Original Article

Longitudinal reference intervals for ductus venosus Doppler indices

Lale Usta[a], Necla Konar Ustyol[b,*], Ragıp Atakan Al[c]

[a]Department of Obstetrics and Gynecology, Avrasya Meditech Hospital, Ordu, Turkey
[b]Department of Obstetrics and Gynecology, Women and Children's Hospital, Van, Turkey
[c]Department of Obstetrics and Gynecology, Atatürk University Faculty of Medicine, Erzurum, Turkey

Abstract. To perform a longitudinal investigation to establish reference intervals for repeated measurements for ductus venosus indices in women in weeks 15-40 of pregnancy.

Ductus venosus Doppler investigation was performed by inviting the pregnant women included in the study for ultrasonography once every four weeks. Several indices were designated in order to define ductus venosus wave form, using peak velocity atrial contraction (a), systolic peak velocity (S) and diastolic peak velocity (D) values. The association between ductus venosus S, A, and D flow rates (V_s, V_d V_a) and the S/A, PVIV and PLI indices calculated using these parameters and week of pregnancy was then investigated.

V_a and PLI exhibited a significant correlation with gestational weeks and increased with gestational age ($p< 0.05$). S/A and PVIV indices decreased significantly with week of pregnancy ($p< 0.05$)

Ductus venosus measurements being performed near the central part of the vein elicited lower absolute flow rates. This resulted in different reference intervals to those of other studies for these designated parameters.

Key words: Ductus venosus, fetal circulation, Doppler

1. Introduction

Although the ductus venosus is a vessel of venous origin, it is one of the fetal shunts containing oxygenated blood. It connects the intrahepatic part of the umbilical vein to the vena cava inferior, bypassing the liver (1). Oxygenated blood passes from the fetal right atrium to the left atrium through the foramen ovale, supplying the heart and brain.

Ductus venosus examination using Doppler ultrasound was first recommended in 1991 (2) and is today used as an important tool in diagnosing intrauterine development retardation and fetal congestive heart failure (3-7). In contrast to the arterial system, a triphasic flow pattern reflecting atrial pressure variations is observed in almost all precordial veins. Several index reference intervals have been described in order to define the ductus venosus wave form (4, 6, 8-14). These include the preload index (PLI), peak velocity index of vein (PVIV) and the DV S/A ratio.

The first phase of the DV Doppler wave form comprises the ventricular systole (S wave) and the second phase comprises ventricular diastole (D wave). Following these two waves, a deceleration in flow rate occurs during atrial contraction (a wave). Hemodynamically, these phases reflect pressure changes between the umbilical vein and the right atrium.

The atrial contraction wave (a wave) is the most important form in diagnostic terms. During atrial contraction, the foramen ovale closes and blood in the atrium is pumped to the right ventricle. This phase therefore permits assessment of end-diastole right ventricular pressure and central venous pressure. Umbilical venous pressure is higher than central venous pressure during atrial contraction in healthy fetuses (15, 16).

Systolic wave is the maximum flow rate throughout ventricular systole. Systolic peak is normally soft and round during ventricular contraction. Myocardial function changes reflect this part of the cardiac cycle. In the event of decreased compliance (of cardiac or extracardiac origin) the decrease part of velocity is more acute. This is particularly observed in placental pathologies (17, 18).

2. Materials and methods

This study was performed with patients in the 15^{th}-40^{th} weeks of pregnancy attending the Atatürk University Faculty of Medicine Gynecology and Obstetrics Department between May and November, 2009. Length of pregnancy was calculated using Naegele's rule and was

