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Original Article

Obstetrics and Gynaecology Section

Maternal and Foetal Outcomes in Early and Late Intrahepatic Cholestasis of Pregnancy and their Association with Maternal Serum Bile Acid Levels: A Prospective Cohort Study

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ABSTRACT

Introduction: Intrahepatic Cholestasis of Pregnancy (IHCP) also known as recurrent jaundice of pregnancy is a pregnancy specific benign liver disease presenting in the second and third trimester of pregnancy and is associated with increased perinatal morbidity and mortality.

Aim: To study and compare the maternal and foetal outcomes in early and late IHCP and to evaluate the Serum Bile Acid (SBA) levels and its association with adverse maternal and foetal outcomes at a tertiary care hospital in New Delhi.

Materials and Methods: This was an observational, prospective cohort study, conducted during September 2018 to March 2020 in the Department of Obstetrics and Gynaecology, ESI PGIMSR, Basaidarapur, New Delhi, India. A total of 196 antenatal women with clinical signs and symptoms suggestive of IHCP with deranged liver function tests were grouped on the basis of period of gestation as early IHCP (diagnosed ≤32 weeks) comprising of 40 women, and late IHCP (diagnosed >32 weeks), comprising of 156 women. They were further divided into four groups A, B, C, D on the basis of the maternal Serum Bile Acid (SBA) levels between 10-19 mmol/L, 20-29 mmol/L, 30-39 mmol/L and ≥40 mmol/L, respectively. Maternal outcomes such as caesarean rates, instrumental delivery, postpartum haemorrhage, blood transfusion, hospital stay and foetal outcomes such as preterm birth, birth weight, Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score, Neonatal Intensive Care Unit (NICU) admission, intrauterine foetal demise and neonatal death were noted and association was found by Pearson's Chi-square test or Fisher's-exact test.

Results: A total of 196 women (mean age 25.64±3.8 years, 40 in Early IHCP and 156 in late IHCP) were analysed for foetomaternal outcomes and were further divided into group A (n=138), group B (n=27), group C (n=13), and group D (n=18) on basis of maternal SBA. Adverse maternal outcomes such as high caesarean rates, instrumental delivery, postpartum haemorrhage, blood transfusion, prolonged hospital stay and adverse foetal outcomes such as preterm birth, low birth weight, low APGAR score, NICU admission, intrauterine foetal demise and neonatal death was more common in early IHCP in comparison to late IHCP ($p<0.05$). It was also observed that risk of adverse foetomaternal outcomes increased with increasing maternal SBA levels with maximum adverse outcomes seen in women with SBA ≥30 mmol/L i.e., Group C and D ($p<0.05$).

Conclusion: Women diagnosed with IHCP at an earlier gestation ≤32 weeks have more propensity towards adverse foetomaternal outcomes and significantly higher rate of adverse outcome was observed in patients with SBA level ≥30 mmol/L.

Keywords: Foetomaternal outcomes, Liver function tests, Meconium staining of liquor, Ursodeoxycholic acid

INTRODUCTION

The IHCP also known as recurrent jaundice of pregnancy, cholestatic hepatosis, and icterus gravidarum is a pregnancy specific benign liver disease presenting in the second and third trimester of pregnancy, typically characterised by pruritis with a predilection for palms and soles without any evidence of skin lesions along with biochemical tests demonstrating elevated serum aminotransferases and/or elevated SBA levels, without any underlying liver pathology such as Haemolysis, Elevated Liver Enzymes, and Low Platelets (HELLP) syndrome, hepatitis, obstructive jaundice. There is a spontaneous relief of symptoms and laboratory abnormalities promptly after delivery or within one month postpartum [1]. IHCP though relatively non threatening to women, has been reported to have important foetal implications.

Affected pregnancies have been associated with increased perinatal morbidity and mortality. It has been found to be associated with increased risk of preterm delivery, meconium staining of amniotic fluid, foetal bradycardia, foetal distress and foetal demise [2]. The incidence of IHCP has been found to be variable, affecting 0.1-1.5% of the population of Central and Western Europe and North America, and 1.5-4% in Chile and Bolivia [1]. There has been a rising trend of IHCP in India, with reported incidence rate rising from 0.79% [3] to 2.73% [4] over the decade. Although specific predictors for poor foetal outcome have not been consistently identified, higher bile acid levels >40 mmol/L were found to be associated with higher rates of foetal complications. Patients with IHCP are induced after 37 weeks of period of gestation [5]. Thus, this group of patients also deals with a higher frequency of complications such as instrumental delivery and higher caesarean rates as compared to spontaneous labour. Studies conducted on IHCP shows adverse foetal outcomes in 30-70% of affected pregnancies [6,7]. According to literature,70% pregnancies with IHCP present in the third trimester (mean 31 weeks) [8].

