ORIGINAL RESEARCH

DOI: 10.5336/jcog.2023-96258

The Predictive Values of Ductus Venosus Pulsatility Index and "A Wave" for Chromosomal Abnormalities

Şafak YILMAZ BARAN[a], Başar ÖNAL[a], Murat YAYLA[a]

[a]Clinic of Obstetrics and Gynecology, Acıbadem Dr. Şinasi Can (Kadıköy) Hospital, İstanbul, Türkiye

ABSTRACT Objective: To establish a reference range for fetal ductus venosus pulsatility index for veins (DV PIV) and investigate the efficacy of the abnormal ductus venosus (DV) Doppler assessment to diagnose the chromosomal abnormalities of the fetus during first-trimester screening. **Material and Methods:** We retrospectively evaluated a total of 3,243 singleton pregnancies at 11+0 to 13+6 weeks of gestation in a 12-year period and assigned the patients into 2 groups to compare the efficacy of DV PIV in predicting chromosome abnormalities. The first group consisted of pregnancies involving fetuses with chromosomal abnormalities and the second group consisted of uncomplicated singleton fetuses with available DV Doppler measurements. We determined a cut-off value for DV PIV measurements to predict chromosomal abnormalities, and analyzed the relationship between chromosome abnormalities, and abnormal DV Doppler measurements. **Results:** A total of 644 fetuses (104 fetuses with an abnormal karyotype (pregnancies involving fetuses with chromosomal abnormalities) and 540 fetuses phenotypically normal or euploid in neonates after birth (pregnancies with normal fetuses) met the study criteria. The 5th and 95th percentiles of DV PIV were 0.78 and 1.21 in pregnancies with normal fetuses. We calculated with 63.6% sensitivity and 60.3% specificity, (95% confidence interval 0.72-0.83) for DV PIV to diagnose chromosomal abnormalities. Abnormal DV blood flow was related to all trisomies. The lowest DV PIV was observed in cases with trisomy 21, while the highest DV PIV values were found in cases with trisomy 18 and 13 in the abnormal karyotype group. **Conclusion:** Routinely monitoring DIV PIV as a first-trimester screening tool may be beneficial to predict fetal chromosomal abnormalities.

Keywords: First-trimester screening; ductus venosus flow; pulsatility index; reference range; chromosomal abnormalities

The ductus venosus (DV) is a blood vessel in the fetal circulatory system that allows highly oxygenated blood from the umbilical vein to bypass the liver and flow directly to the cerebral and coronary circulation.[1,2] The pressure gradient between the umbilical vein and the right atrium influences the DV, and measurement of DV blood flow can be used as an indirect indicator of fetal cardiac function.[3-5]

Prenatal ultrasonographic screening markers have become an important tool for detecting congenital anomalies in recent years.[6] First-trimester risk estimation of common chromosomal anomalies is based on a combination of various factors including maternal age, crown-rump length (CRL), fetal nuchal translucency thickness (NT), nasal bone (NB), maternal serum free β human chorionic gonadotropin (fβ-hCG), and pregnancy-associated plasma protein-A (PAPP-A).[7,8] Measurement of ductus venosus blood flow is an optional part of first-trimester screening, but abnormal DV blood flow patterns (such as reversed/absent a-wave pattern or increased pulsatility index for veins) can be integrated into the screening to improve the prediction of chromosomal abnormalities, major congenital heart defects (CHD), and poor pregnancy outcomes.[9-11]

The most common chromosomal defects detected in the first trimester in the general population are trisomy 21, 18, and 13.[12] Including assessment of ductus venosus flow (abnormal DV "a wave" pattern and/or abnormal ductus venosus pulsatility index) to

Correspondence: Şafak YILMAZ BARAN
Clinic of Obstetrics and Gynecology, Acıbadem Dr. Şinasi Can (Kadıköy) Hospital, İstanbul, Türkiye
E-mail: safakyilmazbaran@gmail.com

Peer review under responsibility of Journal of Clinical Obstetrics & Gynecology.

