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REVIEW ARTICLE

Perinatal death by bile acid levels in intrahepatic cholestasis of pregnancy: a systematic review

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ABSTRACT

Background: Intrahepatic cholestasis of pregnancy (ICP) is characterized by the elevation of total bile acids (TBAs). The primary concern in women with ICP is the increased risk of stillbirth. ICP is generally considered as "mild" when TBA levels range from 10 to 39 μmol/L and "severe" with levels greater than 40 μmol/L, although levels of TBA ≥100 μmol/L have been also considered as a further threshold of severity.

Objective: To quantify the association between different severities of ICP (TBA 10–39, 40–99, and ≥100 μmol/L) and perinatal death.

Data sources: Medline, Embase, Scopus, Web of Sciences, and ClinicalTrial.gov were searched from the inception of each database to February 2019.

Methods of study selection: Randomized, cohort, case-control, or case series studies reporting maternal and perinatal outcomes on women with ICP by the three prespecified TBA levels (10–39, 40–99, and ≥100 μmol/L) were included. We excluded multiple gestations and trials which included an intervention. The analysis was performed with Pearson chi-square and Fisher's exact test as appropriate. Continuous outcomes were compared using metaregression with inverse variance weighting using reported sample sizes and standard deviations. Pairwise comparisons used a Bonferroni correction to control for multiple testing.

Tabulation, integration, and results: Six articles including 1280 singleton pregnancies affected by ICP were included in the systematic review. Out of the 1280 singleton pregnancies affected by ICP included, 118 had ICP with TBA ≥100 μmol/L. Perinatal death was more common in women with TBA ≥100 μmol/L (0.4% for TBA 10-39 μmol/L *versus* 0.3% for TBA 40-99 μmol/L *versus* 6.8% for TBA ≥ 100 μmol/L, $p < .0001$). Of the 8 perinatal deaths in the TBA ≥100 μmol/L group, 3 occurred ≥34 weeks. TBA ≥100 μmol/L increased the risk of spontaneous preterm birth (PTB) (5.4% *versus* 8.6% *versus* 18.2% respectively, $p < .0001$) and iatrogenic PTB (10.8% *versus* 21.6% *versus* 35.8% respectively, $p < .0001$) as well as meconium-stained amniotic fluid (9.0% *versus* 18.4% *versus* 31.6% respectively, $p < .0001$).

Conclusions: Maternal TBA ≥100 μmol/L is associated with a 6.8% incidence of perinatal death, most of which (5.9% overall) are stillbirths, while TBA <100 μmol/L are associated with an incidence of perinatal death of 0.3%. It may be reasonable to consider late preterm delivery (at about 35–36 weeks) in women with TBA ≥100 μmol/L.

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Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a multifactorial disorder, characterized by elevation of total bile acids (TBAs), associated with abnormal liver enzymes levels and pruritus without skin rash or primary skin lesion, and typically developing during the second half of pregnancy [1,2]. It is the most common

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Supplemental data for this article can be accessed here.

liver disease during pregnancy, ranging from 0.3% to 5.6% in USA [2]. Several risk factors, including genetic, ethnical, hormonal, nutritional, and environmental factors have been proposed to explain the etiology and the pathophysiology of ICP, that is still not completely understood [3]. ICP is generally considered as "mild" when TBA levels are from 10 to 39 μmol/L and "severe" with TBA ≥ 40 μmol/L [4], although some experts also suggest TBA ≥100 μmol/L as a further threshold of severity [5,6]. In ICP, the fetal–maternal gradient of bile acids is reversed, and this contributes to the accumulation of bile acids in the fetal compartment [7].

The primary concern in women with ICP is the risk of stillbirth. Fetal demise usually occurs with higher TBA levels and mainly after 37 weeks of gestation or at least at an advanced gestational age (GA) [8]. Intrauterine death may be explained by elevated TBA levels that may cause an abnormal cardiomyocyte contraction and rhythm transmission in the fetal heart [9] or a dose-dependent vasoconstrictive effect on placental chorionic veins [10]. Other adverse fetal outcomes also involve preterm birth (PTB) – both spontaneous and iatrogenic – meconium-stained amniotic fluid, neonatal respiratory distress syndrome (RDS), subsequently increasing the incidence of admission to neonatal intensive care unit (NICU) [8,11].

While TBA levels >40 μmol/L have commonly been considered to have a good predictive role [12] in adverse perinatal outcomes, the difference between TBA 40–99 μmol/L and TBA ≥100 μmol/L cutoff in predicting poor outcomes has been shown only recently [13], mostly due to small sample size of previously published studies and the heterogeneity in prenatal management and outcomes' measures in cases with TBA ≥100 μmol/L. These data reported for the first time a clear association between the most severe disease and the increased risk of stillbirth in singleton pregnancies affected by ICP [13].

The primary aim of this systematic review was to quantify the association between different severities of ICP (TBA 10–39, 40–99, and ≥100 μmol/L) and perinatal death.

Materials and methods

Search strategy

This study was performed according to a protocol recommended for systematic review [14]. The review protocol was designed *a priori* defining methods for collecting, extracting, and analyzing data. The research was conducted using Medline, Embase, Scopus, Web of Sciences, and ClinicalTrial.gov as electronic databases. The articles were identified with the use of a combination of the relevant heading term, key words, and word variants for: "intrahepatic cholestasis of pregnancy" and "maternal outcomes", or "perinatal outcomes", from the inception of each database to February 2019. Review of articles also included the abstracts of all references retrieved from the search.