With increasing prevalence of IHCP in India and its well-known foetomaternal implications, the authors here aimed to compare the foetomaternal outcomes between early (≤32 weeks) and late IHCP (>32 weeks), focusing on determining whether the timing of onset of IHCP affects the foetomaternal outcomes.

MATERIALS AND METHODS

This was a prospective, cohort, observational study conducted in the Department of Obstetrics and Gynaecology, ESI PGIMSR,

New Delhi, India from September 2018 to March 2020. An ethical clearance has also been taken from the Institutional Ethical Committee. (Reg no ESIPGMSR-IEC/2018009). Informed consent was obtained from all the patients for being included in this study.

Inclusion criteria: Pregnant women in second and third trimester with pruritis predominant on the palm and soles along with deranged liver function tests and raised SBA levels (Aspartate transaminase >35 IU/L, Alanine transaminase >45 IU/L, SBA >10 mmol/L) which could not be defined by any other dermatologic, liver, gall bladder pathology were included in the study.

Excluding criteria: Women with underlying skin disorders, allergies, pre-eclampsia, HELLP, acute fatty liver of pregnancy, chronic liver diseases (symptomatic cholelithiasis, cholecystitis, primary biliary cirrhosis) or any ongoing infections affecting the liver were excluded from the study

Sample size calculation: Assuming (p)=50% as the expected foetal outcome [6,7] with 10% margin of error, the minimum required sample size at 5% level of significance was196 patients.

A total of one ninety six (196) antenatal women with clinical signs and symptoms suggestive of IHCP with deranged liver function tests in second or third trimester were included. In this study, 80% of patients presented after 32 weeks of pregnancy therefore patients were grouped as early IHCP (diagnosed ≤32 weeks) and late IHCP (diagnosed > 32 weeks). Forty (40) women were diagnosed before 32 weeks of period of gestation and one fifty six (156) women were diagnosed after 32 weeks. They were further divided into four groups A, B, C, D on the basis of maternal SBA levels ranging between 10-19 mmol/L, 20-29 mmol/L, 30-39 mmol/L and ≥40 mmol/L, respectively. Foetomaternal outcomes (mode of delivery, postpartum haemorrhage, blood transfusion, prolonged hospital stay, foetal birth weight, APGAR scores, meconium stained liquor, preterm, perinatal death, NICU admission) among each group were compared.

The SBA was estimated on automatic biochemistry analyser (Beckman Coulter) using the commercial kit from DIALAB. Patients were followed during their course of pregnancy till their delivery through regular antenatal checkups in the Outpatient Department (OPD) and additional visits if necessary. Topical emmolients and Ursodeoxycholic acid (UCDA 10-15 mg/kg/day upto maximum 300 mg 8 hourly per oral) was advised to all patients depending on the severity of disease, aiming to achieve completion of 37 weeks of gestation according to Royal College of Obstetricians and Gynaecologists (RCOG) Green top guidelines 2011 [5].

STATISTICAL ANALYSIS

Descriptive statistics were analysed with Statistical Package for Social Sciences (SPSS) version 17.0 software. Continuous variables were presented as mean±SD. Categorical variables were expressed as frequencies and percentages. The Pearson's Chi-square test or Fisher's-exact test was used to determine the relationship between two categorical variables. The p-value <0.05 was considered statistically significant and p-value <0.001 was considered highly significant.

RESULTS

Total of 196 pregnant patients , aged 18-40 years, were analysed in the study, with mean and median age of 25.64±3.8 years and 25 years respectively. Majority of patients 79.59% were diagnosed after 32 weeks of period of gestation (range 26.43-40.43) [Table/Fig-1]. The median gestational age at diagnosis was 36 weeks (range 34-37.57) [Table/Fig-1].

In majority of patients (70.41%) SBA values ranged from 10-19 mmol/L [Table/Fig-1].

Maternal outcomes: In present study, 58.16% patients had normal vaginal delivery and 5.61% had instrumental vaginal delivery (p<0.001). The most common indication for caesarean section was foetal distress (29.57%) [Table/Fig-2,3].

