

COMPARISON OF MEAN PLATELET VOLUME AND SERUM BILE ACID LEVELS IN INTRAHEPATIC CHOLESTASIS OF PREGNANCY

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SUMMARY

Objective: The aim of this study was to investigate the relationship between serum bile acid levels (SBA) and mean platelet volume (MPV), a proinflammatory marker and to detect the role of MPV as a marker of fetal well-being in patients with intrahepatic cholestasis of pregnancy (ICP).

Material and methods: We compared the biochemical parameters of pregnant with ICP and the control group retrospectively.

Results: Pregnants with ICP had statistically significantly higher alanine aminotransferase (ALT), aspartate aminotransferase (AST) and fasting SBA levels and the gestational week at delivery was higher in the control group ($p < 0.05$). There was no statistically significant relationship between MPV and hemoglobin, hematocrite, white blood cell count and thrombocyte levels of the groups ($p > 0.05$). Mean gestational week at delivery was statistically significantly lower in pregnant with ICP when compared to the control group (37.95 ± 0.92 weeks and 37.25 ± 1.25 weeks, $p < 0.05$ respectively).

Conclusions: There was no relationship between MPV and biochemical parameters used to define ICP. But the rate of preterm delivery increased as SBA levels increased.

Key words: mean platelet volume, pregnancy, serum bile acid levels

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GEBELİK İNTRAHEPATİK KOLESTAZINDA ORTALAMA TROMBOSİT HACMİ VE SERUM SAFRA ASİTLERİNİN KARŞILAŞTIRILMASI

ÖZET

Amaç: Bu çalışmanın amacı, serum safra asitleri (SSA) ile proinflatuar bir belirteç olan ortalama trombosit hacmi (OTH) arasındaki ilişkiyi ve OTH'nin gebelik intrahepatik kolestazi (GİK) olan hastalarda fetal iyilik halinin belirteci olarak kullanımını tespit etmektir.

Gereç ve yöntemler: Bu retrospektif çalışmada GİK'li hastalar ile kontrol grubunu oluşturan gebelerin biokimyasal parametreleri karşılaştırıldı.

Bulgular: GİK tanısı alan gebelerin ortalama alanine aminotransferaz (ALT), aspartat aminotransferaz (AST), açlık SSA ölçümleri ve kontrol grubundaki gebelerin doğum sırasındaki gebelik haftaları istatistiksel olarak anlamlı düzeyde yüksek saptanmıştır ($p < 0.05$). Her iki grupta yeralan gebelerin hemoglobin, hematokrit, beyaz küre, trombosit ve OTH ölçümleri arasında fark ve OTH ile açlık SSA arasında istatistiksel olarak anlamlı ilişki saptanmamıştır ($p >$

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0.05). GİK'li gebeler, kontrol grubundaki gebelerden daha erken haftada doğum yapmıştır (sırasıyla 37.95 ± 0.92 hafta ve 37.25 ± 1.25 hafta, $p < 0.05$).

Sonuç: OTH ile GİK'i tanımlayan biokimyasal parametreler arasında korelasyon tespit edilemedi. Ancak SSA yükseldiğinde erken doğum gözlenme sıklığında artış izlendi.

Anahtar kelimeler: kolestaz, ortalama trombosit hacmi, serum safra asitleri

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a liver pathology unique to pregnancy and is most frequently encountered in the third trimester of pregnancy⁽¹⁾. Etiology of ICP is not certain but hormonal changes taking place in pregnancy, drugs, ethnic differences, seasonal variations, genetic factors and familial predisposition are considered^(2,3). The condition is very rare in African-Americans, but may have an incidence as high as 5-15% in Chili and Bolivia, in Europe the rate is reported as 1%^(4,5). The rate increases in winter, twin pregnancies, pregnancies conceived with assisted reproductive technologies, with use of progesteron during pregnancy and oral contraceptives before pregnancy and in pregnant older than 35 years of age^(6,7).

Patients present with pruritus in the third trimester of pregnancy due to deposition of serum bile acids (SBA) in the skin, which especially increases at night and also resides the palms⁽⁸⁾. A few weeks after pruritus jaundice, dark urine, anorexia and light-colored stools may develop⁽⁸⁾. Fever, nausea and vomiting that frequently accompany other diseases of the liver and gallbladder are not encountered. Although the most frequently observed laboratory findings are elevated liver enzymes, diagnosis is confirmed with the detection of rising SBA and exclusion of other liver diseases⁽⁹⁾. These patients still carry a higher risk of other liver diseases in the future⁽⁹⁾. After delivery liver function tests normalize promptly without leaving any sequela, but the disease recurs in 45-70% of patients in the future pregnancies⁽¹⁰⁾.