Received: 21 Feb 2023 ***Received in revised form:*** 13 May 2023 ***Accepted:*** 23 Jun 2023 ***Available online:*** 05 Jul 2023

first-trimester screening improves the performance of screening for those aneuploidies.[8] However, there is still uncertainty as to which parameter of DV is more advantageous. Also, there is limited data about ductus venosus pulsatility index for veins (DV PIV) values to discriminate the chromosomal abnormalities from each other. Meanwhile, it is proposed that the addition of DV PIV measurement can result in a detection rate of 94% for aneuploidies.[13]

In this study, we attempted to establish a reference value for the DV PIV during the evaluation of DV waveforms in the first trimester of uncomplicated singleton pregnancies. In addition, we aimed to determine the DV PIV cut-off value which would allow us to establish the sensitivity, specificity, and positive and negative predictive values for the detection of chromosomal abnormalities.

MATERIAL AND METHODS

We reviewed the records of first-trimester ultrasound examinations of the 3,243 pregnant women with mixed risk groups: (both low and high-risk groups included) at 11^{+0} to 13^{+6} weeks of gestation in a retrospective design. Groups were categorized as pregnancies involving fetuses with chromosomal abnormalities (between 2009 and 2021) and pregnancies with normal fetuses (uncomplicated singleton pregnancies with available ductus venosus *'a wave'* and pulsatility index between 2016 and 2021).

Ultrasound examinations were performed with the Voluson E8 and E10 (4- to 8-MHz transducer; GE Healthcare, Little Chalfont, UK) via the transabdominal route by a single maternal-fetal medicine experienced specialist. Our study involved evaluating participants for maternal age, gravidity, parity, and gestational age. CRL, NT, NB, and DV blood flow were routinely examined in all cases at the time of first-trimester ultrasound according to Fetal Medicine Foundation (FMF-UK) Guidelines. Gestational age was determined from the measurement of crown-rump length. The evaluation method for the DV includes assessing the a-wave pattern (atrial contraction in late diastole), DV PIV, and whether DV is present or absent.[14] DV measurements were obtained in compliance with The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) Guidelines. DV blood Doppler assessment was performed in an immobile position and in the right ventral mid-sagittal plane of the fetus. The pulsed Doppler sample was small (0.5-1 mm) to prevent contamination from the adjacent veins. A minimum of 3 measurements were obtained when optimal Doppler traces were generated at lower than insonation angle of 30°. The as low as reasonably achievable principle (ALARA) was followed during the Doppler evaluation.[15]

We selected the fetuses with abnormal karyotypes during the study period which were identified either through an invasive test during pregnancy or after birth. The inclusion criteria of the first group were singleton pregnancies with chromosomal abnormalities with available DV PIV and wave records measured at 11+0 to 13+6 weeks of gestation. The chromosomal abnormalities were detected by chorionic villus sampling or amniocentesis procedures prenatally, or by direct karyotyping postnatally. Besides, we have determined the second group as a control group and have included participants by performing a search of the same database to establish a reference range for DV PIV with an aim of making a comparison with the fetuses of the abnormal karyotype group. The inclusion criteria for the second group were singleton pregnancies with CRL range between 45-84 mm, fetal NT thickness less than 95th centile, and without major structural or chromosomal abnormalities during follow-up or birth or phenotypically normal neonates who were followed up after birth.

Abnormal DV "a wave" was identified as negative "a wave" pattern, reversed "a wave" pattern, and absence of ductus venosus flow. We used the receiver operating characteristic (ROC) curve analysis to determine the optimal DV PIV threshold for diagnosing chromosomal abnormalities. Sensitivity (Sen), specificity (Spe), positive predictive value (PPV), and negative predictive value (NPV) were identified for abnormal DV PIV, and abnormal "a wave" to determine chromosomal abnormalities.

We obtained informed consent from each participant. We followed ethical guidelines when conducting research involving human subjects in accordance with the Declaration of Helsinki. The

study was approved by Acibadem University Ethics Committee (date: March 11, 2022, no: 2022-05/16).

STATISTICAL ANALYSES

Maternal characteristics and fetal ultrasonographic variables were analyzed with SPSS version 21.0 (IBM, Armonk, NY). Categorical variables were presented as numbers and percentages, while continuous variables were presented as mean and standard deviation or median and range values where needed. To establish a reference range for the DV PIV measurements, histogram test was used. The normality of the distribution was assessed using the Kolmogorov-Smirnov test, and appropriate parametric or non-parametric tests were used for comparing continuous measurements between groups. ROC analysis was used to determine the optimal cut-off values of DV PIV for diagnosing chromosomopathies, sensitivity, specificity, and positive likelihood ratios were calculated. Finally, chi-square or Fisher's test statistics were used for comparing categorical variables, and a p-value <0.05 was considered significant in all analyses.

