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Perinatal outcomes of intrahepatic cholestasis of pregnancy in twin versus singleton pregnancies: is plurality associated with adverse outcomes?

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Abstract

Purpose To determine the rate of obstetric and neonatal complications associated with intrahepatic cholestasis of pregnancy in twin versus singleton gestations.

Methods A retrospective cohort study including patients diagnosed with intrahepatic cholestasis of pregnancy at a single tertiary center between 2011 and 2016. Women were allocated into two groups: twin pregnancies ($n=56$) and singleton pregnancies ($n=186$). Obstetric and neonatal outcomes were compared between the two groups.

Results Intrahepatic cholestasis of pregnancy was diagnosed earlier in gestation in twin compared to singleton pregnancies (33.1 ± 2.8 vs. 35.1 ± 3.0 weeks, respectively; adjusted $P<0.001$). Maternal serum levels of fasting total bile acids were significantly higher in twin pregnancies compared to singletons [27 (IQR 16–44) vs. 16 (IQR 10–26) μmol/L, respectively; $P=0.01$]. None of the pregnancies in our cohort was complicated by fetal death. Apgar score at 5 min and umbilical artery and vein PH at delivery were comparable between the two groups.

Conclusions Intrahepatic cholestasis of pregnancy in twin pregnancies appears to be more severe compared to singletons, as reflected by an earlier presentation and higher levels of maternal serum total bile acids. Large prospective studies are required to customize a management strategy specific for women with twin pregnancies and intrahepatic cholestasis of pregnancy.

Keywords Aminotransferase · Bile acid · Intrahepatic cholestasis of pregnancy · Pruritus · Twins

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is characterized by pruritus, elevated levels of serum bile acids and aminotransferases. Intrahepatic cholestasis of pregnancy typically develops from the late second trimester of pregnancy and resolves quickly after delivery. Prevalence ranges from 0.05 to 27.6%, depending on ethnicity and geographical location [1–5]. The etiology of ICP is yet to be resolved, but genetic, environmental and hormonal factors, including estrogen and progesterone, probably have a roll [1, 6–9]. Pruritus is the key clinical finding of ICP, involving primarily the palms and soles and deteriorating at night. Laboratory abnormalities typically include elevated serum bile acids in above 90% of cases [8, 10, 11] and elevated serum aminotransferases in 60% of cases [8].

Intrahepatic cholestasis of pregnancy in singleton pregnancies is associated with perinatal complications including spontaneous preterm birth (30–40%) [1, 2, 8, 12, 13], meconium-stained amniotic fluid (MSAF) (16–58%) [1, 12, 14], neonatal respiratory distress syndrome (RDS) (28.6%) [1, 15, 16], and most critically, sudden fetal death, with the highest risk after 37 weeks gestation [13, 17, 18]. Intrahepatic cholestasis of pregnancy is also associated with other pregnancy-related diseases including preeclampsia [2, 19, 20] and gestational diabetes mellitus (GDM) [2, 19, 21]. The pathophysiologic mechanisms underlying the perinatal complications in ICP are unclear but seem to be related to high levels of maternal bile acids [13, 18, 19, 21–23].

The common practice regarding pregnancies with ICP is active management, which includes medical treatment, close surveillance, and induction of birth at 37 weeks of gestation

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[2, 23–25]. Since the employment of active management policies, the rate of stillbirth has been reduced to 3.5% or less [1, 8, 12, 18, 26].

The prevalence of ICP is higher among twin pregnancies (20–22%), which may be explained by elevated levels of progesterone and estrogen in twins [1, 12, 21, 27]. However, the data in the literature regarding ICP in twins are limited. Moreover, while the management of singleton pregnancies with ICP is well established, there are no guidelines for the management of twin pregnancies complicated by ICP.

The purpose of our study was to comprehensively compare between twin and singleton pregnancies with ICP and to determine the rate of obstetric and neonatal complications associated with ICP in twins versus singleton pregnancies. Our presumptive hypothesis was that plurality is associated with worse perinatal outcomes.