The most important feature of ICP is the occurrence of sudden intrauterine fetal death which cannot be detected with routine tests used to follow up fetal well-being. Present studies demonstrate a relationship between rising SBA levels and serious fetal complications such as fetal distress, meconium aspiration and sudden intrauterine fetal death^(11,12).

Unfortunately SBA results appear relatively late and cannot be studied in every laboratory⁽¹³⁾.

Platelets secrete many mediators that play role in hemostasis, inflammation, thrombosis and atherosclerosis, contain adhesion receptors and large platelets have a greater potential to aggregate and lead to thrombosis. Therefore a relationship can be observed between mean platelet volume (MPV) and diseases accompanied by inflammation⁽¹⁴⁾, including liver diseases⁽¹⁵⁾. A previous study proposed MPV as a marker that can be used in the follow up of fetal well being in pregnant with ICP and detected a correlation between SBA levels and MPV⁽¹⁶⁾. The aim of this study is to understand the relationship between SBA and MPV, a cheap, readily obtained test that can be studied in every laboratory.

MATERIALS AND METHODS

We searched data of women delivering in İstanbul Bilim University Avrupa Florence Nightingale Hospital between January 2008 and May 2013. Charts of 20 women diagnosed with ICP and their neonates were retrospectively analyzed. Diagnostic criteria for ICP were the presence of pruritus together with elevated SBA and/or liver enzymes and exclusion of other liver diseases with ultrasonography and serological tests. The study protocol included age of the patient, the gestational week when the symptoms started, complete blood count, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), SBA, the gestational week at delivery, birth weight, gender and Apgar score of the neonate. Exclusion criteria were the presence of gestational diabetes mellitus, hypertensive diseases of pregnancy, diseases of thyroid gland, hematological abnormalities, pruritus (only for control group) and use of drugs other than multivitamins and iron preparates. The study protocol was in confirmation with the guidelines of Helsinki Declaration.

Statistical analyses were performed using the Number Cruncher Statistical System (NCSS) 2007& Power Analysis and Sample Size (PASS) 2008 Statistical Software (Utah). Data showing normal distribution of parameters were compared with Student's t-test, data showing non-normal distribution of parameters were compared with Mann Whitney U test. The relation of MPV with other parameters was compared with Pearson's and Spearman's correlation analysis. P-values < 0.01 and <0.05 were accepted as significant.

RESULTS

The study group was comprised of 20 patients with ICP and 21 patients were included as the control group. The mean age of the whole study group was 31.07 ± 3.08 years (24 - 38 years), mean gestational week at delivery was 37.61 ± 1.14 weeks (35 - 40 weeks), the mean gestational week at detection of pruritus was 31.86 ± 3.57 weeks (25 - 36 weeks), mean birth weight was 3191.59 ± 363.50 grams (2480 - 4130 grams). Thirty-six patients (87.8%) delivered with cesarean section, and 5 patients (12.2%) delivered vaginally. Fifteen percent of pregnant with ICP delivered vaginally. Girls made up 43.9% (n = 18) and boys made up 56.1% (n = 23) of neonates. Neonatal mortality was not detected in both of the groups.

Mean age of pregnant with ICP was 30.65 ± 3.06 years and mean age of the control group was 31.48 ± 3.11 years (p = 0.397). Mean birth weight of the neonates of pregnant with ICP was 3140.25 ± 313.52 grams and the control group was 3240.48 ± 407.10 grams (p = 0.384). Mean gestational week at delivery

was statistically significantly higher in the control group when compared to pregnant with ICP (37.95 ± 0.92 weeks, 35.1 - 40 weeks and 37.25 ± 1.25 weeks, 35.4 - 40.3 weeks, p < 0.05 respectively).

The biochemical data of the groups was compared with one another in Table I. There was statistically significant difference between the ALT, AST ve SBA levels of the groups (p < 0.01). There was no statistically significant differences between the hemoglobin, hematocrite, white blood cell, platelet and MPV of the groups (p > 0.05).