RESULTS

A total of 644 fetuses from 3,243 pregnancies evaluated within 12 years, were included in the study in accordance with the inclusion criteria (104 pregnancies involving fetuses with chromosomal abnormalities and 540 fetuses with euploid or phenotypically normal in neonates after birth). Maternal features and fetal ultrasonographic variables were presented in Table 1. Mean age, NT, and DV PIV were higher, and mean NB was lower in pregnancies involving fetuses with chromosomal abnormalities (all those p values were lower than 0.001).

The distribution of DV PIV measurements was found to be suitable with the Gaussian distribution (p=0.20), and the mean DV PIV was 0.99±0.12. The 5th and 95th percentiles were also reported as 0.78 and 1.21 (±2 SD). Additionally, a histogram of the DV PIV measurements in pregnancies with normal fetuses was presented in Figure 1.

Fetal trisomy cases (n=76) were observed in 73.1% of pregnancies involving fetuses with chromosomal abnormalities. Consecutively, trisomy-21 was found in 48 (46.2%) cases, trisomy-18 in 20 (19.2%) cases, and trisomy-13 in 8 (7.7%) cases. In addition, triploidy was detected in 10 (9.6%) cases, monosomy X in 9 (8.7%) cases, and other chromo-

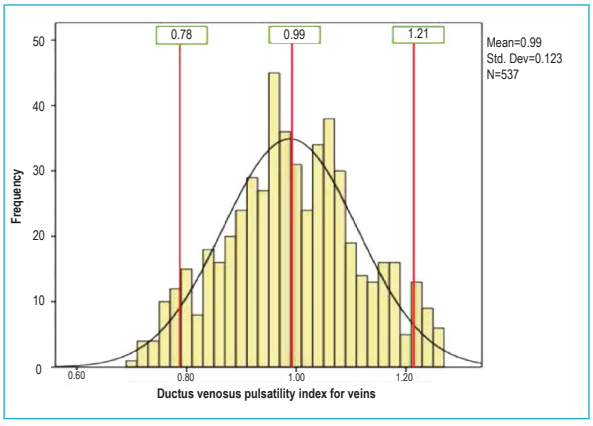

FIGURE 1: Histogram of ductus venosus pulsatility index measurements in pregnancies with normal fetuses.

TABLE 1: Maternal and fetal characteristics of the pregnancies.

	Pregnancies involving fetuses with chromosomal abnormalities (n=104)	Pregnancies with normal fetuses (n=540)	Total (n=644)	p value
Age (years, mean±SD)	34.9±4.9	32±3.9	32.5±4.2	<0.001
Gravidity (median) (maximum-minimum)	1 (1-6)	1 (1-7)	1 (1-7)	0.13
Parity (median) (maximum-minimum)	1 (1-3)	1 (1-5)	1 (1-5)	0.16
Crown-rump length (mm, mean±SD)	61.1±9.7	60±7.1	60.1±7.6	0.15
Weeks of gestation (weeks, mean±SD)	12.4±0.6	12.3±0.5	12.4±0.6	0.34
Nuchal translucency (mm, mean±SD)	4.4±2.8	1.71±0.35	2.14±1.5	<0.001
Nasal bone (mm, mean±SD)	1.8±0.6	2.1±0.3	2.06±036	<0.001
Ductus venosus pulsatility index for veins (mean±SD)	1.38±0.49	0.99±0.14	1.05±0.27	<0.001
Abnormal a wave, n (%)	32 (32.7%)	11 (2%)	43 (6.7%)	<0.001

somal anomalies (balanced translocation, unbalanced translocation, deletion anomaly, etc.) in 9 cases (8.7%). Regarding the prognosis of those chromosomal abnormalities: 92 of them were terminated, 8 of them continued to normal uncomplicated birth, and fetal demise occurred in 4 patients. Cardiac anomalies such as ventricular septal defect, atrioventricular septal defect, and tetralogy of Fallot were suspected during the first-trimester screening in 28 patients, and cardiac anomalies were diagnosed in 17 patients in the further follow-up of in pregnancies involving fetuses with chromosomal abnormalities. Cardiac anomalies could not be confirmed after birth due to the termination of 96 (92.3%) of the cases and a low acceptance rate of autopsies by parents.

