THE JOURNAL OF
Obstetrics and Gynaecology Research

doi:10.1111/jog.13399 J. Obstet. Gynaecol. Res. Vol. 43, No. 9: 1411–1420, September 2017

Bile acid levels and risk of adverse perinatal outcomes in intrahepatic cholestasis of pregnancy: A meta-analysis

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Abstract

Aim: We aimed to determine the association between maternal total bile acid (TBA) levels and the risks of adverse perinatal outcomes in pregnant women with intrahepatic cholestasis of pregnancy (ICP) based on a meta-analysis study.

Methods: We searched PubMed for articles published from 2000 to 2015 with a focus on ICP and restriction to the English language. The main perinatal outcomes were preterm birth (PTB), meconium-stained amniotic fluid (MSAF), asphyxia, or respiratory distress syndrome (RDS). Relative risk (RR) with 95% confidence intervals (CI) was the summary statistic. We used a random- or fixed-effects model to calculate the pooled RR according to the heterogeneity test. Subgroup analyses were performed by region and study design.

Results: Nine eligible related citations fulfilled the inclusion criteria and were included in this study. Compared with pregnant women with a serum TBA < 40 μmol/L, severe ICP (TBA ≥ 40 μmol/L) was associated with a significantly increased risk of adverse fetal outcomes (pooled RR, 1.96; 95%CI, 1.63–2.35), PTB (pooled RR, 2.23; 95%CI, 1.51–3.29), MSAF (pooled RR, 2.27; 95%CI, 1.81–2.85), and asphyxia or RDS (pooled RR, 1.67; 95%CI, 1.18–2.36). Sensitivity analysis suggested that the study design difference may be a major source of heterogeneity. No publication bias was demonstrated by Begg's test ($P > 0.05$).

Conclusion: This meta-analysis indicates that maternal elevated bile acid levels are significantly associated with increased risks of overall adverse perinatal outcomes, PTB, MSAF, and asphyxia or RDS. Serum TBA levels seem to be a useful predictor for the risk of adverse perinatal outcomes.

Key words: bile acid, intrahepatic cholestasis of pregnancy, meta-analysis, perinatal outcomes.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy-specific liver disease, which mainly leads to increased perinatal mortality and is characterized by pruritus and elevated bile acid and transaminase levels.[1] The incidence of ICP has apparent geographic and racial differences, especially in Western Europe and North America, and some populations of Latin origin.[2] Generally, symptoms and laboratory abnormalities resolve spontaneously after delivery. It has been reported that there are several risk factors contributing to the development of ICP, such as a family history of ICP, chronic hepatobiliary diseases, assisted reproduction techniques, oral contraceptive use, and multiple gestation.[3–6] The adverse effects of ICP on the fetus include increased risks of preterm birth (PTB), meconium-stained amniotic fluid (MSAF), asphyxia or respiratory distress syndrome (RDS), neonatal intensive care unit (NICU) admission, and – in extreme cases – fetal distress and fetal death.[7] Therefore, the primary goal of the obstetrician is to evaluate the patient's condition based on clinical experience and auxiliary examination and determine the optimal time and method of delivery to obtain good perinatal outcomes.

A rise in serum bile acids is the most accurate laboratory diagnostic evidence of ICP. In 2004, Glantz *et al.*[8] reported that higher bile acid levels (especially

Received: August 31 2016.
Accepted: April 18 2017.
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>40 μmol/L) are associated with higher rates of adverse fetal outcomes. At present, there is general agreement that total bile acid (TBA) levels >10 μmol/L and <40 μmol/L are considered mild, while TBA levels ≥40 μmol/L are considered to represent severe disease. Recently, more studies have been published and have yielded different and controversial results. Several studies have reported a positive relation between elevated TBA levels and increased risk of perinatal fetal outcomes, suggesting that the maternal bile acid level is an important predictor of fetal risks.[9,10] Conversely, other studies have concluded that maternal clinical and laboratory features, including elevated TBA, do not appear to be significant predictors of fetal complications in gravidas with ICP.[11,12] A study by Oztas *et al.*[13] suggested that there is no association between TBA levels and preterm delivery. Indeed, there are undefined conclusions in this relation between TBA quantitative category levels and perinatal outcomes, such as PTB, MSAF, asphyxia, and RDS. Therefore, the present meta-analysis was conducted to obtain a better estimation of the relation between different TBA levels and fetal complications in gravidas with ICP.

