Intrahepatic cholestasis of pregnancy: Perinatal outcome associated with expectant management

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OBJECTIVE: Our goal was to compare the pregnancy outcomes of patients with intrahepatic cholestasis of pregnancy managed expectantly with antepartum testing with those of other patients who were followed up with a similar testing scheme.

STUDY DESIGN: Cases of intrahepatic cholestasis of pregnancy monitored with antepartum testing at our institution over a 7-year period were reviewed. Their pregnancy outcomes were compared with those of control patients followed up with the same testing scheme for a history of stillbirth. Both groups had at least weekly nonstress tests and amniotic fluid assessment until spontaneous labor or delivery for standard obstetric indications.

RESULTS: Seventy-nine patients were analyzed in each group. The two groups did not differ with respect to the mean gestational age at delivery (38.5 vs 38.8 weeks), birth weight (3216 vs 3277 gm) or incidence of preterm delivery (14% vs 7.6%). Abnormal antepartum testing prompting delivery was more common in the control group (25% vs 7.6%, $p < 0.05$). The risk of meconium passage was higher in the cholestasis group (44.3% vs 7.6%, $p < 0.05$). Two antepartum fetal deaths occurred in the cholestasis group at 36 to 37 weeks' gestation within 5 days of normal results of antepartum testing. Thick meconium and appropriate birth weight were noted in both infants. No gross anomalies were found in either infant.

CONCLUSION: Intrahepatic cholestasis of pregnancy is associated with adverse perinatal outcome not predicted by conventional fetal surveillance. (Am J Obstet Gynecol 1996;175:957-60.)

Key words: Cholestasis, antepartum testing, meconium

Intrahepatic cholestasis of pregnancy is the most common liver disorder that is unique to pregnancy, and it is second only to viral hepatitis as a cause of jaundice during pregnancy.[1, 2] It is characterized by severe pruritus and mild jaundice. Generalized pruritus usually develops after 30 weeks' gestation, becomes progressively severe to term, and is relieved within days after delivery.[3]

The incidence of this disorder appears to vary considerably between geographic areas. In Scandinavia, it is estimated that 1% to 3% of all pregnancies are complicated by this condition in some form.[4] The syndrome is also common in Chile where the incidence ranges from 12% to 22% with overt clinical jaundice in 2.4% to 5.5% of all pregnancies.[5] In North America and other parts of the world the condition is much less common.[6, 7]

Although the symptoms of intrahepatic cholestasis of pregnancy can be severe and incapacitating, there are few if any sequelae for the mother. A prolonged prothrombin time and an increased incidence of biliary tract disease in association with formation of cholesterol gallstones may be seen.[8, 9] In the fetus, however, the course is not as benign. The disease has been related to a high incidence of perinatal complications, including an increased perinatal mortality rate (107/1000) and a higher incidence of meconium passage (45%), abnormal intrapartum fetal heart rate patterns (22%), and preterm delivery (44%).[8, 10]

Fisk and Storey[10] proposed that intensive fetal surveillance, including amniocentesis to detect meconium, and induction of labor at term or when fetal lung maturity is achieved, may reduce the stillbirth rate in such pregnancies. Other authors[11] reported a perinatal mortality rate comparable to that of the general population when patients with cholestasis of pregnancy were managed with antepartum testing and timed intervention. It has not been shown that acceptable perinatal outcome can be achieved in pregnancies complicated by intrahepatic cholestasis when managed expectantly with antepartum testing.