*Corresponding Author: Necla Konar Ustyol, M.D.
Women and Children's Hospital, Department of Obstetrics and Gynecology, Van, TURKEY
Mobile Phone: +90 5054511414
Fax: +90 432 486 54 13
E-mail:necla.konar@hotmail.com
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confirmed with measurement of CRL obtained in the first trimester from all subjects. In the event of inconsistency of more than 1 week between measurements the date of the last menstrual period was adjusted. All pregnant women in less than the 16^{th} week of pregnancy with last menstrual period confirmed or adjusted, with biometric measurements in percentiles 20-90 for length of pregnancy, with normal amniotic fluid and umbilical artery Doppler and with no obstetric or internal disease were included in the study. Women with multiple pregnancy, fetal anomaly, karyotype anomaly, chronic disease (such as chronic hypertension, diabetes mellitus, chronic kidney failure, systemic lupus erythematosus) or poor obstetric histories (pre-eclampsia, intrauterine growth retardation, ablatio placentae, preterm birth, gestational diabetes etc.) were excluded.

All pregnant women attending the antenatal clinic for routine monitoring were enrolled consecutively provided they met the inclusion criteria and provided signed consent forms. All women were monitored until birth, and subjects with any obstetric complication, fetal anomaly or karyotype detected anomaly during monitoring were excluded from the study. After birth, data regarding the baby's sex, weight, Apgar score, type of delivery, indication in the event of cesarean delivery, newborn complications, admission to the neonatal intensive care unit and any complications developing were collected.

Women participating in the study were called for Doppler ductus venosus investigation once four weeks. Doppler ultrasonography was performed using a 2-6 MHz convex probe (Aloka α 5, Aloka α 10, Japan). Mechanical index (MI), or thermal index (TIS) for soft tissues, was kept at 1.1 or less. Doppler color was used in midsagittal or oblique section to determine the ductus venosus as the vein connecting the umbilical vein to the inferior vena cava. Measurements using Doppler color were performed in the midsagittal plane with a typical high flow rate compared to the umbilical vein. Doppler sample volume angle of insonation was always kept as low as possible. It was adjusted at >30°, and all measurements were performed during fetal apnea and inactivity. When at least 5 similar wave forms had been obtained this was regarded as sufficient Doppler imaging, and measurement was performed. All measurements were performed by a single operator. S/A, PVIV and PLI indices were calculated by measuring peak systolic flow rate (S wave), end diastolic flow rate (D wave) and atrium contraction wave (A wave).

Ten ductus venosus measurements each were also taken from 10 subjects in order to calculate intraobserver variability.

Normal distribution by week of pregnancy of ductus venosus S, A and D velocities and S/A, PVIV and PLI indices was established using the Kolmogorov-Smirnov test. An equation for all expected values by gestational age was obtained using regression analysis. All indices and wave velocities were calculated at a 95% prediction interval.

Ductus venosus indices and flow rate intraobserver coefficient of variation (CV) was measured.

Statistical analysis was performed on SPSS 15 (SPSS Inc., Chicago, IL, USA) and SigmaPlot 11 software (Systat Software, Inc, Germany). p values lower than 0.05 were regarded as significant.

3. Results

Forty-two patients enrolled between May and November, 2009, were initially included in the study. One patient was excluded due to intrauterine exitus. Forty-one patients with no obstetric complications and no anomaly or intrauterine developmental retardation in the newborns were finally included in the analysis. All women gave birth after the 36^{th} week of pregnancy, and no newborns required intensive care monitoring or developed any severe neonatal complication. No neonates were beneath the 10^{th} percentile for birth weight for week of pregnancy. Patients' demographic characteristics and obstetric results are shown in Table 1.

Table 1. Demographic characteristics of the patients in the study. Results are shown as mean±standard deviation and median (lowest value – highest value)

Variable	Result
Mother's age (years)	29.3±5 (17-43)
Gravida	3 (1-7)
Parity	1 (0-5)
Nulliparity	12 (29.3%)
Gestational age at birth (weeks)	38.7±1.3 (36.1-41.6)
Newborn weight (grams)	3067±356 (2300-3800)
Baby sex	
Male	12 (29.3%)
Female	29 (70.7%)
Cesarean	11(26.8%)
Apgar < 7	0