Methods

Data collection

PubMed was searched from 2000 to December 2015 for English-language articles using the following keywords: 'intrahepatic cholestasis of pregnancy,' 'ICP,' and 'bile acid;' and 'adverse perinatal outcomes,' 'fetal outcomes,' and 'adverse pregnant outcomes.' All eligible articles and references were reviewed for further analysis.

Studies were limited to relevant articles concerning the association between maternal bile acid category levels and risk for adverse perinatal outcome, such as PTB, MSAF, asphyxia, and RDS, in pregnant women with ICP.

Inclusion criteria

Studies that met the following criteria were included: (i) an observational study, including cross-sectional, case–control, and cohort studies; (ii) maternal TBA as one of the exposure interests (the study must have included at least two TBA levels [mild ICP, 10.00–39.99 μmol/L; and severe ICP, ≥40 μmol/L]); (iii) all adverse fetal outcomes as outcomes of interest, mainly including PTB, MSAF, asphyxia, RDS, and low Apgar scores; and (iv) reported risk estimates with the corresponding 95% confidence intervals (CI), or sufficient data to calculate the 95%CI. Reviews, case reports, case analyses, multiple gestations, women with a history of liver or other disease, and non-human studies were excluded. The meta-analysis was carefully assessed and extracted from all eligible studies. Data retrieved from the studies included authors, country, study period, sample size (ICP or control), mean maternal age, adverse perinatal outcomes, TBA categories, and adjustment covariates (Table 1).

Statistical analysis

Heterogeneity of effects across studies was assessed using the χ^2-test statistic and quantified by I^2, which represented the percentage of total variation across studies that was attributable to heterogeneity rather than chance. The pooled relative risk (RR) was estimated by a fixed-effect model when there was no heterogeneity, otherwise a random-effect model was used. As a result of the limited studies, we could only perform sub-group analysis by region and study design. A sensitivity analysis was performed to evaluate stability by sequential omission of individual studies. Publication bias was tested with Begg's test for funnel plot asymmetry. All analyses were performed with STATA V.12.0.

Results

Characteristics of included studies

The derivation of the relevant studies included in the present meta-analysis is shown in Figure 1. Of the 368 publications initially found in PubMed, nine involving about 1928 patients were included in this meta-analysis.[8–12,14–17] The major characteristics of the nine eligible publications are described in Table 1. Two studies were designed as prospective case–control studies[9,10] six studies were retrospective observational studies;[11,12,14–17] and one study was a prospective cohort study.[8] Three studies were conducted in Europe[8,10,16] three in the USA;[11,12,15] and three in Asia.[9,14,17] Sub-group analysis was performed with stratification by region and study design (Table 2).

TBA and risk of adverse perinatal outcomes

Owing to significant heterogeneity, we used a random-effects model. Severe TBA levels were associated with a 96% increased risk for adverse perinatal outcomes compared with mild TBA levels. Only one study was conducted using a prospective cohort design.[8] The sub-group analysis stratified by study design revealed that there was no heterogeneity in case–control and retrospective observational studies (Fig. 2a). Sub-group

