ORIGINAL ARTICLE

Maternal hepatic vein Doppler velocimetry in normal pregnancy and preeclampsia: a case control study

SIMA FALLAH ARZPEYMA[1], LEILA KARIMI[1], FATEMEH HOSSEINZADEH[2], SODABEH KAZEMI[2*]
[1]*Department of Radiology, Alzahra Hospital, Guilan University of Medical Sciences, Rasht, Iran*
[2]*Department of Obstetric and Gynecology, Alzahra Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran*
**Corresponding author: Sodabeh Kazemi, Department of Obstetric and Gynecology, Alzahra Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran*
Email: drsodabehkazemi@gmail.com, Tel: 00989308864765

ABSTRACT

Background: Preeclampsia is a gestational disease characterized by increased vascular resistance, hypertension, and proteinuria. Vascular and hemodynamic changes are a known feature of this condition and Doppler and spectral ultrasound is a feasible tool to evaluate them. This study aimed at examining the changes which occur in the maximum flow velocity of the maternal hepatic vein during preeclampsia.
Materials and Methods: In this case-control study, 106 women with 28-34 wk of gestational age who had referred to obstetrics and gynecology department of Guilan University of Medical Sciences between November 2017 and May 2018 were enrolled and randomly divided into two groups as control (uncomplicated pregnancy, n=56) and case group (preeclampsia, n=50). Doppler evaluation of the right hepatic vein in both groups was performed and comparison was made using regression models.
Results: Mean age, gestational age, Body Mass Index (BMI), weight, and height were not statistically different between the groups. Maximum A-wave velocities of the right hepatic vein were lower in normal pregnant women compared with the case group ($p<0.001$).
Conclusion: Our study demonstrated that the venous backflow was significantly higher in preeclampsia patients than women with uncomplicated pregnancies.
Keywords: Preeclampsia, Pregnancy, Hepatic veins, Pulse Wave Analysis, Ultrasonography, Doppler.

INTRODUCTION

Gestational hypertension, preeclampsia, and eclampsia are among the pregnancy-related hypertensive complications which affect about 10% of pregnant women worldwide (1). Preeclampsia, the origin of which is still unknown, remains the most remarkable cause of maternal and perinatal morbidity and mortality. This condition begins to show itself after 20 weeks of pregnancy following a disturbance in the adaptive regulation of maternal blood volume (2). Abnormal venous hemodynamic leads to secondary imbalances in some of the body organs including the liver and the kidneys and their abnormalities are reported as a prominent characteristic in preeclampsia (3, 4). During normal pregnancy, the venous compliance and the inferior vena cava diameter increase by 30% and 70%, respectively but women with preeclampsia have lower venous compliance (1). Studies using Doppler ultrasonography have suggested that the maternal venous compartment depends on the gestational adaptation while insisting that blood flow of renal and hepatic veins pattern are not similar in preeclampsia and uncomplicated pregnancies (2, 5, 6). Duplex ultrasound facilitates data collection for the renal interlobar vein resistance index and hepatic vein (HV) pulsed-wave velocities (3, 7). Some researchers have reported remarkable changes in HV Doppler waveforms in the pregnancy period (3, 8). Various HV Doppler-wave patterns have been observed in the course of both normal pregnancies and preeclampsia (3, 6).

Due to the high importance of diagnosing preeclampsia in pregnancy and its related morbidities and mortalities, and to give a better understanding of hemodynamic and hepatic changes during this condition, the main objective of this study was to evaluate the relationship between the Right HV velocities in preeclampsia compared with uncomplicated pregnancies using Doppler ultrasound examination.

MATERIALS AND METHODS

This case-control study was conducted on 106 pregnant women with gestational ages between 28 and 34 weeks who were referred to the obstetrics and gynecology department of Guilan University of Medical Sciences for routine obstetric follow-up during six months (November 2017-May 2018).

Our inclusion criteria were singleton pregnancies without history or symptoms of liver-related complications. The participants were divided into two groups; the control group with 56 women who had an uncomplicated pregnancy and the case group containing 50 women who had preeclampsia with all severities. We included mothers with gestational ages between 28 and 34 weeks, without prior history of immunologic, hepatic, or systemic disorders affecting Doppler features of hepatic veins. All women with an uncertain medical history, medical conditions affecting hepatic vein Doppler waveform, or mothers with emergency conditions leading to premature delivery were excluded. Preeclampsia was defined according to the criteria defined by the Society of Obstetricians and Gynecologists of Canada (SOGC) Clinical Practice Guideline (1) in which preeclampsia is diagnosed based on blood pressure higher than 140/90 mmHg and proteinuria more than 300 mg/24hr or mid-stream 1+ or more by dipstick test. The Doppler ultrasound examination using a single GE Voluson E6 device with a 2.0-5.0 MHz convex transducer was performed in all participants. All women underwent grayscale and pulse Doppler ultrasound of hepatic veins and one radiologist blinded to the status of the participants performed all of the examinations. During the ultrasound examination, the participants were kept in supine position and the long axis of the right hepatic vein was evaluated in subcostal and intercostal views.