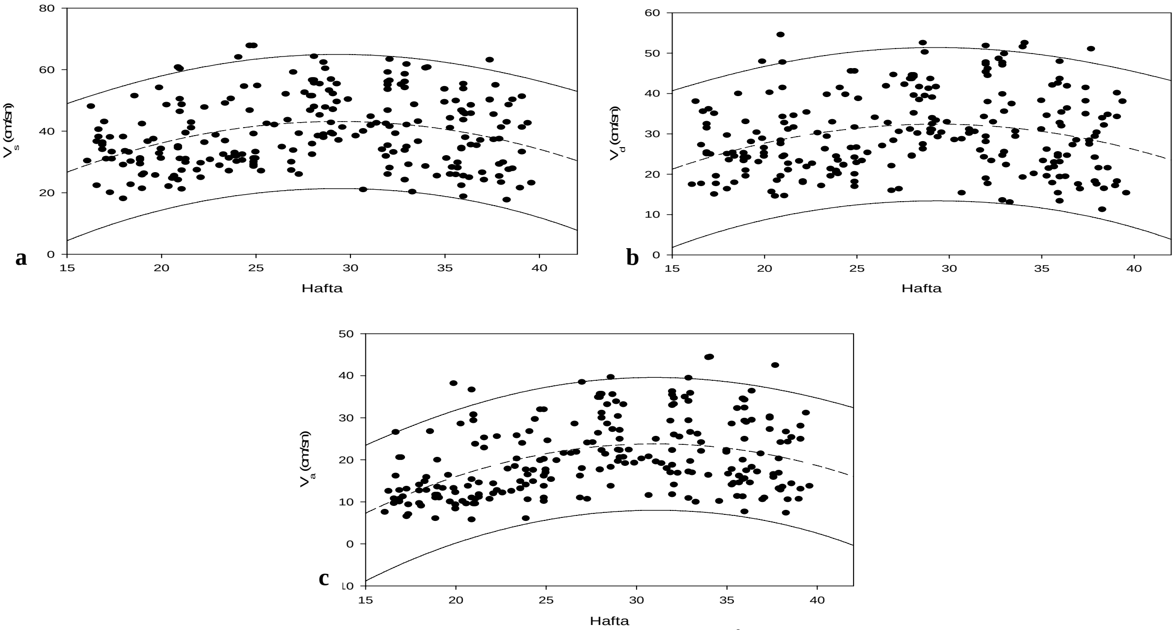

Fig. 1a) Reference interval for S wave (mean and 95% CI). Adjusted R^2=0.10, s = -25.7533 (±13.0605 SE) + 4.6947 (±0.9801)*gestational age – 0.0800 (±0.0175 SE)* (gestational age $)^2$ (SE, standard error).
b) Reference interval for d wave(mean and 95% CI). Adjusted R^2=0.06, s = - 14.4349 (±11.3817 SE) + 3.2005 (±0.8541)*gestational age – 0.0547 (±0.0153 SE)* (gestational age $)^2$ (SE, standard error).
c) Reference interval for a wave (mean and 95% CI). Adjusted R^2=0.19, s = -38.0501 (±9.4634 SE) + 3.9880 (±0.7102)*gestational age – 0.0643 (±0.0127 SE)* (gestational age $)^2$ (SE, standard error).

Table 2. Intraobserver coefficient variability for the indices used in the study

Index	CV%
S	10.69
D	15.48
A	11.84
PLI	4.81
PVIV	24.99
S/A	4.79

A total of 233 measurements were taken from the patients in the study. Measurements covered weeks of pregnancy 14.7 to 39.6. Doppler recording was successfully achieved in all planned measurements. Intraobserver variability for ductus venosus S, A and D flow rates and for S/A, PVIV and PLI indices calculated through gestational weeks and at the start and end of the study are shown in Table 2.

Correlation between week of pregnancy and Vs, Vd, Va, PLI, PVIV and S/A indices was best represented by the second degree equation regression curve. Regression curves for S, D and a flow rates are shown in Figure 1.