Table 1 Summary of studies included in the present study

Author	Country	Study period	Sample size	Mean maternal age (years)	Adverse perinatal outcomes	TBA categories	Adjustment for covariates
Sargın Oruç *et al.* (2014)[9]	Turkey	2012	57/59 (ICP/control)	28.33(ICP) 27.37 (Control)	Preterm birth, MSAF, NICU admission, asphyxia	fTBA < 40 μmol/L (mild), fTBA > 40 μmol/L (severe)	Age, gravidity, BMI
Garcia-Flores *et al.* (2015)[10]	Spain	2012–2014	47/98 (ICP/control)	35.87(ICP) 35.92 (Control)	Threatened preterm labor, Apgar, meconium-stained fluid, global neonatal morbidity, NICU stay	TBA < 40 μmol/L (mild), TBA ≥ 40 μmol/L (severe)	Gestational age, singleton, induction of labor
Glantz *et al.* (2004)[8]	Sweden	1999–2002	693	No found	Spontaneous preterm delivery, meconium-stained amniotic fluid, asphyxial events, green staining of placenta/membranes	SBA < 10 μmol/L (no ICP) 10 μmol/L < SBA < 40 μmol/L (mild), SBA ≥ 40 μmol/L (severe)	Not found
Lee *et al.* (2008)[12]	USA	2000–2007	122	29.7	Spontaneous preterm labor, Apgar, meconium passage, asphyxial events, chorioamnionitis, antepartum fetal death	TBA < 20 μmol/L (mild), 20 μmol/L ≤ TBA < 40 μmol/L (moderate), TBA ≥ 40 μmol/L (severe)	Maternal age, gravidity, parity, gestational age at birth, fetal weight, history of hepatobiliary disease
Rook *et al.* (2012)[11]	USA	2005–2009	101	27.5	Preterm delivery, meconium-stained amniotic fluid, respiratory distress, fetal distress and demise	TBA < 10 μmol/L, 10–40 μmol/L, 40–100 μmol/L, TBA ≥ 100 μmol/L	Maternal age, race/ethnicity, history of hepatic or biliary disease, history of ICP, gravidity, parity
Jin *et al.* (2014)[14]	China	1993–2014	371	29.1	Stillbirth, meconium aspiration, Apgar, NICU, spontaneous preterm delivery, green staining of the placenta, neonatal death	10 μmol/L < SBA < 40 μmol/L (mild), SBA ≥ 40 μmol/L (severe)	Age, BMI, gravidity, history of alcoholism, history of smoking, parity, comorbidity
Brouwers *et al.* (2014)[16]	The Netherlands	2005–2012	215	31	Spontaneous preterm birth, meconium-stained amniotic fluid, asphyxia, perinatal death, NICU admission	Mild (SBA 10–39 μmol/L), moderate (SBA 40–99 μmol/L), severe (SBA ≥ 100 μmol/L)	Maternal age, gestational age, birthweight,
Madazli *et al.* (2015)[17]	Turkey	2003–2013	89	28.7	RDS, meconium, fetal growth restriction, fetal distress, preterm delivery	TBA < 20 μmol/L 20 < TBA < 39, μmol/L TBA > 40 μmol/L	Not found
Kawakita *et al.* (2015)[15]	USA	2009–2014	233	29.9	NICU, hypoglycemia, meconium-stained amniotic fluid, hyperbilirubinemia, RDS, transient tachypnea of newborn, pneumonia, stillbirth	10 μmol/L < TBA < 39.9, μmol/L 40 μmol/L < TBA < 99.9 μmol/L TBA ≥ 100 μmol/L	Maternal age, race, site, any hypertensive disorder, any diabetes, BMI, gestational age at delivery, TBA level, gestational age at diagnosis of ICP, ursodeoxycholic acid use, AST and ALT, pre-existing liver disease

ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; fTBA, fasting total bile acids; ICP, intrahepatic cholestasis of pregnancy; MSAF, meconium-stained amniotic fluid; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; SBA, serum bile acids; TBA, total bile acid.

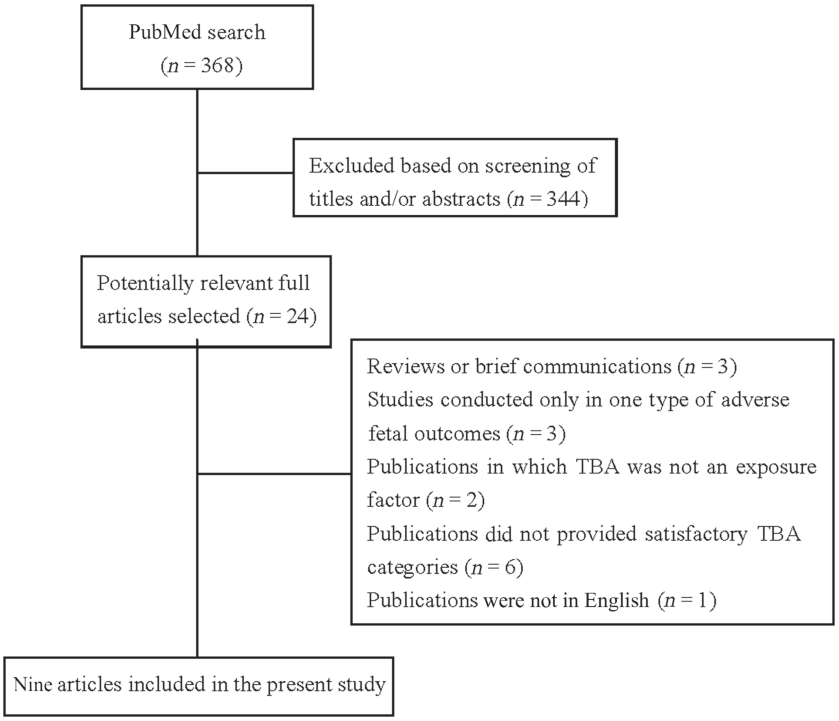


Figure 1 Flow chart of study selection procedure. A total of nine studies were included in our study. TBA, total bile acid.

