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Intrahepatic cholestasis of pregnancy may lead to low birth weight

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Background/aim: To evaluate patients hospitalized in our clinic in the last 5 years with the diagnosis of intrahepatic cholestasis of pregnancy (ICP).

Materials and methods: One hundred and fifty patients hospitalized with a diagnosis of ICP between January 2008 and May 2013 were evaluated retrospectively and age, week at diagnosis, gestational age at delivery, period between diagnosis and delivery, fetal weight, transaminases, and coagulation parameters were recorded. Patients were divided into groups according to their diagnosis weeks and gravida. Accordingly, patients diagnosed before 32 weeks formed group A (n = 49) and those after 32 weeks formed group B (n = 101). Data were evaluated with SPSS 16.0.

Results: There was a significant difference between group A and group B in terms of delivery period and fetal weights (P = 0.001, P = 0.035). Accordingly, the period between diagnosis and delivery and fetal weight were found to be longer and lower, respectively, in the early-onset group. In terms of distribution of ICP according to time of diagnosis, patients were diagnosed mostly in the spring season (60 cases, 40%) and in the month of March (27 cases, 18%).

Conclusion: According to our study, the birth weight of fetuses of patients with ICP diagnosed before 32 weeks are lower, although they have the same gestational age at delivery as the fetuses of the patients with ICP diagnosed after 32 weeks.

Key words: Pregnancy, intrahepatic cholestasis of pregnancy, fetal weight

1. Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disease that usually emerges in the last trimester of pregnancy with generalized pruritus of the skin and resolves itself spontaneously after birth. Although it has a minimal risk for the mother, there are serious risks for the fetus. It is diagnosed based on clinical findings, elevation of serum bile acids, and increased liver transaminases. There are differences in its prevalence in different regions and countries. It is seen in the United States, England, and Sweden at low rates such as 0.01%, 0.07%, and 2.8%, respectively, and in Chile and Bolivia with the highest prevalence of 15% (1). It has been reported that there has been a decrease in the prevalence of these countries in recent years (2,3).

Although the exact etiology is unknown, it is estimated that racial, genetic, hormonal, nutritional, and environmental factors play a role (4). Itching and liver function test abnormalities improve after birth completely. One of the most sensitive tests in the diagnosis of ICP is increase in total serum bile acids. It has been reported that this increase was in parallel with an increase in fetal risks. Fetal risks include preterm birth, low Apgar score, fetal distress, sudden intrauterine fetal death, and meconium-stained amniotic fluid. Despite the use of various agents, ursodeoxycholic acid (UDCA) is the most effective agent in the treatment.

There is no standard method for the treatment and follow-up for ICP. Close monitoring of these patients is recommended in terms of both maternal and fetal risks. In our study, we retrospectively evaluated pregnant women who were treated at our hospital with the diagnosis of ICP over the last 5 years.

2. Materials and methods

The study population was composed of 150 patients hospitalized and treated in the last 5 years with the diagnosis of ICP at our hospital. The patient files were accessed by the ICD-10 computer recording system and reviewed retrospectively. The study was approved by the hospital ethics committee. The patients' liver and biliary tract imaging in terms of organic pathologies, hepatitis

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B and hepatitis C serology for viral hepatitis, coagulation parameters, and complete blood count were recorded in the form of case information. ICP usually arises in the last trimester, and in particular in weeks 32 and 33 (5). We divided the patients with a diagnosis of ICP into two groups according to weeks at diagnosis. Early-onset (before 32 weeks) patients formed group A (n = 49) and late-onset (after 32 weeks) patients formed group B (n = 101). In addition, patients were divided into two groups according to the number of pregnancies. The patients with gravida one formed group I (n = 63), and those with gravida two or more formed group II (n = 87). These groups were compared in terms of age, gravida, transaminases, coagulation parameters, complete blood count, cholestasis diagnostic weeks, period between diagnosis and delivery, gestational weeks, and fetal weight.

The data were analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Student's t-test and the chi-square test were used to compare the groups. $P < 0.05$ was considered significant.