Methods

A retrospective cohort study including all women diagnosed with ICP between 2011 and 2016 at a single tertiary referral perinatal center with a high incidence of high-risk pregnancies. The prevalence of ICP in Israel is 0.25%, with a higher prevalence in twin pregnancies. Exclusion criteria included pregnancies complicated by fetal chromosomal or anatomical abnormalities and monochorionic twins with twin-to-twin transfusion syndrome or selective intrauterine growth restriction.

Women were allocated into study and control groups which comprised of women with twin and singleton pregnancies complicated by ICP, respectively. ICP cases were identified in the hospital discharge database by the tenth International Classification of Diseases (ICD-10) code: 026.6. Data were abstracted from the obstetrical and neonatal computerized medical records and each case was examined thoroughly. Maternal demographic characteristics, obstetric and perinatal outcomes were compared between the two groups. The ethics committee of Sheba medical center approved this study and waived informed consent.

The diagnosis of ICP was made in the presence of pruritus accompanied by elevated levels of fasting total bile acids (TBA) > 10 μmol/L and/or elevated levels of aminotransferases (AST > 40 IU/L or ALT > 45 IU/L), in the absence of other diseases that may cause similar symptoms and laboratory abnormalities. Severe ICP was defined as elevated serum TBA ≥ 40 μmol/L [13].

During the study period, pregnancies with ICP were managed in our center actively with similar management for twin and singleton pregnancies. Women diagnosed with ICP before 37 weeks of gestation received ursodeoxycholic acid (UDCA) at a starting dose of 900 mg a day and were hospitalized in the high-risk pregnancy ward under close surveillance. The inpatient follow-up included vital signs recording three times a day, fetal non-stress test three times a day, daily biophysical profile (BPP), serum aminotransferases levels twice a week and fasting serum TBA level once a week. Induction of labor was performed at 37 + 0 weeks of gestation. In cases of escalating clinical symptoms and/or laboratory abnormalities despite UDCA treatment, the dosage of UDCA was gradually raised until the maximal level of 1500 mg a day. In the occurrence of persistently elevated levels of TBA ≥ 40 despite maximal UDCA treatment, earlier induction of labor was considered.

Neonates with a birthweight below the 10th percentile for gestational age were defined as small for gestational age (SGA), and those with a birthweight above the 90th percentile were defined as large for gestational age (LGA). Birthweight percentiles were calculated according to the Israeli birthweight curves [28].

Obstetric and neonatal outcomes between twin and singleton pregnancies with ICP were compared. Univariate comparisons involving continuous variables were conducted using a *T* test or non-parametric Mann–Whitney test as appropriate. The Chi squared test was employed to compare categorical variables. Multivariate analysis and calculation of various measures of effect size included generalized linear models for continuous variables and binary logistic regressions for categorical (binary) outcome variables. Multivariate analysis was used to evaluate the relationship between the type of pregnancy (twins vs. singleton) and perinatal outcome measures. Adjustments were conducted for maternal age, pregestational body mass index (BMI) and parity. A P value of < 0.05 was considered statistically significant. Statistical analysis was performed using both SPSS 23 and SAS 9.4.

Results

During the study period 57,375 patients delivered in our medical center. 242 women were diagnosed with ICP (56 twin pregnancies and 186 singletons), with an overall prevalence of ICP in our medical center of 0.4% (2.1% in twins vs. 0.3% in singletons). Pruritus was present in 96% of twin pregnancies and 99% of singleton pregnancies with ICP.