analysis showed that there was significant heterogeneity among the three studies in Asia ($I^2 = 74\%$, $P < 0.05$), but no heterogeneity in the US studies (Fig. 2b). The pooled RR across studies in European populations were relatively higher than those of Asian and American populations. Sensitivity analysis suggested that the studies by Glantz *et al.*[8] and Madazli *et al.*[17] might be the major sources of heterogeneity (Fig. 3). After excluding the Glantz *et al.* study, the results showed that the pooled RR for adverse perinatal outcome was 1.88 (95%CI, 1.63–2.16, $P = 0.129$, $I^2 = 37.6\%$) for severe versus mild TBA levels. Of note, we only searched one study from China and two studies from Turkey; the results remain to be seen in Asia.

TBA and PTB risk

Of the nine eligible publications, eight studies investigated the association between serum TBA levels and PTB risk. The results indicated that severe TBA levels were significantly associated with an increased risk of PTB. The pooled RR was 2.23 (95%CI, 1.51–3.29) for PTB in a random-effects model compared with mild TBA levels. Subgroup analyses by region and study design showed that gravidas with severe TBA levels had a significantly increased risk for PTB in various sub-groups (Table 2). Sub-group analysis showed significant heterogeneity among studies conducted in Europe. The possible major source of heterogeneity also came from the Glantz *et al.* study.[8] The pooled RR was 7.57 (95%CI, 3.45–16.62).

TBA and MSAF risk

Meconium staining of the amniotic fluid or membranes is a major adverse fetal outcome. In our meta-analysis, seven eligible studies investigated the association between serum TBA levels and MSAF risk. The results showed that severe TBA levels were significantly associated with an increased risk for MSAF (pooled RR, 2.27; 95%CI, 1.81–2.85) in a fixed-effect model. Sub-group analysis showed no significant heterogeneity ($P > 0.05$).

TBA and asphyxia–respiratory syndrome risk

Based on this meta-analysis, seven studies investigated the association between maternal serum TBA levels and fetal respiratory system risk, including four focusing on fetal asphyxia (defined by low pH value of umbilical arterial blood or low Apgar score), two focusing on low Apgar scores (defined as an Apgar score ≤ 7 at 1 or 5 min), two focusing on RDS (defined by clinical features), and one focusing on fetal distress (defined by CTG or B-ultrasonic tracing criteria). Notably, due to

Table 2 Stratified analysis of pooled relative risks of adverse perinatal outcomes (PTB, MSAF, asphyxia)

Stratified analysis	Number of studies	Reference numbers	Pooled RR (95%CI)	Heterogeneity	
				I2 (%)	*P*-value
Overall adverse perinatal outcomes	9	8–12, 14–17	1.96 (1.63, 2.35)	52.5%	0.032
Study design					
Case–control study	2	9–10	3.40 (2.07, 5.58)	0.0%	0.795
Retrospective study	6	11–12, 14–17	1.72 (1.50, 1.99)	0.0%	0.501
Cohort design	1	8	2.42 (2.00, 2.92)	—	—
Region					
Europe	3	8, 10, 16	2.28 (1.89, 2.76)	23.5%	0.271
USA	3	11–12, 15	1.70 (1.33, 2.17)	0.0%	0.844
Asia	3	9, 14, 17	1.89 (1.19, 3.01)	74.0%	0.021
PTB	8		2.23 (1.51, 3.29)	48.1%	0.061
Study design					
Case–control study	2	9–10	2.48 (1.24, 4.94)	0.0%	0.563
Retrospective study	5	12, 14–17	1.74 (1.30, 2.33)	0.0%	0.899
Cohort design	1	8	7.57 (3.45, 16.62)	—	—
Region					
Europe	3	8, 10, 16	3.57 (1.37, 9.26)	57.9%	0.093
USA	2	12, 15	1.87 (1.23, 2.84)	0.0%	0.465
Asia	3	9, 14, 17	1.77 (1.21, 3.01)	0.0%	0.457
MSAF	7		2.27 (1.81, 2.85)	0.0%	0.611
Study design					
Case–control study	2	9–10	5.73 (1.69, 19.42)	12.9%	0.284
Retrospective study	4	12, 14–16	2.31 (1.61, 3.32)	0.0%	0.797
Cohort design	1	8	1.99 (1.49, 2.66)	—	—
Region					
Europe	3	8, 10, 16	2.09 (1.61, 2.72)	23.5%	0.271
USA	2	12, 15	2.75 (1.67, 4.55)	0.0%	0.795
Asia	2	9, 14	2.62 (0.96, 7.17)	0.0%	0.498
Asphyxia–respiratory syndrome	7		1.67 (1.18, 2.36)	0.0%	0.429
Study design					
Case–control study	1	9	4.50 (0.56, 36.13)	—	—
Retrospective study	5	12, 14–17	1.42 (0.92, 2.17)	0.0%	0.413
Cohort design	1	8	2.13 (1.14, 3.99)	—	—
Region					
Europe	2	8, 16	2.27 (1.22, 4.21)	0.0%	0.579
USA	2	12, 15	1.43 (0.81, 2.53)	0.0%	0.648
Asia	3	9, 14, 17	1.51 (0.80, 2.83)	52.7%	0.121