Parameters	Frequency (n)	Percentage
Age of subjects (years)		
18-20	11	5.61%
21-30	164	83.67%
31-40	21	10.71%
Mean±SD	25.64±3.8	
Median (IQR)	25 (23-28)	
Range	19-38	
Period of gestation at diagnosis (weeks)		
≤32 (Early IHCP)	40	20.41%
>32 (Late IHCP)	156	79.59%
Mean±SD	35.6±2.8	
Median (IQR)	36(34-37.57)	
Range	26.43-40.43	
SBA levels (mmol/L)		
10-19	138	70.41%
20-29	27	13.78%
30-39	13	6.63%
>40	18	9.18%
Mean±SD	20.13±14.1	
Median(IQR)	15 (12-21.7)	
Range	10-78.8	

[Table/Fig-1]: Demographic, clinical and biochemical profile of all study participants.

Mode of delivery	Spontaneous onset of labour (n=78)	Induction of labour (n=101)	Others (n=17)	Total	p-value
Caesarean delivery	10 (12.82%)	44 (43.56%)	17 (100%)	71 (36.22%)	<0.001
Instrumental vaginal delivery	2 (2.56%)	9 (8.91%)	0	11 (5.61%)	
Normal vaginal delivery	66 (84.62%)	48 (47.52%)	0	114 (58.16%)	
Total	78 (100%)	101 (100%)	17 (100%)	196 (100%)	

[Table/Fig-2]: Onset of labour and mode of delivery in study patients.
p-value calculated by Fisher-exact test

Indication of caesarean	Frequency	Percentage
Abruption	1	1.40%
Anhydramnios	3	4.22%
Antepartum Haemorrhage (APH)	2	2.81%
Arrest of descent	1	1.40%
Breech	1	1.40%
Cord prolapse	1	1.40%
Failed induction	13	18.30%
Foetal distress	21	29.57%
Meconium Stained Liquor (MSL)	13	18.30%
Non descent	1	1.40%
Non-progress of Labour (NPOL)	3	4.22%
Previous LSCS	8	11.26%
Scar tenderness	2	2.81%
Twin	1	1.40%
Total	71	100.00%

[Table/Fig-3]: Distribution of indication of caesarean in study subjects.
LSCS: Lower segment caesarean section

A highly significant difference in maternal outcomes between the early and late IHCP group was noted (p<0.05) with a higher rate

of caesarean section, instrumental vaginal delivery, postpartum haemorrhage, prolonged hospital stay and blood transfusion in early IHCP group [Table/Fig-4]. It was observed that the rates of adverse maternal outcomes increased with increasing maternal SBA levels (p<0.001) [Table/Fig-5].

Foetal outcomes: Early IHCP was associated with statistically significant higher chances of low birth weight, low APGAR, Meconium Stained Liqor (MSL), preterm delivery, neonatal death, NICU admission and Intrauterine Deaths (IUDs) as compared to late IHCP (p<0.05) [Table/Fig-6].

The rate of adverse foetal outcomes was observed to be increasing with increasing maternal SBA levels with maximum complications noted in group D (p <0.05) [Table/Fig-7].

DISCUSSION

The main finding was that IHCP diagnosed before 32 weeks of period of gestation is associated with a higher rate of adverse foetal and maternal complications. Over the years foetal outcome in IHCP has been closely studied. However, there is minimal data on adverse maternal outcomes of IHCP as it is thought to be relatively non threatening to women [9,10].

In present study, a significantly higher rate of adverse maternal outcomes such as caesarean section, instrumental vaginal delivery, postpartum haemorrhage, prolonged hospital stay, blood transfusion was noted in group C and D and those diagnosed before 32 weeks. Kenyon AP et al., has reported the incidence of postpartum haemorrhage in women with IHCP to be 17% [11]. On the contrary,

Maternal outcome	Early IHCP (gestational age <=32 years) (n=40)	Late IHCP (gestational age >32 weeks) (n=156)	Total	p-value	Odds ratio (95% CI)
Type of delivery					
Caesarean delivery	24 (60%)	47 (30.13%)	71 (36.22%)	<0.001	7.615 (2.005-28.926)
Instrumental vaginal delivery	5 (12.50%)	6 (3.85%)	11 (5.61%)		4.642 (2.118-10.172)
Normal vaginal delivery	11 (27.50%)	103 (66.03%)	114 (58.16%)		1
Postpartum haemorrhage	9 (22.50%)	9 (5.77%)	18 (9.18%)	**0.001**	4.683 (1.72-12.744)
Prolonged hospital stay	10 (25%)	9 (5.77%)	19 (9.69%)	**0.0002**	5.345 (2.003-14.265)
Blood transfusion	5 (12.50%)	4 (2.56%)	9 (4.59%)	**0.019**	5.25 (1.343-20.524)
Mortality	0 (0%)	0 (0%)	0 (0%)	-	-

