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Authors: Zehra Vural Yılmaz, Oğuz Özdemir, Gözde Yasemin Kurt, Çağanay Soysal, Elif Yılmaz

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The effect of intrahepatic cholestasis of pregnancy and ursodeoxycholic acid treatment on Doppler parameters of fetal and maternal circulation

Zehra Vural Yılmaz, Oğuz Özdemir, Gözde Yasemin Kurt, Çağanay Soysal, Elif Yılmaz

Dr. Sami Ulus Women's and Children's Health Teaching and Research Hospital, Ankara, Türkiye

Corresponding author:
Zehra Vural Yılmaz
Dr Sami Ulus Women Health Education and Research Hospital, Türkiye
e-mail: dilekkaplanoglu@gmail.com

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ABSTRACT

Objectives: We aimed to evaluate feto-maternal blood flow parameters using Doppler ultrasonography (USG) in pregnant women with intrahepatic cholestasis of pregnancy (ICP) and the effect of ursodeoxycholic acid (UDCA) treatment on these parameters.

Material and methods: This prospective cohort study was performed at Dr. Sami Ulus Women's and Children's Health Teaching and Research Hospital, in Turkey between September 2022 and February 2023. Sixty pregnant women, 30 with ICP disease and 30 healthy women were included in the study. Obstetric Doppler parameters were measured by USG at diagnosis and after 48 hours of UDCA treatment for the ICP group.

Results: The obstetric Doppler parameters did not significantly differ in the ICP group and the healthy control group. The Doppler findings were similar after UDCA treatment in the ICP group. Gestational week at delivery and birth weight were lower in the ICP group in our study.

Conclusions: We demonstrated that pregnant women with ICP had similar obstetric Doppler parameters when compared with healthy pregnant women and that the UDCA agent used for treatment of ICP disease did not affect these parameters.
Keywords: intrahepatic cholestasis of pregnancy; fetomaternal circulation; doppler ultrasonography; ursodeoxycholic acid

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is the most frequent liver disease seen only in pregnancy and it affects approximately 0.1–2% of pregnant women [1]. Intrahepatic cholestasis of pregnancy presents mainly with maternal pruritus, increased serum bile acids (BA) and liver dysfunction usually in the third trimester [2, 3]. Enterohepatic circulation of BA ceases and serum BA concentration increases in ICP [4]. Although maternal symptoms resolve after delivery, there are studies in the literature that these affected women are at risk for hepatobiliary disease in later life [5]. Fetal risks such as preterm delivery, fetal hypoxia, meconium-stained amniotic fluid and sudden intrauterine fetal loss increased in pregnant women with ICP [6, 7] and these increased fetal risks are found to be associated with higher BA levels [8].

Ursodeoxycholic acid (UDCA) is a natural bile acid that is found in humans and is usually used to treat hepatobiliary diseases. It is also the most recommended agent in the world for ICP disease [9]. It improves cholestasis by several mechanisms. It increases biliary BA excretion, stimulates hepatocellular secretion, stabilizes plasma membranes and protects cholangiocytes and hepatocytes from cytotoxicity of bile acids [10]. Although UDCA is the most used agent for ICP treatment worldwide, its benefit on fetal outcome is unclear. A Cochrane systematic review of the effectiveness of UDCA for ICP disease concluded that it improves maternal symptoms mildly, however evidence for fetal adverse outcomes was not shown with certainty [11].

In the literature there is insufficient data on fetal and fetomaternal circulation and Doppler Ultrasonography (USG) parameters in pregnant women complicated with ICP and the effect of UDCA treatment on these parameters. In this study we aimed to evaluate Umbilical Artery (UA), Uterine Arteries (UtA) and Middle Cerebral Artery (MCA) Doppler parameters in pregnant women with ICP and compare these parameters with pregnant women without disease, and to determine the effect of UDCA treatment on these Doppler parameters in pregnant women with ICP.

MATERIAL AND METHODS

This prospective cohort study was performed at Dr. Sami Ulus Women's and Children's Health Teaching and Research Hospital, in Turkey between September 2022 and February 2023. This study was approved by the local Ethical Committee of the Hospital (Ethics Number: E-22/09-411). The universal principles of the Helsinki Declaration were applied and informed consent was obtained from all participants. Pregnant women with a diagnosis of ICP and consecutive pregnant women without disease during the same period were recruited for the study.

