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Relationship between Bile Acids Levels and Perinatal Complication Rates in Women with Intra Hepatic Cholestasis of Pregnancy: A Hospital based prospective study

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Abstract

Introduction: Intrahepatic cholestasis of pregnancy (IHCP), characterized by pruritus in the second half of pregnancy, entails an increased risk to the fetus. This study was designed to determine the incidence and fetal complication rates in IHCP, and to define groups at increased risk.

Material and methods: This case-control study compares 50 pregnancies affected by intrahepatic cholestasis (pruritus and bile acid >10µmol/L) with 50 low-risk pregnancies managed between January 2016 and December 2016 at Panna Dhaya Zanana Hospital (PDZH), RNT Medical College, Udaipur. Patients were followed up till delivery for any adverse obstetrical, maternal and neonatal outcome.

Results: There were 30 (60%) cases of mild cholestasis (10≤BA≤39µmol/L), 16 (32%) of moderate cholestasis (40≤BA≤99µmol/L), and 4 (8%) of severe cholestasis (BA ≥100µmol/L). This risk was also significant after adjustment for gestational age at birth and mode of delivery, adjusted. The postpartum haemorrhage rate was twice as high among the case mothers. The rates of admission to neonatal intensive care units was approximately three times higher in the cholestasis than the control group. Moreover, neonatal morbidity was higher in cholestasis cases compared to controls.

Conclusion: After adjustment on the confounding factors we found a higher rate of respiratory distress syndrome and neonatal morbidity among neonates of the cholestasis group.

Keywords: Intra hepatic cholestatis of pregnancy, Bile Acids, Ursodeoxycholic acid, Pruritus, Antenatal care

Introduction

Intrahepatic cholestasis of pregnancy (IHCP) also known as prurigo gravidarum, is the most common liver disease during pregnancy. It occurrs most often during the third trimester and sometimes in the second trimester. It is characterized by pruritus. It persists until delivery, after which it ceases usually within 2-3 weeks postpartum. Studies have shown IHCP to be associated with increased risk of preterm delivery in 19%–60%, [1-4] intrapartum fetal distress in 22%–41%, and

intrauterine fetal death (IUFD) in 0.75% – 1.6% of the affected pregnancies. [2–5]. IHCP is defined by pruritus sine materia (without lesions), with elevated levels of serum bile acids (BA) (>10 μmol/L), and liver enzymes. Its pathogenesis is still unknown, but hormonal influence and the MDR3 mutation gene (multidrug resistance 3) may contribute to it. High bile acid levels have also been associated with increased risk of MSAF [6]. This is very relevant because the exposure of fetal lung to toxic levels of these molecules can result in lung injury, through alteration of secretory phospholipase A2 [7,8]. Previous studies of fetal effects have suggested that IHCP is associated with a higher rate of adverse neonatal outcomes including preterm birth, neonatal respiratory distress syndrome (RDS) [9], meconium-stained amniotic fluid [10], neonatal intensive care unit admission, and stillbirth. Symptoms and abnormal liver function are spontaneously reversible after delivery, with good maternal prognosis. Moreover, maternal treatment with ursodeoxycholic acid (UDCA) improves pruritus and laboratory abnormalities and extends pregnancy [11]. The risk of serious adverse events for the fetus, such as spontaneous and iatrogenic preterm delivery, fetal distress and intrauterine fetal death, is directly proportional to the severity of hypercholanemia [12-14]. The most popular way of establishing the severity of IHCP is based on the magnitude of the highest peak of serum bile acid levels measured at any time after diagnosing IHCP, usually late in the patient follow-up before delivery. A correlation between the degree of hypercholanemia and the occurrence of adverse fetal events was found [12-14].