Study selection and outcomes

Only studies reporting maternal and perinatal outcomes on women with ICP by the three prespecified TBA levels (10–39, 40–99, and ≥100 μmol/L) were included. We excluded multiple gestations, as they are already associated with an increased risk of perinatal death. Trials of women with ICP randomized to an intervention or placebo or randomized to different interventions were also excluded. Only full-text articles were considered eligible for inclusion. Randomized, cohort, case-control, or case series were all accepted study designs. Studies with fewer than five cases were excluded to avoid publication bias.

The primary outcome was perinatal death, defined as including both stillbirths (defined as a fetal death ≥20 weeks or as defined by authors) and neonatal deaths (deaths before 28 d of life). Secondary outcomes were GA at delivery, spontaneous or iatrogenic labor, spontaneous or iatrogenic PTB (sPTB or iPTB) (defined as GA < 37 weeks), cesarean delivery (CD), meconium-stained amniotic fluid, postpartum hemorrhage (PPH) (defined as blood loss >1000 mL), admission to NICU, birthweight, small for GA (SGA) (defined as birthweight <10th percentile), and low Apgar score (<7) at 5 min.

A secondary analysis was carried out in order to estimate the predictive value of TBA ≥100 μmol/L cutoff, compared to TBA 40–99 μmol/L as well as compared to TBA 10–39 μmol/L.

Data extraction and risk of bias assessment

Two authors (DDM, MR) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus. Full-text copies of those papers were obtained and the same reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed by the reviewers and consensus reached or by discussion with a third author (VB). Data not presented in the original publications were requested by the principal investigators.

Quality assessment of the included studies was performed using the Newcastle–Ottawa Scale (NOS) for case-control studies. According to NOS, each study is judged on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment outcome of interest [15]. Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and the demonstration that outcome of interest was not present at start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts based on the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of assessment of the outcome of interest, length, and adequacy of follow-up. According to NOS, a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability [15].

Data analysis

Baseline demographic data for each of the ICP groups within each study was collected and standard means were calculated. Pregnancy and neonatal outcomes were collected for each of the ICP groups. Differences between outcomes were analyzed using a Pearson chi-square for categorical outcomes. When the probability values were noted to be significantly different between groups, Fisher's exact test was used to analyze the difference between each paired group to further detail the interaction. Continuous outcomes were compared using metaregression with inverse variance weighting using reported sample sizes and standard deviations. Pairwise comparisons used a Bonferroni correction to control for multiple testing.

Statistical analyses were performed in SPSS software version 24 (SPSS Inc., Chicago, IL). Probability values of $<.05$ were considered statistically significant.

The systematic review was reported following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [16]. Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42018111642).

Results

Study selection and study characteristics

Figure 1 shows the flow diagram (PRISMA template) of information derived from review of potentially relevant articles. Six articles [5,6,17–20] , including 1280 singleton pregnancies affected by ICP were included in the systematic review. Four of the included studies were retrospective cohort studies [5,6,18,20], one was case–control study [19] while one article was a case series with a total of 13 cases of ICP [17]. Out of the 1280 singleton pregnancies affected by ICP included, 118 had ICP with TBA $\geq$ 100 μmol/L.

Table 1 shows the characteristics of the included studies. For characteristics of excluded studies see Supplementary Appendix 1. The results of the quality assessment of the included studies using NOS are presented in Table 2. The included studies showed an overall moderate score regarding the selection and comparability of the study groups, and for ascertainment of the outcome of interest. Inclusion and exclusion criteria of each study are reported in Table 3. Characteristics of the women included were shown in Table 4. Maternal age, parity, and GA at diagnosis were similar when comparing the study population of each study. The rate of women who had a history of ICP in a previous pregnancy was also comparable.

Synthesis of results

The primary and secondary outcomes are available in Table 5. For comparisons between individual groups, see Supplementary Appendix 2. The risk of perinatal death, defined as including both stillbirths and neonatal deaths, was significantly higher in ICP with TBA $\geq$ 100 μmol/L, compared with TBA 10–39 μmol/L and 40–99 μmol/L (3/789, 0.4% for TBA 10-39 μmol/L *versus* 1/287, 0.3% for TBA 40-99 μmol/L *versus* 8/118, 6.8% for TBA $\geq$100 μmol/L; $p < .0001$). In particular, the risk of stillbirth increased as TBA levels increased (2/789, 0.2% *versus* 1/287, 0.3% *versus* 7/118, 5.9% respectively; $p < .0001$), while no difference was found for neonatal death. Of the six cases of stillbirth where GA data was available, three occurred after 34 weeks, two at 35 weeks, and one at 37 weeks (Table 6).

There was a significantly higher risk of both sPTB (28/523, 5.4% *versus* 19/220, 8.6% *versus* 16/88, 18.2% respectively; $p < .0001$) and iPTB (45/415, 10.8% *versus* 29/134, 21.6% *versus* 24/67, 35.8% respectively; $p < .0001$) as TBA levels increased. The risk of meconium-stained amniotic fluid significantly increased when stratified according to TBA levels (76/840, 9% *versus* 57/310, 18.4% *versus* 37/117, 31.6 respectively; $p < .0001$). There was a significant difference in birthweight only when comparing TBA 10–39 μmol/L and TBA $\geq$ 100 μmol/L (3155 ± 35.5 *versus* 2746 ± 108.5; $p = .035$). Apgar score <7 at 5 min was significantly

