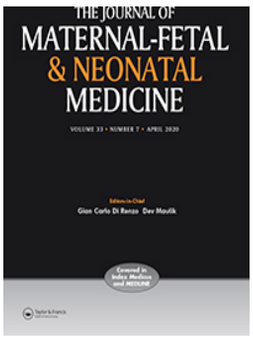

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Reference values of the *ductus venosus* pulsatility index for pregnant women between 11 and 13^{+6} weeks of gestation

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ORIGINAL ARTICLE

Reference values of the *ductus venosus* pulsatility index for pregnant women between 11 and 13^{+6} weeks of gestation

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Department of Obstetrics and Gynecology, Başkent University Faculty of Medicine, Adana, Turkey

ABSTRACT

Purpose: The *ductus venosus* pulsatility index velocity (DV PIV) has become a popular ultrasonographic measurement during the first trimester of pregnancy. The value of the DV PIV has been the topic of ongoing discussion in the literature, and its reference value in the normal population has not yet been established. Therefore, we aimed to determine a reference value for the DV PIV.

Materials and Methods: We retrospectively evaluated our records of first-trimester ultrasonography performed between 2016 and 2017. Our inclusion criteria were as follows: singleton pregnancy; crown-rump length (CRL) between 45 and 84 mm; absence of structural abnormalities on the ultrasound examination; and absence of chromosomal abnormalities. Records of 820 patients were evaluated. According to the inclusion criteria, records of 458 patients were included in this study. All ultrasound examinations were performed by a single operator with the Voluson E8 (5- to 8-MHz 3 D transducer; General Electric Healthcare, Little Chalfont, UK) via the transabdominal route. Gestational weeks were designated according to CRL measurements at the beginning of the examination. Nuchal translucency (NT), nasal bone visualization (NB), tricuspid valve regurgitation (TR), "a"-wave pattern, DV PIV, S-wave (peak systolic velocity), D-wave (peak diastolic velocity), a-wave (atrial contraction in late diastole), and time-averaged maximum velocity (TAMXV) measurements were performed. To evaluate the DV Doppler images, a midsagittal view of the fetal profile was obtained. Color Doppler and pulse Doppler gate were used in the distal portion of the umbilical sinus, and at least three typical DV waveforms were detected. The SPSS 21.0 statistical program (IBM, Armonk, NY) was used to analyze variables.

Results: The mean age, body mass index, CRL, gestational age, and NT values were 30.3 years (range, 18–45), 23.9 kg/m^2 (range, 15.5–46.6), 59.5 mm (range, 45–79), 12.3 weeks (range, 11.2–13.6), and 1.58 mm (range, 0.73–2.62), respectively. The median gravidity and parity were 2 (1–8) and 0 (0–4), respectively. The "a"-wave pattern was identified in all cases, but TR was not detected in any of the cases. Measurements of DV PIV with a Gaussian distribution were suitable according to the Shapiro–Wilk test ($p = .252$). The mean DV PIV was 0.98, and the fifth and 95th percentiles were 0.73 and 1.22 (±2 SD), respectively. A statistical analysis of our cohort revealed that DV PIV values less than 0.73 and more than 1.22 were beyond the normal range. The mean S-wave, D-wave, a-wave, and TAMXV values were 31.18, 25.64, 8.68, and 22.72 cm/s, respectively.

Conclusions: The value of DV PIV measurements is debated in the literature. Using our cohort, we defined the means and ranges of DV PIV. Determining the normal ranges of DV PIV could be helpful to anticipate congenital or chromosomal abnormalities. Further studies are needed to demonstrate the clinical importance of DV PIV, especially for patients with abnormal DV PIV measurements.

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First trimester; *ductus venosus*; Doppler; pulsatility index; reference range

Introduction

The *ductus venosus* (DV) is a small vein that provides a connection between the inferior vena cava and umbilical vein. It allows the transfer of highly oxygenated blood from the placenta to the left atrium through the right atrium and foramen ovale [1].

The flow velocity of the DV on ultrasound is characterized by a peak during ventricular systole (S-wave), another peak during ventricular diastole (D-wave), and depth in the lowest part of atrial contraction during late diastole (a-wave) [2].

Recent studies showed abnormal DV blood flow patterns (reverse "a"-wave or lack of the "a"-wave) during the first trimester, suggesting an association between fetal chromosomal abnormalities, congenital cardiac defects, and adverse pregnancy outcomes

CONTACT Şafak Yilmaz Baran safakyilmazbaran@gmail.com Department of Obstetrics and Gynecology, Adana Seyhan Başkent Hastanesi, Kadın Doğum Kliniği, Gazi Paşa Mah. Baraj Cad. No: 7 Seyhan Adana, Türkiye

Table 1. Evaluation of the *ductus venosus* flow.