The demographic characteristics of women with twin and singleton pregnancies with ICP are presented in Table 1. There was no difference between the two groups regarding maternal age, pregestational BMI, gravidity, and parity. As expected, the prevalence of in vitro fertilization (IVF) was significantly higher in twin compared to singleton pregnancies with ICP (41.8% vs. 9.8%, respectively, $P < 0.001$). The

Table 1 Demographic characteristics of ICP patients with twin and singleton pregnancies

Variable	Twin pregnancies ($N=56$)	Singleton pregnancies ($N=186$)	P value
Maternal age (years)	33.0 ± 6.9	32.07 ± 5.6	0.34
Pregestational BMI (kg/m^2)	21.7 (19.5–24.5)	22.0 (20.3–24.7)	0.32
Gravidity	2 (1–3)	2 (1–3.25)	0.11
Parity	1 (1–2)	2 (1–3)	0.01
Primiparous	24 (42.9)	54 (29)	0.07
IVF	23 (41.8)	18 (9.8)	< 0.001

Data are presented as mean ± SD, median (interquartile range) and *n* (%)

ICP intrahepatic cholestasis of pregnancy, *IVF* in vitro fertilization, *BMI* body mass index

twins group comprised of 52 dichorionic diamniotic twins and 4 monochorionic diamniotic twins.

Table 2 exhibits the clinical and laboratory characteristics of ICP in twin and singleton pregnancies. Adjustments were employed for maternal age, pregestational BMI and parity. The mean gestational week at the onset of symptoms was significantly earlier for twin compared to singleton pregnancies (32.2 ± 3.2 vs. 34.2 ± 3.3 weeks, respectively, adjusted $P < 0.001$), as well as the gestational age at diagnosis (33.1 ± 2.8 vs. 35.1 ± 3.0 weeks, respectively, adjusted $P < 0.001$). The maternal maximal serum level of fasting TBA was significantly higher in twin pregnancies compared to singletons [27 (IQR 16–44) vs. 16 (IQR 10–26) μmol/L, respectively, $P = 0.01$]. Moreover, severe ICP (fasting TBA ≥ 40 μmol/L) was significantly more common in twins compared to singletons (35.5% vs. 16.9%, respectively, $P = 0.04$). However, following adjustment, the difference did not remain significant (adjusted odds ratio 3.12; 95% CI 0.97–10.03, $P = 0.05$). In contrast, maternal maximal serum levels of aminotransferases were not significantly different between the two groups. Moreover, there was no difference regarding the maximal dosage of UDCA used between the two groups.

Table 3 displays the obstetric outcomes in twin and singleton pregnancies with ICP. As could be expected, women with twin pregnancies delivered earlier compared to singletons [35.4 ± 1.7 vs. 37.5 ± 1.2 weeks, respectively, adjusted $P < 0.001$). In both groups, most of the deliveries were iatrogenic and specifically due to ICP (55.4% in twins vs. 82.7% in singletons, adjusted odds ratio 0.21; 95% CI 0.09–0.52, adjusted $P = 0.001$). Iatrogenic preterm birth due to ICP was significantly more common among twins compared to singletons for both preterm birth < 37 weeks and < 35 weeks. However, following adjustment, these differences did not remain significant.

None of the pregnancies in our cohort was complicated by fetal death. In addition, the rates of preeclampsia, GDM and MSAF did not differ significantly between the two groups.

The neonatal outcomes of twin and singleton pregnancies with ICP are presented in Table 4. Odds ratios were adjusted for the confounders mentioned above plus the gestational week at delivery. The mean neonatal birth weight was significantly lower in twins compared to singleton pregnancies (2222 ± 396 vs. 3003 ± 441 g, respectively, adjusted $P < 0.001$), but the rate of SGA neonates was similar among both groups. After adjustment for the variables mentioned above, none of the neonatal outcome measures

Table 2 Clinical and laboratory characteristics of ICP patients in twin and singleton pregnancies