3. Results

The mean age, mean gravida, and mean week of diagnosis of the 150 patients diagnosed with ICP were 28.1 ± 6.2 years, 2.2 ± 1.6, and 31.5 ± 5.8 weeks, respectively. The mean gestational age at delivery, mean time passing until delivery, and mean birth weight were 36.7 ± 2.0 weeks, 4.8 ± 6.3 weeks, and 3070.0 ± 533.9 g, respectively. The laboratory tests averages were: alkaline phosphatase, 217.9 ± 87.0 IU; aspartate aminotransferase, 97.6 ± 71.8 IU; alanine aminotransferase, 158.6 ± 137.9 IU; prothrombin time, 12.9 ± 3.3 s; international normalized ratio, 1.00 ± 0.32; partial thromboplastin time, 29.1 ± 4.6 s, white blood cell count, 10,204 ± 2489.8, hemoglobin, 11.8 ± 1.3 g/dL, hematocrit, 35.2 ± 3.7%, and platelet count, 236.6 ± 75.5 (Table 1).

The numbers of deliveries before the 37th pregnancy week (premature) and after the 37th weeks were 52 (34.6%) and 98 (65.3%), respectively. Cases of vaginal delivery and cesarean section were 37 (24.6%) and 113 (75.3%),

Table 1. Demographic, clinical, and laboratory findings of the patients.

	Mean ± SD	Min–max
Age (years)	28.1 ± 6.2	17–46
Gravida	2.2 ± 1.6	1–9
Gestational week at diagnosis	31.5 ± 5.8	11–39
Gestational week at delivery	36.7 ± 2.0	28–40
Period passing until delivery (weeks)	4.8 ± 6.3	0–35
Fetal weight (g)	3070.0 ± 533.9	1650–4480
ALP	217.9 ± 87.0	23–662
AST	97.6 ± 71.8	16–337
ALT	158.6 ± 137.9	13–652
PT	12.9 ± 3.3	10.7–45.3
INR	1.00 ± 0.32	0.74–3.36
PTT	29.1 ± 4.6	16.1–50.2
WBC	10,204 ± 2489.8	5600–18,600
HB	11.8 ± 1.3	8.2–15.0
HCT	35.2 ± 3.7	24.2–44.8
PLT	236.6 ± 75.5	94–544
T.BIL	0.89 ± 0.34	0.2–2.1

ALP: Alkaline phosphatase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, PT: prothrombin time, INR: international normalized ratio, PTT: partial thromboplastin time, WBC: white blood cell count, HB: hemoglobin, HTC: hematocrit, PLT: platelet count, T.BIL: total bilirubin.

respectively. There were 6 cases of twin pregnancy (4%), and 1 case (0.6%) of IVF pregnancy.

The mean ages of group I and group II were 24.8 ± 5.1 and 30.5 ± 5.8 years, respectively and there was a significant difference between the two groups in terms of the mean age (P = 0.001). Accordingly, patients in group I were younger. There was no significant difference between the two groups in terms of cholestasis diagnosis week, gestational weeks at delivery, period passing until the delivery, fetal weight, alkaline phosphatase, transaminases, or complete blood count and coagulation tests (Table 2).

The mean gestational week at diagnosis in group A and group B was 26.07 ± 6.9 and 34.72 ± 2.0 respectively. In group A (early-onset, before 32 weeks) and group B (late-onset, after 32 weeks) the mean periods passing until delivery were 10.1 ± 7.5 and 2.4 ± 3.8 weeks, respectively, and the mean fetal weights were 2924.3 ± 574.5 g and 3135.6 ± 504.1 g, respectively. There was a significant difference between the two groups in terms of the period passing until delivery and fetal weights (P = 0.001, P = 0.035). The gestational weeks at delivery were 36.3 ± 2.6 and 36.8 ± 1.6 weeks, respectively, and there was no difference in this respect between the two groups (P = 0.166). Accordingly, although mean weeks at delivery was the same in both groups, the period passing until delivery was longer in Group A and fetal weights were lower. There was no significant difference between the two groups in terms of age, alkaline phosphatase, transaminases, or complete blood count and coagulation tests (Table 3).

When the distribution of the months in which the patients were diagnosed was examined, the most common month was March with 27 (18%) patients, and April was the second most common month, with 21 (14%) patients. When the distribution according to the seasons was examined, spring was the most common season in which the patients were diagnosed, with 60 (40%) patients, and the second season was winter, with 44 (29.3%) patients.

4. Discussion

ICP is a liver disease that is the most common cause of jaundice in pregnant women after viral hepatitis. It has been reported that there are serious fetal risks and minimal maternal risks. Despite the maternal risks being minimal, it has been stated that these patients have a predisposition to certain other diseases. In a study conducted recently on the examination of the diseases diagnosed over long-term

Table 2. Comparison of group I and group II.

