Sudden Fetal Death in Intrahepatic Cholestasis of Pregnancy

Richard H. Lee, MD, Marc H. Incerpi, MD, David A. Miller, MD, Bhuvan Pathak, MD, and T. Murphy Goodwin, MD

BACKGROUND: Intrahepatic cholestasis of pregnancy is associated with an increased risk of fetal death. The mechanism of death is unknown.

CASES: The first case involved a young primipara with pruritus and a bile acid concentration of 79 µmol/dL. While undergoing fetal heart rate monitoring, the fetus had a prolonged deceleration resulting in intrauterine death. The second case involved a young multipara with cholestasis who received ursodeoxycholic acid. Her bile acid concentration improved to 13 µmol/dL. At 34 weeks of gestation, she had uterine contractions with prolonged decelerations resulting in delivery of her fetus with Apgar scores of 0, 0, and 5 at 1, 5, and 10 minutes, respectively.

CONCLUSION: Fetal death from intrahepatic cholestasis of pregnancy can be abrupt and not reliably predicted by the characteristics of the fetal heart rate tracing.

(Obstet Gynecol 2009;113:528–31)

Intrahepatic cholestasis of pregnancy is a liver disease unique to pregnancy characterized by pruritus and elevations in total serum bile acids, abnormalities in liver function tests, or both. Intrahepatic cholestasis of pregnancy is associated with adverse obstetric outcomes such as preterm birth, meconium passage, and fetal death. The mechanism of fetal death associated with intrahepatic cholestasis of pregnancy is unknown. Several lines of evidence suggest that it must be a sudden event: 1) newborn examination usually is reported to show a normal appearance and growth, 2) the amniotic fluid volume, although often meconium-stained, is usually of normal volume, 3) death has been reported to occur within a few days or hours of normal antepartum testing. The purpose of this report is to add to our understanding of the events surrounding fetal compromise associated with intrahepatic cholestasis of pregnancy by describing a case of sudden death and a case of near death associated with cholestasis of pregnancy.

CASE 1

The patient was a 29-year-old woman (gravida 1 para 0) with a pregnancy at 33 5/7 weeks of gestation. At 32 weeks of gestation, she had developed intense pruritus and had a total serum bile acid concentration of 79 µmol/dL, and an aspartate aminotransferase (AST) and alanine aminotransferase (ALT) returned 62 U/liter and 91 U/liter, respectively. She was diagnosed with intrahepatic cholestasis of pregnancy and, in light of her elevated total serum bile acid concentration, the decision was made to administer corticosteroids for fetal lung maturity in anticipation of possible preterm delivery. The patient was admitted to the labor and delivery unit at a local community hospital and was placed on a fetal heart rate monitor. The mother’s pulse rate on admission was 86 beats per minute (bpm). Initially, the fetal heart rate had a baseline of 130 bpm with accelerations and no decelerations (Fig. 1A). Approximately 8 hours after admission, there was a sudden, prolonged deceleration, with the fetal heart decreasing to 80–90 bpm (Fig. 1B–E). The nature of the deceleration was not appreciated for approximately 35 minutes. Ten minutes later, bedside ultrasound confirmed fetal bradycardia. Emergency cesarean delivery was performed. Approximately 13 minutes after confirmation of the fetal bradycardia, a male fetus was delivered weighing 2,465 g with Apgar scores of 0 and 0 at 1 and 5 minutes, respectively. Thick meconium was noted at the time of delivery. According to the delivering physician, the placenta appeared grossly normal with no suspicion of abruption; placental pathology results could not be located. The fetus appeared normal, but the mother declined autopsy.

CASE 2

The second patient was a 20-year-old woman (gravida 2, para 0, 1, 0, 1) diagnosed with intrahepatic cholestasis of pregnancy at 29 weeks of gestation. She denied any significant past medical or surgical history. Her total serum bile acid concentration was 36 µmol/dL. Her liver transaminases returned AST of 37 U/liter and ALT of 54 U/L. With ursodeoxycholic acid, the total serum bile acid concentration decreased to 13 µmol/dL, and at 31 weeks the AST and ALT were 52 U/L and 71 U/L, respectively. Twice-weekly modified biophysical profiles were started at 32 weeks of gestation. One week before her delivery, she had a reactive nonstress test with a baseline heart rate of 150 bpm with moderate variability and no decelerations. At 34 weeks of gestation, the patient presented to the labor and delivery unit at a local community hospital complaining of uterine contractions. The fetal heart rate baseline was 170 with minimal variability and no accelerations (Fig. 2). Within 5 minutes, there was a prolonged deceleration with recovery (Fig. 2A). The attending physician was notified by phone.

From the University of Southern California, Los Angeles, California.

Corresponding author: Richard H. Lee, MD, LAC+USC Women’s and Children’s Hospital, 1240 N. Mission Road, Room 5K-40, Los Angeles, CA 90033; e-mail: richarhl@usc.edu.