Variable	Twin pregnancies ($N=56$)	Singleton pregnancies ($N=186$)	P value	Adjusted P value*
Gestational week at onset of symptoms	32.23 ± 3.24	34.2 ± 3.26	< 0.001	< 0.001
Gestational week at diagnosis of ICP	33.12 ± 2.80	35.10 ± 3.05	< 0.001	< 0.001
Maximal level of fasting TBA (μmol/L)	27 (16–44)	16 (10–26)	0.01	–
Fasting TBA ≥ 40 (μmol/L)	11/31 (35.5%)	10/59 (16.9%)	0.04	0.05
Maximal level of AST—IU/L	72 (52.5–114.5)	80 (51–134)	0.56	0.72
Maximal level of ALT—IU/L	85 (51.5–180)	120 (62.5–210.75)	0.13	0.56
Gestational week at starting UDCA	33.45 (32.35–35.50)	34.45 (32.32–35.50)	< 0.001	0.02
Maximal Dosage of UDCA—mg	900 (750–1000)	900 (750–1000)	0.4	–

Data are presented as mean ± SD, median (interquartile range), *n* (%) and *n*/*N* (%)

TBA total bile acids, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *UDCA* ursodeoxycholic acid

*P value was adjusted for maternal age, body mass index (BMI) and parity

Table 3 Obstetric outcomes of twin and singleton pregnancies with ICP

Variable	Twin pregnancies ($N=56$)	Singleton pregnancies ($N=186$)	Odds ratio (95% CI)	*P* value	Adjusted odds ratio (95% CI)*	Adjusted *P* value*
Gestational week at delivery	35.36 ± 1.67	37.48 ± 1.24	–	< 0.001	–	< 0.001
Preterm birth < 37 weeks	44 (78.6%)	35 (18.8%)	15.87 (7.57–33.33)	< 0.001	10.98 (4.40–27.02)	< 0.001
Spontaneous	18 (32.1%)	5 (2.7%)	17.14 (5.99–49.03)	< 0.001	35.36 (7.73–161.71)	< 0.001
Iatrogenic	26 (46.4%)	30 (16.1%)	4.50 (2.34–8.67)	< 0.001	2.55 (1.05–6.20)	0.03
Due to ICP	20 (35.7%)	25 (13.5%)	3.55 (1.78–7.09)	< 0.001	2.10 (0.82–5.38)	0.12
Preterm birth < 35 weeks	18 (32.1%)	4 (2.2%)	21.73 (6.89–66.66)	< 0.001	35.71 (6.66–20)	< 0.001
Spontaneous	11 (19.6%)	0	–	< 0.001	–	–
Iatrogenic	7 (12.5%)	4 (2.2%)	6.5 (1.82–23.10)	0.004	7.65 (0.97–57.24)	0.05
Due to ICP	6 (10.7%)	3 (1.6%)	7.32 (1.77–36.30)	0.006	7.65 (0.97–57.24)	0.05
MSAF	2 (3.6%)	29 (15.6%)	0.2 (0.04–0.86)	0.03	0.82 (0.15–4.34)	0.81
Fetal death	0	0	–	–	–	–
Gestational diabetes mellitus	16 (28.6%)	23 (12.4%)	2.83 (1.37–5.84)	0.005	1.93 (0.71–5.23)	0.19
Preeclampsia	5 (8.9%)	8 (4.3%)	2.17 (0.67–6.9)	0.19	2.31 (0.34–15.62)	0.39
LSCS	47 (83.9%)	48 (25.8%)	14.92 (6.84–33.33)	< 0.001	10 (3.8 to 26.31)	< 0.001

Data are presented as mean ± SD and *n* (%)

MSAF meconium staining of the amniotic fluid, *LSCS* low section cesarean section

*Odds ratio and *P* value were adjusted for maternal age, body mass index (BMI) and parity. The odds ratio and *P* value for meconium staining of the amniotic fluid (MSAF) was also adjusted for gestational week at delivery