Intrahepatic cholestasis of pregnancy was diagnosed when a pregnant woman had unexplained pruritus without skin lesions and with increased serum BA (≥ 10 mmol/L) and/or elevated liver function tests. For all study populations with abnormal liver function test results, viral marker measurements and liver ultrasonography were done for exclusion of other hepatotobiliary diseases such as biliary obstruction, gallstones or hepatitis. Pregnant women with other causes of liver disease were excluded from the study. Pregnant women with chronic systemic disease, multiple gestation and fetuses with malformation or diagnosis of intrauterine growth retardation (defined as estimated fetal weight < 10^{th} percentile and/or abdominal circumference < 10^{th} percentile) and pregnant women with obstetric complications (*e.g.*, preeclampsia, premature rupture of membranes, gestational diabetes mellitus) were also excluded from the study.

Demographic and the laboratory data of pregnant women in study population were recorded at first evaluation. Gestational age was determined according to the first day of the last menstrual period (LMP) and measurement of the crown–rump length (CRL) at first trimester. If there was a difference of more than seven days between them, ultrasound dating was taken as gestational age [12]. All pregnant women in study population were followed to delivery and obstetric outcome in terms of gestational week at delivery, birth weight (BW), and Neonatal Intensive Care Unit (NICU) admission was recorded. UDCA (2 × 300 mg daily) was given to all women in the study group when ICP was diagnosed.

The same perinatologist performed Doppler measurements using a Mindray DC-40 ultrasound device for all pregnant women in the study group. The systole/diastole (S/D) ratio, pulsatility index (PI), and resistance index (RI) were measured for UA, right and left UtAs, MCA and peak systolic velocity (PSV) for MCA with Doppler USG. UA measurement was done on the free loop between the

fetal and placental ends of the cord. UtA measurements were performed bilaterally where it originates from iliac artery at isthmus level. Middle Cerebral Artery Doppler measurement was done with visualizing the Circle of Willis on the axial section of the brain and one of the MCAs was used for the study. The insonation angle was tried to keep to zero degrees as possible and 30 degrees were not exceeded. Cerebro-placental ratio (CPR) was defined by dividing the MCA PI by the UA PI. Measurements were done during fetal inactivity and in the absence of fetal breathing and uterine contraction. Doppler measurements were done in the control group and prior to UDCA treatment at first diagnosis of the disease and after 48-72 hours of treatment in the ICP group.

RESULTS

Totally 60 pregnant women (30 with ICP disease and 30 without disease) were recruited to the study. Demographic parameters were found to be similar between the groups. Mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were significantly higher in the ICP group. The serum mean BA level was 38.75 ± 25.70 in the ICP group at diagnosis. Demographic and laboratory parameters of study population are shown in Table 1.

In our study group no intrauterine fetal loss was observed. BW and gestational week at delivery were lower in the ICP group when compared with the control group. Neonatal Intensive Care Unit admission rate was similar between the groups. The obstetric outcome of the pregnant women with ICP and healthy pregnant women are also presented in Table 1.

There was no statistically significant difference in the S/D ratio, PI and RI values of the UA, MCA and right and left UtAs Doppler between pregnant women with ICP and the control group. CPR values were also similar between the groups. The obstetric Doppler measurements of the pregnant women with and without ICP are presented in Table 2.

The obstetric Doppler parameters before and after treatment with UDCA in the ICP group are shown in Table 3. There was no significant difference in Doppler findings for the ICP group before and after treatment with UDCA.

DISCUSSION

In this study, we evaluated fetal and maternal circulation with routine Doppler

USG parameters in pregnant women with ICP disease and compared the results with pregnant women without disease, and we also aimed to evaluate the effect of UDCA treatment on these parameters. We found that fetomaternal Doppler parameters were similar between pregnant women complicated with ICP and without disease and UDCA had no effect on these parameters.