Reference and year	Number of cases	Gestational age (weeks)	S-wave (cm/s)	D-wave (cm/s)	a-wave (cm/s)	TAMXV (cm/s)	PI
Montenegro [12] 1996	61	10–13	24.8	18.8	3.4	16.5	1.3
Prefumo [10] 2002	198	10–14	29.5	NE	6.8	21.6	1.06
Jaczynska [14] 2006	225	11–14	42.48	NE	11.91	NE	0.94
Pruksanusak [13] 2014	304	11–13^{+6}	41.1	34.87	2.47	31.27	0.92
Peixoto [11] 2015	430	11–13^{+6}	NE	NE	NE	NE	1.1
Kalayci 2018 [This Study]	458	11–13^{+6}	31.18	25.64	8.68	22.72	0.97

S-wave: mean peak systolic velocity; D-wave: mean peak diastolic velocity; a-wave: mean atrial contraction in late diastole; TAMXV: mean time-averaged maximum velocity; PI: mean pulsatility index; NE: not evaluated.

[3–7]. Doppler studies have demonstrated the importance of the DV for monitoring fetuses with intrauterine growth restriction due to placental insufficiency [8–10].

Studies performed in different countries have searched for blood flow velocities and reference ranges of the DV PIV during the first trimester. According to these studies, the mean DV PIV values ranged from 0.92 to 1.93 [10–14] (Table 1). Furthermore, researchers sought a correlation between advanced gestational age and DV Doppler indexes [15–17].

In this study, we aimed to determine DV Doppler indexes and set reference values for the DV pulsatility index velocity (DV PIV) during the evaluation of DV waveforms during the first trimester (11–13^{+6} gestational weeks). We also aimed to provide a scientific basis for future studies investigating the values of DV waveforms and DV PIV.

Materials and methods

We retrospectively evaluated the records of pregnant women who were admitted to our outpatient clinic for screening between 11 and 13^{+6} gestational weeks between January 2016 and September 2017. Our inclusion criteria were singleton pregnancies with crown-rump length (CRL) measurements between 45 and 84 mm and no major structural or chromosomal anomalies during follow-up. A total of 820 records of pregnant women were retrospectively evaluated; 458 of them were included in the study.

All ultrasonographic evaluations were performed by single operator (H.K.) with Voluson E8 (5- to 8-MHz 3 D transducer; General Electric Healthcare, Little Chalfont, UK) using the transabdominal method. During screening, CRL measurements and concordant gestational weeks were determined. Nuchal translucency (NT), the nasal bone (NB), and other structures were evaluated to determine any congenital anomalies. The "a"-wave, S-wave, D-wave, a-wave, and time-averaged maximum velocity (TAMXV) were recorded.

Evaluation of the DV blood flow was performed in an immobile position of the fetus; the fetal thorax and abdomen were viewed on the entire screen with a 0.5–1 Doppler window. Color Doppler was used to measure flow velocity in the right ventral mid-sagittal plane. A pulse Doppler window was used to view the distal portion of the umbilical sinus. The DV Doppler trace was recorded by preventing contamination of the umbilical vein, inferior vena cava, and left hepatic vein flow. At least three measurements were determined when optimal Doppler traces were created using an insonation angle $\leq 30^{\circ}$ (Figure 1). The as low as reasonably achievable (ALARA) principle was used during Doppler evaluation. Figure 1 shows DV Doppler measurements.

Demographic and ultrasonographic variables were collected, and SPSS version 21.0 (IBM, Armonk, NY) was used for statistical analysis. The Shapiro–Wilk test was used to analyze the Gaussian distribution of DV PIV measurements, and $p < .05$ was considered significant.

This study was approved by the Baskent University Institutional Review Board (project no.: KA18/104) and supported by the Baskent University Research Fund.

Results

The demographic results are presented briefly in Table 2. The mean age, body mass index, CRL, gestational age, and NT were 30.3 years (range, 18–45), 23.9 kg/m^2 (range, 15.5–46.6), 59.5 mm (range, 45–79), 12.3 weeks (range, 11.2–13.6), and 1.58 mm (range, 0.73–2.62), respectively. The median gravidity and parity were 2 (range, 1–8) and 0 (range, 0–4), respectively.