Table 4 Neonatal outcomes of twin and singleton pregnancies with ICP

Variable	Twin pregnancies ($N=56$)	Singleton pregnancies ($N=186$)	Odds ratio (95% CI)	*P* value	Adjusted odds ratio (95% CI)*	Adjusted *P* value*
Birth weight (g)	2222 ± 396	3003 ± 441	–	< 0.001	–	< 0.001
Small for gestational age	11 (9.82%)	8 (4.3%)	2.42 (0.94–6.21)	0.06	0.85 (0.18–3.84)	0.83
Large for gestational age	5 (4.46%)	11 (5.91%)	0.74 (0.25–2.19)	0.59	2.12 (0.04–9.70)	0.33
5-min Apgar score < 7	0	1 (0.53%)	–	–	–	–
Umbilical artery PH	7.25 ± 0.06	7.25 ± 0.11	–	0.78	–	0.05
Umbilical vein PH	7.28 ± 0.07	7.27 ± 0.15	–	0.98	–	0.16
Respiratory distress syndrome	4 (3.57%)	1 (0.53%)	6.84 (0.75–62.5)	0.08	1.86 (0.09–38.46)	0.68
Intraventricular hemorrhage	1 (0.53%)	0	–	–	–	–
Mechanical ventilation	3 (2.67%)	2 (1.07%)	2.53 (0.41–15.38)	0.31	2.43 (0.21–27.77)	0.47
Necrotizing enterocolitis	0	0	–	–	–	–
Sepsis	0	0	–	–	–	–
Jaundice requiring phototherapy	12 (10.71%)	25 (13.44%)	0.77 (0.37–1.60)	0.49	0.26 (0.06–1.04)	0.05
Hypoglycemia	32 (28.82%)	1 (11.29%)	3.18 (1.72–5.88)	< 0.001	2.09 (0.79–5.52)	0.13
Neonatal intensive care unit admission	37 (33.03%)	4 (2.15%)	22.22 (7.75–66.66)	< 0.001	0.53 (0.06–4.62)	0.56
Neonatal death	0	0	–	–	–	–

Data are presented as mean ± SD and *n* (%)

*Odds ratio and *P* value were adjusted for maternal age, body mass index (BMI), parity and gestational week at delivery

were significantly different between the two groups, including NICU admission, RDS, necrotizing enterocolitis, sepsis, intraventricular hemorrhage, and hypoglycemia. None of the pregnancies in either group was complicated by neonatal death.

Discussion

Main findings

In this large single-center retrospective cohort study, we demonstrated that ICP was presented and diagnosed earlier in gestation in twins compared to singleton pregnancies. Moreover, women with twin pregnancies had significantly higher serum levels of fasting TBA compared to singletons, and consequently, severe ICP was more common among twin compared to singleton pregnancies. In addition, there was a trend towards a higher rate of iatrogenic preterm birth due to ICP among twins compared to singletons, indicting ICP as an additional factor contributing to the higher rate of preterm birth in twin versus singleton gestations. However, both groups were similar with regards to neonatal outcomes.

Interpretation

Our findings of earlier onset of symptoms and diagnosis of ICP in twin pregnancies compared to singletons are aligned with previous studies [13, 21], whereas a smaller study of 13 twin pregnancies with ICP showed that the gestational age at onset of symptom was similar in twins versus singleton pregnancies with ICP [27]. The contradictory findings may be attributed to differences in sample size.

As far as we know, this is the first study demonstrating significantly higher serum bile acid levels in twins compared to singleton pregnancies with ICP. There are accumulating data indicating that the high levels of maternal serum bile acids play a pivotal role in the perinatal complications associated with ICP, with recent studies showing a positive correlation between TBA levels and the frequency and severity of perinatal complications [13, 18, 19, 21–23]. A prospective cohort study from Sweden showed that there was a 1–2% increased risk of spontaneous preterm delivery, asphyxial events, and MSAF with every 1 µmol/L increase in fasting maternal serum bile acids ≥ 40 µmol/L [18]. Another large prospective cohort study of severe ICP showed that the risks of preterm delivery, MSAF and stillbirth rose with increasing levels of maternal serum bile acids [13]. Brouwers et al. recently showed that every 10 µmol/L increase in serum bile acid concentrations increased the probability of certain fetal complications [22]. Over the years several pathophysiologic mechanisms have been suggested to explain the perinatal complications associated with ICP, all are thought to be mediated via the high levels of maternal serum bile acids. It was found that bile acids increase myometrial contractility as well as response and expression of myometrial oxytocin receptors, which may explain the increased incidence of spontaneous preterm labor in ICP pregnancies [29–31]. MSAF may be explained by an increase in colonic motility or by fetal distress and subsequent meconium passage secondary to bile acids [1, 32]. Bile acid aspiration or accumulation within the fetal circulation is thought to be responsible for the increased incidence of RDS seen in association with ICP [1, 15, 16]. The pathophysiology of fetal death in ICP is yet to be resolved, and there are currently two leading theories: a sudden development of fetal arrhythmia [33] versus vasospasm of the placental chorionic surface vessels [34], both thought to be induced by high levels of bile acids.

