OBSTETRICS

Bile acids in a multicenter, population-based case-control study of stillbirth

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OBJECTIVE: We sought to compare bile acids in women with and without stillbirth in a population-based study.

STUDY DESIGN: The Stillbirth Collaborative Research Network conducted a multisite, population-based case-control study of stillbirth (fetal deaths ≥20 weeks). Maternal sera were obtained at the time of enrollment and frozen at −80°C until assay for bile acids.

RESULTS: Assays were performed in 581 women with stillbirth and 1546 women with live births. Bile acid levels were slightly higher in women with stillbirth (geometric mean [95% confidence interval {CI}] = 3.2 [3.0−3.5]) compared to live births (2.9 [2.7−3.1], P = .0327). However, the difference was not significant after adjustment for baseline risk factors for stillbirth. The proportion of women with elevated levels (≥10 or ≥40 μmol/L) was similar in stillbirths and live births. Results were similar when the analysis was limited to subsets of stillbirths and live births. In women with stillbirths not associated with fetal anomalies or obstetric complications bile acid levels were higher than in women with term live births (geometric mean [95% CI] = 3.4 [3.0−3.8] vs 2.9 [2.7−3.0], P = .0152, unadjusted; P = .06, adjusted). However, a similar proportion of women in both groups had levels ≥10 μmol/L (10.7 vs 7.2%; odds ratio [OR], 1.54; 95% CI, 0.97−2.44; adjusted OR, 1.29; 95% CI, 0.78−2.15) and ≥40 μmol/L (1.7 vs 0.7%; OR, 2.58; 95% CI, 0.85−7.84; adjusted OR, 2.28; 95% CI, 0.79−6.56).

CONCLUSION: Our data do not support testing for bile acids in cases of stillbirth in the absence of clinical evidence of intrahepatic cholestasis of pregnancy.

Key words: bile acids, cholestasis, stillbirth

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Intrahepatic cholestasis of pregnancy (ICP) has been associated with an increased risk of stillbirth.[1-5] Indeed, the risk of stillbirth in women with expectantly managed ICP has been estimated as 2-11%.[1-5] In addition to stillbirth, ICP has been linked to other adverse perinatal outcomes such as spontaneous preterm birth, meconium-stained amniotic fluid and aspiration, and abnormal fetal heart rate tracings.[1-5]

The pathophysiology of fetal death associated with ICP is unknown. It is not thought to be due to placental insufficiency since most fetuses are appropriately grown for gestational age and stillbirth may occur despite normal

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antenatal testing.[3,6,7] Possible mechanisms include bile acid–induced cardiac arrhythmias and impaired contractility[8] and chorionic vein constriction.[9] The critical threshold of maternal serum bile acids that increases the odds of stillbirth is unclear. Although some investigators believe the risk is low if bile acids are <40 umol/L,[10] stillbirths have been reported in cases with lower levels of bile acids.[6,7]

Since a clear threshold for bile acid levels and stillbirth has not been established and since elevated levels of bile acids have been reported in asymptomatic individuals,[11] we hypothesized that elevated levels of bile acids are associated with stillbirth. Also, the association between maternal serum bile acids and stillbirth has not been systematically assessed. Thus, our objective was to compare maternal levels of bile acids in women with and without stillbirth in a large, population-based, racially and ethnically diverse cohort.