While abnormal DV "a wave" pattern (negative "a wave" in 8 cases, absent DV in 3 cases) was observed in 11 (2.0%) fetuses in pregnancies with normal fetuses, abnormal ductus venosus "a wave" pattern was observed in 30.8% (n=32) of pregnancies involving fetuses with chromosomal abnormalities [reversed "a wave" in 17 (16.3%), negative "a wave" in 10 (9.6%), and absence of ductus venosus in 5 (4.8%) of the fetuses]. The DV could not be observed in a total of 5 cases: 2 cases with trisomy 21, 2 cases with trisomy 18, and in 1 case with trisomy 13. Enlarged NT was detected in only 3 of those pregnancies. All cases without DV were terminated. Figure 2 shows a fetus with an reversed 'a wave' in the ductus venosus blood flow.

A DV PIV measurement above the 95th centile was found in 22 (4.1%) patients in pregnancies with normal fetuses, while 50 (50.5%) patients were found to be above the designated range in pregnancies involving fetuses with chromosomal abnormalities ($p<0.001$). Optimal cut-off value for DV PIV to diagnose chromosomal abnormalities was 1.025 with the 63.6% sensitivity, 60.3% specificity, and area under curve was 0.78 (95% confidence interval 0.72-0.83). According to ROC analysis; Sen, Spe, PPV, NPV, LR+, and LR- of abnormal DV PIV in detecting chromosomal abnormalities were 61.5%, 60.5%, 23.1%, 89.1%, 1.56, and 0.64, respectively. Sen, Spe, PPV, NPV, LR+, and LR- of abnormal DV "a wave" in detecting chromosomal abnormalities were 30.8%, 98%, 74.4%, and 88.0%, 15.4, and 0.71, respectively.

In the abnormal karyotype group, enlarged NT (>95th centile) was detected in 58 (55.8%) fetuses and abnormal DV PIV similarly in 50 (48.1%) fetuses. However, only 36 (34.6%) of the fetuses in the abnormal karyotype group had both enlarged NT and

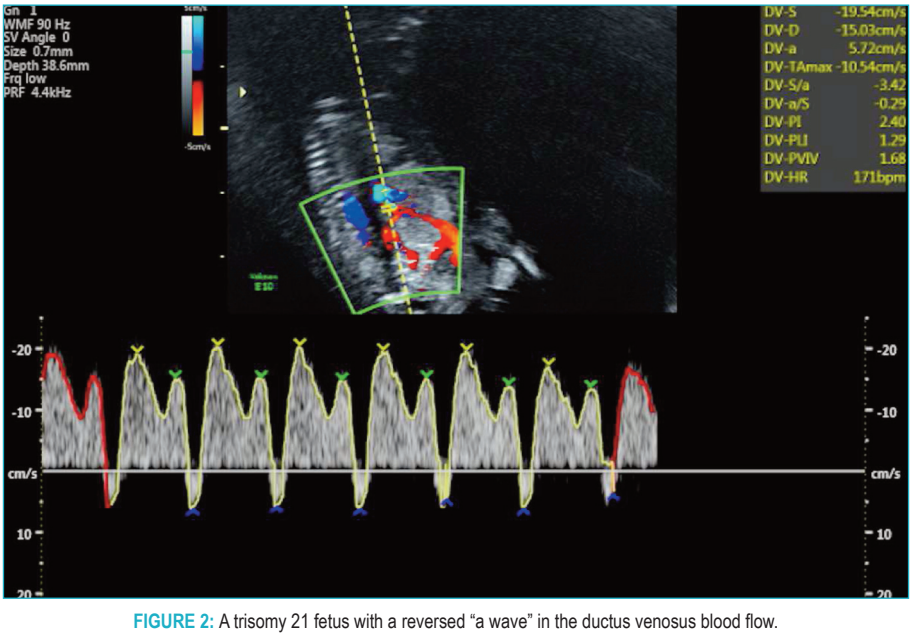

FIGURE 2: A trisomy 21 fetus with a reversed "a wave" in the ductus venosus blood flow.