There was no statistically significant correlation between MPV and SBA levels in pregnant with ICP and the control group (r = - 0.207, p = 0.478 and r = 0.288, p = 0.231 respectively). There was no statistically significant correlation between MPV and gestational week at delivery in pregnant with ICP and the control group (r = 0.337, p = 0.146 and r = 0.071, p = 0.761 respectively). There was no statistically significant correlation between MPV and birth weight of neonates in pregnant with ICP and the control group (r = - 0.051, p = 0.830 and r = 0.046, p = 0.844 respectively).

DISCUSSION

When maternal SBA levels are kept below 40µmol /L in pregnant with ICP fetal complications can be prevented⁽¹²⁾. Glantz et al showed that the risk of adverse obstetric outcomes such as fetal distress, spontaneous preterm delivery, meconium aspiration and sudden fetal death increased 1-2% with every 1µmol /L increase in SBA levels⁽¹²⁾. Yet the level of SBA did not correlate with the severity of maternal symptoms⁽¹²⁾. In the examination of fetuses that were

Table I: Comparison of mean platelet volume and serum bile acid levels in intrahepatic cholestasis of pregnancy .

	Groups		p
	ICP (n=20) Mean ± SD	Control (n=21) Mean ± SD	
ALT (U/L) (median)	270.60 ± 311.33 (184)	14.57 ± 9.08 (13)	^b 0.001**
AST (U/L) (median)	148.05 ± 144.23 (110)	18.09 ± 7.63 (16)	^b 0.001**
SSA (µmol/L) (median)	32.38 ± 20.32 (27.75)	8.36 ± 4.29 (6.60)	^b 0.001**
Hemoglobin (mg/dl)	13.01 ± 5.25	12.08 ± 0.87	^a 0.426
Hematocrit (%)	33.85 ± 6.45	34.60 ± 2.48	^a 0.633
White blood cell count (mm3)	9617.37 ± 2105.61	10874.29 ± 1968.69	^a 0.058
Platelet count (mm3)	202.90 ± 60.21	209.62 ± 56.44	^a 0.714
MPV(fL)	10.80 ± 1.31	11.05 ± 0.96	^a 0.485

^aStudent-T Test, ^bMann-Whitney U Test, **p < 0.01

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, MPV: Mean platelet volume, SBA: Serum bile acids

lost due to ICP, instead of chronic asphyxia signs of acute anoxia were encountered, fetal weights were appropriate for the gestational week of pregnancy and umbilical artery Doppler findings were normal; all of these suggested an acute toxicity related to SBA levels instead of chronic placental insufficiency as the causative agent of fetal loss in ICP⁽¹⁷⁾. Gorelik et al, demonstrated that tauracholic acid was cardiomyotoxic, lead to cardiac arrhythmia and proposed that third trimester sudden fetal deaths were caused by sudden cardiac arrest due to increased taurocholic acid levels^(18,19). Another study inspiring from this study showed a relationship between prolonged intrauterine fetal PR interval and SBA levels⁽²⁰⁾. Another suggestion for asphyxia and sudden intrauterine fetal death was the disruption of fetal oxygenation by SBA that lead to vasoconstriction in placental chorionic veins^(21,22). Although increasing SBA levels had an important role in the identification of fetal well-being, most of the laboratories can give the results only after a few days, this creates a practical difficulty in use of SBA in emergencies⁽¹³⁾. Because that fetal losses in ICP are sudden, we need cheap, reliable and practical tests that can give rapid results. Platelets release many mediators that play role in coagulation, inflammation, thrombosis and atherosclerosis. MPV is a potential marker of platelet activity⁽¹⁴⁾. Large platelets are metabolically and enzymatically more active⁽²³⁾. The rise in MPV in liver diseases is explained with inflammation, but mechanism of the relationship cannot be explained exactly⁽¹⁵⁾. MPV also increases in myocard infarction and atrial fibrillation without coronary artery disease^(4,24). Although the mechanism is not exactly known, two previous studies demonstrated elevated MPV levels in ICP^(16,25). We planned this study by hypothesizing that SBA might increase MPV by direct cardiomyotoxic effect or by liver inflammation, but the level of MPV was not different between the two groups in our study and there was no relationship between SBA and MPV. One of the studies investigating MPV in ICP did not define diagnostic criteria for ICP and did not publish SBA levels⁽²⁵⁾. The other study demonstrated the relationship between MPV and SBA prospectively⁽¹⁶⁾. The differences between the results of this study and our study can be explained by the absence of cases with fetal distress and asphyxia in our study. Also the rise in SBA can occur a few weeks after the appearance of pruritus, in our study exclusion of pregnant with

pruritus but without certain diagnosis of ICP from both case and control groups decreases biases.

