Perinatal outcomes in intrahepatic cholestasis of pregnancy with monochorionic diamniotic twin pregnancy

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Abstract

Background: The primary aim of the study is to investigate the perinatal outcomes in intrahepatic cholestasis of pregnancy (ICP) with monochorionic diamniotic (MCDA) twin pregnancy.

Methods: This study is a retrospective observational study for women with ICP and MCDA twin pregnancy. Included cases were divided into mild ICP group (10–39 mmol/L) and severe ICP group (≥40 mmol/L), whose perinatal outcomes were compared between this two groups and whose predictors of adverse perinatal outcomes were evaluated.

Results: 37 cases and 21 cases are in mild and severe ICP group respectively, of which, the incidence of gestational diabetes mellitus (GDM) and iatrogenic preterm delivery in severe ICP group are higher than those in mild ICP group. Gestational age (GA) at diagnosis of ICP < 32 weeks is an independent risk factor for GA at delivery < 35 weeks and for composite adverse neonatal outcome. Total bile acids (TBA) > 40 mmol/l is an independent risk factor for meconium-stained amniotic fluid.

Conclusion: For women with ICP and MCDA twin pregnancy, GA at diagnosis of ICP < 32 weeks and TBA > 40umol/L are associated with adverse perinatal outcomes.

Keywords: Intrahepatic cholestasis of pregnancy, Monochorionic diamniotic twin pregnancy, Perinatal outcomes, Total bile acids

Background

ICP is characterized by pruritus and rising TBA level [1, 2], which could result in preterm birth, respiratory distress syndrome (RDS) and stillbirth [3–6]. Its incidence in singleton pregnancy was 0.4–15% [7], while it is two times in twin pregnancy [3, 8–10]. Monochorionic diamniotic (MCDA) twin pregnancy is one of the major type, accounting 20–25% of twin pregnancy with continuously increasing incidence [3].

In previous literature, serum TBA level has been reported to be associated with meconium stained amniotic fluid, low Apgar scores, preterm delivery and stillbirth in singleton pregnancy. However, it turns out that no literatures regarding ICP and MCDA twin pregnancy are found. The role of TBA level in MCDA twin pregnancy is not ascertained. Furthermore, the role of other variables such as transaminases and history of cholelithiasis are confusing. Therefore, our study is designed to investigate the perinatal outcomes of patients with ICP and MCDA twin pregnancy and to identify the predictors of adverse perinatal outcomes, whose conclusions may be helpful for better clinical assessments and evaluations of prognosis of patients with ICP and MCDA twin pregnancy.

Methods

This is a retrospective observational study conducted in Chengdu’s women and children’s central hospital. Clinical data from Jan. 2013 to Jun. 2017 was extracted from electronic database after obtaining permission of accessing to clinical data and approval of Ethics Committee. Written consent for data to be used in scientific research was also acquired from patients before operation.
Results
There are 58,862 cases of pregnant women delivering babies in our hospital from Jan. 2013 to Jun. 2017, among which there were 1601 cases of twin pregnancy, 350 cases of ICP with twin pregnancy, and 64 cases of ICP with MCDA pregnancies. Three cases were excluded because of twin-twin transfusion syndrome, and other three cases were because of FGR. Finally, 37 cases and 21 cases were included respectively in mild ICP group and severe ICP in the final analysis, in all which, people delivered babies by caesarean section.

Continuous variables do not normally distribute except mean birth weight. There is no significant difference in baseline characteristics in terms of GA, primipara rate, IVF-ET rate and level of ALT, AST, ALP, albumin, TBIL, and DBIL between two groups (Table 1). The incidence of GDM and iatrogenic preterm delivery in severe ICP group are significantly higher than those in mild ICP group \( (P < 0.05) \). Although the rate of meconium-stained amniotic fluid is higher in severe ICP group than those in mild ICP group, the difference is not statistically significant. Other outcome measures are not dissimilar in both groups (Table 2). One case shows severe ICP and GDM suffered single fetal death in our study. In this case, one fetal was found dead at 31 + 4 gestational weeks, but cesarean section was performed at 31 + 5 weeks to be found with one alive neonate. Only 18 patients had complete course of blood test, among which, 17 patients’ TBA level had decreased on increasing. One case shows severe ICP and GDM suffered single fetal death in our study.

IBM SPSS Statistics for Windows, Version 19.0 is used for data analysis. Student’s T test or Mann-Whitney U test are used to assess continuous variables according to its distribution. \( \chi^2 \) analysis is utilized to assess categorical variables. Logistic regression analysis was performed to identify predictors of adverse perinatal outcomes. \( P < 0.05 \) indicates significant differences.