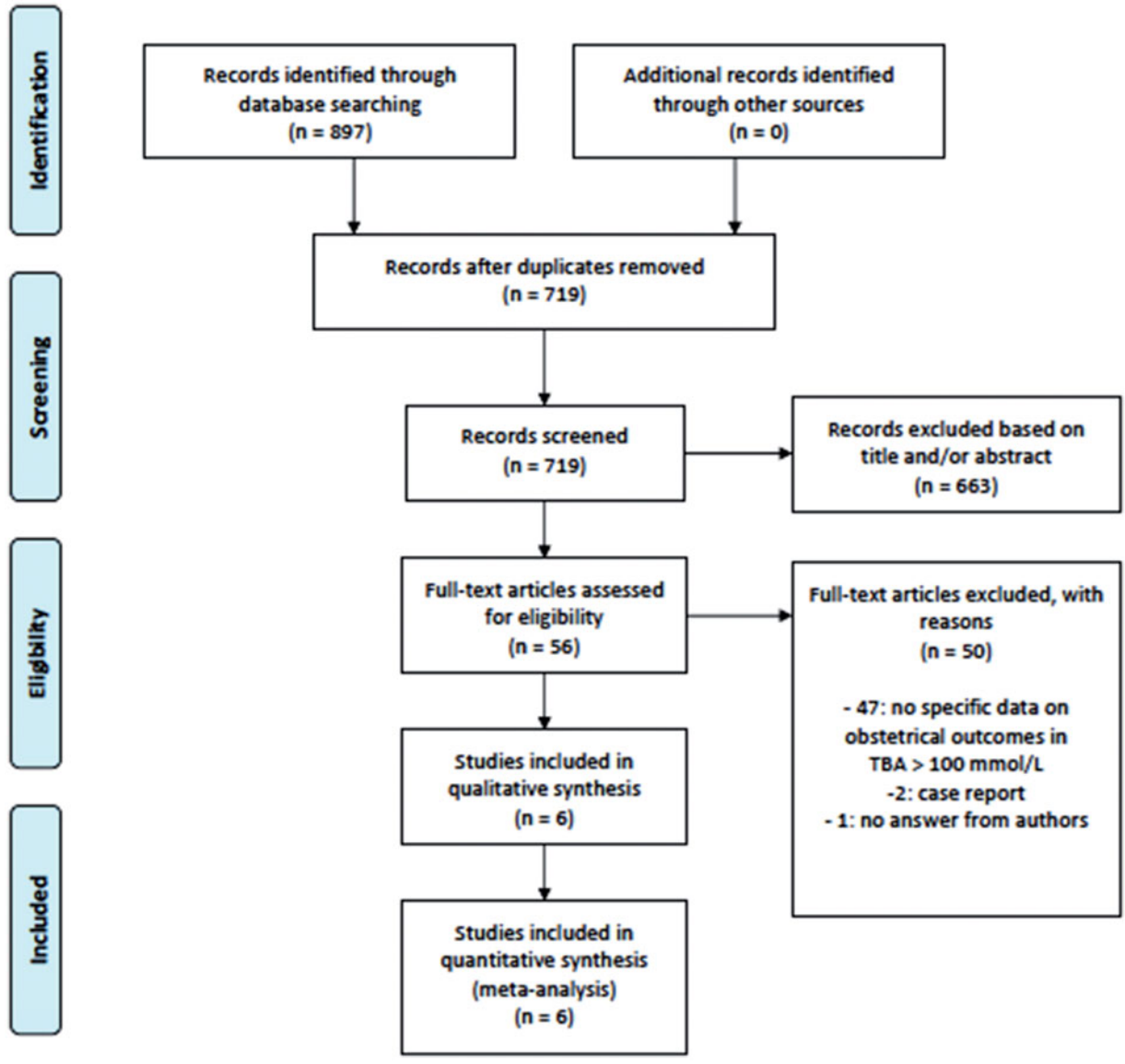

Figure 1. Prisma flow diagram.

more frequent as TBA levels increased (5/762, 0.7% *versus* 2/310, 0.6% *versus* 6/116, 5.2% respectively; $p = .001$). Conversely, a significant difference between TBA 10–39 and 40–99 μmol/L was found only in case of iPTB and meconium-stained amniotic fluid, and no significant difference was found in neonatal deaths, GA at delivery, CD, PPH, SGA, and admission to NICU when stratifying the analysis according to ICP severity.

Discussion

Main findings

This systematic review, including 1280 singleton pregnancies affected by ICP, showed that TBA $\geq$ 100 μmol/L was associated with a significantly higher incidence of perinatal death and adverse perinatal outcomes, including sPTB, iPTB, meconium-stained amniotic fluid, Apgar score <7 at 5 min compared with TBA < 100 μmol/L, and the strength of this association persisted when comparing TBA $\geq$ 100 μmol/L both with TBA 40–99 μmol/L and TBA 10–39 μmol/L.

Conversely, a significant difference between TBA 10–39 and 40–99 μmol/L was reported only for the risk of iPTB and meconium-stained amniotic fluid. Of the six cases of stillbirth where GA data were available, two of those cases occurred at 35 weeks and one at 37 weeks.

Comparison with existing literature

Data shown in this review are concordant with the largest meta-analysis published on this topic in February 2019 [13]. Authors collected individual participant data from 27 studies as well as from 2 large

Table 1. Characteristics of the included trials.