Our findings that ICP in twin pregnancies presents earlier and is characterized by higher serum TBA levels suggest that the disease is more severe in twins and consequently the risk of fetal death may be increased compared to singletons. However, none of the pregnancies in our cohort was complicated by fetal death. Therefore, no conclusion could be reached regarding the incidence and timing of fetal death among the two groups. This could be partly explained by the active management of pregnancies with ICP, which is the common practice in our medical center and is reflected by the high percentage of iatrogenic preterm birth due to ICP, especially in twin gestations. The primary question arising from these data is whether women with twin pregnancies and ICP should be delivered earlier compared to singletons? Early iatrogenic preterm delivery could potentially decrease the risk of fetal death on the one hand, but increases the risk associated with late prematurity on the other hand. Liu et al. showed an increased risk of stillbirth of 3.9% among twin pregnancies with ICP, and that stillbirth in twins with ICP occurred at 33–35 weeks of gestation compared to 36–38 weeks among singletons, suggesting that earlier scheduled delivery should be considered in these women [21]. Nevertheless, the optimal time of delivery of women with twin pregnancies and ICP is yet to be determined in large prospective studies.

Strengths and limitations

The strengths of this study include meticulous data collection from medical records, detailed pregnancy follow-up, including comprehensive data on serum TBA levels, and being a single-center study applying the same diagnostic criteria and management protocol of ICP for all participants.

The primary limitation of the study is its retrospective design, which limits the ability to control for potential confounders. To minimize the effect of bias, the comparisons were adjusted for potential confounders including maternal age, pre-pregnancy BMI, parity and gestational week

at delivery. As twin pregnancies are associated with earlier delivery, lower birth weight percentiles and a higher rate of perinatal complications compared to singletons, the primary challenge of the study was to isolate the additive effect of ICP on the perinatal outcomes in twins. Consequently, the major outcome measures of the study were chosen to reflect specifically ICP severity (gestational age at diagnosis, maximal level of maternal serum TBA and iatrogenic preterm birth due to ICP). Twin pregnancies are usually followed more closely than singletons, which could theoretically contribute to the earlier diagnosis of ICP but cannot explain the higher level of maternal serum TBA. Our study included 52 dichorionic diamniotic twins and 4 monochorionic diamniotic twins. Owing to the small number of monochorionic diamniotic twins, we were not able to conclude about the role of chorionicity in ICP.

Conclusions

ICP in twin pregnancies appears to be more severe compared to singletons, as reflected by earlier onset of symptoms and diagnosis, and higher levels of maternal serum TBA. Accordingly, women with twin pregnancy and ICP warrant increased surveillance for adverse perinatal outcomes, including consideration of earlier hospitalization and earlier delivery at 35–36 depending on severity of the disease. Large prospective studies are required to customize a management strategy specific for women with twin pregnancy and ICP and to determine the optimal time of delivery for these women.

Author contributions LB: data collection and management, data analysis, manuscript writing, and editing. KZ: data collection. AK: data collection. MB: data collection. SMT: project development and manuscript editing. YY: project development, data analysis, and manuscript editing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights statement This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent The study was approved by the ethics committee of Sheba medical center, which waived informed consent.

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