[Table/Fig-4]: Comparison of maternal outcomes in early and late IHCP.
IHCP: Intrahepatic cholestasis of pregnancy; No mortality was reported in this study; Blood transfusion parameter's significance was calculated by Fisher-exact test while all other parameters significance was calculated by Chi-square test

Maternal outcome	Group A 10-19 mmol/L (n=138)	Group B 20-29 mmol/L (n=27)	Group C 30-39 mmol/L (n=13)	Group D ≥40 mmol/L (n=18)	Total	p-value
Type of delivery						
Caesarean delivery	37 (26.81%)	16 (59.26%)	8 (61.54%)	10 (55.56%)	71 (36.22%)	<0.001
Instrumental vaginal delivery	0	3 (11.11%)	3 (23.08%)	5 (27.78%)	11 (5.61%)	
Normal vaginal delivery	101 (73.19%)	8 (29.63%)	2 (15.38%)	3 (16.67%)	114 (58.16%)	
Postpartum haemorrhage	0	0	7 (53.85%)	11 (61.11%)	18 (9.18%)	<0.001
Prolonged hospital stay	3 (2.17%)	5 (18.52%)	4 (30.77%)	7 (38.89%)	19 (9.69%)	<0.001
Blood transfusion	0	0	2 (15.38%)	7 (38.89%)	9 (4.59%)	<0.001

[Table/Fig-5]: Association of maternal outcome with Serum Bile Acid (SBA) (mmol/L).
Fisher-exact test used to find significance

Foetal outcome	≤32 (n=40)	>32 (n=156)	Total	p-value	Odds ratio (95% CI)
Low birth weight	14 (35%)	14 (8.97%)	28 (14.29%)	<0.001	5.462 (2.333-12.786)
Low APGAR score	12 (30%)	8 (5.13%)	20 (10.20%)	<.0001	7.929 (2.971-21.158)
Meconium stained liquor	14 (35%)	22 (14.10%)	36 (18.37%)	**0.002**	3.280 (1.487-7.233)
Preterm	29 (72.50%)	32 (20.51%)	61 (31.12%)	<0.001	10.216 (4.611-22.632)
Neonatal death	8 (20%)	6 (3.85%)	14 (7.14%)	**0.0004**	6.250 (2.029-19.255)
NICU	21 (52.50%)	19 (12.18%)	40 (20.41%)	<0.001	7.970 (3.637-17.462)
Intrauterine death	4 (10%)	2 (1.28%)	6 (3.06%)	**0.017**	8.556 (1.508-48.536)

[Table/Fig-6]: Comparison of foetal outcome and in early and late IHCP.
p-value for IUD was calculated by Fisher-exact test while those of all other parameters were calculated by Chi-square test

Foetal outcome	Group A 10-19 mmol/L (n=138)	Group B 20-29 mmol/L (n=27)	Group C 30-39 mmol/L (n=13)	Group D >40 mmol/L (n=18)	Total	p-value
Low birth weight	10 (7.25%)	7 (25.93%)	5 (38.46%)	6 (33.33%)	28 (14.29%)	**0.0002**
Low APGAR score	4 (2.90%)	6 (22.22%)	4 (30.77%)	6 (33.33%)	20 (10.20%)	<0.001
Meconium stained liquor	13 (9.42%)	10 (37.04%)	3 (23.08%)	10 (55.56%)	36 (18.37%)	<0.001
Preterm	24 (17.39%)	16 (59.26%)	9 (69.23%)	12 (66.67%)	61 (31.12%)	<0.001
Neonatal death	2 (1.46%)	3 (11.11%)	3 (23.08%)	6 (33.33%)	14 (7.18%)	<0.001
NICU	10 (7.25%)	14 (51.85%)	6 (46.15%)	10 (55.56%)	40 (20.41%)	<0.001
Intrauterine death	0 (0%)	0 (0%)	2 (15.38%)	4 (22.22%)	6 (3.06%)	<0.001