Therefore the goal of this study was to compare the perinatal outcome of pregnancies complicated by intrahepatic cholestasis managed expectantly with antepar-

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Presented at the Sixteenth Annual Meeting of the Society of Perinatal Obstetricians, Kamuela, Hawaii, February 4-10, 1996.
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0002-9378/96 $5.00 + 0 6/6/75294

Table I. Pregnancy outcomes in patients with cholestasis and control patients

Parameter	*Cholestasis (n = 79)*	*Control (n = 79)*
Indication for delivery		
Abnormal antepartum testing	6 (7.6%)	20 (25%)*
Abnormal NST result	2†	6
Low amniotic fluid index (<5)	4	14*
Spontaneous labor	60	37
Maternal indications	10	15
Others	3	7
Mode of delivery		
Vaginal	63 (80%)	59 (75%)
Abdominal	16 (20%)	20 (25%)
Perinatal outcome		
Gestational age at delivery (wk)	38.5 ± 1.9	38.8 ± 1.7
Intrapartum fetal distress	6 (7.6%)	1 (1.3%)
Preterm delivery (<37 wk)	11 (14%)	6 (7.6%)
Birth weight (gm)	3216 ± 472	3277 ± 586
Small-for-gestational-age infant	6 (7.6%)	3 (3.8%)
Meconium passage	35 (44.3%)	6 (7.6%)*
Meconium aspiration syndrome	3	0
Apgar score <7 at 1 min	0	0
Neonatal death	0	0
Stillbirth	2	0

Data are presented as number, number and percent, or mean ± SD.
*$p < 0.05$.
†Prolonged bradycardia necessitating an immediate operative delivery.

tum testing with those of a group of pregnant women at an increased risk of abnormal perinatal outcome undergoing the same management protocol.

Material and methods

We reviewed the medical records of all patients who underwent antepartum testing for intrahepatic cholestasis of pregnancy at Los Angeles County/University of Southern California Medical Center over a 7-year period (1988 through 1995). The diagnosis of intrahepatic cholestasis of pregnancy was based on the presence of generalized pruritus in the absence of other skin or medical conditions that could produce pruritus. When suspected, viral hepatitis and obstructive gallstones were excluded with appropriate tests. Patients with other conditions associated with adverse perinatal outcomes when antepartum testing started were excluded from the study.

A group of patients who underwent antepartum testing for a history of unexplained fetal death were used as controls. Both groups underwent the same antepartum testing scheme until delivery. The testing scheme included a nonstress test (NST) at least weekly and an amniotic fluid volume assessment with the four-quadrant amniotic fluid index.[12] Antepartum testing started at 34 weeks' gestation or at the time of diagnosis in patients who were first seen later than 34 weeks' gestation. Both groups were followed up until spontaneous onset of labor. Pregnancy was interrupted at 42 weeks' gestation or when antepartum testing became nonreassuring (nonreactive NST or amniotic fluid index <5 cm). Other pregnancy complications were managed in accordance with standard obstetric care.

We noted the incidence of abnormal results of antepartum testing prompting delivery, gestational age at delivery, passage of meconium, intrapartum fetal distress, and mode of delivery. We also noted Apgar scores at 1 and 5 minutes, birth weight, and the presence of meconium aspiration syndrome in the neonates. Intrapartum fetal distress was defined as fetal bradycardia, severe variable decelerations, or persistent late decelerations.

Statistical tests used were Student's t test and χ^2 test where appropriate. A p value <0.05 was considered statistically significant.

Results

During the study period 79 patients underwent antepartum testing for intrahepatic cholestasis of pregnancy, and management was undertaken as described. Seventy-nine consecutive patients who underwent antepartum testing for a history of unexplained fetal death were used as a control group. There was no significant difference between the two groups in maternal age; however, the control patients had higher parity because none was primigravid. Labor induction was more common in control patients than in the cholestasis patients (42% vs 19%, $p < 0.05$). Indications for delivery and pregnancy outcomes are summarized in Table I.

The incidence of abnormal results of antepartum testing prompting delivery was higher in the control group than in the cholestasis patients (25% vs 7.6%, $p < 0.05$). However, most of the abnormalities in antepartum testing were caused by a low amniotic fluid index rather than a nonreactive NST in both groups. Two of the cholestasis patients had episodes of prolonged fetal bradycardia during nonstress testing that prompted an immediate operative delivery. Although the incidence of abnormal an-

tepartum testing was higher in the control group, cholestasis patients had a higher but not statistically significant risk of intrapartum fetal distress requiring operative delivery (7.6% vs 1.3%, $p = 0.12$).