CI, confidence interval; MSAF, meconium-stained amniotic fluid; PTB, preterm birth; RR, relative risk.

the low incidence of various diseases in this meta-analysis, we combined them all in a single mixed category (redefined as 'asphyxia–respiratory syndrome') and we synthesized the statistic of serum TBA levels and related disease risks. The pooled RR for asphyxia–respiratory syndrome was 1.67 (95%CI, 1.18–2.36) for severe versus mild TBA levels (Table 2). The possible major source of heterogeneity was the Madazli *et al.* study[17] with a relatively lower risk of RDS in severe versus mild ICP (RR, 0.67; 95%CI, 0.24–1.87).

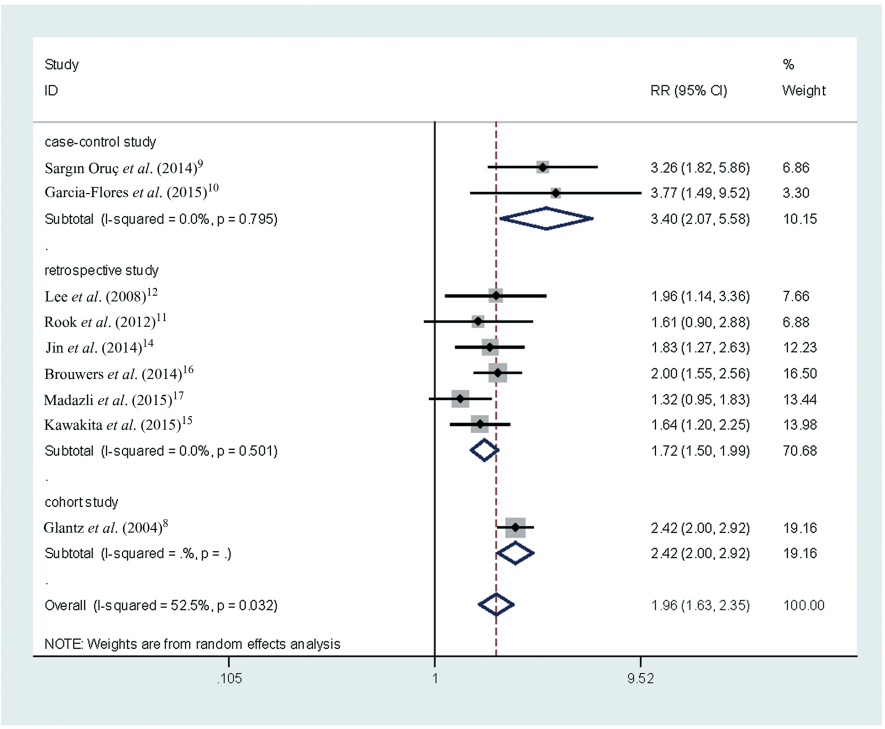
Sensitivity analysis and publication bias

One study at a time was excluded in the sensitivity analysis (Fig. 3). When excluding the Glantz *et al.* study, the relative risk of adverse perinatal outcomes was 1.88 (95%CI, 1.63–2.16) for severe versus mild TBA levels. The RR of PTB was 1.86 (95%CI, 1.42–2.43). A funnel plot and Begg's test were used to estimate the publication bias of studies. There was no obvious funnel plot asymmetry. The Begg's test score of the *P*-values was >0.05, suggesting that publication bias was not evident in all studies (Fig. 4).

