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Retrospective analysis of maternal, fetal, and neonatal outcomes of intrahepatic cholestasis of pregnancy at Gazi University

Berrin GÜNAYDIN[1,*], Merih BAYRAM[2], Melis ALTUĞ[2], Semra CEVHER[1], Nuray BOZKURT[2]
[1]Department of Anesthesiology, School of Medicine, Gazi University, Ankara, Turkey
[2]Department of Obstetrics and Gynecology, School of Medicine, Gazi University, Ankara, Turkey

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Background/aim: Maternal, fetal, and neonatal outcomes in parturients with intrahepatic cholestasis of pregnancy (ICP) have been retrospectively documented. We aimed to present pregnancy outcomes of parturients with ICP who underwent delivery. The study was conducted during a 1-year period.

Materials and methods: After ethics committee approval, data from 1 January to 31 December 2015 were collected to identify parturients with ICP.

Results: Ten out of 37 patients underwent normal spontaneous vaginal delivery (NSVD), and the remaining 27 parturients underwent cesarean section (CS). Five of 27 parturients underwent nonelective cesarean section, while 22 had elective cesarean delivery. As for NSVD deliveries, only one parturient received combined spinal and epidural anesthesia (CSE) for labor. Neuraxial (n = 22 for spinal and n = 1 for CSE) and general anesthesia (n = 4) rates for CSs were 85% and 15%, respectively. Approximately 96% of neuraxial anesthesia choices were spinal anesthesia. Nearly 18.5% of CSs were not elective. Adverse outcomes included 2 preterm births, 2 preterm labors, 2 newborns with hepatitis, and one perinatal fetal death.

Conclusion: Parturients with ICP who had normal coagulation parameters despite increased liver enzymes preoperatively underwent cesarean delivery under spinal anesthesia without complication. Although maternal outcomes were generally positive, adverse fetal and neonatal outcomes are more likely to occur, particularly in cases with severe ICP.

Key words: Intrahepatic cholestasis of pregnancy, cesarean delivery, anesthesia outcome, maternal, fetal, neonatal

1. Introduction

Certain liver diseases that are uniquely associated with pregnancy include hyperemesis gravidarum, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy (ICP), and HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome. Among these, ICP generally occurs in the second or third trimester with a mean onset at 30 weeks' gestation, and it occurs approximately 1 to 2 times per 1000 pregnancies. Generalized peripheral pruritus is commonly the first sign of the disease, but it is usually resolved within 48 h of delivery. Approximately 10% to 25% of patients develop jaundice, while some patients may occasionally suffer from chills and abdominal pain. Some may also develop diarrhea or steatorrhea. The differential diagnosis includes viral or autoimmune hepatitis, primary biliary cirrhosis, and cholelithiasis (1–4). ICP may be a challenge for health care providers such as obstetricians and/or anesthesiologists because of the potential of severe fetal consequences, including prematurity and stillbirth. Therefore, early obstetric management of the disease is essential when diagnosed by measuring the high levels of bile acid levels in the serum. The medical treatment of choice is ursodeoxycholic acid (UDCA) to relieve pruritus and improve liver enzyme dysfunction. According to the FDA, UDCA is a category B drug when used during pregnancy and breastfeeding. Possible early delivery of the fetus should be considered at the most appropriate fetal maturity stage. Incidences of coagulopathy in parturients with ICP and maternal and fetal-neonatal outcomes associated with elevated bile acid levels have been retrospectively documented (5,6). According to these recent studies, a lack of abnormal coagulation results even in the presence of 5-fold increased liver enzymes does not require to delay or avoid neuraxial blocks for delivery. However, severe ICP at a bile acid level of ≥100 μmol/L could be correlated with an adverse pregnancy outcome (5–7). Therefore, we aimed to document maternal and pregnancy outcomes of parturients with ICP who

* Correspondence: gunaydin@gazi.edu.tr

underwent delivery during a 1-year period in our unit to compare the results with international data.