The DV "a"-wave was recorded for all cases. However, TR was not found in any case. NB hypoplasia was recorded for five cases (1.1%). According to the Shapiro–Wilk test, measurements of DV PIV using the Gaussian distribution were suitable ($p = .252$). The mean DV PIV was 0.98, and the 5th and 95th percentiles were 0.73 and 1.22 (±2 SD). Statistical analysis of our cohort revealed that DV PIV values less than 0.73 and more than 1.22 were out of the normal range

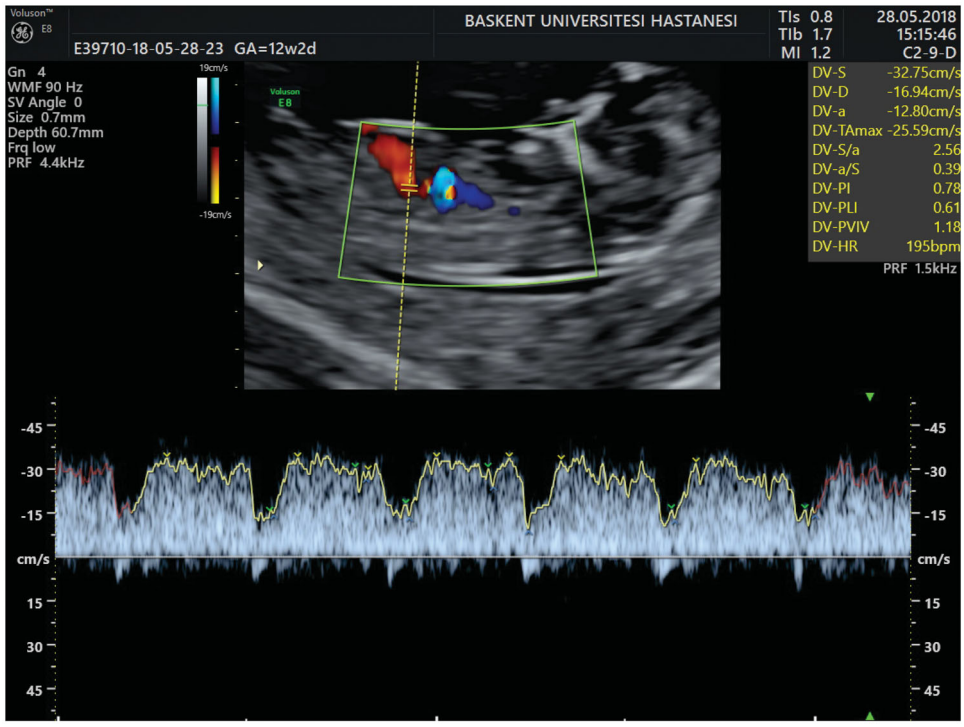

Figure 1. *Ductus venosus* Doppler measurements.

Table 2. Maternal and fetal characteristics and *ductus venosus* doppler measurements of the cohort.

	Minimum	Maximum	Mean
Maternal age	18	45	30.3 ± 4.96
Maternal BMI	15.5	46.6	23.9 ± 4.14
CRL (mm)	45	79	59.5 ± 7.15
Gestational week	11.2	13.6	12.3 ± 0.52
NT (mm)	0.73	2.62	1.57 ± 0.33
S-wave (cm/s)	12.99	60.87	31.18 ± 8.07
D-wave (cm/s)	9.07	53.36	25.64 ± 7.23
a-wave (cm/s)	3.75	22.17	8.68 ± 2.72
TAMXV (cm/s)	6.3	44.29	22.72 ± 6.22
PIV	0.56	1.37	0.98 ± 0.14

BMI: body mass index; CRL: crown-rump length; NT: nuchal translucency; S-wave: mean peak systolic velocity; D-wave: mean peak diastolic velocity; a-wave: mean atrial contraction in late diastole; TAMXV: mean time-averaged maximum velocity; PIV: mean pulsatility index volume.

(Figure 2). The mean S-wave, D-wave, a-wave, and TAMXV were 31.18, 25.64, 8.68, and 22.72 cm/s, respectively (Table 2).

According to the Pearson correlation analysis, our data indicated no correlation between gestational week and S-wave, D-wave, a-wave, TAMXV, and DV PIV ($p = .44$).

Discussion

The routine ultrasonographic evaluation during the first trimester does not include measurements of DV waveforms or DV PIV. Furthermore, the clinical importance of DV and DV PIV during the first trimester is the subject of ongoing debate in the literature. However, studies investigating the importance of DV waves during the first trimester have shown that abnormal DV waves accompany congenital heart disease and poor perinatal outcomes, thereby suggesting they are helpful tools for the first-trimester evaluation [5–7]. Therefore, setting normal values should be the first step of defining a new parameter.