The risk of perinatal mortality has been shown to be reduced by delivery at 36 weeks of gestation as compared with expectant management [15], although this study did not consider bile acid concentrations when deciding about timing of delivery [16]. A recent meta-analysis has shown that the close monitoring of IHCP patients and treatment with UDCA are beneficial and account for a reduction in the rate of adverse pregnancy outcomes reported in the last years [17]. Furthermore, IHCP is associated with long-term effects on the health of the offspring, including susceptibility to increased adiposity and metabolic disease [18]. Changes in serum levels of estrogens [19] and progesterone derivatives have been described in asymptomatic hypercholanemia of pregnancy [20] and IHCP [21], but no clear association with the severity of hypercholanemia has been reported except for progesterone sulphates, which have been proposed as prognostic indicators for IHCP [22]. Using a decision-analytic model to determine the optimal gestational age, delivery at 36 weeks of gestation without amniocentesis or corticosteroid administration has been found by another study to reduce neonatal morbidity and mortality [23]. It was also found that induction of labour at 37 weeks of gestation in high-risk IHCP (>40 μmol/L total bile acid concentration) was justified and led only to a reduction in birth weight compared to women with lower serum bile acids [24]. Our level III reference centre, uses active management of IHCP, defined by weekly clinical and laboratory monitoring with systematic induction of labor before or by 38 weeks of gestation. The exact term depends on its severity. This active attitude aims to avoid stillbirth [25], although its imputability to cholestasis has not been clearly established [26,27]. Nowadays, elevation of serum bile acids is considered to be the most appropriate laboratory parameter for diagnosis of the condition.[28-31]. It is reasonable to believe that IHCP constitutes a continuum, ranging from light to severe

forms, but there has been an absence of algorithms to identify pregnancies entailing increased fetal risk. The aims of this prospective study were to determine the incidences of pruritus of pregnancy and IHCP, and to investigate whether fetal complication rates correlated to the severity of the disease, measured by bile acid levels in maternal serum.

Aim And Objective

The objective was to compare the neonatal and maternal consequences in pregnancies affected by intrahepatic cholestasis and normal pregnancies.

Material and methods

Patient selection

This investigation was conducted using data collected prospectively from January 2016 to December 2016 at the Panna Dhaya Zanana Hospital, RNT Medical College, Udaipur. Women with fasting hypercholanemia (serum bile acid levels _10 μmol/L) and pruritus of unexplained cause were invited to participate in the study. A total of 50 women with IHCP were compared to 50 women with normal S.bile acids and no pruritus serving as control group.

The exclusion criteria were:

Patients with any other hepatic disease or other diseases affecting liver function tests

Multiple-fetal pregnancies

Patients delivering at another institution.

Patients with previous history of preterm delivery

According to the amount of hypercholanemia at diagnosis, the study patients were classified into 3 groups. Apart from the well recognised severe ICP (>40 μmol/L), two additional groups of mild (10±19.9 μmol/L) and moderate (20±39.9 μmol/L) ICP were defined for fine-tuning of the relationship between hypercholanemia and adverse outcome. Maternal age, parity and adverse events were evaluated: stillbirth, perinatal death (between 24th week of gestation and 4 weeks after delivery), meconium aspiration syndrome (babies with infiltrates on chest X-ray), gestational age at delivery, preterm birth (<37 weeks of gestation, spontaneous or elective), MSAF, placental abruption, altered fetal vitality (5 min Apgar <7), fetal well-being (normal cardiotocograph trace), and neonatal intensive care unit admission.

Statistical analysis

Where the data are shown as mean±SD, an ANOVA test was performed and the Bonferroni method of multiple-range testing was used to calculate the statistical significance of differences among groups. Categorical variables were compared with Chi-square or Fisher's exact tests. A probability of <0.05 was considered statistically significant. Stata software 11 (StataCorp, College Station, Texas, USA) was used for statistical analyses. The study is reported according to STROBE guidelines.

Ethical approval

Written informed consent from all patients was obtained. The study was reviewed and approved by the Medical Ethics Committee of the Hospital.

Results

Table 1: Maternal characteristics of women with intrahepatic cholestasis of pregnancy and the control group.