The left and middle hepatic veins were not examined because of the cardiac motion artifact. The Right hepatic vein evaluation was performed at a distance of least 4-6 cm from inferior vena cava (5) and the participants were asked to halt breath during the exam. Then the spectrum of hepatic vein flow was recorded for measurement of maximum flow velocity.

A normal hepatic vein spectral wave typically consists of four peaks (Figure 1) including two upward peaks (toward the liver) representing atrial (A-wave) and late ventricular (V-wave) contractions, and two downward peaks (toward the heart) showing ventricular early systole (S wave) and diastole (D wave).

As the A-wave represents the velocity changes more consistent than other waves and previous studies found no appreciable change between uncomplicated pregnancies and pre-eclampsia in S, V, and D hepatic vein wave velocities, we evaluated A-wave hepatic vein alone (3, 9). Figure 2 shows the Right hepatic vein spectral Doppler evaluated by ultrasound in a patient with preeclampsia.

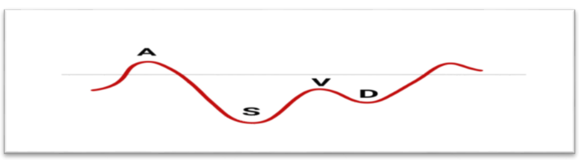

Figure 1: Normal hepatic spectral waveform: A-wave: atrial contraction showing retrograde flow toward the liver, S-wave: ventricular systole, V wave: the opening of the tricuspid valve, D-wave: ventricular diastole

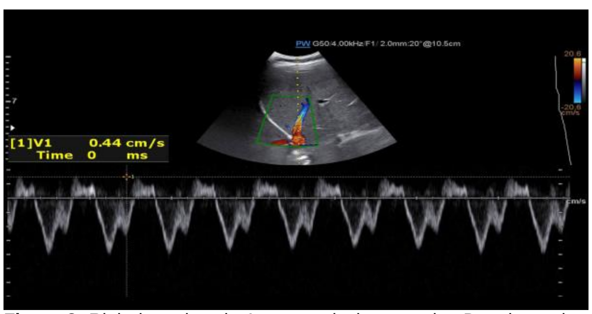

Figure 2: Right hepatic vein A-wave velocimetry using Doppler and spectral ultrasound

Ethical consideration: This research has been approved by the medical ethics committee of Guilan University of Medical Sciences (with registration code IR.GUMS.REC.1397.442). The process and purpose of the study were described to participants and after answering their questions, written informed consent was obtained before enrollment.

Statistical analysis: The analysis was performed using STATA SE v13.1. Independent t-test and Mann-Whitney U test were performed to compare the groups. Ordinary Least Square regression models were estimated to show the difference of velocity in case and control groups and the relationship between different factors and velocity. Statistical differences were considered significant at P<0.05.

RESULTS

Table 1 shows the descriptive statistics. The mean ages of the case and control groups were 29.3±5.9 and 27.7±5.0 years respectively and no significant differences were found between the ages of two groups. Also, there were no significant differences in mean gestational age and body mass indexes. Besides, a significant difference in the mean of systolic and diastolic blood pressure between the two groups was observed as expected.

Table 1: The demographic characteristics of study groups

	Case group	Control group	P-values
Age (yrs)	29.32 + 5.90	27.75+5.00	0.14
Gestational age (wk)	31.26 + 1.79	30.71+1.90	0.13
Weight (Kg)	77.06+7.28	75.39+8.86	0.29
Height (Cm)	169.94+7.04	169.77+6.64	0.90
BMI	26.72+2.38	26.17+3.34	0.34
Systolic BP (mmHg)	135.80+7.17	108.75+7.15	<0.001
Diastolic BP (mmHg)	84.70+8.17	73.98+6.94	<0.001

Data presented as mean±SD. Independent t-test
BMI: Body mass index
BP: Blood pressure

In the evaluation of Right hepatic vein A-wave velocities, the numbers did not follow a normal distribution pattern and were analyzed using the Mann-Whitney U test. In the group with uncomplicated pregnancies, the mean and standard deviation was 5.43 ± 2.0 cm/s, respectively. Also in the case group, the mean and standard deviations were 0.57 and 1.85 cm/s. This difference was statistically significant between the groups (p<0.001) as shown in Table 2.