The PIV is calculated from the following formula: [(S-wave – a-wave)/TAMXV] [18]. When DV waveforms found during the first-trimester evaluation showed an increase in flow of the S-wave and D-wave, this increase is thought to be caused by trophoblastic migration. Spiral arteries are destroyed and placental vascular resistance decreases. This decrease occurs when cardiac afterload decreases and cardiac compliance increases [9,10]. During atrial contraction, the DV blood flow increases and PIV decreases inversely proportional to each other [17,18].

Physiologic changes occur with chromosomal or congenital abnormalities due to the impaired diastolic function of the heart. Ventricular afterload increases with high placental resistance, and peripheral vasoconstriction and ventricular end-diastolic pressure increase. Atrial contraction occurs against increased impedance to forward flow. Blood flow ejected retrogradely to great vessels and a reverse or absence of the "a"-wave can be seen [5].

These physiologic changes reflect different sonographic waveforms, and measurements of these

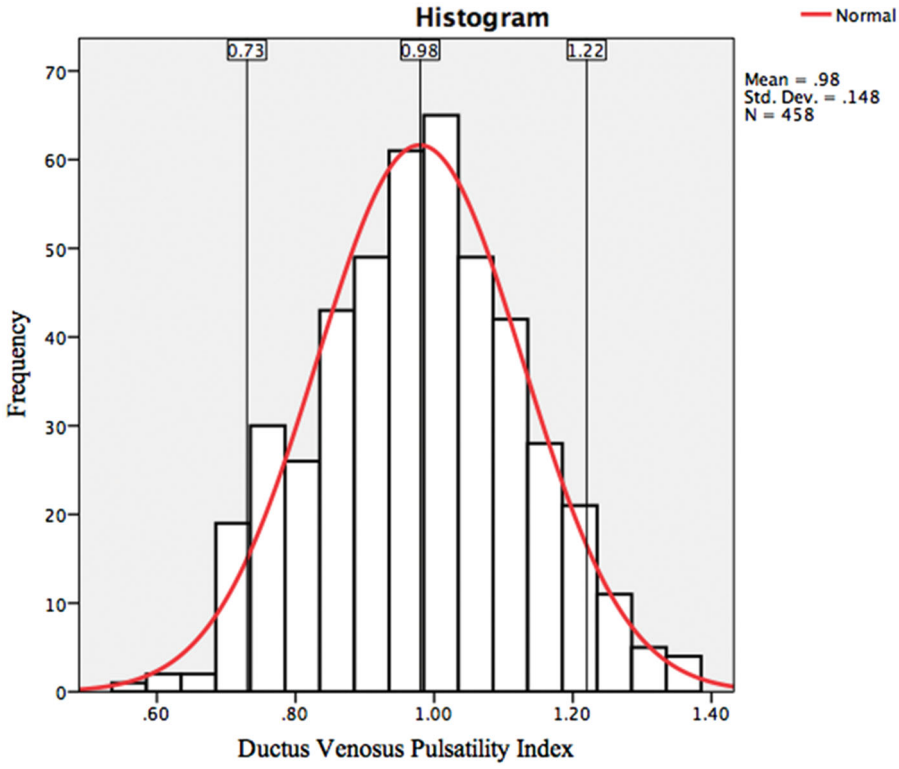

Figure 2. Histogram of *ductus venosus* pulsatility index measurements. Std. Dev.: standard deviation.

waveforms provide significant information for clinicians. Therefore, it is crucial to define normal ranges for all sonographic variables. Our statistical analysis showed that the mean DV PIV for our cohort was 0.98. The 5th and 95th percentiles were 0.73 and 1.22 (±2 SD). Similar results were presented by Peixoto et al., who performed a study involving a Brazilian population and found that the mean DV PIV was 1.1. Their cohort consisted of 430 singleton pregnancies, and their inclusion criteria were quite similar to those of our cohort; however, ongoing follow-up of pregnancies after DV PIV measurements and perinatal outcomes were lacking in their study [11]. We excluded patients from our cohort if their follow-up data and/or perinatal outcome data were lacking. We also excluded patients who had normal findings during the first-trimester evaluation; however, we subsequently determined structural or chromosomal abnormalities. Peixoto et al. [11] defined the DV PIV values according to CRL determined using polynomial regression and made adjustments to determine the coefficient, thus indicating that their DV PIV results did not have a Gaussian distribution and needed statistical determination. However, our DV PIV results had a Gaussian distribution and easily defined normal ranges. We also could not find any correlation between the DV PIV, a-wave, D-wave, S-wave, TAMXV, and CRL measurements ($p = .44$). Differences between the two cohorts could have depended on patient selection. Our data included follow-up information and perinatal outcomes of only those with normal pregnancies.