Author	Year	Country	Study design	Time frame	Singletons with ICP	Daily therapy
Ambros Rudolph	2007	Austria	Case series	2000–2005	13	UDCA 15 mg/kg
Lee	2008	USA	Retrospective cross-sectional	2000–2007	104	UDCA, diphenhydramine topical hydrocortisone hydroxyzine cholestyramine
Brouwers	2015	The Netherlands	Retrospective cohort study	2005–2012	215	UDCA
Kawakita	2015	USA	Retrospective cohort study	2009–2014	233	UDCA
Furrer	2016	Switzerland	Retrospective case-control (controls matched to cases by propensity analysis)	2004–2014	266	UDCA 900 mg
Herrera	2017	USA	Retrospective cohort study	2005–2015	449	UDCA

ICP: intrahepatic cholestasis of pregnancy; TBA: total bile serum; UDCA: ursodeoxycholic acid

UK hospitals and reported a threefold increase in stillbirth in women with TBA levels ≥ 100 μmol/L when compared with those with milder disease and the general population [13]. They suggest that women with TBA levels ≥ 100 μmol/L should probably deliver at about 35–36 weeks of gestation [21].

The prognostic value of maternal TBA levels > 40 μmol/L has been explored in both prospective and retrospective studies, and higher TBA levels – mostly >40 μmol/L – were reported to predict poor fetal outcomes [4–6,11,22]. A recent systematic review and meta-analysis of nine studies involving 1928 patients showed that TBA > 40 μmol/L was associated with a significant increase of the risk of PTB, meconium-stained amniotic fluid, RDS and asphyxia, and authors suggested to consider TBA > 40 μmol/L as a threshold to identify pregnancies at high risk for fetal complication [12].

This threshold was also adopted in one of the largest prospective studies of perinatal outcomes in women affected by ICP, demonstrating that TBA > 40 μmol/L was associated with both sPTB and iPTB, meconium-stained amniotic fluid, admission to NICU, and stillbirth [11], and, therefore, authors suggested to carefully consider this threshold for delivery from 37 weeks of gestation, as benefits could balance the risks of an anticipated delivery [11].

In a retrospective cohort study on over a million and a half pregnancies, perinatal mortality was lowest with delivery at 36 weeks and significantly lower than mortality with expectant management in women with ICP. However, the main limitation of this study is that no data on TBA levels were available and, therefore, it was not possible to highlight a potential subgroup of patients with ICP who may face a much higher risk of stillbirth compared to those with lower TBA [23].

Current guidelines on ICP do not clearly focus on a specific threshold of TBA levels to determine the management of these patients: the American College of Gastroenterology only mentions TBA > 40 μmol/L as a predictive value for pregnancy complications [1], while the Royal College of Obstetricians and Gynecologists suggests to offer delivery after 37 weeks of gestation, particularly in case of severe transaminases and TBA elevations, without specifying those values [2]. Our study does demonstrate the increased risk of perinatal death in patients with TBA ≥ 100 μmol/L, and delineates further that the severity of ICP increases as TBA levels increase.

The majority of women included in this review were treated with ursodeoxycholic acid. Evidence showed that UDCA was effective in reducing adverse

Table 2. Quality assessment of the included studies according to Newcastle–Ottawa Scale (NOS).

Author	Year	Selection (max four stars)	Comparability (max two stars)	Outcome (max three stars)
Ambros Rudolph	2007	**	*	**
Lee	2008	***	*	**
Brouwers	2015	***	*	**
Kawakita	2015	***	*	**
Furrer	2016	***	*	**
Herrera	2017	***	*	**

Table 3. Inclusion and exclusion criteria of the women included in the studies.

	Inclusion criteria	Exclusion criteria
Ambros Rudolph (2007)	The diagnosis of ICP was based on: (1) generalized pruritus with or without skin changes starting in the second half of pregnancy; (2) elevated total serum bile acid levels (11 μmol/L)2 (to convert to μg/mL, divide by 2.448); and (3) exclusion of other dermatologic and/or internal conditions known to cause pruritus. The clinical parameters evaluated included age, ethnicity, and medical history (particularly, personal, and/or family history of pregnancy-associated pruritus, time of disease onset, presenting signs and symptoms, disease duration, treatment, and maternal outcome)	NR
Lee (2008)	Women were included if they were of Hispanic ethnicity and delivered by 37 weeks, as determined from charted demographic data	Women were excluded if they were of non-Hispanic ethnicity
Brouwers (2015)	All cases of ICP were identified through the laboratory computer systems. ICP was diagnosed when BA levels were $\geq$ 10 mmol/L and signs of pruritus during pregnancy where found in the hospital records	All pregnancies that were complicated by severe congenital malformations, which consisted of chromosomal abnormalities and/or multiple congenital anomalies, and all twin pregnancies were excluded from the study.
Kawakita (2015)	Women with the diagnosis of ICP were identified through the electronic perinatal database in each hospital. Subsequent chart abstraction was undertaken to collect relevant outcome data. ICP was diagnosed by presence of pruritus without a rash and documented maximum serum TBA level of $\geq$ 10 μmol/L	Women with TBA level $<$10 μmol/L and pregnancies complicated by multiple gestations or infants with congenital and chromosomal abnormalities were excluded
Furrer (2016)	All deliveries after 22 weeks of gestation were included. The study examined 15,083 women including 348 women with intrahepatic cholestasis of pregnancy (2.3%). Propensity score matching was performed and women without ICP were matched to the women with ICP in a 5:1 ratio	Exclusion criteria for both women in the case group and those in the control group were known risk factors for postpartum bleeding such as placentation pathology, known coagulation disorders, and liver dysfunction
Herrera (2017)	Women were included if they met initial ICD9 coding criteria and had serum bile acid testing performed. Women were considered to have intrahepatic cholestasis of pregnancy with TBA $\geq$10 μmol/L	Women were excluded if they had a major fetal chromosomal or structural abnormality

NR: not reported; ICP: intrahepatic cholestasis of pregnancy; TBA: total bile acid; ICD: international classification of diseases.

maternal and fetal outcomes in pregnant women with ICP [24], even when compared with other medications [25] but no data on effectiveness stratified according to ICP severity were available, and, therefore, we support the current management of ICP with UDCA from diagnosis until delivery.