Table 2 represents the Ordinary Least Square (OLS) regression model to indicate the A-wave velocity of Right hepatic vein (cm/s) difference between case and control groups, after adjustment of age, gestational age, and BMI. As shown in the table, the coefficient of case group was 4.67432 (positive) and significant (p<0.001), suggesting that after adjustment of age, gestational age and BMI, the A-wave velocity of Right hepatic vein (cm/s) is significantly higher in preeclampsia in comparison with normal pregnancy.

Table 3 shows the relationship between different variables and the maximum flow velocity of the maternal hepatic vein in the preeclampsia and control groups. As shown in the table, age, weight, height, BMI and systolic and diastolic BP did not have any significant relationship with the maximum flow velocity of the maternal hepatic vein. However, pregnancy age had a negative significant relationship with the maximum flow velocity of the maternal hepatic vein (Correlation coefficient=-0.337, P-value=0.017). Thus, it can be concluded that by an increase in pregnancy age, the maximum flow velocity of the maternal hepatic vein would decrease in preeclampsia pregnant women. In the control group, a significant relationship was found between the maximum flow velocity of the maternal hepatic vein and pregnancy age (Correlation coefficient=-0.429, P-value=0.001), weight (correlation coefficient= -0.281, P-value=0.036) and BMI (Correlation coefficient=-0.345, P-value=0.009).

Table 2: Comparison of the assessments of right HV A-wave velocity in normal pregnancy and preeclampsia

A-wave velocity of Right hepatic vein (cm/s)		Case group	Control group	IIIP-value
	Mean	0.57	5.43	<0.001
	Standard Deviation	1.85	2.00	
	Median	1.00	5.35	
	Minimum	-3.00	2.20	
	Maximum	3.40	9.20	
	95.0% Lower CI for Mean	0.05	4.89	
	95.0% Upper CI for Mean	1.10	5.97	

* Mann–Whitney U test

Table 3: The relationship between different variables and the maximum flow velocity of the maternal hepatic vein in preeclampsia and control group

Study group			Age	Pregnancy age	Weight	Height	BMI	Systolic BP	Diastolic BP
Preeclampsia	Maximum flow velocity of the maternal hepatic vein	Correlation Coefficient	.182	-.337	-.060	-.064	-.027	-.155	.097
		Sig. (2-tailed)	.205	.017	.678	.658	.855	.282	.501
		N	50	50	50	50	50	50	50
Control	Maximum flow velocity of the maternal hepatic vein	Correlation Coefficient	.140	-.429	-.281	.036	-.345	-.034	-.297
		Sig. (2-tailed)	.302	.001	.036	.795	.009	.805	.026
		N	56	56	56	56	56	56	56

Table 4: The regression model with the dependent variable of the maximum flow velocity of the maternal hepatic vein

Variable	Coefficient	SE	P-value	Lower limit	Upper limit
pregnancy age	-0.41675	0.094371	<0.001	-0.60391	-0.22959
case group	-4.62755	0.350758	<0.001	-5.32319	-3.9319
constant	18.22872	2.908311	<0.001	12.46077	23.99667

Table 4 shows the regression model with the dependent variable of the maximum flow velocity of the maternal hepatic vein in preeclampsia in the case group compared with the control group after adjustment of the mother's pregnancy age. As shown in the table, the coefficient of the case variable was -4.627 and significant, indicating that in preeclampsia group the maximum flow velocity of the maternal hepatic vein was lower than the control group after adjustment of mother's pregnancy age. The pregnancy age variable had a negative relationship with the maximum flow velocity of the maternal hepatic vein (coefficient=-0.416, P-value<0.001).

DISCUSSION

Preeclampsia is a disorder of high blood pressure in pregnant women. This makes pregnancy difficult and can increase the risk of fetal growth restriction as well as dysfunction of multiple organs in the mother (10). The successful outcome of pregnancy is due to severe arterial dilatation in the mother's bloodstream. The use of Doppler ultrasound (US) to assess maternal circulatory changes can be useful in the follow-up of high-risk pregnancies with preeclampsia (11). The standard examination of the United States in pregnant women is the evaluation of uterine circulation and the prediction of preeclampsia. Other vascular substrates that may be considered during pregnancy are those affected by preeclampsia such as cerebral, renal, and hepatic circulation (12). Using Doppler ultrasound on the surface of the hepatic veins, various developments of maximum and minimum blood flow velocities (Doppler waveforms of hepatic vein) in uncomplicated pregnancies have been observed (13).

