient. Although this case presented with fetal distress that needed urgent delivery, the complicating symptoms and signs needed correction and optimization.

A gastroenterologist's opinion on jaundice in the third trimester of pregnancy

This 36-week-pregnant woman had jaundice 3 days before admission, after symptoms of an upper respiratory tract infection 2 weeks previously. Her jaundice seemed clinically to be hepatocellular since she had symptoms of malaise, anorexia, nausea and vomiting without pruritus or pale stools. The liver function tests confirmed the presence of hepatocellular jaundice. Although her alkaline phosphatase was elevated 5-6 times that of normal, the normal GGT convinced us that the elevated AP came from another source, which was likely to be the placenta. Furthermore, we found she had a marked coagulopathy with a high D-Dimer value, and hypoglycemia on admission, all of which showed that she had severe hepatocellular disease. If she had had hepatic encephalopathy following this she would have fulfilled the diagnostic criteria of acute fulminant hepatic failure.

Causes of severe hepatocellular disease in late pregnancy can be classified into 1) Liver disease unique to pregnancy i.e. acute fatty liver of pregnancy (AFLP) or the most severe form of preeclampsia known as **H**emolysis **E**levated **L**iver Enzymes **L**ow **P**latelets (HELLP) syndrome. 2) Concurrent liver disease during pregnancy i.e. acute viral hepatitis (A, B or E), herpes simplex viral hepatitis (HSV), other viral causes of hepatitis such as cytomegalovirus (CMV) or Epstein-Barr virus (EBV), drug-induced hepatitis or acute Budd-Chiari syndrome. Data from western country shows that AFLP is the most common cause of acute liver failure in pregnancy (70%), followed by the HELLP syndrome (15%).[1] Other less common causes are acute viral hepatitis (A or B) and HSV hepatitis. In contrast, in some areas of the world such as India, acute viral hepatitis E is the most common cause of acute liver failure in pregnancy.[2] HSV hepatitis usually has some clues to the diagnosis such as buccal or genital lesions (50%), markedly

elevated transaminases (may be up to 10,000 U/L) and most are anicteric.[3] Drug-induced hepatitis is uncommon since most pregnant women usually avoid unnecessary drug prescriptions. Budd-Chiari syndrome was unlikely in this patient because most of the reports in pregnancy are found in the postpartum period and nearly all cases had abdominal pain, ascites and hepatomegaly.[4] Hence, in this patient we should be aware of AFLP, HELLP syndrome, acute viral hepatitis A,B or the less common acute viral hepatitis E since in Thailand, only a few cases of acute viral hepatitis E have been reported.

From the clinical picture, this patient was likely to have AFLP or acute viral hepatitis rather than the HELLP syndrome. Since the former 2 conditions are "true" hepatocellular disease, they can manifest as marked jaundice, severe coagulopathy, hypoglycemia and even hepatic encephalopathy, DIC and acute renal failure as in this patient. In contrast, the HELLP syndrome is a severe form of preeclampsia so in nearly all cases, evidence of preeclampsia (edema, proteinuria and hypertension) should be present. HELLP syndrome is not a true hepatocellular disease, thus, unlikely to have marked jaundice, hypoglycemia, encephalopathy and severe coagulopathy unless DIC is present.[5] So it is not compatible with the clinical picture in this patient.

It is difficult to differentiate AFLP from acute viral hepatitis in this patient. Serological tests for acute viral hepatitis A (anti HAV IgM), B (HBsAg, anti HBc IgM) and E (anti HEV IgM) should be performed in all cases, although anti HEV is not yet available routinely. However, there are some clinical clues to differentiate AFLP from acute viral hepatitis. Half of the patients with AFLP have associated preeclampsia[6] and 60% have polyuria and polydipsia from transient central diabetes insipidus, whose mechanism is not understood.[7,8] AFLP seldom has a transaminase level above 1,000 U/L and in the majority of cases they are usually less than 500 U/L.[9,10] In contrast, a transaminase level greater than 1,000 U/L is very common in acute viral hepatitis.[10] Nearly all cases of AFLP have leukocytosis and a high serum uric acid, which is different from an acute viral hepatitis, which may show a normal white cell count and usually has a low serum uric acid level.[8,10]

This patient had severe hepatocellular jaundice, since she had a marked coagulopathy and hypoglycemia, together with leukocytosis, DIC, acute renal failure and a high uric acid. Even though she did not have preeclampsia, we should diagnose her with AFLP rather than acute viral hepatitis.

Serological tests for acute viral hepatitis are very important to differentiate acute viral hepatitis from AFLP but they usually take many days to complete. Although liver biopsy, is the best method for making a definite diagnosis; it is usually not justified or cannot be done due to the severe coagulopathy which is usually seen in these patients. In the real situation, we have to make the most likely diagnosis on clinical grounds alone.

Acute Fatty Liver of Pregnancy (AFLP)

The pathogenesis remains unclear. However, the hepatic histology of AFLP is similar to Reye's syndrome seen in children. Recent studies have shown that infants born to mothers with AFLP may have a deficiency in one of the enzymes used in mitochondrial beta oxidation of fatty acids, long chain3-hydroxyl-acyl CoA dehydrogenase (LCHAD).[11] These infants are at risk of developing a Reye-like syndrome when faced with stress or fasting and usually die.[9] These infants were found to have homozygous LCHAD deficiency. Some women with AFLP were found to have heterozygous LCHAD deficiency. Thus it seems that many AFLP women and their spouses might be heterozygous for LCHAD deficiency. These women are usually asymptomatic since they are partially deficient. Unfortunately, their offspring have a 1 in 4 chance of being homozygous for LCHAD deficiency, since it is autosomal recessive. These mothers might not be able to cope with the stresses of pregnancy or pre-eclampsia, because of overspill of unmetabolized free fatty acids from the fetus (because they were completely deficient in LCHAD) to their mothers. Subsequently, these mothers develop AFLP.[11-14]

