OBSTETRICS

The risk of infant and fetal death by each additional week of expectant management in intrahepatic cholestasis of pregnancy by gestational age

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OBJECTIVE: The objective of the study was to characterize the risk of infant and fetal death by each additional week of expectant management vs immediate delivery in pregnancies complicated by cholestasis.

STUDY DESIGN: This was a retrospective cohort study of 1,604,386 singleton, nonanomalous pregnancies of women between 34 and 40 weeks' gestation with and without intrahepatic cholestasis of pregnancy (ICP) in the state of California during the years of 2005-2008. *International Classification of Diseases*, 9th version, codes and linked hospital discharge and vital statistics data were utilized. For each week of gestation, the following outcomes were assessed: the risk of stillbirth, the risk of delivery (represented by the risk of infant death at a given week of gestation), and the composite risk of expectant management for 1 additional week. Composite risk combines the risk of stillbirth at this gestational age week plus the risk of infant death if delivered at the subsequent week of gestation.

RESULTS: Among women with ICP, the mortality risk of delivery is lower than the risk of expectant management at 36 weeks' gestation (4.7 vs 19.2 per 10,000). The risk of expectant management remains higher than delivery and continues to rise by week of gestation beyond 36 weeks. The risk of expectant management in women with ICP reaches a nadir at 35 weeks (9.1 per 10,000; 95% confidence interval, 1.4—16.9) and rises at 36 weeks (19.2 per 10,000; 95% confidence interval, 7.6—30.8).

CONCLUSION: Among women with ICP, delivery at 36 weeks' gestation would reduce the perinatal mortality risk as compared with expectant management. For later diagnoses, this would also be true at gestational ages beyond 36 weeks. Timing of delivery must take into account both the reduction in stillbirth risk balanced with the morbidities associated with preterm delivery.

Key words: expectant management, intrahepatic cholestasis of pregnancy, stillbirth

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Intrahepatic cholestasis of pregnancy (ICP) is characterized by pruritus, elevated bile acid, and liver enzyme levels. ICP is predominantly observed in the third trimester of pregnancy and has been associated with increased fetal morbidity and mortality but resolves postpartum with no known long-term maternal morbidity. The incidence of ICP has been reported between 0.2% and 2%. However, higher figures are reported in particular Scandinavian and South American populations, such as Chile where the incidence has been reported to be as high as 15.6%.[1-5] A prevalence of 5.6% of ICP has been reported in a Los Angeles population that was primarily Latina.[6]

Adverse fetal outcomes associated with ICP reported in literature include spontaneous and iatrogenic preterm birth, fetal distress, respiratory distress syndrome, meconium staining, neonatal intensive care unit admission, and stillbirth.[4,7-10] Fetal mortality is reported up to 1.5-7% but as high as 20% in some studies.[8-9,11]

Recently it has been hypothesized that the risk of stillbirth may correlate with higher bile acid levels.[9,12-14] However,

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numerous retrospective studies and case reports describe the unpredictable nature of antepartum fetal deaths in pregnancies complicated by ICP after 36 weeks' gestation.[10,15] To date, there are no proven antenatal monitoring methods that are predictive or preventive of stillbirth in ICP.[5,15] However, there is little evidence regarding the neonatal or infant mortality and no examination of the optimal time for delivery that considers the trade-off between delivery at a particular week of gestation vs expectant management for another week.

Given this background, we sought to ascertain the prospective risk of stillbirth and risk of infant death at each week of gestation. We then sought to ascertain the optimal gestational age that would minimize the risk of overall perinatal mortality.

Materials and Methods

This is a retrospective cohort study of 1,604,386 pregnancies of women between 34 and 40 weeks' gestation in the state of California during the years of 2005-2008. *International Classification of Diseases*, 9th version (ICD-9), codes were used to identify 5545 pregnancies complicated by ICP. Our control group consisted of pregnant women without ICP at the same gestational week. Both groups excluded multiple gestations and congenital anomalies to avoid confounders. Approval from the institutional review boards at Oregon Health and Science University and the state of California was obtained.