	Group I (n = 63)	Group II (n = 87)	P-value
Age (years)	24.8 ± 5.1	30.5 ± 5.8	0.001
Gestational week at diagnosis	31.6 ± 6.1	32.1 ± 5.6	0.614
Gestational week at delivery	36.4 ± 2.1	36.8 ± 1.8	0.279
Period passing until delivery (weeks)	5.0 ± 6.7	4.7 ± 6.0	0.791
Fetal weight (g)	3043.3 ± 476.8	3089.6 ± 574.6	0.625
ALP	213.2 ± 71.0	221.3 ± 97.2	0.575
AST	87.9 ± 68.4	104.7 ± 73.8	0.157
ALT	144.4 ± 131.9	168.9 ± 141.9	0.284
PT	13.2 ± 5.0	12.8 ± 1.2	0.566
INR	1.06 ± 0.52	0.97 ± 0,10	0.322
PTT	29.3 ± 5.1	28.9 ± 4.1	0.691
WBC	10,504 ± 2358.4	9919.5 ± 2569.0	0.179
HB	11.9 ± 1.3	11,8 ± 1.3	0.737
HCT	35.2 ± 4.0	35.1 ± 3.6	0.861
PLT	236.6 ± 77.3	236.6 ± 74.6	0.999

Values are mean ± SD.
ALP: Alkaline phosphatase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, PT: prothrombin time, INR: international normalized ratio, PTT: partial thromboplastin time, WBC: white blood cell count, HB: hemoglobin, HTC: hematocrit, PLT: platelet count.

Table 3. Comparison of group A (n = 49, <32 weeks) and group B (n = 101, ≥32 weeks).

	Group A	Group B	P-value
Age (years)	27.04 ± 6.1	28.4 ± 6.1	0.209
Gestational weeks at delivery	36.3 ± 2.6	36.8 ± 1.6	0.166
Period passing until delivery (weeks)	10.1 ± 7.5	2.4 ± 3.8	0.001
Fetal weight (g)	2924.3 ± 574.5	3135.6 ± 504.1	0.035
ALP	216.1 ± 88.9	223.2 ± 88.1	0.657
AST	101.6 ±76.1	95.8 ± 72.2	0.664
ALT	172.4 ± 143.8	151.5 ± 137.7	0.410
PT	12.6 ± 1.0	13.2 ± 4.2	0.366
INR	0.94 ± 0.08	1.03 ± 0.39	0.401
PTT	29.7 ± 5.2	28.8 ± 4.3	0.369
WBC	9577 ± 1848	10,366 ± 2784	0.087
HB	11.9 ± 1.2	11.8 ± 1.3	0.453
HCT	35.3 ± 3.5	35.1 ± 3.8	0.800
PLT	241.9 ± 76.4	236.0 ± 76.1	0.671

Values are mean ± SD.
ALP: Alkaline phosphatase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, PT: prothrombin time, INR: international normalized ratio, PTT: partial thromboplastin time, WBC: white blood cell count, HB: hemoglobin, HTC: hematocrit, PLT: platelet count.

periods in patients with cholestasis, hepatobiliary diseases, breast cancer, and hypothyroidism were more common and hypertension, cholesterolosis, and cardiac arrhythmia were seen to a lesser degree in these patients (6).

When the week of diagnosis of the patients was evaluated, despite the fact that there were patients who were diagnosed during the first trimester, in general, they were diagnosed with ICP at average of the third trimester, consistent with the literature. In the study conducted by Kenyon et al. on 70 patients with cholestasis, the initiation of itching, week of diagnosis, cesarean rate, and delivery rate before the 37th week were found to be 30 weeks, 33.7 weeks, 36%, and 17%, respectively, while there was no intrauterine fetal loss and 14% of infants were sent to the neonatal intensive care unit after birth (5). In our study, diagnosis of ICP was performed at a mean of 31.5 weeks, and the delivery rate before the 37th week and the cesarean rate were 34.6% and 75.3%, respectively. According to our evaluation, the increase in cesarean rate is due to the patients undergoing repeated cesarean sections. In parallel with our study, the preterm delivery rate has been reported as 36%–38 % in the literature (7,8).