The pruritus related to increased SBA in ICP can be managed with ursodeoxycholic acid (UDCA). UDCA relieves pruritus, regulates maternal-fetal SBA transport and decreases SBA levels⁽²⁶⁾. UDCA was shown to protect myocardium from arrhythmia by decreasing umbilical cord SBA levels in vitro⁽²⁷⁾. Our patients used UDCA after detection of increased levels of SBA. Although UDCA is the most effective known treatment, it cannot prevent all of the fetal complications totally. Dexamethasone decreases placental estrogen production by decreasing secretion of precursors from the adrenal glands⁽²⁸⁾. But these drugs may not prevent fetal complications. Induction of labor is advised in pregnant with ICP, because of the increasing adverse fetal events after 37 weeks of gestation⁽²⁹⁾. The risk of intrapartum fetal loss is not increased during labor and vaginal delivery in pregnant with ICP and labor progressed more rapidly when compared to pregnancies at the same gestational week⁽³⁰⁾. In our study patients with ICP delivered at earlier weeks of pregnancy when compared to the control group, but the difference between the gestational weeks at delivery may be smaller than expected because of inclusion of patients undergoing elective cesarean section on maternal demand. We induced labor or performed cesarean section in patients with ICP when levels of SBA could not be controlled. We did not observe the increased rate of fetal distress or intrapartum fetal asphyxia pronounced in previous studies⁽³⁰⁾.

In conclusion we detected a higher rate of preterm labor due to increased SBA levels, but there was no relationship between SBA levels and MPV. Prospectively designed larger studies may evaluate this relationship more satisfactorily.

REFERENCES

1. Wikström Shemer E, Marschall HU, Ludvigsson JF, Stephansson O. Intrahepatic cholestasis of pregnancy and associated adverse pregnancy and fetal outcomes: a 12-year population-based cohort study. *BJOG*. 2013 May;120(6):717-23.
2. Reyes H, Simon FR. Intrahepatic cholestasis of pregnancy: an estrogen related disease. *Semin Liver Dis* 1993 Aug;13(3): 289-301.