Table 1 Baseline characteristic of both groups

|                      | Mild ICP group | Severe ICP group | P    |
|----------------------|----------------|------------------|------|
| Mean maternal age(y,±SD) | 27.65 ± 4.61  | 27.29 ± 3.62     | 0.819|
| BMI                  | 22.8 ± 2.61   | 22.74 ± 3.38     | 0.744|
| Nulliparous          | 28(75.7%)     | 14(66.7%)        | 0.546|
| IVF-ET               | 5(13.5%)      | 1(4.8%)          | 0.402|
| GA at diagnosis< 32 weeks | 32.92 ± 2.51  | 31.8 ± 5.48      | 0.878|
| GA at diagnosis< 32 weeks | 12(32.4%)     | 8(38.1%)         | 0.776|
| ALT(U/L,±SD)         | 173.8 ± 162.1 | 217.9 ± 156.6    | 0.314|
| AST(U/L,±SD)         | 136.2 ± 128.8 | 144.7 ± 94.5     | 0.361|
| ALP(U/L,±SD)         | 352.3 ± 105.7 | 322 ± 125.1      | 0.304|
| Albumin(g/L,±SD)     | 31.1 ± 4.1    | 31.9 ± 3.7       | 0.476|
| TBIL(umol/L,±SD)     | 14.5 ± 7.3    | 19.4 ± 15.2      | 0.313|
| DBIL(umol/L,±SD)     | 8.1 ± 5.3     | 12.8 ± 13.8      | 0.418|
| TBA(umol/L,±SD)      | 204 ± 6.3     | 75.3 ± 33.8      | 0    |
| ICP history          | 1(2.7%)       | 0                | 1    |
The risk factors of major perinatal outcomes are as follows. DBIL level > 7 mmol/l, GDM and GA at diagnosis of ICP < 32 weeks are related with GA at delivery < 35 weeks in \( \chi^2 \) analysis, while GA at diagnosis of ICP is an independent risk factor in logistic regression analysis. TBA level > 40 umol/l is related with meconium stained amniotic fluid in both \( \chi^2 \) analysis and logistic regression analysis. DBIL level > 7 umol/l, GA at diagnosis < 32 weeks and ALP level > 400 U/L are associated with composite adverse neonatal outcomes in \( \chi^2 \) analysis, while GA at diagnosis of ICP < 32 weeks is an independent risk factor in logistic regression analysis (Tables 3, 4 and 5).

**Discussion**

Maximum TBA level was used to determine the severity of ICP in previous literature [3, 11–13]. Due to various impact of ICP on perinatal outcomes, composite adverse neonatal outcome was created and defined to evaluate

### Table 2

Maternal and neonatal outcomes of both groups

|                      | Mild ICP group(n,%) | Severe ICP group(n,%) | P       | OR               |
|----------------------|---------------------|-----------------------|---------|------------------|
| GDM                  | 5(13.5%)            | 8(38.1%)              | 0.049   | 3.938(1.084–14.307) |
| Pre-eclampsia        | 2(5.4%)             | 2(9.5%)               | 0.615   | 1.842(0.24–14.138) |
| Hypothyroidism       | 2(5.4%)             | 1(4.8%)               | 1       | 0.875(0.075–10.268) |
| placental abruption  | 1(2.7%)             | 0                     | 1       | 0.632(0.518–0.77) |
| PPROM                | 2(5.4%)             | 0                     | 0.53    | 0.625(0.51–0.766)  |
| postpartum hemorrhage| 2(5.4%)             | 0                     | 0.53    | 0.625(0.51–0.766)  |
| meconium stained amniotic fluid | 18.9% | 42.9% | 0.069 | 3.214(0.975–10.6) |
| GA at delivery (weeks,± SD) | 34.95,1.5 | 34.7,1.4 | 0.408 |
| spontaneous preterm delivery | 13(35.1%) | 4(19.1%) | 0.245 | 0.434(0.121–1.564) |
| iatrogenic preterm delivery | 20(54.1%) | 17(81%) | 0.05 | 3.613(1.018–12.822) |
| iatrogenic preterm delivery with GA < 35 weeks | 4(10.8%) | 6(28.6%) | 0.089 | 3.3(0.81–13.445) |
| Mean birth weight(g,± SD) | 2223.43±16.8 | 2177.13±96.6 | 0.628 |
| NICU                 | 25(67.6%)           | 13(61.9%)             | 0.776   | 0.78(0.255–2.385) |
| neonatal asphyxia    | 5(13.5%)            | 3(14.3%)              | 1       | 1.067(0.228–4.993) |
| aspiration syndrome  | 2(5.4%)             | 1(4.8%)               | 1       | 0.875(0.075–10.268) |
| neonatal respiratory distress syndrome | 2(5.4%) | 2(9.5%) | 0.615 | 1.842(0.24–14.138) |
| pneumonia            | 9(24.3%)            | 9(42.9%)              | 0.237   | 2.333(0.743–7.332) |
| respiratory failure  | 4(10.8%)            | 2(9.5%)               | 1       | 0.868(0.145–5.195) |
| hyperbilirubinemia   | 2(5.4%)             | 1(4.8%)               | 1       | 0.875(0.075–10.268) |
| hypoglycemia         | 3(8.1%)             | 0                     | 0.547   | 0.618(0.502–0.761) |
| ventilator-assisted breathing | 3(8.1%) | 3(14.3%) | 0.657 | 1.889(0.345–10.332) |
| tracheal intubation assisted breathing | 2(5.4%) | 2(9.5%) | 0.615 | 1.842(0.24–14.138) |
| encephalopathy       | 3(8.1%)             | 0                     | 0.547   | 0.618(0.502–0.761) |
| still-birth          | 2(5.4%)             | 1(4.8%)               | 1       | 0.87(0.075–10.268) |
| adverse composite neonatal outcome | 8(67.6%) | 13(61.9%) | 0.438 | 0.78(0.255–2.385) |