GA at diagnosis is another important clinical information when assessing patients with ICP: while earlier onset of pruritus was reported to be associated with a higher risk of spontaneous PTB in a series of 352 pregnancies, no significant differences in GA at the onset of pruritus was found in ICP complicated by intrauterine death [8], and GA at diagnosis was similar when stratifying the analysis according to ICP severity also in this review.

Strengths and limitations

The main limitations are those of the included studies, such as their retrospective approach, differences among the included populations and differences in prenatal management of pregnancies with ICP. Notably, our study does not compare the risk of stillbirth to that of the general population and should not be interpreted as indicating that ICP with TBA $<$ 100 μmol/L is a benign disease. We continue to

Table 4. Characteristics of the women included in the studies.

	Ambros Rudolph (2007)			Lee (2008)			Brouwers (2015)			Kawakita (2015)			Furrer (2016)			Herrera (2017)			Total or mean		
	10–39.9	39.9– 99.9	≥100	10–39.9	39.9– 99.9	≥100	10–39.9	39.9– 99.9	≥100	10– 39.9	39.9– 99.9	≥100	10–39.9	39.9– 99.9	≥100	10– 39.9	39.9– 99.9	≥100	10– 39.9	39.9– 99.9	≥100
Maternal age (years) (Mean ±SD)	NR	NR	NR	29.6 ± 6.5	30.4 ± 6.3	26.3 ± 5.0	32[a]	31[a]	33[a]	29.7 ± 6.0	30.4 ± 5.6	30.2 ± 7.4	30.9 ± 5.5	31.2 ± 5.0	32.0 ± 5.4	28.0 ± 5.2	27.7 ± 5.1	30.0 ± 6.3	29.55	29.93	29.63
Parity = 0	4/8 (50%)	3/4 (75%)	1/1 (100%)	1.8 ± 1.5[b]	2.1 ± 1.8[b]	1.4 ± 1.3[b]	1[a]	0[a]	1[a]	66/152 (43.4%)	28/55 (50.9%)	12/26 (46.2%)	106/196 (54.1%)	27/48 (56.3%)	12/22 (54.5%)	111/325 (34.2%)	28/94 (29.8%)	7/30 (23.3%)	287/681 (42.1%)	86/201 (42.8%)	32/79 (40.5%)
GA at diagnosis	34.4 ± 3.4	34.0 ± 2.6	36.0 ± 0	NR	NR	NR	37[a]	35.4[a]	33.4[a]	34.2 ± 3.9	33.6 ± 4.3	30.6 ± 5.8	NR	NR	NR	34.7 ± 3.5	34.3 ± 3.7	33.9 ± 4.1	34.43	33.97	33.5
TBA (Mean ±SD)	23.0 ± 8.2	59.6 ± 23.9	138.0 ± 0	23.3 ± 8.6	64.9 ± 17.2	141.2 ± 48.0	21[a]	60[a]	149[a]	NR	NR	NR	17.9 ± 6.4	60.5 ± 17.9	183.9 ± 76.9	20.6 ± 8.0	61.2 ± 17.0	146.5 ± 55.4	21.2	61.55	152.4
Previous ICP	NR	NR	NR	11/58 (19.0%)	6/26 (23.1%)	2/17 (11.8%)	19/108 (17.6%)	8/86 (9.3%)	5/21 (23.8%)	22/152 (14.5%)	10/55 (18.2%)	4/26 (15.4%)	NR	NR	NR	NR	NR	NR	52/318 (16.4%)	24/167 (14.4%)	11/64 (17.2%)
Pre-pregnancy BMI (Mean ±SD)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	23.4 ± 4.4	22.0 ± 3.0	21.8 ± 1.9	25.4 ± 5.8	24.2 ± 5.3	26.9 ± 6.3	24.4	23.1	24.35
Smoking	NR	NR	NR	NR	NR	NR	6/108 (5.6%)	1/86 (1.2%)	1/21 (4.8%)	9/152 (5.9%)	0/55 (0%)	0/26 (0%)	NR	NR	NR	11/347 (3.2%)	1/108 (0.9%)	0/32 (0%)	26/607 (4.3%)	2/249 (0.8%)	1/79 (1.3%)
Any diabetes	NR	NR	NR	16/58 (27.1%)	6/26 (23.1%)	3/17 (17.6%)	NR	NR	NR	13/152 (8.6%)	10/55 (18.2%)	1/26 (3.8%)	NR	NR	NR	22/325 (6.8%)	2/94 (2.1%)	3/30 (10%)	41/535 (8.9%)	18/175 (10.3%)	7/73 (9.6%)
Any hypertensive disease	NR	NR	NR	NR	NR	NR	NR	NR	NR	16/152 (10.5%)	5/55 (9.1%)	0/26 (0%)	NR	NR	NR	8/325 (2.5%)	3/94 (3.2%)	1/30 (3.3%)	24/477 (5.0%)	8/149 (5.4%)	1/56 (1.8%)

SD: standard deviation; GA: gestational age; TBA: total bile acids; ICP: intrahepatic cholestasis of pregnancy; BMI: body mass index; NR, not reported.

