

Original Article

Can the ductus venosus doppler predict the hemoglobinopathies?

Atilla Karateke¹, Dilek Benk Silfeler², Arif Güngören², Raziye Keskin Kurt², Ayşe Güler Okyay², Recep Dokuyucu³, Turker Ulutas⁴, Burak Un⁵, Hacer Paksoy⁶, Ali Ulvi Hakverdi²

¹Antakya State Hospital, Obstetrics and Gynecology Clinic, Hatay, Turkey; ²Departments of ²Obstetrics and Gynecology, ⁶Physical Medicine and Rehabilitation, Mustafa Kemal University, Faculty of Medicine, Hatay, Turkey; ³Department of Medical Physiology, Medical Faculty, Mustafa Kemal University, Hatay, Turkey; ⁴Kadirli State Hospital, Biochemistry Clinic, Osmaniye, Turkey; ⁵Kadirli State Hospital, Obstetrics and Gynecology Clinic, Osmaniye, Turkey

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Abstract: Objective: The aim of our study was to investigate the ductus venosus doppler between 11-13+6 (week-day) in pregnant women with hemoglobinopathies and its relation with fetal outcomes. Material and methods: A total of 100 pregnant women with hemoglobinopathies and 100 healthy pregnant women were included in our study. Ultrasonography (USG) was performed to all pregnant women and the ductus venosus doppler (DVD) flows were evaluated. The results were statistically analyzed. Results: The mean hemoglobin level was significantly lower in hemoglobinopathy group (9.7 ± 0.7) than control group (10.67 ± 0.82) ($P < 0.001$). There was a significant relationship between Vmax, Vmin, S/D and reverse 'a' wave in fetuses with hemoglobinopathies. Vmax, Vmin and S/D parameters were higher in the group of hemoglobinopathies (respectively mean value, 31.3 ± 1.66 , 8.90 ± 0.81 , 2.97 ± 0.49). Reverse 'a' wave was detected especially in all fetuses with sickle cell anemia. There was no significantly relationship between the groups in terms of PI, RI and HR. In a logistic regression analyses, fetal hemoglobinopathy was independently associated with Vmin ($\beta = 1.07$, $P = 0.001$), S/D ($\beta = 2.61$, $P = 0.001$) and reverse 'a' wave ($\beta = 2.46$, $P = 0.004$). Conclusion: Pregnant women with hemoglobinopathies had changed ductus venosus doppler values in compared to normal pregnant women. Maternal anemia may cause this doppler changes. Furthermore all fetuses with sickle cell anemia ($n = 5$) had abnormal ductus venosus doppler findings. Further studies are needed to investigate the relationship between abnormal ductus venosus doppler findings and fetuses diagnosed with sickle cell anemia.

Keywords: Hemoglobinopathies, ductus venosus doppler, ultrasonography

Introduction

Hemoglobinopathy is a hereditary disease frequently seen in the Mediterranean region due to consanguineous marriages. The most common hemoglobinopathies are sickle cell anemia and thalassemia. Incidence of sickle cell anemia in Turkey ranged from 13.6 to 16.8, while those of thalassemia were reported as 4.3% [1, 2]. Pregnant women with anemia might have high probability to have these hemoglobinopathies in Mediterranean region of Turkey. Although anemia is a physiological result of pregnancy, symptoms of anemia increase further by existence of hemoglobinopathy. Blood flow rate that is transmitted to the fetus

differs in pregnant women with hemoglobinopathy. To get enough blood flow in case of fetal anemia, fetus increases the blood flow rate from the vessels reaching itself. The changes in blood flow rate may affect fetal Doppler indices via different ways. The best method to detect difference in fetal blood flow velocity is ductus venosus doppler.

The sphincter-like ductus venosus (DV) is an essential regulator of fetal circulation. It transports oxygenated blood from umbilical vein to the inferior vena cava and foramen ovale, thus bypasses hepatic circulation. Highly oxygenated blood passes through the right atrium and goes to the left atrium to perfuse the fetal brain