Financial Disclosure

The authors did not report any potential conflicts of interest.

© 2009 by The American College of Obstetricians and Gynecologists. Published by Lippincott Williams & Wilkins.

ISSN: 0029-7844/09
about this initial fetal heart rate deceleration and its recovery. Approximately 38 minutes later, a second prolonged deceleration occurred (Fig. 2C). The physician arrived 9 minutes afterward and proceeded with cesarean delivery. A female neonate was delivered (Fig. 2E), weighing 2,095 g. The time from the initiation of the second prolonged heart rate deceleration to time of delivery of the fetus was 20 minutes. Thick meconium was noted at the time of amniotomy. The
newborn was intubated at 4 minutes of life and resuscitated by the emergency room physician until the neonatologist arrived. A femoral pulse was detected after 10 minutes. Apgar scores were 0, 0, and 5 at 1, 5, and 10 minutes, respectively. No epinephrine was required. There was no initial fetal cord gas analysis; however, the infant’s initial umbilical arterial blood gas after intubation revealed a pH 7.19, paCO₂ 32 mm Hg, paO₂ 251 mm Hg, bicarbonate 12 mmol/L, and base deficit –16 mmol/L. The newborn was extubated inadvertently at 20 minutes of life and noted to have spontaneous respiratory effort, but she required supplemental oxygen by nasal cannula for 3 days. The placenta weighed 391 g and appeared grossly normal; microscopic examination revealed mild chorioamnionitis and mild acute funisitis. Blood cultures of the newborn were negative. Head ultrasound showed no intracranial hemorrhage, and an electroencephalogram was normal. The newborn was discharged on day 21 of life in good condition.

At this time, the child is approximately 1 year old, and no neurodevelopmental or physical disability has been detected.

**COMMENT**

A PubMed search of articles written or translated to English from 1970 to July 2008 using the search terms “cholestasis, pregnancy, fetal, heart, tracing, monitoring” yielded no articles that have shown an actual electronic fetal heart rate tracing of a sudden fetal death associated with intrahepatic cholestasis of pregnancy. The mechanism by which intrahepatic cholestasis of pregnancy causes fetal death is not known. In isolated rat cardiac myocytes, exposure to the bile acid taurocholate has been shown to affect cardiac contractility directly.4,5 Others have shown that the
bile acid cholate induces human chorionic vein constriction, which possibly could lead to an abrupt reduction in oxygenated blood flow to the fetus.6

These studies presume that bile acids are the cause of fetal death, but the evidence is conflicting. Glantz et al found an association between bile acid concentration and meconium passage and asphyxial events and have suggested that early delivery to prevent fetal complications is not needed if the bile acid concentration is less than 40 μmol/dL.7 Case 2, reported here, and another previously reported case suggest that fetal death can occur with total bile acid concentrations much lower than 40 μmol/dL.8 This report supports the concept that factors other than serum bile acids are responsible for fetal compromise in intrahepatic cholestasis of pregnancy.

The cases described here, especially the first case, reinforce the concept that antepartum testing cannot be relied on to predict fetal loss in intrahepatic cholestasis of pregnancy.2 In case 1, sudden death occurred in the context of a completely normal fetal heart rate tracing, an extremely rare event. Although the diminished variability in case 2 could be consistent with a chronic process, the prompt recovery of the newborn suggests that the insult was not longstanding. The modified biophysical profile had been entirely normal 1 week before. The false-negative rate of the modified biophysical profile has been reported to be 0.8 per 1,000, with a false-positive rate of 1.5%, leading to preterm delivery in those tested before term.9 Because fetal deaths in intrahepatic cholestasis of pregnancy tend to cluster later in pregnancy, premature delivery, often around 37 weeks of gestation, has been advocated as a means of avoiding fetal death.10

Although intrahepatic cholestasis of pregnancy is believed to be the primary cause of fetal death in case 1, we admit that we cannot completely exclude other potential causes of fetal death that were not fully evaluated, such as antiphospholipid syndrome and massive fetal–maternal hemorrhage. Although abruption is associated with the highest risk of intrapartum fetal death, case 1 demonstrated no clinical signs or symptoms of placental abruption and case 2 had no documented evidence of abruption.11

Despite the abrupt nature of the prolonged decelerations seen in these two cases, it is still our practice to institute nonstress testing on making the diagnosis of intrahepatic cholestasis of pregnancy or at 34 weeks of gestation, whichever is later. We base our practice on hopes that fetal heart decelerations or prolonged decelerations such as the ones depicted in these two cases might be detected—leading to intervention and delivery of a viable fetus. The optimal frequency of testing has yet to be determined.

In summary, these two cases demonstrate that in utero fetal death from intrahepatic cholestasis of pregnancy can be abrupt in nature and cannot be predicted reliably from reactive nonstress tests.

REFERENCES