[a]number reported as a median with standard deviation.

[b]number reported as mean with standard deviation.

Table 5. Obstetrical and perinatal outcomes in TBA 10–39.9 μmol/L versus TBA 40–99.9 μmol/L versus TBA ≥ 100 μmol/L.

	Ambros Rudolph (2007)			Lee (2008)			Brouwers (2015)			Kawakita (2015)			Furrer (2016)			Herrera (2017)			Totals or mean ± SE			
Bile acid levels	10 − 39.9	39.9–99.9	≥ 100	10 − 39.9	39.9–99.9	≥ 100	10 − 39.9	39.9–99.9	≥ 100	10 − 39.9	39.9–99.9	≥ 100	10 − 39.9	39.9–99.9	≥ 100	10 − 39.9	39.9–99.9	≥ 100	10 − 39.9	39.9–99.9	≥ 100	*p* Values
Perinatal death*	0/8 (0%)	0/4 (0%)	0/1 (0%)	0/0 (0%)	0/0 (0%)	1/18 (5.6%)	0/108 (0%)	0/86 (0%)	2/21 (9.5%)	0/152 (0%)	0/55 (0%)	4/26 (15.4%)	2/196 (1%)	0/48 (0%)	1/22 (4.5%)	1/325 (0.3%)	1/94 (1.1%)	0/30 (0%)	3/789 (0.4%)	1/287 (0.3%)	8/118 (6.8%)	**<.0001**[bd]
Stillbirth	0/8 (0%)	0/4 (0%)	0/1 (0%)	0/0 (0%)	0/0 (0%)	1/18 (5.6%)	0/108 (0%)	0/86 (0%)	2/21 (9.5%)	0/152 (0%)	0/55 (0%)	4/26 (15.4%)	1/196 (0.5%)	0/48 (0%)	0/22 (0%)	1/325 (0.3%)	1/94 (1.1%)	0/30 (0%)	2/789 (0.2%)	1/287 (0.3%)	7/118 (5.9%)	**<.0001**[bd]
Neonatal death	NR	NR	NR	0/0 (0%)	0/0 (0%)	0/18 (0%)	0/108 (0%)	0/86 (0%)	0/21 (0%)	0/152 (0%)	0/55 (0%)	0/26 (0%)	1/196 (0.5%)	0/48 (0%)	1/22 (4.5%)	0/325 (0%)	0/94 (0%)	0/30 (0%)	1/781 (0.1%)	0/283 (0%)	1/117 (0.8%)	**.149**
GA at delivery	38.6 ± 1.3	35.3 ± 3.7	37.0 ± 0	37.0 ± 1.7	37.0 ± 1.5	35.6 ± 2.9	38.9[a]	37.9[a]	37[a]	37.3 ± 1.2	37.1 ± 1.3	36.0 ± 3.0	38.5 ± 2.0	37.7 ± 1.7	36.3 ± 2.1	37.5 ± 1.4	37.2 ± 1.2	36.8 ± 1.4	37.6 ± 0.1	37.2 ± 0.2	36.5 ± 0.5	.444
sPTB	0/8 (0%)	1/4 (25%)	0/1 (0%)	3/59 (5.1%)	1/27 (3.7%)	1/18 (5.6%)	3/108 (2.8%)	3/86 (3.5%)	4/21 (19.0%)	7/152 (4.6%)	4/55 (7.3%)	1/26 (3.8%)	15/196 (7.7%)	10/48 (20.8%)	10/22 (45.5%)	NR	NR	NR	28/523 (5.4%)	19/220 (8.6%)	16/88 (18.2%)	**<.0001**[bd]
iPTB	2/8 (25%)	2/4 (50%)	0/1 (0%)	19/59 (32.2%)	13/27 (48.1%)	11/18 (61.1%)	NR	NR	NR	22/152 (14.5%)	13/55 (23.6%)	12/26 (46.2%)	2/196 (1%)	1/48 (2.1%)	1/22 (4.5%)	NR	NR	NR	45/415 (10.8%)	29/134 (21.6%)	24/67 (35.8%)	**<.0001**[bcd]
Cesarean delivery	0/8 (0%)	0/4 (0%)	1/1 (100%)	15/59 (25.4%)	6/27 (22.2%)	5/18 (27.8%)	14/108 (13.0%)	14/86 (16.3%)	1/21 (4.8%)	58/152 (38.2%)	22/55 (40%)	9/26 (34.6%)	73/196 (37.2%)	20/48 (41.7%)	10/22 (45.5%)	58/325 (17.8%)	25/94 (26.6%)	6/30 (20%)	218/848 (25.7%)	87/314 (27.8%)	32/118 (27.1%)	.773
Meconium stained amniotic fluid	NR	NR	NR	6/59 (10.2%)	3/27 (11.1%)	7/18 (38.9%)	15/108 (13.9%)	19/86 (22.1%)	10/21 (47.6%)	15/152 (9.9%)	14/55 (27.3%)	9/26 (34.6%)	20/196 (10.2%)	13/48 (27.1%)	6/22 (27.3%)	20/325 (6.2%)	8/94 (8.5%)	5/30 (16.7%)	76/840 (9.0%)	57/310 (18.4%)	37/117 (31.6%)	**<.0001**[bcd]
PPH	NR	NR	NR	5/59 (8.5%)	0/27 (0%)	2/18 (11.1%)	3/108 (2.8%)	11/86 (12.8%)	2/21 (9.5%)	15/152 (9.9%)	7/55 (12.7%)	0/26 (0%)	5/196 (2.6%)	3/48 (6.3%)	0/22 (0%)	NR	NR	NR	28/515 (5.4%)	21/216 (9.7%)	4/87 (4.6%)	.075
Admission to NICU	NR	NR	NR	13/59 (22.0%)	6/27 (22.2%)	6/17 (35.3%)	1/108 (0.9%)	2/86 (2.3%)	2/21 (9.5%)	31/152 (20.4%)	15/55 (27.3%)	4/26 (15.4%)	10/196 (5.1%)	7/48 (14.6%)	4/22 (18.2%)	55/325 (16.9%)	17/94 (18.1%)	8/30 (26.7%)	110/840 (13.1%)	47/310 (15.2%)	24/116 (20.7%)	.08
Birthweight	NR	NR	NR	3067 ± 483	3071 ± 585	2716 ± 690	3290	3180	2930	3096 ± 444	3012 ± 454	2751 ± 650	3256 ± 538	3125 ± 545	2758 ± 514	NR	NR	NR	3155 ± 35.5	3057 ± 65.1	2746 ± 108.5	**.029**[b]
SGA	NR	NR	NR	NR	NR	NR	8/108 (7.4%)	4/86 (4.7%)	1/21 (4.8%)	NR	NR	NR	12/196 (6.1%)	1/48 (2.1%)	1/22 (4.5%)	20/325 (6.2%)	6/94 (6.4%)	3/30 (10%)	40/629 (6.4%)	11/228 (4.8%)	5/73 (6.8%)	.673
Apgar score <7 at 5 min	NR	NR	NR	1/59 (1.7%)	0/27 (0%)	1/17 (5.9%)	0/108 (0%)	0/86 (0%)	0/21 (0%)	1/152 (0.7%)	0/55 (0%)	4/26 (15.4%)	1/196 (0.5%)	1/48 (2.1%)	1/22 (4.5%)	2/325** (0.6%)	1/94** (1.1%)	0/30** (0%)	5/762 (0.7%)	2/310 (0.6%)	6/116 (5.2%)	**<.0001**[bd]