Regression curves for PLI, PVIV and S/a are shown in Figure 2. V_a and PLI exhibited a significant correlation with week of pregnancy and increased with it ($p<0.05$). PVIV and S/A decreased significantly with week of pregnancy ($p< 0.05$).

Coefficients of curves with a 95% prediction interval for V_s, V_d, V_a, PLI, PVIV and S/a indices are shown in Table 3.

4. Discussion

Ductus venosus measurements are frequently performed in risky pregnancies. The great majority of these measurements are assessed using reference values obtained from cross-sectional studies. In this study, reference values for various commonly used indices were produced in a group of women observed longitudinally.

The ductus venosus flow rate and indices characteristics in our study are compatible with previous board cross-sectional and longitudinal studies, although the reference intervals are not in complete agreement (12-14,19). In their longitudinal observation, Kessler et al. (19) calculated the S wave at approximately 20 cm/sec higher and the a wave at approximately 30-40 cm/sec higher. Kessler et al.'s (19) findings are in agreement with other wide-scale studies (13, 14), and are approximately 10 cm/sec slower than Hecher et al.'s (12) measurements. Bahlmann et al. (13) conducted another broad study involving

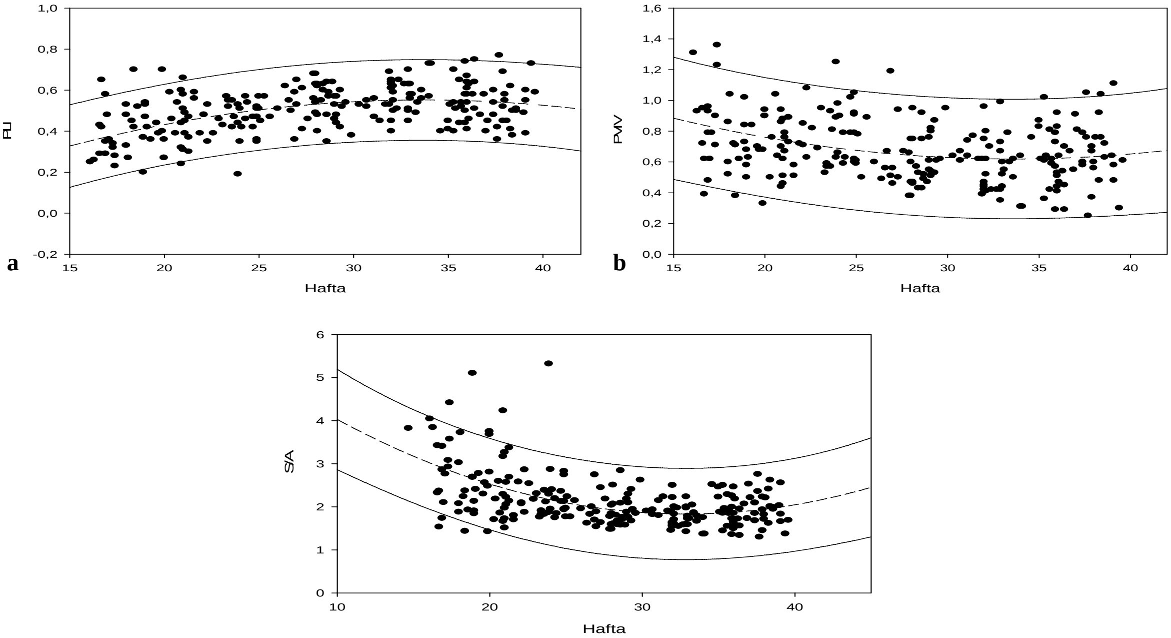

Fig. 2 a) Reference interval for PLI index (mean and 95% CI). Adjusted R^2=0.25, s = -0.1795 (±0.1179 SE) + 0.0435 (±0.0089)*gestational age – 0.0006 (±0.0002 SE)* (gestational age)^2 (SE, standard error) ($p < 0.05$).
b) Reference interval for PVIV index (mean and 95% CI). Adjusted R^2=0.10, s = - 1.4874 (±0.2328 SE) – 0.0518 (±0.0175)*gestational age – 0.0008 (±0.0003 SE)* (gestational age)^2 (SE, standard error) ($p < 0.05$).
c) Reference interval for s/a (mean and 95% CI). Adjusted R^2=0.29, s/a = 6.3698 (±0.6353 SE) -0.2762 (±0.0477)*gestational age + 0.0042 (±0.0009 SE)* (gestational age)^2 (SE, standard error) ($p<0.05$)

Table 3. Regression equation coefficients showing Vs, Vd, Va, PLI, PVIV and S/A indices upper 95% and lower 95% prediction intervals (f=y0+fixed +b_1*[gestational age] + b_2*[gestational age]^2

		Coefficient		
Index	Interval	Fixed	b_1	b_2
V_s	95% Upper	.113	4.389	-.074
	95%Lower	-51.619	5.001	-.085
V_d	95% Upper	-51.619	5.001	-.085
	95%Lower	-36.976	3.467	-.059
V_a	95% Upper	-19.308	3.766	-.060
	95%Lower	-56.792	4.210	-.068
PLI	95% Upper	-.068	.041	-.001
	95%Lower	-.413	.046	-.001
PVIV	95% Upper	1.949	-.057	.001
	95%Lower	1.026	-.046	.001
s/a	95% Upper	7.628	.291	.004
	95%Lower	5.112	-.261	.004

697 pregnant women. While S, a and D wave flow rates were comparable to those of other studies, the reference values determined for PLI, S/A and PVIV indices were compatible with our study.