Increase in maternal serum bile acids is a significant predictor. There is a correlation between serum bile acids and perinatal outcomes. It has been reported that when maternal serum levels were under 40 μmol/L, perinatal outcomes were good, and when they were above 40 μmol/L, the incidence of intrauterine mortality increased (9,10). Sudden intrauterine fetal loss rates in ICP were reported to be 7%, and 90% of these losses happened after the 37th gestational week (11). In our study, the low rate of fetal loss of 1/150 (0.6%) can be related with mean delivery week of our patients being 36.7 weeks. UDCA is started as a routine in our hospital for the patients with the diagnosis of ICP. UDCA is selected as the first choice due to its improvement of the maternal symptoms, acceleration of bile transport from placental trophoblasts, and the absence of a negative impact on the mother and fetus. Although it is highly effective in healing the maternal symptoms and reducing the transaminases, the positive impact on the results of fetal healing is not clear. It was reported in the metaanalysis of nine randomized controlled trials conducted recently that UDCA reduced preterm birth, fetal distress, respiratory distress syndrome, and the need for neonatal care (12). Because no other treatment was received other than UDCA, the low fetal loss rate in our study is controversial as it is difficult to discern whether it was caused by UDCA treatment or not.

Many factors are culpable in the etiology of ICP. At a basic level, there are genetic, hormonal, nutritional, and environmental factors. It has been determined that ICP showed seasonal changes, and this was seen especially during the winter months. The reason for this was failure to obtain sufficient diet and selenium during the winter (13). Selenium plays a role in the detoxification of the liver as a cofactor of glutathione peroxidase, and bile secretion and formation are impaired in the event of its deficiency (14,15). In our study, when the time of diagnosis of ICP is examined, it is noteworthy that the spring and winter seasons are the most common seasons. Estrogen and progesterone have been considered among hormonal factors. The findings such as emergence in the second and third trimesters, being more common in twin pregnancies, spontaneous disappearance after birth, and reemergence of cholestasis with oral contraceptives in patients who had ICP support the possibility that hormonal mechanisms play an important role in the etiology (16). It is known that, although there was no difference with normal pregnancies in terms of high estrogen and progesterone, metabolites in the liver impair the expression of the canalicular protein providing transport of bile acids in patients genetically predisposed (17,18). We found that the twin and IVF pregnancy rate was 4% and 0.6%, respectively. Twin pregnancy and IVF pregnancy have been reported as 20%–22% and 2.7%, respectively, in the literature (19–21).

In our study, we evaluated patients separated into two groups as primigravid and multigravid. Our aim here was to determine the effect of first exposure to high estrogen and progesterone metabolites on the course of ICP. There was no significant difference between primigravid and multigravid patients in terms of diagnosis week of ICP, period passing until delivery, gestational age at delivery, fetal weights, transaminases, and coagulation parameters.

We determined that fetal weights were lower in early-onset ICP than late-onset ICP, although there was no difference between the two groups in terms of the mean gestational weeks at delivery. Taking into account that there was no significant difference in terms of age, hematocrit, transaminases, and coagulation parameters between the two groups, further studies should be done for the cause of the difference between the fetal weights. On the other hand, the period passing until delivery was longer in early-onset group. Because of waiting until the 37th gestational week in order to proceed with labor, it is an expected result that the period passing until delivery in early-onset ICP is longer.

When we evaluated ICP in terms of intrauterine fetal death, intrauterine fetal death rates were relatively high at 15% in old studies and 3.5% in more recent studies (22). In a study conducted by Turunen et al., intrauterine fetal death rate was found to be 1.2%, and in our study, it was found to be 0.6%. In the same study, ICP increased the rates of induction of delivery and cesarean section. In our study, the rate of cesarean section was 75.3% (6). When it is taken into account that ICP is not an indication for cesarean section alone, we can further say that this increase is mostly due to the cases of repeated cesareans.

In conclusion, according to our study, the fetuses of patients with ICP diagnosed at under 32 weeks have lower birth weights although they have the same gestational age as the fetuses of the patients with ICP diagnosed after 32 weeks, and ICP is encountered mostly in the spring season. Among primigravid and multigravid patients, there is no difference in terms of week of diagnosis, gestational week at delivery, fetal weights, complete blood count, transaminase levels, and coagulation parameters.