Intrahepatic cholestasis of pregnancy is a benign and temporary disease for pregnant women and after birth the symptoms resolve, and prognosis is excellent. However, ICP disease is associated with significant fetal risks such as preterm delivery, meconium-stained amniotic fluid, sudden intrauterine fetal demise and NICU admission and fetal complications are found to be more common with higher BA concentrations [13, 14]. In a recent Swedish cohort study, preterm labor and fetal asphyxia were found to be significantly increased when maternal serum BA concentrations were more than 40 μmol/L [8] and a UK cohort study also supported these findings that increased stillbirths were only increased in pregnant women with ICP when bile acids increased more than 40 μmol/L [15]. The long-term outcome of these children is not well known, and data is insufficient in the literature [16]. Increased bile acids and their toxic metabolites are thought to be a reason for increased fetal morbidity associated with ICP. In animal studies it was shown that bile acids might have toxic effects on myometrium and placenta. In an animal study, Williamson et al reported that elevated serum taurocholate might cause fetal dysrhythmia by impairing cardiac conduction and destroy synchronous contraction by altering the function of gap junctions in cardiomyocytes [17]. In another animal study it was found that tauro-conjugated cholic acid administration to adult and neonatal rat cardiomyocytes caused arrhythmias and abnormal contraction and neonatal rat cardiomyocytes were found to be more sensitive than adult cardiomyocytes [18].

Although in the literature it is known that ICP is associated with increased fetal risks, there are limited studies and data is conflicting about obstetric Doppler findings in pregnant women with ICP. Guerra et al found that obstetric Doppler patterns were similar in pregnant women with a diagnosis of ICP [19]. Suri et al. [20] showed that a S/D ratio above 2 SD was significantly higher in pregnancies with ICP compared with gestation matched reference values of the umbilical artery of a normal healthy pregnant population, however adverse fetal outcome was not associated with Doppler findings. Kurtulmuş et al. [21] found that UA and MCA Doppler S/D ratio, PI, and RI in pregnant women with ICP were not different when compared with

healthy pregnant women. In our study there was no statistically significant difference between Doppler findings in the ICP group and the control group. CPR was found to be similar between groups. To our knowledge, this is the first study that evaluated CPR in pregnant women with ICP disease.

Different pharmacological agents, such as UDCA, cholestyramine, dexamethasone, s-adenosylmethionine and, most recently, rifampicin have been used for pregnant women with ICP diagnosis [7]. Although the effectiveness of these agents has not been shown with evidence-based studies, UDCA is the most frequently suggested agent in the treatment of ICP in most guidelines. UDCA is thought to remove more hydrophobic endogenous bile salts from the BA pool, protects hepatocyte membranes from bile acid toxicity, and causes BA clearance from the placenta [22]. There are a few studies on UDCA effects on neonatal outcome in ICP disease in the literature. In a recent placebo controlled RCT, Chappell et al found that UDCA treatment showed a small reduction in pruritus in pregnant women with ICP of any severity, but no effect on adverse perinatal outcomes that included intrauterine fetal demise, preterm delivery and NICU admission [23]. In a systematic review of the Cochrane library, the authors reported that UDCA treatment may cause a decrease in pruritus to a small extent in pregnant women with ICP, however definitive evidence for improvement in perinatal outcomes was not found and further large-scale trials are needed to determine fetal risks or benefits [11].

Although in clinical studies the impact of UDCA treatment on adverse fetal outcomes has not been demonstrated clearly, in an in vitro study UDCA was shown to protect rat cardiomyocytes from damage due to BAs [24]. Vasavan et al found an increased fetal NT-proBNP concentration, which is used as a marker for ventricular dysfunction in untreated ICP disease when compared with normal healthy pregnant women and pregnant women with treated ICP disease and they suggested that the cardiac phenotype of ICP fetuses showed arrhythmic activity and that UDCA may have cardioprotective effects on the fetus [25].

In this study we evaluated UDCA treatment effects on maternal and fetal Doppler parameters and found that Doppler parameters were not affected at 48 hours after UDCA treatment. The influence of UDCA treatment on fetal Doppler parameters has not previously been studied and this is the first study that evaluated UDCA treatment effects on fetal and maternal Doppler parameters. We found lower BW and gestational week at birth in pregnant women with ICP compared to healthy pregnant

women, similar to the literature, due to our policy of early timing of birth in these pregnant women. Stillbirth or neonatal death was not observed in each group. Neonatal Intensive Care Unit admission rate was similar between the groups.