3. Schreiber A, Simon F. Estrogen induced cholestasis: clues to pathogenesis and treatment. *Hepatology* 1983 Jul-Aug;3(4): 607-13.
4. Lammert F, Marschall HU, Glantz A, Matern S. Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management. *J Hepatol* 2000 Dec;33(6):1012-21.
5. Reyes H, Gonzalez MC, Ribalta J, Aburto H, Matus C, Schramm G, et al. Prevalence of intrahepatic cholestasis of pregnancy in Chile. *Ann Intern Med.* 1978 Apr;88(4):487-93.
6. 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 Sep; 80(1):31-8.
7. Koivurova S, Hartikainen AL, Karinen L, Gissler M, Hemminki E, Martikainen H, et al. The course of pregnancy and delivery and the use of maternal healthcare services after standard IVF in Northern Finland 1990-1995. *Hum Reprod.* 2002 Nov;17(11): 2897-903.
8. 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 Mar;109(3): 282-8.
9. Marschall HU, Shemer EW, Ludvigsson JF, Stephansson O. Intrahepatic cholestasis of pregnancy and associated hepatobiliary disease: A population-based cohort study. *Hepatology.* 2013 Apr 8. doi: 10.1002/hep. 26444. [Epub ahead of print].
10. Bacq Y, Sapey T, Bréchet MC, Pierre F, Fignon A, Dubois F. Intrahepatic cholestasis of pregnancy: a French prospective study. *Hepatology* 1997 Aug;26(2):358-64.
11. Lee RH, Kwok KM, Ingles S, Wilson ML, Mullin P, Incerpi M, et al. Pregnancy outcomes during an era of aggressive management for intrahepatic cholestasis of pregnancy. *Am J Perinatol.* 2008 Jun;25(6):341-5.
12. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. *Hepatology.* 2004 Aug;40(2):467-74.
13. Egerman RS, Riely CA. Predicting fetal outcome in intrahepatic cholestasis of pregnancy: is the bile acid level sufficient? *Hepatology* 2004 Aug;40(2):287-8.
14. Canpolat F, Akpınar H, Eskioglu F. Mean platelet volume in psoriasis and psoriatic arthritis. *Clin Rheumatol* 2010 Mar; 29(3):325-8.
15. Ceylan B, Fincanci M, Yardimci C, Eren G, Tözalgan Ü, Müderrisoğlu C, et al. Can mean platelet volume determine the severity of liver fibrosis or inflammation in patients with chronic hepatitis B? *Eur J Gastroenterol Hepatol.* 2013 May; 25(5):606-12.
16. Kebapçılar AG, Taner CE, Kebapçılar L, Bozkaya G. High mean platelet volume, low-grade systemic coagulation, and fibrinolytic activation are associated with pre-term delivery and low APGAR score in intrahepatic cholestasis of pregnancy. *J Matern Fetal Neonatal Med;* 2010 Oct;23(10):1205-10.
17. Fisk NM, Bye WB, Storey GN. Maternal features of obstetric cholestasis: 20 years experience at King George V Hospital. *Aust N Z J Obstet Gynaecol* 1988 Aug;28(3):172-6.
18. Williamson C, Gorelik J, Eaton BM, Lab M, de Swiet M, Korchev Y. The bile acid taurocholate impairs rat cardiomyocyte function: a proposed mechanism for intra-uterine fetal death in obstetric cholestasis. *Clin Sci (Lond).* 2001 Apr;100(4):363-9.
19. Gorelik J, Harding SE, Shevchuk AI, Korlage D, Lab M, de Swiet M, et al. Taurocholate induces changes in rat cardiomyocyte contraction and calcium dynamics. *Clin Sci (Lond).* 2002 Aug;103(2):191-200.
20. Strehlow SL, Pathak B, Goodwin TM, Perez BM, Ebrahimi M, Lee RH. The mechanical PR interval in fetuses of women with intrahepatic cholestasis of pregnancy. *Am J Obstet Gynecol.* 2010 Nov;203(5):455.e1- 5.
21. Sepúlveda WH, González C, Cruz MA, Rudolph MI. Vasoconstrictive effect of bile acids on isolated human placental chorionic veins. *Eur J Obstet Gynecol Reprod Biol.* 1991 Dec; 42(3):211-5.
22. Martin JF, Trowbridge EA, Salmon G, Plumb J. The biological significance of platelet volume: its relationship to bleeding time, platelet thromboxane B2 production and megakaryocyte nuclear DNA concentration. *Tromb Res* 1983 Dec 1;32(5): 443-60.
23. Feng C, Mei W, Luo C, Long M, Hu X, Huang Y, et al. Relationship between mean platelet volume and coronary blood flow in patients with atrial fibrillation. *Heart Lung Circ.* 2013 Jan;22(1):43-9.
24. Khode V, Sindhur J, Kanbur D, Ruikar K, Nallulwar S. Mean platelet volume and other platelet volume indices in patients with stable coronary artery disease and acute myocardial infarction: A case control study. *J Cardiovasc Dis Res* 2012 Oct;3(4):272-5.
25. Evsen MS, Soydinc HE, Ozler A, Basaranoglu S, Karacor T, Yalinkaya A, et al. Evaluation of platelet function in intrahepatic cholestasis of pregnancy. *Perinatal Journal* 2012; 20:45-8.
26. Serrano MA, Brites D, Larena MG, Monte MJ, Bravo MP, Oliviera N, et al. Beneficial effect of ursodeoxycholic acid on alterations induced by cholestasis of pregnancy in bile acid

- transport across the human placenta. *J Hepatol* 1998 May;28(5): 829-39.
27. Mazzella G, Rizzo N, Azzaroli F, Simoni P, Bovicelli L, Miracolo A, et al. Ursodeoxycholic acid administration in patients with cholestasis of pregnancy: effects on primary bile acids in babies and mothers. *Hepatology*. 2001 Mar;33(3): 504-8.
28. Kauppila A, Jouppila P, Karvonen P, Tuimala R, Ylikorkala O. Effect of dexamethasone on blood levels of ACTH, cortisol, progesterone, estradiol and estriol during late pregnancy. *Int J Gynaecol Obstet*. 1976;14(2):177-81.
29. Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. *World J Gastroenterol* 2009 May 7;15(17):2049-66.
30. Wikström Shemer EA, Thorsell M, Marschall HU, Kaijser M. Risks of emergency cesarean section and fetal asphyxia after induction of labor in intrahepatic cholestasis of pregnancy: a hospital-based retrospective cohort study. *Sex Reprod Healthc* 2013 Mar;4(1):17-22.