References

1. Abedin P, Weaver J, Egginton E. Intrahepatic cholestasis of pregnancy: prevalence and ethnic distribution. Ethn Health 1999; 4: 35–37.
2. Reyes H. Sex hormones and bile acids in intrahepatic cholestasis of pregnancy. Hepatology 2008; 47: 376–379.
3. Lammert F, Marschall HU, Glantz A, Matern S. Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management. J Hepatol 2000; 33: 1012–1021.
4. Diken Z, Usta IM, Nassar AH. A Clinical approach to intrahepatic cholestasis of pregnancy. Am J Perinatol 2014; 31: 1–8.
5. 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: 282–288.
6. Turunen K, Sumanen M, Haukilahti RL, Kirkinen P, Mattila K. Good pregnancy outcome despite intrahepatic cholestasis. Scand J Prim Health Care 2010; 28: 102–107.
7. Pathak B, Sheibani L, Lee RH. Cholestasis of pregnancy. Obstet Gynecol Clin North Am 2010; 37: 269–282.
8. Sheikh Abdul Kadir SH, Miragoli M, Abu-Hayyeh S, Moshkov AV, Xie Q, Keitel V, Nikolaev VO, Williamson C, Gorelik J. Bile acid induced arrhythmia is mediated by muscarinic M2 receptors in neonatal rat cardiomyocytes. PLoS One 2010; 15: 5 e9689.
9. Lee RH, Kwok KM, Ingles S, Wilson ML, Mullin P, Incerpi M, Pathak B, Goodwin TM. Pregnancy outcomes during an era of aggressive management for intrahepatic cholestasis of pregnancy. Am J Perinatol 2008; 25: 341–334.

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

11. Williamson C, Hems LM, Goulis DG, Walker I, Chambers J, Donaldson O, Swiet M, Johnston DG. Clinical outcome in a series of cases of obstetric cholestasis identified via a patient support group. BJOG 2004; 111: 676–681.

12. Bacq Y, Sentilhes L, Reyes HB, Glantz A, Kondrackiene J, Binder T, Nicastri PL, Locatelli A, Floreani A, Hernandez I et al. Efficacy of ursodeoxycholic acid in treating intrahepatic cholestasis of pregnancy: a meta-analysis. Gastroenterology 2012; 143: 1492–1501.

13. 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 an high incidence area: Portugal. Eur J Obstet Gynecol Reprod Biol 1998; 80: 31–38.

14. Reyes H, Báez ME, González MC, Hernández I, Palma J, Ribalta J, Sandoval L, Zapata R. Selenium, zinc and copper plasma levels in intrahepatic cholestasis of pregnancy, in normal pregnancies and in healthy individuals, in Chile. J Hepatol 2000; 32: 542–554.

15. Kauppila A, Korpela H, Mäkilä UM, Yrjänheikki E. Low serum selenium concentration and glutathione peroxidase activity in intrahepatic cholestasis of pregnancy. Br Med J (Clin Res Ed) 1987; 294: 150–152.

16. Schreiber A, Simon F. Estrogen induced cholestasis: clues to pathogenesis and treatment. Hepatology 1983; 3: 607–613.

17. Meng LJ, Reyes H, Axelson M, Palma J, Hernandez I, Ribalta J, Sjovall J. Progesterone metabolites and bile acids in serum of patients with intrahepatic cholestasis of pregnancy: effect of ursodeoxycholic acid therapy. Hepatology 1997; 26: 1553–1579.

18. Simon FR, Fortune J, Iwahashi M, Gartung C, Wolkoff A, Sutherland E. Ethinyl estradiol cholestasis involves alterations in expression of liver sinusoidal transporters. Am J Physiol 1996; 271: 1043–1052.

19. Gonzales MC, Reyes H, Arrese M, Figueroa D, Lorca B, Andresen M, Segovia N, Molina C, Arce S. Intrahepatic cholestasis of pregnancy in twin pregnancies. J Hepatol 1989; 9: 84–90.

20. Rioseco AJ, Ivankovic MB, Manzur A, Hamed F, Kato SR, Parer JT, Germain AM. Intrahepatic cholestasis of pregnancy: a retrospective case-control study of perinatal outcome. Am J Obstet Gynecol 1994; 170: 890–895.

21. Koivurova S, Hartikainen AL, Karinen L, Gissler M, Hemminki E, Martikeinen, Tuomivaara L, Jarvelin MR . The course of pregnancy and delivery and the use of maternal healthcare services after standard IVF in Northern Finland 1990-1995. Hum Reprod 2002; 17: 2897–2903.

22. Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. World J Gastroenterol 2009; 15: 2049–2066.