2. Materials and methods

After obtaining ethics committee approval, a retrospective study was conducted with data from 1 January to 31 December 2015, meeting the criteria of parturients with ICP diagnosis that were identified using ICD-33 and ICD-10 codes (pregnancy and cholestasis diagnosis together). The severity of ICP was classified according to fasting serum bile acid levels (bile acid levels of ≥10–39 μmol/L, 40–99 μmol/L, and ≥100 μmol/L regarded as mild, moderate, or severe ICP, respectively) (6).

Results were expressed as mean ± standard error of mean (SEM), number, or median, as appropriate. Comparisons between preoperative and postoperative coagulation parameters, liver enzymes, and bilirubin levels were performed with t-tests. $P < 0.05$ was considered as statistically significant.

3. Results

Although we identified 38 parturients with ICP out of 1900 deliveries in a 1-year period, the data of 37 parturients who delivered in our hospital were documented in the current study because one patient with ICP decided to deliver in another hospital. The overall rate of ICP was calculated as 2%, based on admission to our unit. Demographic properties and fasting serum bile acid levels of the parturients with reference levels of ICP are shown in Table 1.

Preoperative and postoperative coagulation parameters, liver enzymes, and bilirubin levels are shown in Table 2. There were no significant differences between preoperative and postoperative data in the coagulation studies. Except LDH and bilirubin levels, all preoperative liver enzymes were significantly higher than those from postoperative measurements (Table 2).

The distribution of delivery modes and the urgency of deliveries were documented. Ten out of 37 parturients

Table 1. Demographic properties and fasting serum bile acid levels of parturients (n = 37) (mean ± SEM).

Age (years)	34.0 ± 0.8
Weight (kg)	72.4 ± 2.8
Height (cm)	160.9 ± 1.4
BMI (kg/cm^2)	27.9 ± 0.9
Gestational age (weeks)	37.3 ± 0.4
Bile acid (μmol/L)	53.1 ± 14.2

Reference levels for severity of ICP (6): Mild: 10–39 μmol/L,
Moderate: 40–99 μmol/L,
Severe: ≥100 μmol/L.

Table 2. Coagulation studies, liver enzymes, and bilirubin levels (mean ± SEM).

	Preoperative	Postoperative
APTT (s) (ref. range: 18–26)	23.4 ± 0.5	24.6 ± 1.4
PT (s) (10–14)	10.1 ± 0.5	10.9 ± 0.3
INR (0.8–1.25)	1.3 ± 0.4	0.9 ± 0.03
Thrombocytes (10^{-3}/μL)	210 ± 9.5	215 ± 20.5
AST (U/L) (0–40)	77.1 ± 10.7*	37.2 ± 8.5
ALT (U/L) (0–40)	119.9 ± 17.6*	41.6 ± 9.7
GGT (U/L) (0–38)	38.1 ± 11.7*	26.6 ± 7.6
ALP (U/L) (30–120)	182.6 ± 15.3*	128.1 ± 11.8
LDH (U/L) (0–248)	241.5 ± 13.5	240.1 ± 20.3
Bilirubin (mg/dL) (0.3–1.2)	0.9 ± 0.2	0.6 ± 0.08

*$P < 0.05$ versus postoperative.

underwent normal spontaneous vaginal delivery (NSVD) and the remaining 27 parturients had cesarean delivery. Five of 27 parturients underwent nonelective cesarean section, while 22 had elective cesarean delivery. Regarding the anesthesia choices for NSVD delivery, only 1 out of 10 parturients received combined spinal and epidural anesthesia (CSE) during labor. As for cesarean delivery, 22 elective cases received either neuraxial (n = 22 for spinal and n = 1 for CSE) or general anesthesia (n = 4).