The data used for outcome analysis were obtained from the California Vital Statistics Birth Certificate Data, California Patient Discharge Data, Vital Statistics Death Certificate Data, and Vital Statistics Fetal Death File.[16] These data are part of the public record and deidentified; therefore, informed consent was not required. The state of California maintains linked maternal and infant data sets, starting 9 months prior to delivery and up to 1 year after delivery. The data sets also include infant birth records and all hospital admissions up to 1 year of life. A unique record linkage number is assigned to the mother-infant pair by the California Office of Statewide Health Planning and Development Healthcare Information Resource Center under the state of California.

For each week of gestation, the following outcomes were assessed for both the ICP and control subjects: the risk of stillbirth defined as fetal demise at or after 20 weeks' gestation, the risk delivery represented by the risk of infant death following delivery at a given week of gestation, and the composite mortality risk of expectant management for 1 additional week.

The risk of stillbirth was calculated by dividing the number of stillbirths that occurred at a particular week of gestation by the number of ongoing pregnancies at that particular gestation. Composite mortality risk of expectant management was calculated by combining the risk of stillbirth at a given gestational age week plus the risk of infant death if delivery occurs at the subsequent week of gestation per 10,000 fetuses at risk.

χ^2 tests were used for statistical analysis. A value of $P < .05$ was considered statistically significant. The data are also presented as odds ratios (ORs) with 95% confidence intervals (CIs) with an assumption of statistical significance if the 95% CI did not contain 1.

Results

Of 1,604,386 singleton pregnancies without congenital anomalies, 5545 pregnancies in the cohort were complicated by ICP with a calculated incidence of 0.35%. Women with ICP were more likely to be Hispanic or Asian, older, and have other comorbidities such as chronic hypertension, diabetes, and gestational diabetes (Table 1).

The risk of stillbirth was higher in women with ICP than in our control group at each gestational age between 34 and 40 weeks compared with our control group (overall this was 63.8 vs 21.2 per 10,000; $P < .001$) with a peak at 40 weeks' gestation. The increased risk of stillbirth remains statistically significant in ICP between 32 and 40 weeks' gestational age (OR, 2.17; $P = .004$), even when controlling for confounders including race, maternal age, chronic hypertension, diabetes, gestational diabetes, nulliparous status, and limited prenatal care.

The risk of delivery represented by the risk of infant death is lowest at 36 weeks and increased thereafter in women with ICP. In contrast, in women without ICP, the risk of delivery reaches a nadir at 39 weeks (9.8 per 10,000; 95% CI, 9.3−10.3) before beginning to rise again (Table 2).

Among women with ICP, the risk of delivery is lower than the risk of expectant management at 36 weeks' gestation (4.7 per 10,000 [95% CI, 0.0−10.5] vs 19.2 per 10,000 [95% CI, 7.6−30.8]). After 36 weeks' gestation, the risk of expectant management remains higher than delivery and continues to rise at each week of gestation thereafter (Figure).

When the same comparison was made in the control group, the rate of mortality was lower in the expectant management group at 37 weeks and earlier, no different at 38 weeks, and greater in the expectant management group at 39 weeks of gestation (Table 3).

Comment

In our large cohort of women with ICP in pregnancy, we found that the risk of fetal, neonatal, or infant mortality was minimized by delivery at 36 weeks of gestation for those diagnosed at 36 weeks or earlier. Immediate delivery continued to minimize perinatal mortality beyond 36 weeks' gestation as well. Thus, from a mortality consideration, the ideal delivery timing for pregnancies complicated by ICP is at 36 weeks' gestation. However, it may be that the perinatal morbidity at 36 weeks' gestation outweighs the mortality risk of expectant management.

Given that the risk of hyaline membrane disease and need for intubation is about 1% higher at 36 weeks than 37 weeks and that the mortality difference of delivery 1 week earlier was approximately 1 per 1,000, 10 neonates would be intubated to prevent 1 mortality. If the neonatal intensive care unit admission rate is 8% higher, then it would be 80 admissions to prevent 1 mortality.[17] It is beyond the scope of the current study to either evaluate the trade-off between these outcomes or the cost-effectiveness of immediate delivery at 36 weeks' gestation, but certainly these trade-offs appear to favor