A wide range of hepatic vein Doppler waves has been observed in both normal and complex pregnancies with preeclampsia (14). The liver is commonly seen in severe preeclampsia in the form of HELLP syndrome, which is one of the most severe acute conditions of pregnancy (15). So far, only absolute amounts of liver blood flow in normal pregnancies have been evaluated. Munnell and Taylor reported hepatic vein catheterization with no change in hepatic blood flow during pregnancy, while Nakai et al. Showed by Doppler measurements that hepatic perfusion increased in the third trimester. And is the main cause of increased portal venous flow, while hepatic arterial flow remains unchanged (16, 17).

However, in our study, doppler waveforms of hepatic vein was compared in normal pregnant women and preeclamptic pregnancies, which in turn is the first comparative study of Doppler waveforms of hepatic vein among normal pregnant women and mothers with preeclampsia in Iran.

The velocity of the hepatic artery in the hepatic venous circulation is significant because vascular changes in preeclampsia involve most of the arteries (11). Many studies have shown that abnormal Doppler waveforms are seen in 36% of patients in the first 20 weeks of pregnancy when the uterus is still small. It has also been observed that the Doppler velocity in the portal vein (mean: 28 cdsec) is significantly higher than the portal vein in non-pregnant women (18). This may be a reflection of increased cardiac output and decreased vascular resistance in the vascular system and possibly the abdominal arteries during pregnancy.

Using Doppler ultrasound at the level of relative interstitial volume (RIV), various changes of maximum and minimum blood flow velocity were observed during uncomplicated pregnancy, leading to lower values of RIV impedance index in the third trimester compared to the first trimester of pregnancy (19). In addition, it has been reported that the RIV impedance index in preeclampsia is higher than in uncomplicated pregnancies; the Doppler waveform of the hepatic vein (HV) has been reported to change significantly during pregnancy. A range of venous

HV Doppler wave patterns has been observed in both uneven pregnancies and those with preeclampsia (20). A limited number of studies have evaluated the liver blood flow velocities during pregnancy. The most important of these were performed by Nakai et al. who measured the liver blood flow velocities with Pulsed wave (PW) doppler and calculated the volume of flow in the hepatic artery and portal vein. They found that the rate of hepatic blood flow increased in the third trimester (up to 160%), but was associated with no change in flow through the hepatic artery due to increased flow through the portal vein (up to 150%). HV Doppler waveform patterns are very different in healthy people. This may reflect natural human diversity or may depend on congenital anatomical changes, liver or heart disease, excessive fluid, respiration, orthostasis, venous obstruction, and the distance between the measuring point and the heart (17).

One of our key points is that hepatic vein A wave was faster on doppler ultrasound in women with preeclampsia than in uncomplicated pregnancies at 28-34 weeks of gestation, this is consistent with the results of a study by Nakai et al (17). These results suggest that venous blood flow in preeclampsia was significantly higher than in normal pregnancies and is consistent with a study by Gyselaers et al., which similarly confirmed that the maternal venous system is involved in preeclampsia (3). Our study also showed that the A-wave of the right hepatic vein (cm/s) in preeclampsia was significantly higher than in normal pregnancy, whereas in a study by Erkoc et al. maximum rate was reported in the third trimester of pregnancy to be less than the second trimester, which differs from ours (21).

In our study, it was found that age, weight, height, BMI, and systolic and diastolic had no significant relationship with the maximum velocity of the mother's hepatic venous flow. However, gestational age showed a significant negative relationship with the maximum velocity of the mother's hepatic vein flow. In other words, it was shown that the maximum velocity of the mother's hepatic vein flow after adjusting the gestational age of the mother was lower in the preeclampsia group than the control group, which indicates a negative relationship between wave A and gestational age. These results are consistent with the results of Gyselaers et al. and Daher et al. (2015), which measured the doppler flow rate of the kidneys and liver of pregnant mothers (3, 8). The findings of this study can be justified by the increase in uterine size and the pressure on the IVC, which increases the preload of the heart, but should be confirmed by further evaluation using echocardiography. Our study had limitations because the cross-sectional design of this study led to a lack of time evaluation. Also, some confounding variables such as blood lipids were not available and were not adjusted in the two groups.

CONCLUSION

The results of our study confirm previous studies. In our study, it was shown that gestational age had a significant negative relationship with the maximum velocity of the mother's hepatic vein. In other words, it can be concluded that with increasing gestational age, the maximum rate of maternal hepatic vein flow in preeclampsia pregnant women decreases. Evaluation of hepatic artery Doppler indices in the third trimester of pregnancy has significant diagnostic value in predicting adverse pregnancy outcomes and should be considered as part of routine evaluation in high-risk pregnancies.

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