CONCLUSIONS

In conclusion, the pathogenesis of increased fetal morbidity and especially sudden intrauterine fetal demise in ICP is not fully understood. In this study we aimed to evaluate Doppler USG parameters of fetomaternal circulation in pregnant with ICP to understand the fetal pathophysiology associated with disease and we found that Doppler results were similar in the ICP group and healthy group so it is not useful in monitoring fetal health in pregnant with ICP. We also showed that UDCA treatment had no effect on these parameters in the short term. However further multicenter prospective studies with larger patient series are needed to evaluate fetomaternal circulation in ICP disease and the effect of UDCA treatment in both short and long term on fetomaternal Doppler parameters in pregnant with ICP to confirm our results.

Article information and declarations

Data availability statement

Data used in this study can be provided on reasonable request.

Ethics statement

This study was approved by the local Ethical Committee of our Hospital (Ethics Number: E-22/09-411).

Author contributions

Zehra Vural Yılmaz: first author, conception and design the study, analyses and interpretation of data, drafting of the manuscript.

Oğuz Özdemir: acquisition of data, analysis and interpretation of data.

Gözde Yasemin Kurt: acquisition of data, drafting the manuscript.

Çağanay Soysal: conception and design of the study, supervision.

Elif Yılmaz: statistical analysis, critical revision of the manuscript for important intellectual content.

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None.

Conflict of interest

Authors declare no conflict of interest.

Supplementary material

None.

REFERENCES

1. Marathe JA, Lim WH, Metz MP, et al. A retrospective cohort review of intrahepatic cholestasis of pregnancy in a South Australian population. Eur J Obstet Gynecol Reprod Biol. 2017; 218: 33–38, doi: 10.1016/j.ejogrb.2017.09.012, indexed in Pubmed: 28926728.
2. Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. World J Gastroenterol. 2009; 15(17): 2049–2066, doi: 10.3748/wjg.15.2049, indexed in Pubmed: 19418576.
3. Wolf MF, Sgayer I, Yaron L, et al. Intrahepatic cholestasis of pregnancy - prevalence and ethnic distribution in northern Israel. Ginekol Pol. 2022 [Epub ahead of print], doi: 10.5603/GP.a2021.0172, indexed in Pubmed: 35072239.
4. Ovadia C, Williamson C. Intrahepatic cholestasis of pregnancy: Recent advances. Clin Dermatol. 2016; 34(3): 327–334, doi: 10.1016/j.clindermatol.2016.02.004, indexed in Pubmed: 27265070.
5. Marschall HU, Wikström Shemer E, Ludvigsson JF, et al. Intrahepatic cholestasis of pregnancy and associated hepatobiliary disease: a population-based cohort study. Hepatology. 2013; 58(4): 1385–1391, doi: 10.1002/hep.26444, indexed in Pubmed: 23564560.
6. Williamson C, Geenes V. Intrahepatic cholestasis of pregnancy. Obstet Gynecol. 2014; 124(1): 120–133, doi: 10.1097/AOG.0000000000000346, indexed in Pubmed: 24901263.
7. Hague WM, Callaway L, Chambers J, et al. A multi-centre, open label, randomised, parallel-group, superiority Trial to compare the efficacy of URsodeoxycholic acid with RIFampicin in the management of women with severe early onset Intrahepatic Cholestasis of pregnancy: the TURRIFIC randomised trial. BMC Pregnancy Childbirth. 2021; 21(1): 51, doi: 10.1186/s12884-020-03481-y, indexed in Pubmed: 33435904.
8. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. Hepatology. 2004; 40(2): 467–474, doi: 10.1002/hep.20336, indexed in Pubmed: 15368452.
9. Carey EJ, Lindor KD. Current pharmacotherapy for cholestatic liver disease. Expert Opin Pharmacother. 2012; 13(17): 2473–2484, doi: 10.1517/14656566.2012.736491, indexed in Pubmed: 23094715.
10. Roma MG, Toledo FD, Boaglio AC, et al. Ursodeoxycholic acid in cholestasis: linking action mechanisms to therapeutic applications. Clin Sci (Lond). 2011; 121(12): 523–544, doi: 10.1042/CS20110184, indexed in Pubmed: 21854363.
11. Walker KF, Chappell LC, Hague WM, et al. Pharmacological interventions for treating intrahepatic cholestasis of pregnancy. Cochrane Database Syst Rev. 2020; 7(7): CD000493, doi: 10.1002/14651858.CD000493.pub3, indexed in Pubmed: 32716060.