Discussion

ICP is transient and generally follows a benign course in gravidas, but may adversely affect the prognosis of the

(a)



(b)

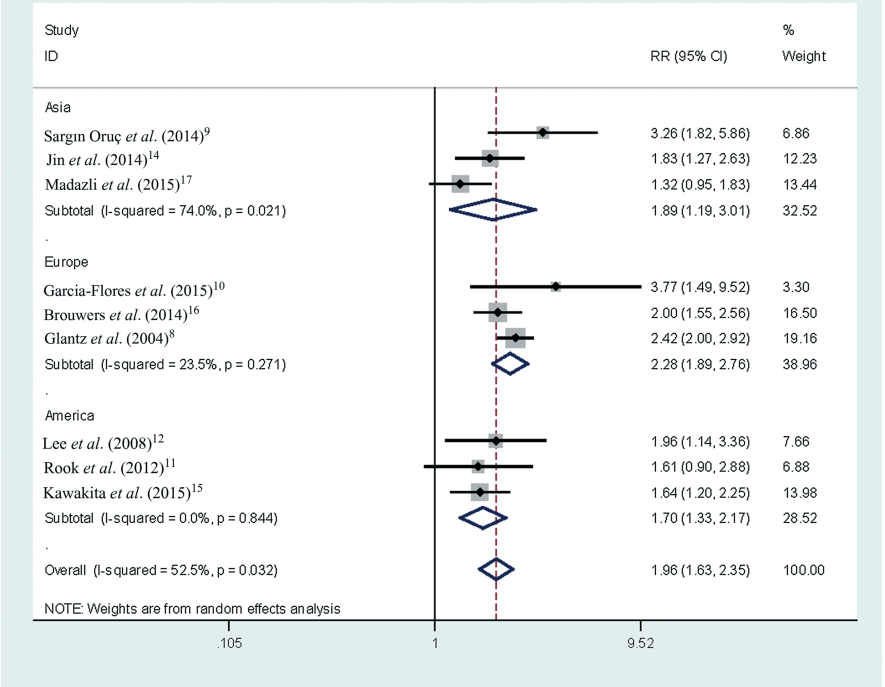


Figure 2 Meta-analysis (forest plot) of nine evaluable studies assessing the relative risk of adverse perinatal outcomes for severe versus mild total bile acid (TBA) levels. (a) Sub-group analysis stratified by study design. (b) Sub-group analysis stratified by region.

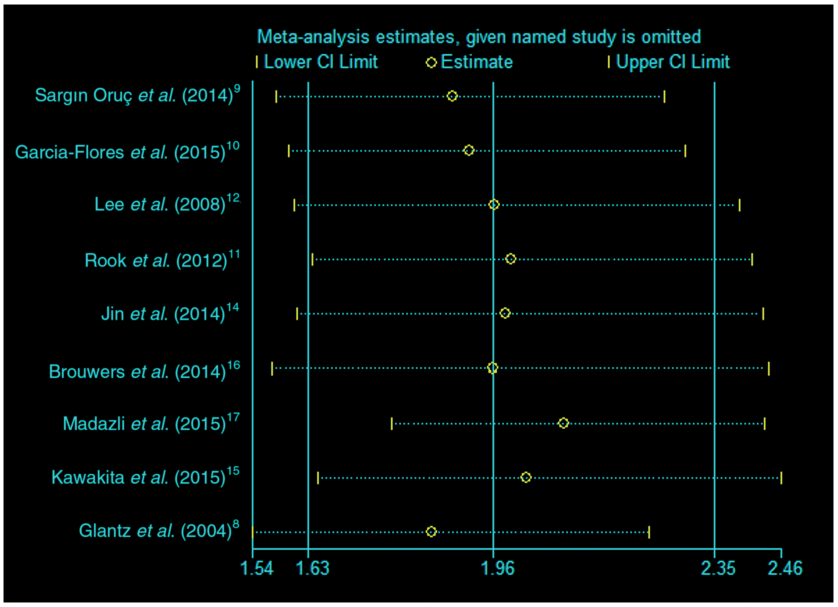


Figure 3 Sensitivity analysis by stepwise omitting one study at a time.