### Table 3

Predictors of GA at delivery< 35 weeks

| GA at delivery< 35 weeks | chi square value | P      | OR     | 95%CI lower | 95%CI upper |
|--------------------------|------------------|--------|--------|-------------|-------------|
| DBIL > 7 umol/l          | 7.917            | 0.01   | 5.385  | 1.587       | 18.264      |
| GDM                      | 5.429            | 0.043  | 4.4    | 1.201       | 16.114      |
| GA at diagnosis< 32 weeks| 22.182           | 0.000  | 19.800 | 4.973       | 78.837      |
| binary logistic analysis | B                | P      | adjusted OR\(^a\) | 95%CI lower | 95%CI upper |
| GA at diagnosis< 32 weeks| 2.917            | 0      | 18.48  | 4.611       | 74.068      |

\(^a\) means adjusted for age, nulliparous, IVF-ET, GA at diagnosis< 32 weeks, ALT> 200 U/L, AST > 200 U/L, ALP > 400 U/L, TBIL> 17.1 umol/l, DBIL> 7 umol/l, TBA > 40 umol/l
the perinatal outcomes of ICP [14, 15]. And our study drew on these methodologies. A large number of studies about single pregnancy had found that the higher TBA level exists, the higher rate of adverse perinatal outcomes [3, 11–13, 16]. The study of LIU Xiaohua [17] and SHAN Dan [18] about twin pregnancy also made similar conclusions. However, our study reveals that the major perinatal outcomes is similar between severe ICP group and mild ICP group, which is consistent with the studies of Gonzalez MC [10] and Andrea Y. Lausman [19]. The reason is probably that the rigorous monitoring, standardized treatment, and timely termination of pregnancy have reduced the harm of high TBA level on neonates. The rate of iatrogenic preterm birth in severe ICP group is higher than that in mild ICP group presenting in our study, which is consistent with the studies of SHAN Dan [18] and Maria C. Estiu [12].

SHAN Dan’s study concluded the incidence of GDM increased in twin pregnancy with ICP [18], while our study revealed the incidence of GDM in severe ICP group is higher than that in mild ICP group. The mechanism may be that bile acids could increase the expression of farnesoid receptors (FXR), and destroy homeostatic pathways for glucose balance system [20]. It was also found the rate of preeclampsia increased in ICP patients with twin pregnancy in previous studies [21]. However, the preeclampsia rate was not different between mild ICP group and severe ICP group in our study. But the sample size of preeclampsia in our study is too small (four cases) to make a conclusion.

According to SHAN Dan [18] and R. Madazli’s [22] studies, the rate of adverse perinatal outcomes would increase in patients with earlier ICP onset gestational age, which is also the same result found in our study. Therefore, more concerns should be given to these patients. Our study’s result is in keeping with previous literature, which makes the conclusion that higher TBA level leads to higher rate of meconium stained amniotic fluid [14]. The reason may be that elevated bile acids altered colonic motility [7]. Stillbirth with ICP and twin pregnancy usually occurs at 33–35 weeks [17], and stillbirth’s rate increases with higher TBA levels or combination with GDM or other complications [13, 23]. In our study, there was only one case shows dead fetal, in which severe ICP and GDM are suffered.