12. Committee opinion no 611: method for estimating due date. Obstet Gynecol. 2014; 124(4): 863–866, doi: 10.1097/01.AOG.0000454932.15177.be, indexed in Pubmed: 25244460.
13. Rioseco AJ, Ivankovic MB, Manzur A, et al. Intrahepatic cholestasis of pregnancy: a retrospective case-control study of perinatal outcome. Am J Obstet Gynecol. 1994; 170(3): 890–895, doi: 10.1016/s0002-9378(94)70304-3, indexed in Pubmed: 8141222.
14. Ovadia C, Seed PT, Sklavounos A, et al. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: results of aggregate and individual patient data meta-analyses. Lancet. 2019; 393(10174): 899–909, doi: 10.1016/S0140-6736(18)31877-4, indexed in Pubmed: 30773280.
15. Geenes V, Chappell LC, Seed PT, et al. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population-based case-control study. Hepatology. 2014; 59(4): 1482–1491, doi: 10.1002/hep.26617, indexed in Pubmed: 23857305.
16. Papacleovoulou G, Abu-Hayyeh S, Nikolopoulou E, et al. Maternal cholestasis during pregnancy programs metabolic disease in offspring. J Clin Invest. 2013; 123(7): 3172–3181, doi: 10.1172/JCI68927, indexed in Pubmed: 23934127.
17. Williamson C, Gorelik J, Eaton BM, et al. The bile acid taurocholate impairs rat cardiomyocyte function: a proposed mechanism for intra-uterine fetal death in obstetric cholestasis. Clin Sci (Lond). 2001; 100(4): 363–369, indexed in Pubmed: 11256973.
18. Abdul Kadir SH, Ali NN, Mioulane M, et al. Embryonic stem cell-derived cardiomyocytes as a model to study fetal arrhythmia related to maternal disease. J Cell Mol Med. 2009; 13(9B): 3730–3741, doi: 10.1111/j.1582-4934.2009.00741.x, indexed in Pubmed: 19438812.
19. Guerra F, Guzmán S, Campos G. [Evaluation of maternal and fetal blood flow indices in intrahepatic cholestasis of pregnancy]. Rev Chil Obstet Ginecol. 1994; 59(1): 17–21, indexed in Pubmed: 7809426.
20. Suri V, Jain R, Aggarwal N, et al. Usefulness of fetal monitoring in intrahepatic cholestasis of pregnancy: a prospective study. Arch Gynecol Obstet. 2012; 286(6): 1419–1424, doi: 10.1007/s00404-012-2482-4, indexed in Pubmed: 22854875.
21. Kurtulmuş S, Gür EB, Öztekin D, et al. The impact of intrahepatic cholestasis of pregnancy on fetal cardiac and peripheral circulation. J Turk Ger Gynecol Assoc. 2015; 16(2): 74–79, doi: 10.5152/jtgga.2015.15173, indexed in Pubmed: 26097388.
22. Serrano MA, Brites D, Larena MG, 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; 28(5): 829–839, doi: 10.1016/s0168-8278(98)80234-1, indexed in Pubmed: 9625319.
23. Chappell LC, Bell JL, Smith A, et al. PITCHES study group. Ursodeoxycholic acid versus placebo in the treatment of women with intrahepatic cholestasis of pregnancy (ICP) to improve perinatal outcomes: protocol for a randomised controlled trial (PITCHES). Trials. 2018; 19(1): 657–860, doi: 10.1186/s13063-018-3018-4, indexed in Pubmed: 30482254.
24. Gorelik J, Shevchuk AI, Diakonov I, et al. Dexamethasone and ursodeoxycholic acid protect against the arrhythmogenic effect of taurocholate

in an *in vitro* study of rat cardiomyocytes. BJOG: An International Journal of Obstetrics & Gynaecology. 2003; 110(5): 467–474, doi: 10.1046/j.1471-0528.2003.02273.x.
25. Vasavan T, Deepak S, Jayawardane IA, et al. Fetal cardiac dysfunction in intrahepatic cholestasis of pregnancy is associated with elevated serum bile acid concentrations. J Hepatol. 2021; 74(5): 1087–1096, doi: 10.1016/j.jhep.2020.11.038, indexed in Pubmed: 33276032.