[Table/Fig-7]: Association of foetal outcome with bile acid (mmol/L).
NICU: Neonatal Intensive Care, APGAR: Appearance, pulse, grimace, activity and respiration; *p-value for neonatal death was calculated by Fischers-exact test and rest parameters significance was calculated by Chi-square test

DeLeon A et al., found postpartum haemorrhage in only 2.6% patients after normal vaginal delivery and 6.3% in caesarean delivery in women with IHCP [12]. Similarly, Furrer R et al., evaluated 348 women with IHCP and came to the conclusion that women with IHCP do not show increased postpartum blood loss when actively managed with ursodeoxycholic acid [13]. In this study 9.18% women had postpartum haemorrhage, out of which 61.11 % women had SBA greater than 40 mmol/L and postpartum haemorrhage was observed in patients who did not receive ursodeoxycholic acid for a substantial amount of time owing to non compliance and late presentation to OPD.

In present study, a higher rate of adverse foetal outcomes such as low birth weight, low APGAR, meconium staining of liquor, preterm birth, NICU admission, intrauterine death, neonatal death was noted in early IHCP group and women with SBA ≥30 mmol/L. Similar conclusions have been made by Labbe C et al., in a retrospective study conducted to compare the risk for adverse pregnancy and foetal outcomes in early (<33 weeks) or late IHCP (≥33 weeks) particularly threatened preterm birth and prematurity [1]. Jin J et al., in his retrospective study, divided IHCP patients into early onset (≥28 weeks) and late onset group (<28 weeks), they further divided the women into two groups on the basis of SBA level, these groups were A: mild IHCP (SBA <40 mmol/L) and B: severe IHCP (SBA ≥40 mmol/L) and found significantly elevated SBA levels and higher incidence of meconium staining, foetal distress, neonatal asphyxia, premature delivery and caesarean section in early onset group when compared to late onset IHCP. Also, the proportion of women with adverse foetomaternal outcomes was higher in group B than in group A [14]. Higher SBA levels (≥40 mmol/L) have been found to be associated with higher rate of foetal complications [1,15]. Herrera CA et al., examined the perinatal outcomes associated with cholestasis of pregnancy according to bile acid level in 487 women with IHCP and also came to a conclusion that severe cholestasis (SBA ≥100 mmol/L) is associated with neonatal morbidity that antenatal testing may not predict [16], similar to this study where antenatal testing could not predict the neonatal outcomes.

In present study, although adverse foetomaternal outcomes were highest in group D, the rate of adverse outcomes were comparable between the two groups, C and D. These adverse foetomaternal maternal outcomes could be owing to detrimental effect of high bile acid levels on cardiomyocytes causing arrhythmias which explains the incidence of stillbirth and sudden intrauterine foetal demise in IHCP. The vasoconstrictive effect of bile acid on placental chorionic veins also possibly explains the occurrence of foetal distress, asphyxia and death [17]. Although treatment with UDCA has been seen to bring about improvement in liver function tests and SBA levels, clear evidence of improvement in neonatal outcomes is sparse [18]. Genetic defect in canalicular transporters have been found to be associated with IHCP, such as mutations associated with ABCB4 (MDR3) which is a transporter responsible for bile salt dependent bile flow, ABCB2 which is responsible for transport of bilirubin and bile acid across canalicular membrane and variations in NR1H4, a bile acid sensor that protects liver from bile acid toxicity by regulation of transcription genes involved in bile acid homeostasis [15].

Thick meconium was observed in all 6 cases of IUD (3.06%), belonging to group C and D. Some research in animals suggest that bile acids stimulate foetal colonic motility signifying the presence of meconium in amniotic fluid in IHCP to be a physiological reaction rather than assign of distress [1], which may be the reason behind the unpredictability of antenatal tests in foreseeing the adverse foetal outcomes. Delivery of IHCP patients has been recommended at 37-38 weeks [5]. Various studies have come to a conclusion that a more aggressive approach of elective delivery at <37 weeks of Period of Gestation (POG) in women with SBA ≥100 mmol/L and that if SBA is ≤40 mmol/L, expectant management can be considered [17]. The strengths of this study were that a large number of patients were included in this study (196) with both deranged liver function test as well as raised SBA level along with clinical signs and symptoms being taken into consideration for diagnosis of IHCP. No other study has been conducted focusing on the impact of earlier onset of disease on the foetomaternal outcomes.

Limitation(s)

Only a single highest value of SBA was taken into consideration, the possible improvement in SBA levels following treatment with ursodeoxycholic acid has not been taken into consideration due to lack of resources.