Meconium passage occurred more frequently in the cholestasis patients (44.3% vs 7.6%, $p < 0.05$). Meconium aspiration syndrome requiring prolonged intensive care developed in three infants in the cholestasis group.

Two stillbirths were observed in the cholestasis group. Both occurred at 36 to 37 week's gestation within 3 and 5 days of a normal antepartum test result. Although autopsies were not performed, both infants appeared grossly normal at delivery with appropriate weights for gestational age and normal placentas. Thick meconium was identified at delivery in both cases.

Comment

The role of antepartum testing in the management of pregnancies complicated by intrahepatic cholestasis of pregnancy is unclear. We used antepartum testing in the management of such patients, but it did not successfully predict fetal compromise, as shown by two intrauterine fetal deaths within 5 days of a normal nonstress test result. The two fetal deaths observed in the cholestasis group correspond to a perinatal mortality rate of 25 per 1000. Because of the limited number of cholestasis patients undergoing antepartum testing, it is difficult to draw firm conclusions. Nevertheless, the perinatal mortality rate after a normal antepartum test result observed among pregnancies complicated by intrahepatic cholestasis in this study is significantly higher than the 0.8 per 1000 rate reported from our institution with the same antepartum testing scheme used for all indications.[13] The two fetal deaths and the two cases of unremitting fetal bradycardia identified during antepartum testing in the cholestasis patients are worrisome. These findings raise questions about the reliability of the current antepartum testing schemes in the expectant management of cholestasis.

The causes of the stillbirths in cholestasis of pregnancy are unknown. The absence of intrauterine growth restriction among stillbirths in our study and previously published studies combined with the evidence of an acute anoxic insult in those infants who underwent autopsies does not support chronic uteroplacental insufficiency as the likely cause of fetal death.[10] Additionally, studies of placental intervillous perfusion and umbilical circulation have not shown a significant difference between cholestasis patients and controls.[14, 15] In vitro studies have shown that meconium can cause umbilical vein constriction.[16, 17] Such constriction may cause an acute reduction in the umbilical blood flow leading to fetal hypoxia and death. Two of our patients had prolonged episodes of fetal bradycardia without recovery during a nonstress test necessitating an immediate operative delivery. Thick meconium was identified at delivery in both cases. Such episodes of fetal bradycardia may have been caused by an acute interruption of umbilical blood flow.

The observed high incidence of meconium staining in the amniotic fluid is consistent with the findings of other investigators.[10, 11] The mechanism of meconium passage in cholestasis of pregnancy is not understood. Although bile acids stimulate colonic motility in fetal sheep,[18] in humans meconium passage was not found to correlate with high values of bile acids in maternal serum, umbilical cord serum, or amniotic fluid.[19]

Although some investigators used bile acid measurements in the diagnosis of cholestasis,[20] we made the diagnosis in our patients on a clinical basis only. The role of bile acid measurements in the diagnosis of cholestasis of pregnancy is unclear. Lunez et al.[6] have measured bile acids in pregnant women. Only 48% of patients with elevated bile acid levels and 20% of those who had normal bile acid levels had pruritus. Additionally, other investigators demonstrated poor correlation between bile acid levels and adverse pregnancy outcomes.[19]

In contrast to previous reports our study did not show a significant increase in preterm deliveries among cholestasis patients.

In summary, the most likely explanation for fetal death in pregnancies complicated by intrahepatic cholestasis is an acute anoxic event rather than chronic uteroplacental insufficiency. Such an event may not be predicted by conventional antepartum testing. Delivery of the infant when maturity is confirmed may minimize the risk of stillbirth.

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