	CASE GROUP	CONTROL GROUP	P VALUE
MATERNAL AGE(YEARS)	26(20-32)	26.5 (21-30)	0.59
PRIMIPAROUS(Y/N)	35(70%)	30(60%)	0.29
MULTIPAROUS(Y/N)	15(30%)	20(40%)	0.29
BMI	23.5(21.8-26.7)	22.65 (20.8-24.7)	<0.0001
PERSONAL HISTORY OF IHCP	13 (26%)	0	0.02
FAMILY HISTORY OF IHCP	6 (12%)	0	0.02
GESTATIONAL DIABETES	11 (22%)	5 (10%)	0.16

Table 1 shows maternal characteristics of women with intrahepatic cholestasis of pregnancy and the control group. Median age of case group is 26 and of control group it is 26.5 years. We calculated median for various parameter shown in table 1. There is significant difference in BMI and family history of IHCP as their p value is <0.05.

Table 2: Neonatal and maternal outcomes of pregnancies with intrahepatic cholestasis of pregnancy (IHCP).

	CASE GROUP	CONTROL GROUP	P- VALUE
OBSTETRIC OUTCOMES			
GESTATIONAL AGE AT BIRTH	37.5 (37-38)	39.5(39-40)	<0.0001
PRETERM DELIVERY BEFORE 37 WEEK	9(18%)	5(10%)	0.25
MECONIUM-STAINED FLUID	12(24%)	10(20%)	0.63
BIRTH WEIGHT(GRAMS)	3032(2890-3350)	3315(3150-3610)	<0.0001
MATERNAL OUTCOMES			
INDUCTION OF LABOUR	39(78%)	10(20%)	<0.0001
VAGINAL DELIVERY	33(66%)	45(90%)	0.003
CESAREAN DELIVERY DURING LABOUR	7(14%)	5(10%)	0.54
SCHEDULED CESAREAN DELIVERY	6(12%)	5(10%)	0.7
POSTPARTUM HEMORRHAGE	7(14%)	10(20%)	0.42
MATERNAL TRANSFUSION	1(2%)	5(10%)	0.09
NEONATAL OUTCOMES			
5-MIN APGAR SCORE <7	7(14%)	6(12%)	0.76
RESPIRATORY DISTRESS SYNDROME	12(24%)	7(14%)	0.2

MECHANICAL VENTILATION OR INTUBATION	2(4%)	5(10%)	0.24
ADMISSION TO NEONATAL INTENSIVE CARE UNIT	8(16%)	8(16%)	1
STILLBIRTH	0	0	0

In table 2, we found neonatal and maternal outcomes of pregnancies with intrahepatic cholestasis of pregnancy (IHCP). Here we classified this table in 3 categories named as Obstetric outcomes, Maternal outcomes and Neonatal outcomes. Their corresponding outcome is shown in table 2. We found significant difference in gestational age at birth and induction of labours between women with IHCP and controls as their p value is < 0.05.

Table 3: Clinical and laboratory characteristics according to the severity of intrahepatic cholestasis of pregnancy (IHCP)