GA: gestational age; sPTB: spontaneous preterm birth; iPTB: iatrogenic preterm birth; CD: cesarean delivery; PPH: postpartum hemorrhage; NICU: neonatal intensive care unit; SGA: small for gestational age; NR, not reported.

p values are reported in bold when reaching statistical significance.

*Defined as including both stillbirths (defined as a fetal death ≥ 20 weeks or as defined by authors) and neonatal deaths (deaths before 28 d of life).

**Apgar score <5 at 5 min.

[a]Number reported as a median.

[b]Significant difference between mild and severe.

[c]Significant difference between mild and moderate.

[d]Significant difference between moderate and severe.

Table 6. Available details on perinatal deaths.

Stillbirth/ neonatal deaths	Highest TBA level (μmol/L)	GA at death/ neonatal days of life	Circumstances of death	Stillbirth/ neonatal deaths	Highest TBA level (μmol/L)	Fetal neonatal autopsy
Lee						
Patient 1	Stillbirth	113.5	30 0/7	Chief complaint of no fetal movement for 1 day, no cardiac motion seen on ultrasound	Ursodeoxycholic acid, 900 mg daily (selfdiscontinued after taking the medication for only 1 month)	Declined
Kawakita						
Patient 1	Stillbirth	261	37 1/7	Came to L&D for induction and found to have stillbirth.	NR	Declined
Patient 2	Stillbirth	509.1	35 3/7	Normal BPP one day before stillbirth. Presented with decreased fetal movements	Ursodeoxycholic acid, 1200 mg daily (compliant)	Declined
Patient 3	Stillbirth	128	24 1/7	Diagnosed at 23 weeks.	Ursodeoxycholic acid 1000 mg daily	Declined
Patient 4	Stillbirth	114	35 5/7	Stillbirth even with improving bile acid	Urosodeoxycholic acid 1000 mg daily	Declined
Furrer						
Patient 1	Extreme prematurity	18.4	22 1/7	Chorioamnionitis, extreme premature delivery	None	Declined
Patient 2	neonatal death	114.6	29 4/7	Hydrops fetalis, hydrothorax, polyhydramnios, pathologic CTG, death in the first hour after birth, intubation not possible	Ursodeoxycholic acid, 1350 mg daily, Colestyramine 8 g daily	Declined
Patient 3	Stillbirth	13	33 2/7	PPROM at 32 5/7, fetal lung maturation and tocolysis because of contraction, no sign of chorioamnionitis, stillbirth at 33 2/7	Ursodeoxycholic acid 1800 mg daily	Declined
Herrera						
Patient 1	Stillbirth	47	35	Decreased fetal movement after reactive NST one day prior	NR	Acute hypoxemia, placental infarction, wavy cardiac myocytes
Patient 2	Stillbirth	31	23	Decreased fetal movement	NR	Short umbilical cord with tight nuchal, acute asphyxia

L&D: labor and delivery; BPP: biophysical profile; CTG: cardiotocography; PPROM: premature prelabor rupture of membranes; NST: nonstress test; NR: not reported
Data from Brouwers were not available.

support the previous recommendation to deliver all cases of ICP 10-99 μmol/L by 37 weeks of gestation [2,11]. Additionally, the included studies report differences in the timing of delivery of the explored population. Lastly, TBA results may be affected by different laboratory tests ordered or by the institution or type of lab. Thus utilizing absolute numbers of 40 or 100 μmol/L may be misleading if the scale of a local laboratory differs widely from the scales used by the included studies.