There are several factors that may account for the differences in our study regarding S, D and a flow rates in particular. The reference interval variations are probably associated with equipment used, insonation technique, angle correction and population. However, the main difference between this and other studies stems from the site of ductus venosus measurement. In this study, ductus venosus measurement was performed, not from the beginning of the ductus venosus or where it joins the inferior vena cava, but from the approximate center of the vessel. The ductus venosus typically has a greater velocity compared to neighboring veins throughout the cardiac cycle (20-25). Velocity increases, starting from early pregnancy (for example, the 10th week) and reaches a plateau on the 22nd week (20, 24). In measurements performed from the beginning of the vein, peak velocity in the remaining part of pregnancy ranges between 40 and 85 cm/sec (21,23-25). Velocity pattern reflects the entire cardiac, with one peak in systole (S), another peak during passive diastolic filling (D), reaching the lowest point (a) during active diastolic filling (atrial contraction). The decrease during atrial contraction typically does not reach the zero line in the second half of pregnancy, in contrast to the other precordial veins, although before the 15th week an increasing number or zero or below-zero velocities have been observed in normal fetuses (18). In our study, a wave measurements close to zero were included in analysis, not excluded. In measurements from the center of the vein there is a decrease in velocity in S and D waves compared to the initial section of the vessel. Absolute blood velocity both directly reflects the portacaval pressure gradient that regulates hepatic perfusion (26) and also reflects the cardiac events that modify velocity wave form (23). A lower flow is probably obtained in the a wave from a point closer to the heart.

The intra-observer variation coefficient in this study was within acceptable levels for S and a waves (19). Limits for intraobserver variation had been reported as -13;12 cm/s for S wave and -15;12 cm/s during a wave (21). However, the D wave value determined was higher than those in other studies. This may be due to the ductus venosus form having a wide normal variation.

The variation coefficient for the PLI and S/A indices was also within reasonable limits in our study. However, the intraobserver variation coefficient in the PVIV index was higher, probably in association with the variation coefficient in D wave flow rate.

Our study includes 233 measurements. This number is sufficient to establish a reference interval. However, the variation coefficients obtained from the study being high will probably reduce the natural variation rate for the ductus venosus in sampling involving more pregnant women.

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