TABLE 2: Mean DV PIV values, abnormal/normal DV PIV, and abnormal/normal DV a wave characteristics in all chromosomal abnormalities.

	Mean±SD DV PIV	[1]Abnormal DV PIV (n=72)	Normal DV PIV (n=567)	[2]Abnormal DV "a wave" (n=43)	Normal DV "a wave" (n=601)
All chromosomopathies (n=104)	1.38±0.5	50 (69.4%) p<0.001	49 (8.6%)	32 (74.4%) p<0.001	72 (12%)
Trisomy 21 (n=48)	1.35±0.4	24 (33.3%) p<0.001	22 (3.9%)	13 (30.2%) p<0.001	35 (5.8%)
Trisomy 18 (n=20)	1.53±0.6	13 (18%) p<0.001	6 (1.1%)	8 (18.6%) p<0.001	12 (2%)
Trisomy 13 (n=8)	1.39±0.6	2 (2.8%) p=0.14	4 (0.7%)	4 (9.3%) p<0.001	4 (0.7%)
Triploidy (n=10)	1.42±0.6	5 (6.9%) p=0.003	5 (0.9%)	3 (7.0%) p=0.02	7 (1.2%)
Monosomy X (n=9)	1.38±0.5	4 (5.6%) p=0.012	5 (0.9%)	3 (7.0%) p=0.018	6 (1%)
Others (n=9)	1.14±0.7	2 (2.8%) p=0.27	7 (1.2%)	1 (2.3%) p=0.47	8 (1.3%)

[1]Abnormal DV PIV was defined as DV PIV>1.21; [2]Abnormal DV "a wave" was defined as a negative "a wave", reversed "a wave", or absent ductus venosus; DV PIV: Ductus venosus pulsatility index for veins.

abnormal DV PIV. Abnormal DV PIV and normal NT were found in 14 (13.5%) fetuses in pregnancies involving fetuses with chromosomal abnormalities and CHD was detected in 7/22 (31.8%) of these fetuses. There were 27 (26%) cases in the abnormal karyotype group that had neither enlarged NT nor abnormal DV PIV.

Mean DV PIV values, abnormal/normal DV PIV, and abnormal/normal DV a wave characteristics in all chromosomal abnormalities were presented in Table 2. While the lowest DV PIV values were observed in cases with trisomy 21, the highest DV PIV values were found in cases with trisomy 18 and 13 in the abnormal karyotype group.

DISCUSSION

The mean DV PIV value for uncomplicated singleton pregnancies was 0.99, which can serve as a reference value for future studies. However, the mean DV PIV value for the group of pregnancies with chromosomal abnormalities was higher, at 1.38. Also, the lowest DV PIV values were found in cases with trisomy 21, and the highest DV PIV values in cases with trisomy 18 and 13. The more severe findings of anomalies except trisomy 21 (Tr 18-13, and triploidy) seemed to be correlated with the higher DV PIV measurements or with the detection of abnormal "a wave" patterns. According to Wright et al, fetuses with trisomy 18 had higher DV PIV than trisomy 21 and 13, and the difference in DV PIV values in trisomy 21, 18, and 13 could depend on cardiac defects or severe multiple abnormalities.[16]

We presented DV PIV reference values (0.78-1.21) for 11^{+0} to 13^{+6} weeks of gestation which is rather similar to the literature.[17-19] The rate of fetuses with DV PIV beyond the 95th centile was 69.4% in pregnancies involving fetuses with chromosomal abnormalities and 8.6% in pregnancies with normal fetuses. According to Antolin et al., the overall detection rate of chromosomal abnormalities was 65%, similar to our findings when using the 95th centile DV PIV pulsatility index as a cut-off.[20] On the other hand, their 95th centile of DV PIV value was higher than our cut-off values (DV PIV: 1.33-1.49 vs 1.21-1.38). Also, Wagner et al. reported higher values for DV PIV than our study in fetuses with trisomy 21 regardless of CHD (median DV PIV 1.50-1.61).[21] The differences in DV PIV cut-off values observed between studies can be attributed to a number of factors, including patient selection, ethnic variations, or differences in methodology.[15]