	MILD CHOLESTASIS	MODRATE CHOLESTASIS	SEVERE CHOLESTASIS	P-VALUE
MEDIAN GESTATIONAL AGE AT DIAGNOSIS (WEEKS)	36(33-38)	35(33-38)	32.55(31.5-35)	0.003
MEDIAN GESTATIONAL AGE AT DELIVERY(WEEKS)	38(38-38)	38(37-38)	37.5(37-38)	0.0001
RESPIRATORY DISTRESS SYNDROME	6(20%)	5(31.2%)	2(50%)	0.16
BIOCHEMISTRY AT DIAGNOSIS				
BILE ACID	16(12-23)	40(21.2-55)	49.5(38-58)	0.001
ASPARTATE TRANSAMINASE	52(32-85)	96(46.5-170)	242.5(224-304)	0.0001
ALANINE TRANSAMINASE	88(40.6-154.2)	138(57-308)	468.5(158-478)	0.16
MOST SEVERE BIOCHEMISTRY				
BILE ACID	19(14-26)	55.5(43.2-207.9)	134.5(131-140)	0.0001
ASPARTATE TRANSAMINASE	53(34-96)	95.5(54-206.4)	237.5(224-323)	<0.001
ALANINE TRANSAMINASE	78(38-160)	112(54-296)	468.5(246-478)	<0.001
TREATMENT				
URSODEOXYCHOLIC ACID TREATMENT	9(30%)	14(87.5%)	3(75%)	0.3
TERM AT BA NORMALIZATION	36(35-38).	36(35-38)	32(32-32)	<0.0001
STANDARDIZATION TIME	7.5(3.8-28)	12.25(10-28)	16(16-16)	0.0006

PRURITUS DISAPPEARANCE	9(30%)	4(25%)	0	0.72
BIOCHEMISTRY AT DELIVERY				
BILE ACID	12(8-23)	29.5(13-48)	74(46.1-78.1)	<0.001
ASPARTATE TRANSAMINASE	37(27-89)	56(26-94)	119.5(34-250)	<0.0001
ALANINE TRANSAMINASE	58(30-138)	58(27-157	189.5(42.5-540)	<0.001
PROTHROMBIN TIME	102(92-112)	100(98-112)	100(98-100)	0.87
POSTPATUM HEMOGLOBIN	12.1(12-13)	11.7(10.6-13)	11.55(11.4-12.2)	0.9

In table 3, we found clinical and laboratory characteristics according to the severity of intrahepatic cholestasis of pregnancy (IHCP). Their data are shown in table 3.

Discussion

During our study period, no stillbirths occurred in either group. After adjusting the confounding factors, a higher rate of RDS and neonatal morbidity was found among neonates of the cholestasis group. Mothers with IHCP had more postpartum hemorrhages than control women, without a proportionate rise in requirement for blood transfusions. The RDS rate was three times higher among neonates of the cholestasis group, similar to findings from other studies. Zecca et al, in a case-control study (matching on gestational age) showed a risk of RDS in IHCP newborns 2.5 times higher than in control infants regardless of the magnitude of hypercholanemia [9]. A study by Sengupta S et al morbidity in the IHCP cases was higher than that in the control population delivered in the same late preterm period [Z13]. Hypothesis by Zecca E et al to explain increased neonatal morbidity among case infants include a direct effect of BA on neonatal lung, which could be induce a “bile acid pneumonia” [9,33]. Kawakita T et al however showed, no significant differences in acid-base status or meconium staining during labor, contrary to other studies [34]. Chappell L C showed the PITCHES trial outcome was to evaluate perinatal outcome in IHCP-affected pregnancies of ursodesoxycholic acid versus placebo [35]. Authors funded that treatment with ursodeoxycholic acid does not reduce adverse perinatal outcomes. Wikstrom S E et al found the proportion of women with diabetes was higher among IHCP cases compared with control, as expected from previous studies [36]. Kawakita T et al found the risk of stillbirth seems to increase after 37 weeks and is rare before 34 weeks. Ovadia C et al found increase with BA level [34], when serum bile acids concentrations are of 100μmol/ L or more [37]. Sentilhes L found that the bile acids are not an infallible surveillance marker, and the level can rise abruptly, as shown by the serious accidents reported in this context [26]. Ethnicity (Latino, native American) is also a reported risk factor for stillbirths associated with cholestasis [38], but these ethnicities were not represented in our study. Similar study by Quigley M A et al in IHCP, stillbirth prevention must be weighed against the long-term consequences of “late preterm” birth [39]. Although the American College of Obstetricians and Gynecologists recommends active management, the ideal time for termination of pregnancy has not been advised. Similar study by Quigley M A et al advocate that 36 weeks of gestation is the best compromise between the risks of preterm delivery and the risk of stillbirth or neonatal death [39]. However, our results do not support systematic delivery at this late preterm gestational age. The Royal College of Obstetrics and Gynaecology also, does not