It was recommended that 36 weeks was the proper gestational age to terminate pregnancy in ICP patients with singleton pregnancy [24, 25]. However, there was no recommendation for twin pregnancy with ICP. In our study, the mean GA at delivery was 34.7 ± 1.4 weeks in severe ICP group, while 34.95 ± 1.5 weeks in mild ICP group, which may provide some suggestions about timing of delivery for these patients.

Advantages of our study are as follows. 1. Our study is one of the largest studies assessing MCDA twin pregnancy with ICP. 2. It only includes patients of MCDA twin pregnancy, avoiding bias of different chorionicity. 3. A wide variety of factors are included, leading to comprehensive conclusions. The major limitation of our study is that it is a retrospective and observational study. Some patients’ conditions were not fully documented. As a result, we could not evaluate outcomes based on change of blood test’s result. Furthermore, the concept of adverse composite

### Table 4 Predictors of meconium-stained amniotic fluid

|                        | chi square value | P     | OR     | 95%CI lower | 95%CI upper |
|------------------------|-----------------|-------|--------|-------------|-------------|
| TBA > 40 umol/l        | 3.843           | 0.069 | 3.214  | 0.975       | 10.6        |
| binary logistic analysis | B               | P     | adjusted OR<sup>b</sup> | 95%CI lower | 95%CI upper |
| TBA > 40 umol/l        | 1.322           | 0.035 | 3.75   | 1.095       | 12.842      |

<sup>b</sup> means adjusted for age, nulliparous, IVF-ET, GA at diagnosis< 32 weeks, ALT> 200 U/L, AST > 200 U/L, ALP > 400 U/L, TBIL> 17.1 umol/l, DBIL> 7 umol/l

### Table 5 Predictors of adverse composite neonatal outcome

|                        | chi square value | P     | OR     | 95%CI lower | 95%CI upper |
|------------------------|-----------------|-------|--------|-------------|-------------|
| DBIL> 7 umol/l         | 3.728           | 0.094 | 3.063  | 0.963       | 9.736       |
| GA at diagnosis< 32 weeks | 5.129         | 0.04  | 4.587  | 1.15        | 18.306      |
| ALP > 400 U/L          | 4.634           | 0.061 | 0.276  | 0.083       | 0.920       |
| binary logistic analysis | B               | P     | adjusted OR<sup>c</sup> | 95%CI lower | 95%CI upper |
| GA at diagnosis< 32 weeks | 1.463         | 0.039 | 4.317  | 1.076       | 17.318      |

<sup>c</sup> means adjusted for means adjusted for age, nulliparous, IVF-ET, GA at diagnosis< 32 weeks, ALT> 200, AST > 200, ALP > 400, TBIL> 17.1, DBIL> 7, TBA > 40 umol/l
neonatal outcome was drawn from previous studies but not the same. Therefore, comparison with other studies should be interpreted with caution.

**Conclusion**

GA at diagnosis of ICP < 32 weeks and TBA > 40umol/L are associated with adverse perinatal outcomes in our study. Further large prospective trials are required to identify the predictors of adverse neonatal outcomes and the optimal timing of delivery for patients with ICP and MCDA twin pregnancy.

**Abbreviations**

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; DBIL: Direct bilirubin; DCDA: Dichorionic diamniotic; FXR: Farnesoid receptors; GA: Gestational age; GDM: Gestational diabetes mellitus; ICP: Intrahepatic cholestasis of pregnancy; MCDA: Monochorionic monoamniotic; NICU: Neonatal intensive care unit; PPROM: Preterm premature rupture of membrane; TBA: Total bile acid; TBIL: Total bilirubin

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**Availability of data and materials**

The datasets analysed during the current study are available from the corresponding author on reasonable request.

**Authors’ contributions**

YWM drafted the manuscript and participated in data collection and analysis. YHL participated in the design of the study and performed the statistical analysis. DL conceived of the study, and participated in its design and coordination. LG and LH participated in data collection and analysis. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

The authors confirmed that approval of ethics committee of Chengdu women and children’s central hospital had obtained. Written Consent for data to be used in scientific research was also acquired from patients before operation.

**Consent for publication**

Not applicable.

**Competing interests**

All the authors declare that they have no competing interests.

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