Previous studies mostly reported DV Doppler only by evaluating DV as a waveform.[8,20-25] The results of our study demonstrate that each parameter indicating abnormal DV blood flow (abnormal DV "a wave" pattern and abnormal DV PIV) could be found associated with chromosomal abnormalities when compared with controls. On the contrary, Wagner et al. reported the combining the DV "a wave" with DV PIV for assessment of the DV did not significantly improve the detection rates of trisomy 21.[26] The concern of that study was the computed risk for trisomies based on the combination of DV "a wave" and DV PIV measurements may not accurately reflect the true risks. Recent studies have compared the detection rates of increased DV PIV with the detection rates of reversed "a wave" for trisomies and found that the DV PIV measurement alone may be more effective in detecting these chromosomal abnormalities.[27,28]

The use of the quantitative DV flow (DV PIV) for screening trisomy 21 has been shown in recent literature to provide more accurate results compared to the qualitative flow assessment with a low positive predictive value.[6,16,29] By using the ROC curve, our study shows that abnormal DV blood flow was present in 61.5% fetuses with chromosomal abnormalities with 63.6% sensitivity, and specificity of 60.3%. A study by Bilardo et al. found an abnormal DV PIV or an abnormal "a wave" in the DV waveform sensitivity of 65% for detecting chromosomal abnormalities.[30] Also, Maiz et al. reported that the inclusion of DV flow in a combination of maternal age, fetal NT, maternal serum fβ-hCG, and PAPP-A markers can improve the performance of first-trimester screening for aneuploidies.[8]

On the other hand, Martinez et al. conducted a study that the abnormal DV blood flow was a significant predictor of CHD in fetuses with normal NT and normal karyotype.[31] We have detected abnormal DV PIV with the absence of enlarged NT in 22 (21.2%) fetuses in the abnormal karyotype group and CHD was detected in 7/22 of these fetuses. A previous meta-analysis showed that the predictive value of abnormal DV during early pregnancy for CHD, regardless of NT status, had a sensitivity and specificity of 50% and 93%, respectively.[4] Certainly, NT measurement and DV blood flow evaluation should be presented as complementary methods in the prediction of aneuploidies in the first-trimester.

There are some concerns about the accuracy of DV blood flow Doppler evaluation due to errors in measurement techniques that could lead to misinterpretation. It could be difficult to distinguish adjacent vessels or DV may not be visible in some cases.[30] Therefore, it is necessary to receive appropriate training and be experienced in DV Doppler studies for obtaining the waveform properly. Concerns about assessment of DV flow "a wave" pattern, which could be susceptible to operator bias has been overcome with the use of DV PIV by reducing the bias and facilitating assurance comparable with that for NT.[6] In our study, we could not detect DV in 4.8% of the chromosomally abnormal group that was a similar rate with literature (the incidence of absent DV was 5.8% in aneuploidy cases according to Wiechec et al. study).[32] The appropriate evaluation of the reversed "a wave" or absence of DV is crucial because these kinds of DV pathologies are usually observed in severe cases.[32,33] In a study, which analyzed 26 cases with absent DV, the incidence of the aneuploidies was higher in cases with absent DV and enlarged NT.[34] We observed that all cases with absent DV were trisomies regardless of NT.

DV-PIV can be used as a continuous variable to increase the specificity of screening for CHD. The detection rate for CHD with enlarged NT and increased DV PIV was 73%.[35] However, prenatal detection rates of CHD are still insufficient. One of the limiting factors for our study was that the number of CHD cannot exactly be known due to the termination of some of the fetuses in the early weeks of gestation. The other limiting factor of the study was its retrospective and monocentric design. Furthermore, maternal age and NT were observed to be higher in the chromosome abnormality group, which may indicate that these could be the possible confounders for DV evaluation. On the other hand, the strengths of the study that utilizes DV Doppler studies for prenatal screening would include having a single perinatologist, who is highly experienced in the said field and who has routinely measured DV PIV during first-trimester screening. Since our clinic is a referral center, chromosomal abnormalities have been detected more frequently.

CONCLUSION

DV PIV measurements could lead to a significant improvement in risk assessment for chromosomal abnormalities. We suggest that the measurement of DV PIV between 11-14 weeks of gestation should be added to first-trimester screening. Moreover, if abnormal DV PIV were to be present, a careful follow-up scan should be performed. DV PIV exceeding 95th centile could be typical for the detection of trisomies. Patterns of "a wave" could point out rigorously but fewer cases. However, we could not make a statement on such little study population, further studies with larger series are required to evaluate clinical importance.