recommend systematic active management [40]. Henderson E et al on the other hand conclude that if IHCP is associated with stillbirth, which it does not consider statistically proven, the risk is clinically insignificant [27]. Regarding maternal outcomes, the planned cesarean rate was significantly higher in IHCP cases. Induction of labor for women with IHCP did not increase the emergency cesarean rate [41]. Khireddine et al found the postpartum hemorrhage rate was higher in IHCP cases, probably related to their higher rates of cesarean delivery and of oxytocin-induced labor [42]. In our study, however, we did not observe any differences in the transfusion rates or maternal hemostasis problems, consistent with Brouwers et al. [43]. Our study nonetheless has some limitations. It was a retrospective study with potential bias. Thus, we chose to report and analyze the rates of RDS rather than neonatal unit admission to limit reporting bias.

Conclusion

Although no marker can rule out the onset of in utero fetal death, weekly clinical and laboratory monitoring appear beneficial and essential. Treatment with ursodeoxycholic acid does not reduce adverse perinatal outcomes, but may provide symptomatic relief [35]. The adverse pregnancy outcomes associated with intrahepatic choles tasis of pregnancy have been clarified by thus study and also identified that women with serum bile acids of 100 µmol/L or more have a significantly increased risk of stillbirth. Future research should target mechanistic explanations for the increased risk of stillbirth in intrahepatic cholestasis of pregnancy and the potential of specific treatments to prevent fetal death.

References

1. Bacq Y, Sapey T, Brechot MC, Pierre F, Fignon A, Dubois F. Intrahepati cholestasis of pregnancy: a French prospective study. HEPATOLOGY 1997; 26:358 –364.
2. Fisk NM, Storey GN. Fetal outcome in obstetric cholestasis. Br J Obstet Gynaecol 1988;95:1137–1143.
3. Rioseco AJ, Ivankovic MB, Manzur A, Hamed F, Kato SR, Parer JT, et al. Intrahepatic cholestasis of pregnancy: a retrospective case-control study of perinatal outcome. Am J Obstet Gynecol 1994;170:890–895.
4. Alsulyman OM, Ouzounian JG, Ames-Castro M, Goodwin TM. Intrahepatic cholestasis of pregnancy: perinatal outcome associated with expectant manegement. Am J Obstet Gynecol 1996;175:957–960.
5. Laatikainen T, Tulenheimo A. Maternal serum bile acid levels and fetal distress in cholestasis of pregnancy. Int J Gynaecol Obstet 1984;22:91–94.
6. Kawakita T, Parikh LI, Ramsey PS, Huang CC, Zeymo A, Fernandez M, et al. Predictors of adverse neonatal outcomes in intrahepatic cholestasis of pregnancy. Am J Obstet Gynecol. 2015; 213: 570 e1±8.
7. De Luca D, Minucci A, Zecca E, Piastra M, Pietrini D, Carnielli VP, et al. Bile acids cause secretory phospholipase A2 activity enhancement, revertible by exogenous surfactant administration. Intensive Care Med. 2009; 35: 321±6.
8. Herraez E, Lozano E, Poli E, Keitel V, De Luca D, Williamson C, et al. Role of macrophages in bile acid induced inflammatory response of fetal

lung during maternal cholestasis. J Mol Med (Berl). 2014; 92:359±72.

