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

TABLE 1
Characteristics of women with and without ICP between 34 and 40 weeks' gestation

Characteristics	ICP (n = 5545)		Control (n = 1,598,841)		
	n	%	n	%	*P* value
Ethnicity					< .001
White	1261	21.2	499,457	27.0	
African American	120	2.0	90,495	4.9	
Hispanic	3448	58.1	1,005,661	54.4	
Asian	1027	17.3	218,416	11.8	
Other	80	1.4	34,890	1.9	
Nulliparous	2376	40.1	734,283	39.7	.556
Chronic hypertension	86	1.5	18,824	1.0	.001
Diabetes	97	1.6	12,980	0.7	< .001
Gestational diabetes	652	11.0	116,583	6.3	< .001
Maternal age >35 y	1256	21.2	315,916	17.1	< .001
Maternal age <20 y	327	5.5	173,480	9.4	< .001
Public insurance	2900	48.9	890,568	48.1	.251
Education >12 y	2891	46.0	808,940	45.0	.114
Limited prenatal care (<5 prenatal visits)	221	3.5	63,558	3.5	.915

ICP, intrahepatic cholestasis of pregnancy.

Puljic. Perinatal mortality risk associated with expectant management in intrahepatic cholestasis of pregnancy. Am J Obstet Gynecol 2015.

immediate delivery. In a recent decision analysis, indeed, delivery at 36 weeks was found to be the optimal strategy.[18]

There has been recent debate in the literature about whether ICP actually connotes an increased risk of stillbirth.[14] Certainly in our modern cohort, we found an increased risk of stillbirth in a group of women being cared for in California. The exact pathogenesis of ICP is still poorly understood, specifically what causes the fetal mortality.

Proposed hypotheses and animal data suggest that increased bile acids play a role in worse fetal outcomes by increased oxytocin bioaction, oxidative stress in the placenta, impairing fetal cardiomyocyte function, and even increasing colonic motility, which may explain why ICP is an independent risk factor for meconium staining of amniotic fluid irrespective of gestational age.[19-21] A recent study of women with ICP confirmed that bile acids indeed crossed the placenta and were potentially causally related to adverse fetal outcomes because maternal bile acid levels were positively associated with measured umbilical cord bile acid levels at delivery.[14]

The only proven method to prevent fetal mortality in ICP is delivery because antenatal testing alone does not clearly reduce the risk of stillbirth in women with ICP.[22] Fortunately, a recent study demonstrated that early-term labor induction for ICP does not lead to an increased risk of cesarean deliveries.[23]

Additionally, there are no studies to date evaluating whether symptomatic relief of pruritus or normalization of bile

TABLE 2
Risk of stillbirth and infant death in women with and without ICP

Variable	Stillbirth per 10,000 ongoing pregnancies (95% CI)		Infant death per 10,000 live births (95% CI)	
GA, wks	ICP	Control	ICP	Control
34	2.3 (0.0–6.2)	1.7 (1.5–1.9)	22.2 (10.2–34.2)	42.1 (41.1–43.0)
35	4.4 (0.0–9.9)	1.9 (1.7–2.1)	26.9 (13.5–40.3)	27.1 (26.4–27.9)
36	6.8 (0.0–13.8)	2.1 (1.9–2.3)	4.7 (0.0–10.5)	22.9 (22.2–23.6)
37	8.0 (0.0–16.0)	2.3 (2.1–2.5)	12.3 (2.4–22.3)	18.0 (17.3–18.6)
38	4.7 (0.0–11.9)	3.2 (2.9–3.5)	13.7 (1.5–26.0)	11.8 (11.3–12.3)
39	11.1 (0.0–25.1)	4.2 (3.8–4.5)	18.3 (0.5–36.2)	9.8 (9.3–10.3)
40	26.5 (0.0–56.5)	5.8 (5.2–6.4)	22.5 (0.0–50.2)	10.4 (9.8–11.0)

CI, confidence interval; *GA*, gestational age; *ICP*, intrahepatic cholestasis of pregnancy.

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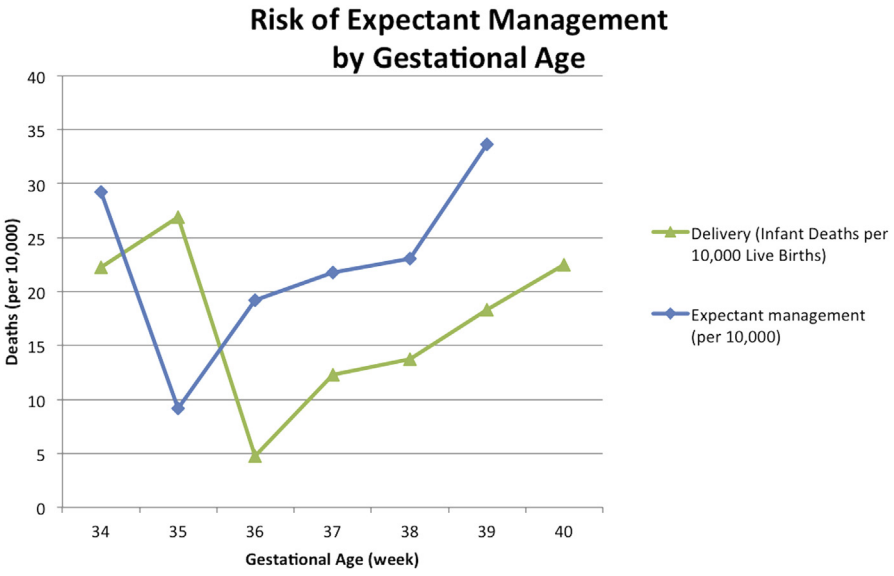
FIGURE
Risk of delivery vs expectant management



Risk of delivery (infant death) vs expectant management for 1 week by gestational age in women with ICP is shown.

