ANTEPARTUM FETAL CEREBRAL HEMORRHAGE NOT PREDICTED BY CURRENT SURVEILLANCE METHODS IN CHOLESTASIS OF PREGNANCY

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Background: **The reason for increased fetal mortality in cholestasis of pregnancy is not completely understood. Intracerebral hemorrhage due to coagulation disorders, similar to those reported in the mother, is a possible explanation.**

Case: **Antepartum fetal death occurred at 37 weeks in a primigravida with cholestasis of pregnancy. The woman was taking no medication. Autopsy revealed extensive cerebral hemorrhage. A cardiotocogram and biophysical profile performed 24 hours and 5 days, respectively, before fetal death had been normal.**

Conclusion: **Antepartum fetal death may occur in patients with mild cholestasis who are taking no medication. Intracerebral hemorrhage is a possible cause, and this may be unpredictable with current methods of fetal surveillance. This possibility constitutes an argument in support of delivering these pregnancies as soon as lung maturity is achieved. (Obstet Gynecol 1997;89:803–4. © 1997 by The American College of Obstetricians and Gynecologists.)**

Increased perinatal mortality in intrahepatic cholestasis of pregnancy has been found by many authors,[1–4] but the reason for it is still a matter of debate. An increased rate of preterm deliveries,[1–5] stillbirths,[2,3] and intrapartum fetal distress[2,3,5] has been found in some series. More recently, maternal coagulation disorders have been reported,[6,7] perhaps explaining the increased rate of postpartum hemorrhage found in older series.[1–3] Such coagulation disorders are probably caused by defective intestinal absorption of vitamin K,[6] which may be further impaired by cholestyramine administration[7] used to alleviate pruritus. An increased prothrombin ratio has been reported in 20% of cases.[7] To our knowledge, fetal intracranial hemorrhage has been documented only once by autopsy in cholestasis of pregnancy.[6] In that case, death occurred in the immediate neonatal period, after labor induction and extended treatment with cholestyramine.

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Case Report

A 21-year-old primigravid woman was referred to our hospital at 37 weeks' gestation because of mild generalized pruritus and dark urine, which had developed during the previous week. There was no history of liver disease, jaundice with oral contraceptives, or use of hepatotoxic drugs.

No fever, jaundice, hepatosplenomegaly, or other signs of liver disease were detected on admission. Liver enzymes were mildly elevated: alkaline phosphatase 133 U/L (normal 38–126), alanine aminotransferase 94 U/L (normal 7–56), and aspartate transaminase 83 U/L (normal 5–40). Total bilirubin was 15.8 mg/L (normal 2–13) and conjugated bilirubin was 8.8 mg/L (normal 0–3). The coagulation profile was normal, and the platelet count was 168×10^9/L. Serology for hepatitis B and C was negative. Ultrasound scan of the upper abdomen showed normal hepatic dimensions and no alterations of the gallbladder or intrahepatic or extrahepatic canals. A normal cardiotocogram was recorded, and fetal ultrasound revealed normal amniotic fluid, normal respiratory and body movements, and an umbilical artery Pourcelot index of 0.57.

No medication was prescribed, and induction of labor was planned for the 38th week of gestation. The fetus was monitored daily with cardiotocograms, which were invariably normal. On the fourth day of hospitalization, an analytic control revealed a slight increase in liver function enzymes and bilirubin: alanine aminotransferase 171 U/L, alkaline phosphatase 253 U/L, and total bilirubin 23.2 mg/L. On routine evaluation the following day, no fetal heart sounds were heard; fetal death was subsequently diagnosed by ultrasound. The mother had perceived normal fetal movements during the previous hours. A female infant weighing 3205 g was delivered vaginally 9 hours later, after oxytocin induction.

Postmortem examination of the fetus showed marked congestion, petechial multi-organ hemorrhage, and parenchymal hemorrhage of the lungs, kidneys, and liver. A large subcapsular hepatic hematoma was present. The brain showed marked meningeal congestion and hemorrhage, particularly in the brainstem. Intraventricular hemorrhage was found, probably secondary to rupture of vessels in the periventricular white matter. Multifocal brain-cell necrosis was present. No fetal maceration, congenital malformations, or signs of infection were detected. Histologic examination of the placenta revealed no signs of abruption, infection, or other abnormality. A small number of erythroblasts were found in the circulation. The fetal membranes were deeply stained with meconium.

The mother's pruritus spontaneously disappeared 2 days after delivery. At 60 days postpartum, her liver enzymes and bilirubin were normal.

Discussion

In this case, antepartum death occurred in the absence of clinical, biophysical, or postmortem evidence of chronic fetal distress, fetal malformations, or other known situations leading to acute fetal distress (eg,

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abruption, infection, premature rupture of membranes, or cord abnormalities). The most probable cause of fetal death was cerebral hemorrhage, which is very rare in term fetuses in the absence of infection.[8] Fetal cholestasis-induced coagulation disorders are a possible explanation for this event; this would also account for the extensive multi-organ hemorrhages.

Management of patients with intrahepatic cholestasis of pregnancy is controversial. Frequent cardiotocographic monitoring has been proposed,[3] as well as administration of parenteral vitamin K and cholestyramine if needed. Some authors propose delivery as soon as lung maturity is achieved.[3-5]

With respect to fetal surveillance, our case suggests that current methods do not anticipate all antepartum fetal deaths in this disease. A normal cardiotocogram and biophysical profile were obtained 24 hours and 5 days, respectively, before fetal death. These methods will only detect cases of sudden intracerebral hemorrhage by chance because they evaluate the fetal state only intermittently. Perhaps with continued (ie, round-the-clock) cardiotocographic monitoring, early signs of neurologic compromise can be detected before overt hemorrhage, irreparable neurologic damage, or death occur.

In a large series from Chile,[4] three apparently similar cases of stillbirths were reported, with normal cardiotocograms recorded 2, 5, and 6 days before death and fetal movements perceived by the mother in the previous hours. However, no postmortem information was provided. Two cases of normal cardiotocograms recorded on the day before fetal death were also reported by Fisk and Storey.[3] Autopsy revealed petechial hemorrhages attributed to acute uterine anoxia, but no overt hemorrhage. In a case of neonatal death due to intracranial hemorrhage,[6] a nonreactive cardiotocogram was obtained before delivery.

Our case suggests that antepartum fetal death can occur even in patients with mild cholestasis of pregnancy who are taking no medication. Fetal intracranial hemorrhage is a possible cause of death for some of these cases, and this could be due to fetal coagulation disorders similar to those described in the mother. If this is confirmed by further reports, more frequent evaluations of the coagulation profile or even prophylactic parenteral vitamin K administration may be warranted. This case also suggests that current methods of fetal surveillance do not anticipate all antepartum fetal deaths in this disease. In our view, this constitutes an argument in support of delivering pregnancies with intrahepatic cholestasis as soon as lung maturity is achieved.

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