9. Allen AM, Kim WR, Larson JJ, et al. The epidemiology of liver diseases unique to pregnancy in a US community: a population-based study. Clin Gastroenterol Hepatol 2016;14: 287–94.
10. Marathe JA, Lim WH, Metz MP, Scheil W, Dekker GA, Hague WM. A retrospective cohort review of intrahepatic cholestasis of pregnancy in a South Australian population.
11. Lin J, Gu W, Hou Y. Diagnosis and prognosis of early-onset intrahepatic cholestasis of pregnancy: a prospective study.J Matern Fetal Neonatal Med 2017; published online Nov 7.DOI:10.1080/14767058.2017.1397124 (preprint).
12. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. Hepatology. 2004; 40: 467±74. https://doi.org/10.1002/hep.20336 PMID: 15368452
13. Geenes V, Chappell LC, Seed PT, Steer PJ, Knight M, Williamson C. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population-based case-control study. Hepatology. 2014; 59: 1482±91. https://doi.org/10.1002/hep.26617 PMID: 23857305
14. Brouwers L, Koster MP, Page-Christiaens GC, Kemperman H, Boon J, Evers IM, et al. Intrahepatic cholestasis of pregnancy: maternal and fetal outcomes associated with elevated bile acid levels. Am J Obstet Gynecol. 2015; 212: 100 e1±7.
15. Puljic A, Kim E, Page J, Esakoff T, Shaffer B, LaCoursiere DY, 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: 667 e1±5.
16. Wensink MJ. The risk of infant and fetal death by each additional week of expectant management in intrahepatic cholestasis of pregnancy by gestational age: various objections. Am J Obstet Gynecol. 2016; 215: 807±8. https://doi.org/10.1016/j.ajog.2016.07.033 PMID: 27448733
17. Bacq Y, Sentilhes L, Reyes HB, Glantz A, Kondrackiene J, Binder T, et al. Efficacy of ursodeoxycholic acid in treating intrahepatic cholestasis of pregnancy: a meta- analysis. Gastroenterology. 2012; 143: 1492±501. https://doi.org/10.1053/j.gastro.2012.08.004 PMID: 22892336\
18. Papacleovoulou G, Abu-Hayyeh S, Nikolopoulou E, Briz O, Owen BM, Nikolova V, et al. Maternal cholestasis during pregnancy programs metabolic disease in offspring. J Clin Invest. 2013; 123: 3172±81. https://doi.org/10.1172/JCI68927 PMID: 23934127
19. Leslie KK, Reznikov L, Simon FR, Fennessey PV, Reyes H, Ribalta J. Estrogens in intrahepatic cholestasis of pregnancy. Obstet Gynecol. 2000; 95: 372±6. PMID: 10711547
20. Pascual MJ, Serrano MA, El-Mir MY, Macias RI, Jimenez F, Marin JJ. Relationship between asymptomatic hypercholanaemia of pregnancy and progesterone metabolism. Clin Sci (Lond). 2002; 102: 587±93.