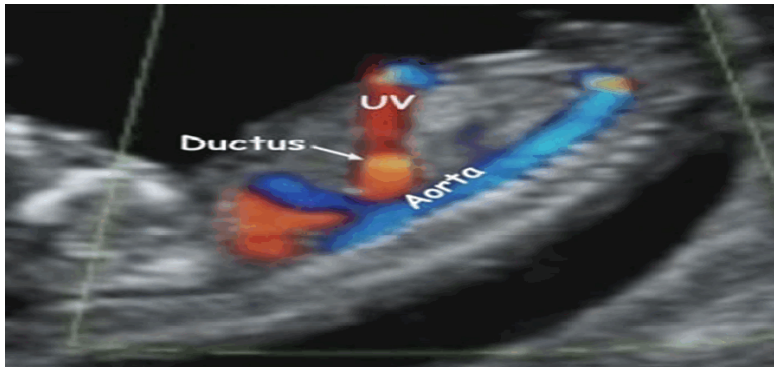


Figure 1. The anatomy of ductus venosus Doppler.

and trunk [3-5]. Doppler measurements of the DV have been accepted as an important indicator in monitoring the fetus in cases of cardiac defects, intrauterine growth restriction and fetal anemia [2, 6-8]. The analysis of the DV has also been used to determine fetuses at risk of acidemia and perinatal death [2, 9]. An abnormal DV blood flow velocity waveform is also related with fetal twin-to-twin transfusion syndrome and anemia [10]. In some studies on A-wave of DV have showed the importance of the ductus venosus in first trimester screening for fetal chromosomal abnormalities [11].

In this study, ductus venosus Doppler indices were investigated in women with hemoglobinopathies, which has not been previously reported in the literature. Additionally, the success of ductus venosus Doppler indices to diagnose fetal hemoglobinopathies were studied.

Material and methods

This study was performed in Obstetrics and Gynecology Department of Mustafa Kemal University between October 2012 and October 2013. 100 pregnant women with hemoglobinopathies (group 1) and 100 healthy pregnant women (group 2) were included in the study. All the participants were pregnant (11-13 week +6 days based on last menstrual period). Of 100 patients with hemoglobinopathies, 60 patients had thalassemia, 36 patients were carriers for sickle cell anemia and 4 patients had sickle cell anemia. Fetal age was calculated from the last menstrual period, and it was confirmed by ultrasonography measurement of the crown-rump length. Exclusion criteria were as follows; multiple pregnancies, pregnant women with hypertension, diabetes mellitus, uterine anom-

aly, recurrent pregnancy loss or abortus imminens, additional medical illness. Ethical committee approval was obtained. After giving the detailed information to the patients, the signed informed consent was obtained.

All data including age, blood groups, wives blood groups of pregnant women, types of hemoglobinopathies and obstetric history were recorded. Venous blood was taken

to determine hemoglobin levels. All subjects had fetal pulsed Doppler studies with color Doppler flow mapping at 11 weeks 0 days to 13 weeks 6 days of gestation. First, pregnant women were evaluated by transabdominal ultrasonography (Toshiba brand Xario PVT-375 BT, 3.5 MHz). When optimal image could not be obtained, transvaginal ultrasonography (Acuson 128XP10, 5 or 7-MHz) was performed. Ductus venosus was measured by Doppler seeing umbilical valve, ductus venosus and inferior vena cava under the positioned fetus to dorso-posterior vertex. It is done from the nearest place that ductus venosus spilled to the inferior vena cava, by using doppler angle less than 30 degrees and lower filter (50 Hz) (**Figure 1**). Measured values were the peak velocity during ventricular systole (Vmax), pulsatility index (PI), resistance (RI), systole/diastole (S/D), heart rate (HR) and reverse 'a' waves. Ultrasonography evaluation of pregnant women were made by the same person. In group 1, chorionic villus sampling (CVS) was performed to determine whether or not the fetuses had hemoglobinopathies. Statistical analysis was performed by SPSS software (version 15.0, packet program for windows systems). Normal distribution for continuous variables was checked with histogram plot. Doppler variables among pregnant with hemoglobinopathy and control groups were analyzed by Mann-Whitney U test or two-tailed Student's t-test, whichever was appropriate. Binary logistic regression analyze was performed between doppler parameters, maternal Hb and fetal hemoglobinopathy. A *P*-value < 0.05 was considered statistically significant.