Another study of the mean DV PIV that was performed in Italy stated that the average DV PIV was 1.07 for 10- to 14-week fetuses whose CRL measurements were up to 88 mm [10]. In that study, Prefumo et al. [10] found that the flow velocity increased in the "a"-wave and "S"-wave, and that TAMXV was correlated with gestational week. However, the S/A rate and DV PIV measurements were not altered with advanced gestational age. They explained this entity by describing the immaturity of fetomaternal circulation due to high umbilical artery resistance during the first trimester [10]. Our data showed that no DV Doppler indexes were correlated with advanced gestational age.

Tseng et al. [15] presented their results regarding DV PIV, resistivity index (RI), "S" wave, and "D" wave of 252 fetuses at 11–14 gestational weeks. They reported that during the next gestational weeks, the peak velocities of the "D" wave and "S" wave increased and the PIV decreased; however, the correlation between variables was not statistically significant or concordant with our results. In addition, they reviewed the RI of their Taiwanese cohort and reported that it decreased while the gestational age increased [15].

Another interesting study by Teixeira et al. [17] highlighted the biphasic pattern of DV PIV and included 843 cases. DV PIV values increased for CRL up to 63 mm and then decreased thereafter. The S-wave, D-wave, and a-wave velocities and TAMXV increased with CRL. This might have occurred because of inadequate trophoblastic migration, high afterload, or low blood flow velocity during atrial contraction before 12^{+6} weeks (CRL: 63 mm) [17].

In our study, we did not find any correlation between CRL and DV PIV ($p = .44$). Similarly, Montenegro et al. [12] reported that DV blood flow was not correlated with gestational age in their study that consisted of 61 fetuses. However, they explained that their study suffered from inadequate fetal volumes and cardiac compliance as a result of a lack of trophoblastic migration [12].

Sabria et al. [16] reported their results after studying 14,444 singleton pregnancies for 4 years. They found that DV PIV measurements had changed over the course of the years and concluded that new ultrasonography techniques, advanced instruments, and increased experience could have affected the results [16]. In the present study, one experienced perinatologist obtained measurements using advanced ultrasonography to minimize interference.

In a recent study that included 410 euploids (group1) and 136 aneuploids (trisomy 21) fetuses (51 with major cardiac defects (group2) and 85 without major cardiac defects (group3), the a-wave was reversed in 3.2%, 66.7%, and 57.6% of the groups. DV PIV values were significantly higher in the trisomy subgroups (1.07 (group1), 1.6 (group2), 1.54 (group3)). It was also found that a:S and a:D ratios were significantly lower for the trisomy 21 groups. The DV a:S ratio was superior to PIV, with a false-positive rate of 2.5%; furthermore, the detection rate increased from 52.1% to 60.4% with DV PIV [19].

Different studies in the literature have indicated the importance of DV blood flow as a screening tool for structural and chromosomal anomalies [20,21]. The Fetal Medicine Foundation recommends DV evaluation for patients whose estimated risk for trisomy 21 is between 1:100 and 1:1000 (intermediate risk group) [22]. In the present study, we defined a DV PIV reference value (0.73–1.22) for our institution that is quite similar to that reported in the literature. The limitations of the study are; retrospective design and single center experience. Further studies are needed to compare normal and abnormal DV PIV results according to perinatal outcomes and to determine the importance and efficacy of DV PIV as a screening tool during the first trimester.

Disclosure statement

No potential conflict of interest was reported by the authors.

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ORCID

Hakan Kalayci http://orcid.org/0000-0003-2054-7102
Şafak Yilmaz Baran http://orcid.org/0000-0001-5874-7324
Gülşen Doğan Durdağ http://orcid.org/0000-0002-5064-5267
Selçuk Yetkinel http://orcid.org/0000-0002-2165-9168
Songül Alemdaroğlu http://orcid.org/0000-0003-4335-6659
Serdinç Özdoğan http://orcid.org/0000-0002-1767-1527
Seda Yüksel Şimşek http://orcid.org/0000-0003-3191-9776
Esra Bulgan Kiliçdağ http://orcid.org/0000-0002-0942-9108

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