21. Estiu MC, Monte MJ, Rivas L, Moiron M, Gomez-Rodriguez L, Rodriguez-Bravo T, et al. Effect of ursodeoxycholic acid treatment on the altered progesterone and bile acid homeostasis in the mother-Prediction of meconium-stained fluid in ICP PLOS placenta-foetus trio during cholestasis of pregnancy. Br J Clin Pharmacol. 2015; 79: 316±29. https://doi. org/10.1111/bcp.12480 PMID: 25099365
22. Abu-Hayyeh S, Ovadia C, Lieu T, Jensen DD, Chambers J, Dixon PH, et al. Prognostic and mechanistic potential of progesterone sulfates in intrahepatic cholestasis of pregnancy and pruritus gravidarum. Hepatology. 2016; 63: 1287±98. https://doi.org/10.1002/hep.28265 PMID: 26426865
23. Lo JO, Shaffer BL, Allen AJ, Little SE, Cheng YW, Caughey AB. Intrahepatic cholestasis of pregnancy and timing of delivery. J Matern Fetal Neonatal Med. 2015; 28: 2254±8. https://doi.org/10.3109/14767058.2014.984605 PMID: 25371372
24. Friberg AK, Zingmark V, Lyndrup J. Early induction of labor in high-risk intrahepatic cholestasis of pregnancy: what are the costs? Arch Gynecol Obstet. 2016; 294: 709±14. https://doi.org/10.1007/s00404-016-4019-8 PMID: 26825731
25. Laatikainen T, Ikonen E. Serum bile acids in cholestasis of pregnancy. Obstet Gynecol 1977; 50: 313–18. 26. Reddy UM, Goldenberg R, Silver R, et al. Stillbirth classification—developing an international consensus for research. Obstet Gynecol2009; 114: 901–14.
26. Herrera CA, Manuck TA, Stoddard GJ, et al. Perinatal outcomes associated with intrahepatic cholestasis of pregnancy. J Matern Fetal Neonatal Med 2018; 31: 1913–20.
27. Shaw D, Frolich J, Wittman BA, Willms M. A prospective study of 18patients with cholestasis of pregnancy. Am J Gynecol 1982;142:621– 625.
28. Fisk N, Bye WB, Storey B. Maternal features of obstetric cholestasis: 20 years experience at King George V Hospital. Aust N Z J Obstet Gynaecol 1988;28:172–176.
29. Brites D, Rodrigues CM, van-Zeller H, Brito A, Silva R. Relevance of serum bile acid profile in the diagnosis of intrahepatic cholestasis of pregnancy in a high incidence area: Portugal. Eur J Obstet Gynecol Reprod Biol 1998;80:31–38.
30. Laatikainen T, Ikonen E. Serum bile acids in cholestasis of pregnancy. Obstet Gynecol 1977;50:313–318.
31. Tran TT, Ahn J, Reau NS. ACG clinical guideline: liver disease and pregnancy. Am J Gastroenterol 2016; 111: 176–94.
32. Henderson CE, Shah RR, Gottimukkala S, Ferreira KK, Hamaoui A, Mercado R. Primum non nocere: how active management became modus operandi for intrahepatic cholestasis of pregnancy. Am J Obstet Gynecol 2014; 211: 189–96.
33. MacKay DF, Smith GCS, Dobbie R, Pell JP. Gestational age at delivery and special educational need: retrospective cohort study of 407 503 schoolchildren. PLoS Med 2010; 7: e1000289.
34. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008; 371: 261–69.
35. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile

range. BMC Med Res Methodol 2014; 14: 1–13.

36. Abbott DS, Radford SK, Seed PT, Tribe RM, Shennan AH. Evaluation of a quantitative fetal fibronectin test for spontaneous preterm birth in symptomatic women. Am J Obstet Gynecol 2013;208: 122.e1–6.
37. Sunkara SK, Khalaf Y, Maheshwari A, Seed P, Coomarasamy A. Association between response to ovarian stimulation and miscarriage following IVF: an analysis of 124 351 IVF pregnancies. Hum Reprod 2014; 29: 1218–24.
38. Kramer MS, Liu S, Luo Z, Yuan H, Platt RW, Joseph KS. Analysis of perinatal mortality and its components: time for a change? Am J Epidemiol 2002; 156: 493–97.
39. Geenes V, Chappell LC, Seed PT, Steer PJ, Knight M, Williamson C. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population-based case-control study. Hepatology 2014; 59: 1482–91.
40. Furrer R, Winter K, Schaffer L, Zimmermann R, Burkhardt T, Haslinger C. Postpartum blood loss in women treated for intrahepatic cholestasis of pregnancy. Obstet Gynecol 2016; 128: 1048–52.
41. Grymowicz M, Czajkowski K, Smolarczyk R. Pregnancy course in patients with intrahepatic cholestasis of pregnancy treated with very low doses of ursodeoxycholic acid. Scand J Gastroenterol 2016; 51: 78–85.
42. Zhang Y, Hu L, Cui Y, et al. Roles of PPARγ/NF-κB signaling pathway in the pathogenesis of intrahepatic cholestasis of pregnancy. PLoS One 2014; 9: 1–11.