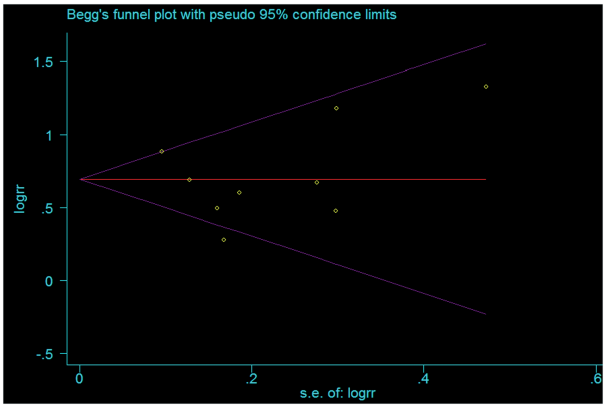


Figure 4 Begg's funnel plot analysis of publication bias.

fetus. The major adverse fetal outcomes that have been reported include PTB, MSAF, fetal distress, RDS, and asphyxia.[18] The most dreadful complication that gravidas with ICP will experience is intrauterine fetal death without any early warning signs. The mechanism underlying the pathogenesis of ICP and the mechanisms by which ICP leads to poor fetal outcome are unclear, and the prognosis of ICP remains obscure. Thus, specific markers and/or methods for the prediction of adverse fetal outcomes in gravidas with ICP need to be determined. A recent prospective population-based case–control study with national coverage was conducted in the UK.[19] The findings demonstrated significantly increased risks of adverse perinatal outcomes in gravidas with severe ICP. It has become the general consensus that serum TBA levels are associated with the risk for adverse fetal complications. Furthermore, some research conclusions about other laboratory examination parameters in ICP – such as bilirubin and hepatic transaminase levels – are controversial and there is a lack of evidence-based medicine. The association between quantitative categories of TBA levels and fetal outcomes remains poorly understood. We therefore conducted this meta-analysis to provide a reference for prevention and management of fetal outcomes in gravidas with ICP.

At present, there is no unified standard regarding the categorization of ICP severity based on TBA levels. Glantz *et al.*[8] concluded that the risk for fetal complications does not occur until bile acid levels exceed 40 μmol/L. Chen *et al.*[20] showed that the critical value of TBA above which adverse perinatal outcomes are observed is 40.15 μmol/L. In the current study, we selected those studies that included at least two different TBA levels. With reference to guidelines published by the Chinese Medical Association, patients were classified into two groups according to TBA concentration: mild ICP (10.00–39.99 μmol/L) and severe ICP (≥40 μmol/L).[21] Nine studies examined the association between TBA with adverse perinatal outcomes, but no consistent conclusions were drawn. We found that higher TBA concentrations are associated with adverse perinatal outcomes in patients with ICP. Our results are consistent with the results of Favre *et al.*,[22] who found that a threshold of 40 μmol/L could be a way of defining a

group at risk for complications. Of note, in order to exclude the influence of some bias factors on the results, such as data duplication, when calculating the pooled RR for adverse perinatal outcomes in two case–control studies,[9,10] the total number of NICU admissions was not included.

In the present study, we found that the main source of heterogeneity was derived from the Glantz *et al.* study,[8] especially with respect to the description of PTB. The rate of PTB in this cohort study was higher than that reported in other studies. This study showed that the total prematurity rate was 11.7%, including PTB in multiple pregnancies and iatrogenic PTB due to the severity of complications or symptoms. We speculate that the study by Glantz *et al.* probably increased iatrogenic PTB due to the concern for intrauterine fetal death; therefore, the PTB rate was higher in their study. The major design deficiencies in our study were the retrospective data collection and inadequacy of follow-up cohort studies, which may influence the accuracy of the data and increase bias. In addition, although the efficacy of ursodeoxycholic acid (UDCA) therapy is uncertain, it is the only therapy that has shown some results, such as a decrease in itching and extending the pregnancy period.[23] In most of the nine studies included in our study, ICP patients underwent treatment with UDCA and/or other drugs, which may affect the objectivity of the results. The finding also highlights the need for research on the association between TBA and risk for adverse perinatal outcomes with adjustment for more confounding factors.