ICP, intrahepatic cholestasis of pregnancy.

Puljic. Perinatal mortality risk associated with expectant management in intrahepatic cholestasis of pregnancy. Am J Obstet Gynecol 2015.

acid or liver enzymes reduces the risk of stillbirth associated with ICP. Patients should be counseled on the unpredictable nature of fetal and infant mortality associated with ICP in the setting of expectant management past 36 weeks and that this outcome cannot be foreseen by conventional antenatal surveillance and symptomatic reduction.[10] Given this known risk, some providers have chosen to induce women with ICP prior to 37 weeks of gestation because iatrogenic preterm deliveries in women with ICP have been reported up to 17% of the time.[9]

One important issue with ICP is the challenges of making a rapid diagnosis. In most clinical settings, it may take several days to obtain the bile acid levels that are commonly used to make the diagnosis. However, if a woman presents at 37 weeks' gestation with extreme pruritus, particularly of the palms and soles, or if she has elevated transaminases in such a setting, management with presumed ICP seems reasonable. In one study, the authors used a pruritus scale and if the woman reported a score of 8 or higher (on a scale of 1-10), the positive predictive value for ICP was greater than 50%.[6] In such a setting, even with delayed bile acid laboratory results, one must consider the active management approach rather than expectant management, given the increased risk of fetal mortality. The UK Royal College of Obstetricians and Gynecologists has existing guidelines that recommend making a diagnoses based on typical pruritus and abnormal liver function tests with the resolution of symptoms after delivery, even without the availability of bile acid results.[24]

TABLE 3
Risk of perinatal mortality associated with delivery vs expectant management stratified by GA in women with and without ICP

Variable	ICP (n = 5545)		Control (n = 1,598,841)	
GA, wks	Infant death per 10,000 live births (95% CI)	Risk of expectant management per 10,000 (95% CI)[a]	Infant death per 10,000 live births (95% CI)	Risk of expectant management per 10,000 (95% CI)[a]
34	22.2 (10.2–34.2)	29.2 (15.5–43.0)	42.1 (41.1–43.0)	28.8 (28.0–29.6)
35	26.9 (13.5–40.3)	9.1 (1.4–16.9)	27.1 (26.4–27.9)	24.7 (24.0–25.5)
36	4.7 (0.0–10.5)	19.2 (7.6–30.8)	22.9 (22.2–23.6)	20.0 (19.4–20.7)
37	12.3 (2.4–22.3)	21.7 (8.5–35.0)	18.0 (17.3–18.6)	14.1 (13.5–14.6)
38	13.7 (1.5–26.0)	23.1 (7.2–38.9)	11.8 (11.3–12.3)	13.1 (12.5–13.6)
39	18.3 (0.5–36.2)	33.6 (9.5–57.8)	9.8 (9.3–10.3)	14.6 (13.9–15.3)
40	22.5 (0.0–50.2)	25.18 (0.0–54.51)	10.4 (9.8–11.0)	5.83 (5.25–6.40)

CI, confidence interval; *GA*, gestational age; *ICP*, intrahepatic cholestasis of pregnancy.

[a] Composite risk is the risk of stillbirth at this gestational age (weeks) plus the risk of infant death following delivery at the subsequent gestational age (weeks).

Puljic. Perinatal mortality risk associated with expectant management in intrahepatic cholestasis of pregnancy. Am J Obstet Gynecol 2015.

Although the current study provides evidence from a large cohort regarding both prospective risk of stillbirth and the optimal time of delivery, there are limitations. To obtain such a large cohort, administrative data were utilized and diagnoses were confirmed with ICD-9 codes. In general, women with such codes likely have the diseases noted, but undercoding can be a problem. For instance, our ICP group consists of 5545 cases (0.3%) among 1,604,386 pregnancies in California. The reported prevalence of ICP in the literature is noted to be 0.2-2% and even 5.6% in a primarily Latina population in Los Angeles. Thus, we expected to have a number of cases between 3208 and 89,845. Such misclassification bias would lead to only an underestimation of the effect difference between women with ICP and the control subjects.

Given that the optimal time of delivery was examined only in women with a diagnosis of ICP, the risk of misclassification bias is very low in that cohort alone. As a retrospective study, there is also concern of accuracy of outcome diagnoses. However, we used actual death certificates, as opposed to ICD-9 codes for both stillbirth and infant mortality, which have been shown to be accurate and are unlikely to be false-positive results.

Additionally, our study subjects did not have specific metrics assessing the severity or timing of disease such as the bile acid or transaminase levels. It may be that large future studies may be able to delineate different risks of stillbirth based on such levels.

Finally, despite the fact that these cases were drawn from a population of more than 1.5 million births, when examining stillbirth and infant death rates by week, the numbers were relatively small in each week, making our estimates more prone to the instability seen in smaller studies.

Despite these potential limitations, our study of the composite fetal and infant death risk in pregnancies complicated by ICP demonstrated that the risk of mortality was minimized by delivery at 36 weeks of gestation or immediate delivery in those women diagnosed beyond that gestation, and therefore, preterm delivery at this gestational age may be optimal. Although a randomized control trial would be best to confirm the outcomes and safety of delivery at 36 weeks' gestation as compared with 37 weeks of gestation or beyond, it seems unlikely that an adequately powered trial is forthcoming. Until then, these data can help clinicians counsel patients and guide clinical decision making. ■

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