Results

Age of the group 1 ranged from 17 to 41, as the mean age was 27.5 ± 5.08 . Age of the group 2

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Table 1. The ductus venosus doppler findings of patient and control group

	Patient group n= 100	Control group n= 100	P value
Vmax	31.3 ± 1.66	30.83 ± 1.69	0.032
Vmin	8.90 ± 0.81	8.19 ± 0.87	0.001
PI	1.15 ± 0.16	1.11 ± 0.17	0.085
RI	0.64 ± 0.52	0.66 ± 0.37	0.057
S/D	2.97 ± 0.49	2.26 ± 0.49	0.001
HR	165.87 ± 98.91	165.96 ± 7.83	0.729
Reverse 'a' wave	12 (12%)	3 (3%)	0.001

Table 2. Correlation between fetal hemoglobinopathy and ductus venosus doppler findings of patient group

	P value	B	OR	95.0% C.I. for OR	
				Lower	Upper
Fetal hemoglobinopathy					
Vmax	0.13	0.30	1.35	1.06	1.71
Vmin	0.001	-1.07	0.34	0.20	0.56
S/D	0.001	2.61	13.60	6.26	29.59
Reverse 'a' wave	0.004	2.46	11.74	2.20	62.54

ranged from 16 to 38, as the mean age was found to be 26.68 ± 5.24 . There was no significant difference between group 1 and 2 in terms of ages ($P > 0.05$). Hemoglobin (g/dl) levels of the pregnant women were between 7.1-12.5, and the average value was measured as 10.1 ± 0.9 . Mean hemoglobin level was 9.7 ± 0.7 in Group 1, while it was found to be 10.67 ± 0.82 in Group 2. There was a significant difference between group 1 and 2 in terms of hemoglobin ($P < 0.001$).

There was statistically significant difference at some Doppler parameters of ductus venosus (**Table 1**). Number of Reverse 'a' wave was 15 in all pregnant women. 12 of that were detected in Group 1. A significant statistical difference was found in terms of Reverse 'a' wave ($P: 0.001$). As a result of CVS, while one of the patients was determined as thalassemia, 16 were thalassemia trait, 5 were sickle cell disease, and 24 were sickle cell trait. Reverse 'a' wave was detected in all fetuses with sickle cell disease, while only 6 were detected in of the fetuses with sickle cell trait. A reverse 'a' wave detected only in one fetus with thalassemia. In a logistic regression analyze for fetal hemoglobinopathy with Vmax, Vmin, S/D and reverse 'a' wave was independently associated with Vmin

($\beta = 1.07$, $P = 0.001$), S/D ($\beta = 2.61$, $P = 0.001$) and reverse 'a' wave ($\beta = 2.46$, $P = 0.004$) (**Table 2**).

All pregnancies were followed until the end of the birth. Some pregnancies were terminated at 2th trimester based on the request of the family because fetuses suffering from sickle cell disease and thalassemia. Five pregnancies with thalassemia resulted in IUGR. Of 3 resulted in prematurity and 1 was fetal death. Three of this complicated cases had abnormal umbilical artery doppler findings as diastolic flow loss and reverse diastolic flow. Seven pregnancies with sickle cell resulted in IUGR. Prematurity and fetal death were observed in 4 and 3 pregnancies, respectively. Five pregnant women with sickle cell resulted had abnormal doppler findings as mentioned above.

Discussion

The present study results indicate that ductus venosus doppler parameters may be guide to diagnose the fetal hemoglobinopathies in pregnant women with hemoglobinopathy. Also there were significant correlations between Vmin, S/D and reverse 'a' wave and fetal hemoglobinopathy.

Ductus venosus directly transports oxygen-rich blood to the brain and left side of heart bypassing right atrium. Any adverse effects on ductus venosus affects heart and brain [3]. In cases of fetal anemia and cardiac pathologies, blood flow of ductus venosus is impaired. Since this impairment directly affect brain and heart of fetus, fetal complications such as intrauterine growth retardation (IUGR), prematurity, low birth weight babies, fetal death and fetal anomaly may arise.

In a study conducted to women population with thalassemia in Thailand, Traislisp et al. have found increase in incidence of IUGR infants, premature birth, and prematurity, low birth weight infants and abnormalities via fetal outcomes [12]. In our study, 5 patients with thalassemia resulted in IUGR pregnancies, as 3 resulted in prematurity and one in fetal death. In 2009, in a study of Al Jama et al. done in the Arabian Peninsula, the birth outcomes were

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investigated in pregnant women with sickle cell anemia. They observed an increase in the incidence of problems that we have mentioned above [1]. In our study, 7 sickle cell anemia ended up with IUGR pregnancies, while 4 of them had prematurity and 3 of them had fetal death.