Table 1. Comparison of demographic and laboratory findings of study groups

Variables	**Control Group (n = 30)**	**ICP Group (n = 30)**	**p value**
Age [years]	27.93 ± 5.25	28.40 ± 5.03	p = 0.727
GW at assessment	34.87 ± 2.92	33.39 ± 3.05	p = 0.060
Gravidity	2.0 (1.0–6.0)	2.0 (1.0–6.0)	p = 0.195
Parity	0.0 (0.0–2.0)	0.0 (0.0–4.0)	p = 0.186
BMI [kg/m^2]	27.5 ± 5.24	28.7 ± 4.53	p=0.35
ALT [U/L]	13.0 (8.0–43.0)	95.5 (16.0–374.0)	**p < 0.0001**
AST [U/L]	17.0 (12.0–76.0)	67.5 (15.0–232.0)	**p < 0.0001**
Hemoglobin [g/dL]	11.52 ± 1.01	11.59 ± 1.16	p = 0.801
WBC × 10^3 mL	10.41 ± 3.01	10.72 ± 3.64	p = 0.720
Platelets × 10^3 mL	223.60 ± 63.19	253.13 ± 66.52	p = 0.083
Fasting TBA [mmol/L]	–	38.75 ± 25.70	–
GW at delivery	38.8 (35.0–41.0)	36.0 (32.0–38.0)	**p < 0.0001**
Birth weight [g]	3410.66 ± 504.84	2982.50 ± 455.96	**p = 0.001**
NICU admission. n [%] No Yes	 26 (86.7%) 4 (13.3%)	 25 (83.3%) 5 (%16.7%)	p = 0.718

ICP — intrahepatic cholestasis of pregnancy; GW — gestational week; BMI — body mass index; ALT — alanine aminotransferase; AST — aspartate aminotransferase; WBC — white blood cell; TBA — total bile acid; NICU — Neonatal Intensive Care

Unit; p < 0.05 was considered statistically significant

Table 2: Comparison of Doppler index values in intrahepatic cholestasis of pregnancy (ICP) and control groups

Doppler parameters	Control group (n = 30)	ICP group (n = 30)	p value
UA-S/D	2.34 ± 0.48	2.48 ± 0.48	p = 0.264
UA-PI	0.85 ± 0.24	0.92 ± 0.17	p = 0.205
MCA-S/D	3.46 ± 0.46	3.24 ± 0.52	p = 0.097
MCA-PSV	39.30 ± 10.04	41.36 ± 9.01	p = 0.407
MCA-PI	1.86 ± 0.47	1.85 ± 0.51	p = 0.948
CPR	2.28 (1.29–3.7)	2.11 (0.74–3.90)	p = 0.395
Right UtA-PI	0.67 (0.40–1.20)	0.66 (0.33–1.60)	p = 0.848
Left UtA-PI	0.64 (0.37–1.14)	0,66 (0.32–1.60)	p = 0.787

UA — umbilical artery; S/D — systole/diastole; MCA — middle cerebral artery; PSV — peak systolic velocity; CPR — cerebro-placental ratio; PI — pulsatility index; RI — resistance index; UtA — uterine artery; p < 0.05 was considered statistically significant

Table 3. Comparison of Doppler index values before and after treatment in intrahepatic cholestasis of pregnancy (ICP) group

Doppler parameters	Before treatment (n = 30)	After treatment (48 hours) (n = 30)	p value
UA-S/D	2.47 (1.73–3.50)	2.41(1.80–3.00)	p = 0.34
UA-PI	0.90 (0.61–1.35)	0.92 (0.68–1.40)	p = 0.94
MCA-S/D	3.35 (1.98–4.20)	3.00 (1.80–3.90)	p = 0.358
MCA-PSV	41.36 ± 9.01	42.02 ± 8.66	p = 0.077
MCA-PI	1.85 ± 0.51	1.87 ± 0.43	p = 0.05
CPR	2.10 ± 0.72	2.18 ± 0.64	p = 0.36
Right UtA-PI	0.66 (0.33–1.60)	0.67 (0.44–1.40)	p = 0.87

Left UtA-PI	0.66 (0.32–1.60)	0.61 (0.44–1.40)	p = 0.16

UA — umbilical artery; S/D — systole/diastole; MCA — middle cerebral artery; PSV — peak systolic velocity; CPR — cerebro-placental ratio; PI — pulsatility index; RI — resistance index; UtA — uterine artery; $p < 0.05$ was considered statistically significant