Conclusions and implications

Maternal TBA $\geq$ 100 μmol/L is associated with a 6.8% incidence of perinatal death, most of which (5.9% overall) are stillbirths, while TBA $<$ 100 μmol/L are associated with an incidence of perinatal death of 0.3%. It may be reasonable to consider late preterm delivery (at about 35–36 weeks) in women with TBA $\geq$ 100 μmol/L.

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References

[1] Tran TT, Ahn J, Reau NS. ACG clinical guideline: liver disease and pregnancy. Am J Gastroenterol. 2016; 111(2):176–194.

[2] Royal College of Obstetricians and Gynaecologists. Obstetric cholestasis. Green-top guideline no. 43. London: Royal College of Obstetricians and Gynaecologists; 2011.

[3] Diken Z, Usta IM, Nassar AH. A clinical approach to intrahepatic cholestasis of pregnancy. Am J Perinatol. 2014;31(1):1–8.

[4] Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: relationships between bile acid levels and fetal complication rates. Hepatology. 2004;40(2):467–474.

[5] Brouwers L, Koster MP, Page-Christiaens GC, et al. Intrahepatic cholestasis of pregnancy: maternal and fetal outcomes associated with elevated bile acid levels. Am J Obstet Gynecol. 2015;212(1):100.e1–100.e7.

[6] Kawakita T, Parikh LI, Ramsey PS, et al. Predictors of adverse neonatal outcomes in intrahepatic cholestasis of pregnancy. Am J Obstet Gynecol. 2015;213(4): 570.e1–570.e8.

[7] Geenes V, Lövgren-Sandblom A, Benthin L, et al. The reversed feto-maternal bile acid gradient in intrahepatic cholestasis of pregnancy is corrected by ursodeoxycholic acid. PLoS One. 2014;9(1):e83828.

[8] Williamson C, Hems LM, Goulis DG, et al. Clinical outcome in a series of cases of obstetric cholestasis identified via a patient support group. BJOG. 2004;111(7): 676–681.

[9] Williamson C, Miragoli M, Sheikh Abdul Kadir S, et al. Bile acid signaling in fetal tissues: implications for intrahepatic cholestasis of pregnancy. Dig Dis. 2011; 29(1):58–61.

[10] Sepúlveda WH, González C, Cruz MA, et al. Vasoconstrictive effect of bile acids on isolated human placental chorionic veins. Eur J Obstet Gynecol Reprod Biol. 1991;42(3):211–215.

[11] Geenes V, Chappell LC, Seed PT, et al. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population-based case-control study. Hepatology. 2014;59(4): 1482–1491.

[12] Cui D, Zhong Y, Zhang L, et al. Bile acid levels and risk of adverse perinatal outcomes in intrahepatic cholestasis of pregnancy: a meta-analysis. J Obstet Gynaecol Res. 2017;43(9):1411–1420.

[13] Ovadia C, Seed PT, Sklavounos A, et al. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: results of aggregate and individual patient data meta-analyses. Lancet. 2019;393(10174):899–909.

[14] Higgins JPT, Altman DG ,Sterne JAC. 2001. Cochrane handbook for systematic reviews of interventions. The Cochrane Collaboration, version 5.1.0 [updated 2011 March; accessed 2015 Dec 20]. Available at www.cochrane-handbook.org

[15] Wells GA, Shea B, O'Connell D et al. Newcastle-Ottawa Scale for assessing the quality of non randomised studies in meta-analyses. Available at www.ohri.ca/programs/clinical_epidemiology/oxford.asp

[16] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10): 1006–1012.

[17] Ambros-Rudolph CM, Glatz M, Trauner M, et al. The importance of serum bile acid level analysis and treatment with ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: a case series from central Europe. Arch Dermatol. 2007;143(6):757–762.

[18] Lee RH, Kwok KM, Ingles S, et al. Pregnancy outcomes during an era of aggressive management for intrahepatic cholestasis of pregnancy. Amer J Perinatol. 2008;25(6):341–345.

[19] Furrer R, Winter K, Schäffer L, et al. Postpartum blood loss in women treated for intrahepatic cholestasis of pregnancy. Obstet Gynecol. 2016;128(5):1048–1052.

[20] Herrera CA, Manuck TA, Stoddard GJ, et al. Perinatal outcomes associated with intrahepatic cholestasis of pregnancy. J Matern Fetal Neonatal Med. 2018;31(14): 1913–1920.

[21] Palmer KR, Xiaohua L, Mol BW. Management of intrahepatic cholestasis in pregnancy. Lancet. 2019; 393(10174):853–854.

[22] Oztekin D, Aydal I, Oztekin O, et al. Predicting fetal asphyxia in intrahepatic cholestasis of pregnancy. Arch Gynecol Obstet. 2009;280(6):975–979.

[23] Puljic A, Kim E, Page J, et al. The risk of infant and fetal death by each additional week of expectant management in intrahepatic cholestasis of pregnancy by gestational age. Am J Obstet Gynecol. 2015;212(5): 667.e1–667.e5.

[24] Kong X, Kong Y, Zhang F, et al. Evaluating the effectiveness and safety of ursodeoxycholic acid in treatment of intrahepatic cholestasis of pregnancy: a meta-analysis (a prisma-compliant study). Medicine (Baltimore). 2016;95(40):e4949.

[25] Gurung V, Middleton P, Milan SJ, et al. Interventions for treating cholestasis in pregnancy. Cochrane Database Syst Rev. 2013;6(6)CD000:493.