Recent studies showed that abnormal flow patterns of ductus venosus increase risk of fetal acidemia and perinatal death. Moreover, DVD is a specific indicator of fetal acidemia [2, 9]. Abnormal flow patterns that have mostly seen in this case associated with fetal anemia and cardiac pathologies. As mentioned above, decreased blood flow due to anemia may cause some problems in the fetus. Basic mechanism of this result is hypoxic response of fetal brain secondary to decreased blood flow of ductus venosus. Brain will get the blood flow by increasing the ductus venosus blood flow to protect itself as a response to hypoxic condition. Thus, ductus venosus doppler parameters regarding blood flow will change. The most important doppler parameters are slow blood flow during atrial contraction and increased ventricular end-diastolic pressure [13]. In our study, fetus will not be able to receive adequate blood flow from the placenta due to maternal hemoglobinopathy and in this case, the abnormal flow patterns will be seen in the fetal ductus venosus.

In a study conducted in pregnant women who has inadequate blood flow to placenta, Hechler et al. detected abnormal DVD flow patterns with fetal and cardiac involvement [14]. This abnormal flow patterns are more increased parameters including Vmax, Vmin, S/D and the reverse 'a' wave. In particular, Vmax and Vmin were seen as increased. Vmax and Vmin, and DVD index were similarly found as increased in our study. S/D values increased at the same time. An important marker showing developmental abnormalities in the fetus is the reverse 'a' wave. When a reverse 'a' wave is observed, that commonly means an upcoming problem for fetus. Murat et al. conducted a study with 372 pregnant women and DVD were applied. Reverse 'a' wave was determined in fetuses with developmental abnormalities approximately at the rate of 86.2% by fetal Doppler [15].

According to CVS results, the reverse 'a' wave was determined in all 5 sickle cell fetus. The

result indicated that reverse 'a' wave was important for showing abnormal flow pattern in fetus DVD. Similarly, a single fetus with thalassemia had the same wave. Reverse 'a' wave presence was detected in 6 of 24 fetus with sickle cell trait. In the light of all results, reverse 'a' wave is seen very important to show abnormal DVD flow patterns caused by fetal anemia. In this process, applying ductus venosus Doppler at 11-13+6 (week-day) weeks of gestation may help us to previously predict the likelihood of such problems. Any Doppler study related to ductus venosus have not been conducted in pregnant women with hemoglobinopathies in the literature so far. A single study closest was performed to fetuses who were diagnosed with homozygous alpha-thalassemia. It was done by Lam et al., in 1999, China's Hong Kong with 96 women. Of 96 women, 20 fetus had homozygous alpha-thalassemia. Ductus venosus Doppler were performed these fetuses between 11 and 13+6 (week-day) weeks of gestation like our study. Vmax and Vmin values found to be significantly increased in fetuses with hemoglobinopathy via Doppler results compared to normal fetuses. The reason was that fetuses had deep anemia due to homozygous alpha-thalassemia [16].

In our study, Vmax and Vmin values were found significantly increased in the fetuses of pregnant women with hemoglobinopathy than the control group. PI, RI and HR values were detected as significantly increased, while there was no significant change at S/D values compared to control group. When we compare the fetuses with hemoglobinopathy among themselves, Vmax and Vmin values increased at higher rates in fetuses with sickle cell anemia compared to thalassemia. Among thalassemics, fetuses with BTM had higher Vmax and Vmin rates compared to ones without BTM. S/D value was found to be increased at higher rates in sickle cell anemia compared to thalassemic fetuses as well. In our study, reverse 'a' wave was detected in 12 people with hemoglobinopathy, whereas in only 3 of the control group. Therefore, the reverse 'a' wave could be a valuable marker for predicting fetal developmental pathologies in people with hemoglobinopathy.

Pregnant women with hemoglobinopathy had changed DVD values in compared to normal pregnant women. Although fetal aneuploidy, fetal heart abnormalities, fetal anemia and twin to twin syndrome may cause these doppler

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changes [10], maternal anemia can be pronounced as the most important reason. All fetuses with sickle cell anemia had abnormal ductus venosus Doppler findings in this study. Further studies are needed to investigate the relationship between abnormal ductus venosus Doppler findings and fetuses diagnosed with sickle cell anemia.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Atilla Karateke, Antakya State Hospital, Obstetrics and Gynecology Clinic, Hatay 31100, Turkey. Tel: +90 536 977 76 72; Fax: +90 326 224556; E-mail: drkarateke@gmail.com

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