AFLP must be suspected in every woman in late pregnancy who has signs and symptoms of acute hepatocellular jaundice, especially with acute liver failure; coagulopathy, hypoglycemia and in severe cases, hepatic encephalopathy. The presence of pre-eclampsia, DIC and acute renal failure will raise the possibilitiy of AFLP. Usually, the HELLP syndrome

can be differentiated from AFLP without much difficulty. However, exclusion of acute viral hepatitis, especially A, B and E, may be very difficult, so hepatitis serology tests are essential. In selected cases, we may have to exclude HSV, CMV or EBV hepatitis too. Liver biopsy is rarely needed, because it is usually too risky and the decision concerning treatment would not be changed after biopsy. Whether the patient has AFLP or the HELLP syndrome, prompt delivery is the treatment of choice. The exception is if we suspect acute viral hepatitis rather than AFLP, the we can wait for the hepatitis serology tests. However, if the mother or the condition of the fetus deteriorates, prompt delivery must ensue without hesitation. Thus, in this patient, we decided to deliver her as soon as possible.

Obstetric management of acute fatty liver in pregnancy

In this case of a twin pregnancy with a gestational age of 36 weeks with previous cesarean section and late decelerations on cardiotochogram, it is appropriate to terminate the pregnancy. Over 50 percent of twins reach sufficient maturity for survival at 36 weeks or more.[15] Termination of pregnancy for any reasonable cause can be done safely. When late decelerations of the fetal heart rate are seen in the late second trimester or third trimester, it implies that there is uteroplacental insufficiency. In uteroplacental insufficiency, the fetus should be delivered urgently because the fetus is at risk of hypoxia. In cases in which cesarean section can not be done promptly, intrauterine resuscitation should be given. Intrauterine resuscitation is composed of intravenous fluid replacement, oxygenation of the mother, and left lateral positioning.

The medical team who took care of this patient decided to terminate the pregnancy as soon as possible, but the associated coagulopathy delayed the obstetric intervention. She appeared sick and moderately jaundiced. The venous clotting time (VCT) was 25 minutes and her blood sugar was 22 mg/dl. VCT is a crude investigation of the coagulation system. If the VCT is prolonged, the PT and PTT are also prolonged. Hypoglycemia indicates that glycogenolysis is decreased, which is found in severe hepatic dysfunction.[16] Even though further investigations will not affect the management, they should be done to predict outcome. The route of delivery chosen in this patient was caesarian section as a result of many factors i.e: fetal distress (late deceleration on electronic fetal monitoring), previous cesarean section and deep jaundice in pregnancy from acute fatty liver in pregnancy or severe pre-eclampsia. The gastroenterologist strongly pushed for rapid delivery to stop the process of hepatic dysfunction. However the general condition of the patient had to be improved by a team approach of an obstetrician, a hepatologist and an anesthesiologist.

*Data collected in Siriraj Hospital from 1990-1999, Acute fatty liver in pregnancy 4 cases, incidence 0.24/10,000 (average number of deliveries / year = 16,864.1)

*Mortality rate in acute fatty liver in pregnancy was found to be 2/4.

Anesthetic management

"Acute fatty liver in pregnancy" patients who need expeditious operative delivery need prompt aggressive supportive treatment preoperatively, intraoperatively and postoperatively. Because hepatic function is seriously impaired, both the metabolic and hepatic synthetic functions should be assessed and corrected to give as optimal a condition as possible. Coagulopathy from abnormal clotting factors which are synthesized by liver and malabsorption of vimatin K should be corrected by giving vitamin K, fresh frozen plasma and cryoprecipitate. Prophylactic H2 blockers should be given to prevent GI bleeding and units cross matched for perioperative bleeding. Quite often, decreased fibrinogen, platelet and antithrombin III are found together with increased FDP.[16] One should pay attention to metabolic abnormalities such as hypoglycemia, hyponatremia, hypokalemia and acid base disturbance. The serious hepatorenal syndrome should be prevented by optimizing the hemodynamics and renal perfusion. Hepatic encephalopathy should be avoided by correcting hypokalemia, correcting alkalosis, minimizing sedatives, stopping GI bleeding and giving an enema. Optimizing hepatic blood flow and oxygenation, avoiding overuse of paracetamol, preventing hypotension and monitoring LFT and PT can help to preserve hepatic function.[17] The way to optimize he-

patic blood flow and oxygenation includes stabilizing hemodynamics, monitoring and anesthetic technique. The choice of anesthesia is regional[18] or general. Indications for general anesthesia are coagulopathy, obstetric hemorrhage, fetal distress and altered mental state. The other important thing is that the fetal conditon should be helped by intrauterine resuscitation. Nevertheless fetal distress and death from secondary uteroplacental insufficiency have been report. After delivery, the patient should be closely monitored for postoperative hepatic dysfunction and postpartum hemorrhage and postpe-rative problems should continue to be corrected. Orthotopic liver transplant is an option for the rare parturient who shows no evidence of recovery by 3 days postpartum.[19,20]

CONCLUSION

Acute fatty liver in pregnancy is a rare clinical entity unique to the third trimester of pregnancy. Mortality is lower if early detection is made. Intensive care support should be provided and early delivery should be performed. The obstetric team must be familiar with and clinicians must have a high index of suspicion for this condition. A high index of suspicion, early diagnosis, timely and appropriate management can improve the outcome of this serious complication of pregnancy.

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