According to the level of fasting serum bile acids, the rates of mild, moderate, and severe ICP were 65% (n = 24), 21% (n = 8), and 14% (n = 5), respectively (Table 3). Gestation age, neonatal demographics, and adverse outcomes were also documented. The worst adverse fetal outcome was perinatal fetal death, which was observed in only one case of severe ICP at 34 weeks' gestation. The patient underwent cesarean delivery under spinal anesthesia using midazolam for sedation. Birth weights, Apgar scores, and newborn sex were comparable among mild, moderate, and severe ICP cases, as shown in Table 3 ($P > 0.05$).

4. Discussion

We retrospectively documented maternal and fetal-neonatal outcomes in parturients with ICP delivered at the Gazi University School of Medicine in the present study. Maternal outcomes were generally positive, as indicated in many previous reports (1–4). Twenty-seven percent of our patients had NSVD while the rest (73%) underwent cesarean delivery. Approximately 18.5% of cesarean deliveries were emergent. When anesthesia and/or analgesia choices were evaluated, we performed CSE labor analgesia for only one patient. According to the records on cesarean deliveries, the rates of neuraxial and general anesthesia were 85% and 15%, respectively. Among neuraxial anesthesia choices, spinal anesthesia (96%) was the most preferred one.

Regarding neonatal outcomes in terms of birth weight and Apgar scores at 1 and 5 min, they were positive, as well. However, there were 2 preterm births and 2 preterm labors from mild and severe ICP cases (one from each). Hepatitis in 2 newborns was observed in parturients with mild ICP. However, the worst fetal outcome observed in a parturient with severe ICP was perinatal fetal death at 34 weeks' gestation.

Anesthesia choices for delivery might be challenging in patients with liver diseases unique to pregnancy. Because of the physiologic decrease in gall bladder contractility, pregnant women tend to have a sort of physiologic cholestasis. Additionally, in the event of ICP, cholestasis might lead to malabsorption of vitamin K, which is a cofactor in the synthesis of coagulation factors II, VII, IX, and X. Therefore, coagulation abnormalities might be expected in parturients with ICP. Furthermore, increased liver enzymes, and AST and ALT predominantly, are considered to be determinants of liver diseases (1–4,7,8). However, in a recent retrospective study investigating the incidence of coagulopathy in parturients with ICP, no abnormal coagulation studies were found, even in the presence of significantly increased liver enzymes (5). The authors reported that the incidence of coagulopathy in parturients with isolated ICP was extremely low, and routine coagulation studies were not necessary, except for patients who had ICP with coexisting preeclampsia (5). Similarly, we had neither abnormal coagulation parameters nor any patients with coexisting preeclampsia in our study.

Table 3. Gestation age and neonatal demographics (median); adverse outcomes (n) according to severity of intrahepatic cholestasis of pregnancy.

	Mild (n = 24)	Moderate (n = 8)	Severe (n = 5)
Gestation age at delivery (weeks)	37	37	35
Birth weight (g)	2950	2995	2940
Newborn sex (female/male) (n)	9/15	3/5	3/2
Apgar score 1 min (min)	9	9	9
Apgar score 5 min (min)	10	10	9
Preterm birth (n)	1	-	1
Perinatal fetal death (n)	-	-	1
Spontaneous preterm labor (n)	1	-	1
Newborn hepatitis (n)	2	-	-

The severity of ICP, especially in cases of bile acid levels exceeding 40 μmol/L, may affect pregnancy outcomes (6,9). Based on these studies, we similarly classified cases with a bile acid level of ≥10–39 μmol/L, 40–99 μmol/L, and ≥100 μmol/L as mild, moderate, and severe ICP, respectively. In the present study, the rates of mild, moderate, and severe ICP were 65%, 21%, and 14%, respectively. When we compare studies in this regard, our incidence of mild ICP was higher but that of severe ICP was lower than in Brouwers et al.'s study (6). In mild cases, obstetric management includes delivery at 38 weeks' gestation, but early delivery at 36 weeks can be considered in severe cases due to the high risk of fetal distress/death, jaundice, or unbearable maternal pruritus, despite UDCA treatment (1–7). In contrast to the 14% cesarean section rate in Brouwers et al.'s study (6), we documented a much higher rate of 73%. This cesarean section rate was consistent with the 65% rate in DeLeon et al.'s study (5). In our cases, we observed adverse outcomes, including preterm labor and birth and perinatal fetal death in parturients with severe ICP.