We also explored the association between TBA levels and PTB, MSAF, asphyxia, and RDS in this meta-analysis. Compared with mild ICP patients, we found that the summary RR of PTB were significantly increased for severe ICP patients (2.23 [1.51–3.29]). After excluding the Glantz *et al.* study,[8] severe ICP had an 86% increased risk for PTB in comparison to mild ICP. Furthermore, we also found that MSAF was more likely in gravidas with severe ICP (pooled RR, 2.27; 95%CI, 1.81–2.85). In addition, several studies recently reported that there is an increased risk for PTB in gravidas with early onset ICP. The Kondrackiene *et al.* study[24] indicated that early onset of pruritus and high levels of TBA were the most important factors associated with preterm delivery in a cohort of patients with ICP; however, in the study by Pata *et al.*,[25] the findings indicated that the onset time of pruritus and response to UDCA treatment were not correlated with PTB. Therefore, further evaluation of the relation is needed in the future. Of note, in our study, the pooled RR for asphyxia–respiratory syndrome was composed of fetal asphyxia, RDS, and fetal distress. Although these factors are obviously related, there are evident differences in the methodology used for selecting them, which might bias the results. Madazli *et al.*[17] reported a relatively lower risk of RDS in gravidas with severe versus mild TBA levels (RR, 0.67; 95%CI, 0.24–1.87), which could be due in part to the earlier gestational age at the time of delivery. Oztekin *et al.*[26] reported that levels of TBA and exposure time to ICP are the two most important predictive factors for fetal asphyxia. It seems that the timing of ICP onset may affect the risk of adverse fetal outcomes. This opinion could not be determined in this meta-analysis due to the lack of data provided by each study.

Of the selected studies, five examined the association between TBA levels and NICU admission,[9,10,14–16] as well as the rate of NICU admission for severe (13.8%) versus mild TBA levels (10.8%). When extracting data and calculating the RR for adverse outcomes risk, there may be duplicated data between the number of NICU admissions and other outcomes. Therefore, our meta-analysis was not carried out to evaluate TBA levels and NICU admission risk. Four studies investigated the association between TBA levels and stillbirths[12,14,15] or perinatal deaths[16] however, the number of subjects in the four studies concerning this relation was relatively small, as was the rate of stillbirth for severe (10/330, about 3%) versus mild TBA levels (3/511, about 0.6%). Thus, our meta-analysis was not sufficient to evaluate these rare outcomes. However, ICP must be recognized as a condition that is associated with increased perinatal mortality. A recent study showed that a TBA $>$ 100 μmol/L is associated with stillbirth.[15] Bile acids can induce lung injury, leading to surfactant depletion, surfactant dysfunction, lung inflammation, and other fetal multiple organ function damage. Therefore, it is possible that the increased risk of stillbirth may be directly related to ICP.

In addition, according to the survey, the incidence of ICP among pregnancies in the USA is 0.7%, while it is 0.1–1.5% in Europe, and considerably higher in Chile (1%–10%). Therefore, the prevalence of ICP may be associated with geography, ethnicity, and environmental factors. One study reported that genetic predisposition and hormonal factors have crucial roles in the pathogenesis of ICP[27] however, the exact underlying mechanism is obscure at present. The incidence of ICP in our hospital is 0.36%. In our meta-analysis, all included studies were conducted in American and European populations; only one study from China and two studies from Turkey were included. Our results

suggest that the high heterogeneity existed in the subgroup analysis by region. Data for other continents were lacking, especially in Asia. Indeed, different lifestyles, living environments, and economic development may have different effects on the global occurrence of disease. Therefore, investigators in these regions should pay more attention to the assessment of risks of adverse perinatal outcomes.

In summary, various strategies have been proposed to predict and obtain better fetal outcomes in ICP patients. Our study confirmed that perinatal outcomes are worse and risks increased among gravidas with severe TBA levels compared to mild TBA levels. A TBA concentration of 40 μmol/L in maternal serum may be a critical value for predicting adverse perinatal outcomes in ICP. Maternal bile acid levels are not only related to fetal outcomes in a qualitative way, but importantly there is a quantitative positive relation to most of them. More studies focusing on the association between TBA levels and various fetal outcomes are needed in the future.

Acknowledgments

The authors have no support or funding to report.

Disclosure

The authors declare that they have no conflicts of interest.

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