Materials and Methods

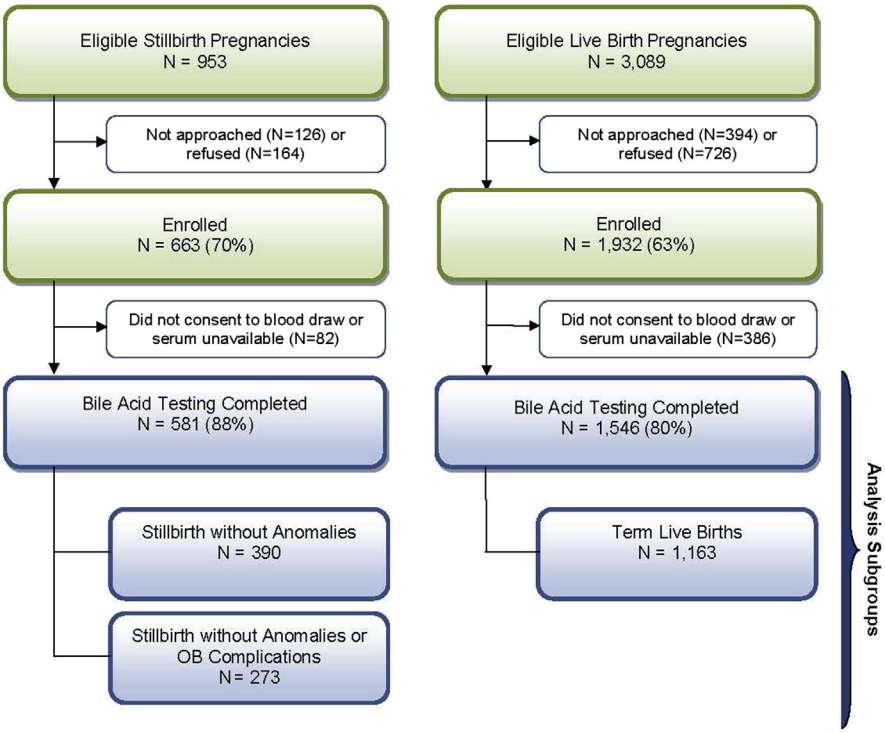
The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Stillbirth Collaborative Research Network (SCRN) conducted a population-based case-control study of stillbirth, with participant enrollment at the time of delivery from March 2006 through September 2008. The study design and methods have been described in detail.[12] The study was approved by the institutional review board of each clinical site and the data-coordinating center. An advisory board reviewed the progress and safety of the study. All participants gave written informed consent.

A stillborn fetus was defined by Apgar scores of 0 at 1 and 5 minutes, and no signs of life by direct observation. Deliveries resulting from the termination of a live fetus were excluded. Residents of a SCRN catchment area were eligible for participation. Catchment areas were defined by state and county boundaries and included portions of 5 states: Rhode Island, Massachusetts, Georgia, Texas, and Utah. Daily surveillance and enrollment occurred at 59 tertiary care and community hospitals servicing the catchment areas. These hospitals deliver >80,000 infants per year.[12] Attempts were made to enroll all stillbirths and a representative sample of live births with oversampling of preterm births and non-Hispanic black women to ensure adequate numbers for stratified analyses.[12]

Study components included a comprehensive standardized fetal postmortem examination and uniform placental pathology evaluation performed by a perinatal pathologist in both stillbirths and live births.[13,14] A standardized maternal interview during the delivery hospitalization and detailed chart abstraction of prenatal office visits, antepartum hospitalizations, and the delivery hospitalization was performed. Biospecimens collected included maternal blood for serum and DNA, fetal blood from the umbilical cord (when available), placental samples, and fetal tissue (in cases). Maternal serum was stored at −80°C for 2-5 years prior to assay.

Gestational age was determined by the best clinical estimate. Multiple sources were utilized including assisted reproduction with documentation of the day of ovulation or embryo transfer, first day of the last menstrual period, and obstetrical sonograms.[15] Fetal deaths at 18 or 19 weeks and without good dating were included in the study to ensure inclusion of all possible eligible stillbirths.[12]

FIGURE
Study enrollment and inclusion in cholestasis analysis



This analysis compares bile acid testing results from stillbirth and live birth pregnancies. Pregnancy was categorized as stillbirth pregnancy if there were any stillbirths delivered and as live birth pregnancy if all live births were delivered. Fetal death was defined by Apgar scores of 0 at 1 and 5 minutes and no signs of life by direct observation. Fetal deaths were classified as stillbirths if best clinical estimate of gestational age at death was ≥20 weeks. Fetal deaths at 18 and 19 weeks without good dating were also included as stillbirths. Analysis includes comparison of: all stillbirths to all live births; all stillbirths to term live births; nonanomalous stillbirths to term live births; and nonanomalous stillbirths without obstetric (OB) complications to term live births.

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