CONCLUSION(S)

Antenatal women who were diagnosed with IHCP before 32 weeks of gestation have a greater risk of adverse maternal and foetal outcomes as compared to women who present with IHCP after 32 weeks. Adverse foetomaternal outcome also associates with increasing maternal SBA level and significantly, higher rate of adverse outcome was observed in patients with SBA level ≥30 mmol/L. An earlier onset of symptoms and gestational age at diagnosis should also be considered in predicting the disease course and probable outcome in IHCP.

REFERENCES

[1] Labbe C, Delesalle C, Creveuil C, Dreyfus M. Early and later intrahepatic cholestasis of pregnancy (ICP): Study of adverse pregnancy outcomes. Gynecol Obstet Fertil Senol. 2018;46(4):388-94.

[2] Alakananda, Bhattacharya A, Kavita. Fetomaternal outcome in intrahepatic cholestasis of pregnancy. Scholars Journal of Applied Medical Sciences. 2016;4(10D):3837-41.

[3] Dang A, Agarwal N, Bathla S, Sharma N, Balani S. Prevalance of liver disease in pregnancy and its outcome with emphasis on obstetric cholestasis: An Indian scenario. The Journal of Obstetrics and Gynaecology of India. 2010;60(5):413-18.

[4] Pegu B, Mehrotra M, Yadav A, Sahoo PSK. Cholestasis of pregnancy: A prospective analysis from a South Andaman teaching hospital. Int J Reprod Contracept Obstet Gynecol. 2019;8(5):1895-98.

[5] Obstetric Cholestasis. RCOG Green-top guideline No. 43, 2011. https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg43/.

[6] Kondrackiene J, Beuers U, Zalinkevicius R, Taushel HD, Gintautas V, Kucsinkas C. Predictors of premature delivery in patients with intrahepatic cholestasis of pregnancy. World Journal of Gastroenterology. 2007;13(46):6226-30

[7] Rook M, Vargas J, Caughey A, Bacchetti P, Rosenthal P, Bull L. Fetal outcomes in pregnancy complicated by Intrahepatic cholestasis of pregnancy in a Northern California Cohort. PLoS ONE. 2012;7(3):e28243.

[8] Ghosh S, Chaudhuri S. Intrahepatic cholestasis of pregnancy: A comprehensive review. Indian J Dermatol. 2013;58(4):327.

[9] Fisk NM, Storey GNB. Fetal outcome in obstetrics cholestasis. British Journal of Obstetrics and Gynaecology. 1998;95(11):1137-43.

[10] 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. American Journal of Obstetrics and Gynaecology. 1994;170(3):890-95.

[11] Kenyon AP, Piercy CN, Girling J, Williamson C, Tribe RM, Shennan AH. Obstetric cholestasis, outcome with active management: a series of 70 cases. BJOG. 2002;109(3):282-88.

[12] DeLeon A, De Oliveira GS, Kalayil M, Narang S, McCarthy RJ, Wong CA. The incidence of coagulopathy in pregnant patients with IHCP: Should we delay or avoid neuraxial analgesia? J Clin Anesth. 2014;26:623-27. 10.1016/j.jclinane.2014.04.013.

[13] Furrer R, Katarina W, Schaffer L. Postpartum blood loss in women treated for intrahepatic cholestasis of pregnancy. The American College of Obstetrics and Gynaecology. 2016;128(5):1048-52.

[14] Jin J, Pan SL, Huang LP, Yu YH, Zhong M, Zhang GW. Risk factors for adverse fetal outcomes among women with early- versus late– onset intrahepatic cholestasis of pregnancy. International Journal of Gynaecology and Obstetrics. 2015;128(3):236-40.

[15] Floreani A, Gervasi TM. New insights on intrahepatic cholestasis of pregnancy. Cin Liver Dis. 2016;(20):177-89.

[16] Herrera CA, Manuck TA, Stoddard GJ, Varner MW, Esplin S, Clark EAS, et al. Perinatal outcomes associated with intrahepatic cholestasis of pregnancy. The Journal of Maternal-Fetal and Neonatal Medicine. 2018;31(14):1913-20.

[17] 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. American Journal of Obstetrics and Gynaecology. 2015;212(1):100.e1-7.

[18] Ovadia C, Sajous J, Seed PT, Patel K, Williamson NJ, Attilakos G. Ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: A systematic review and individual participant data meta-analysis. The Lancet Gastroenterology and Hepatology. 2021;6(7):547-58.

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