Pregnancy-associated liver diseases and/or abnormalities in conjunction with their interpretation have been extensively studied (10–14). Thus, maternal and fetal-neonatal outcomes in parturients with ICP associated with elevated bile acid levels have been retrospectively documented similar to recent retrospective studies for comparison (5,6). One of the limitations of our study could be the inadequacy of our 1-year documentation to represent national data for international comparison. However, this small retrospective study, which included the records of 37 cases, might be helpful for both anesthesiologists and obstetricians in order to provide better management of parturients with ICP for delivery.

In conclusion, parturients with ICP who had normal coagulation parameters despite increased liver enzymes preoperatively underwent cesarean delivery mostly under spinal anesthesia without complications. Although maternal outcomes were generally positive, adverse fetal and neonatal outcomes are more likely to occur, particularly in severe ICP cases.

References

1. Kamimura K, Abe H, Kawai H, Kamimura H, Kobayashi Y, Nomoto M, Aoyagi Y, Terai S. Advances in understanding and treating liver disease during pregnancy. World J Gastroenterol 2015; 21: 5183-5190.
2. Ahmed KT, Almashhrawi AA, Rahman RN, Hammoud GM, Ibdah JA. Liver diseases in pregnancy: Diseases unique to pregnancy. World J Gastroenterol 2013; 19: 7639-7646.
3. Goel A, Jamwal KD, Ramachandran A, Balasubramanian KA, Eapen CE. Pregnancy-related liver disorders. J Clin Exp Hepatol 2014; 4: 151-162.
4. Bacq Y. Liver diseases unique to pregnancy: a 2010 update. Clin Res Hepatol Gastroenterol 2011; 35: 182-193.
5. DeLeon A, De Oliveira GS, Kalayil M, Narang S, McCarthy RJ, Wong CA. The incidence of coagulopathy in pregnant patients with ICP: should we delay or avoid neuraxial anesthesia? J Clin Anesth 2014; 26: 623-627.
6. Brouwers L, Koster MP, Page-Christiaens GC, Kemperman H, Boon J, Evers IM, Bogte A, Oudijk MA. Intrahepatic cholestasis of pregnancy: maternal and fetal outcomes associated with elevated bile acid levels. Am J Obstet Gynecol 2015; 212: 100. e1-7.
7. Rahimzadeh P, Safari S, Faiz SH, Alavian SM. Anesthesia for patients with liver disease. Hepat Month 2014; 1: 19881.
8. Sasaki KJ. Liver Disease and Pregnancy. Emedicine Medscape Webpage; 2015. Available online at http://emedicine.medscape.com/article/188143-overview#a1.
9. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: relationship between bile acid levels and fetal complication rates. Hepatology 2004; 40: 467-474.
10. Joshi D, James A, Quaglia A, Westbrook RH, Heneghan MA. Liver disease in pregnancy. Lancet 2010; 13: 594-605.
11. Than NN, Neuberger J. Liver abnormalities in pregnancy. Best Prac Res Clin Gastroenterol 2013; 27: 565-575.
12. Kia L, Rinella ME. Interpretation and management of hepatic abnormalities in pregnancy. Clin Gastroenterol Hepatol 2013; 11: 1392-1398.
13. Hepburn IS, Schade RR. Pregnancy-associated liver disorders. Dig Dis Sci 2008; 53: 2334-2358.
14. Gunaydin B, Tuna AT. Anesthetic considerations for liver diseases unique to pregnancy. World J Anesthesiol 2016; 5: 54-61.