Acknowledgements

We would like to thank Emel Timucin for assistance with the statistical analysis and Serra Onal for editing the language of the manuscript.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

***Idea/Concept:** Şafak Yılmaz Baran, Murat Yayla; **Design:** Şafak Yılmaz Baran, Murat Yayla; **Control/Supervision:** Şafak Yılmaz Baran, Murat Yayla; **Data Collection and/or Processing:** Şafak Yılmaz Baran, Murat Yayla; **Analysis and/or Interpretation:** Şafak Yılmaz Baran, Başar Önal, Murat Yayla; **Literature Review:** Şafak Yılmaz Baran, Murat Yayla; **Writing the Article:** Şafak Yılmaz Baran, Başar Önal, Murat Yayla; **Critical Review:** Şafak Yılmaz Baran, Başar Önal, Murat Yayla; **References and Fundings:** Şafak Yılmaz Baran, Murat Yayla; **Materials:** Şafak Yılmaz Baran, Murat Yayla.*

REFERENCES

1. Kiserud T, Eik-Nes SH, Blaas HG, Hellevik LR. Ultrasonographic velocimetry of the fetal ductus venosus. Lancet. 1991;338(8780):1412-4. [Crossref] [PubMed]
2. Baschat AA, Gembruch U, Harman CR. The sequence of changes in Doppler and biophysical parameters as severe fetal growth restriction worsens. Ultrasound Obstet Gynecol. 2001;18(6):571-7. [Crossref] [PubMed]
3. Baschat AA. Fetal growth restriction-from observation to intervention. J Perinat Med. 2010;38(3):239-46. [Crossref] [PubMed]
4. Papatheodorou SI, Evangelou E, Makrydimas G, Ioannidis JP. First-trimester ductus venosus screening for cardiac defects: a meta-analysis. BJOG. 2011;118(12):1438-45. [Crossref] [PubMed]
5. Wagner P, Eberle K, Sonek J, Berg C, Gembruch U, Hoopmann M, et al. First-trimester ductus venosus velocity ratio as a marker of major cardiac defects. Ultrasound Obstet Gynecol. 2019;53(5):663-8. [Crossref] [PubMed]
6. Kagan KO, Wright D, Nicolaides KH. First-trimester contingent screening for trisomies 21, 18 and 13 by fetal nuchal translucency and ductus venosus flow and maternal blood cell-free DNA testing. Ultrasound Obstet Gynecol. 2015;45(1):42-7. [Crossref] [PubMed]
7. Ghaffari SR, Tahmasebpour AR, Jamal A, Hantoushzadeh S, Eslamian L, Marsoosi V, et al. First-trimester screening for chromosomal abnormalities by integrated application of nuchal translucency, nasal bone, tricuspid regurgitation and ductus venosus flow combined with maternal serum free β-hCG and PAPP-A: a 5-year prospective study. Ultrasound Obstet Gynecol. 2012;39(5):528-34. [Crossref] [PubMed]
8. Maiz N, Valencia C, Kagan KO, Wright D, Nicolaides KH. Ductus venosus Doppler in screening for trisomies 21, 18 and 13 and Turner syndrome at 11-13 weeks of gestation. Ultrasound Obstet Gynecol. 2009;33(5):512-7. [Crossref] [PubMed]
9. Borrell A, Grande M, Bennasar M, Borobio V, Jimenez JM, Stergiotou I, et al. First-trimester detection of major cardiac defects with the use of ductus venosus blood flow. Ultrasound Obstet Gynecol. 2013;42(1):51-7. [Crossref] [PubMed]
10. Oh C, Harman C, Baschat AA. Abnormal first-trimester ductus venosus blood flow: a risk factor for adverse outcome in fetuses with normal nuchal translucency. Ultrasound Obstet Gynecol. 2007;30(2):192-6. [Crossref] [PubMed]
11. Minnella GP, Crupano FM, Syngelaki A, Zidere V, Akolekar R, Nicolaides KH. Diagnosis of major heart defects by routine first-trimester ultrasound examination: association with increased nuchal translucency, tricuspid regurgitation and abnormal flow in ductus venosus. Ultrasound Obstet Gynecol. 2020;55(5):637-44. [Crossref] [PubMed]
12. Czuba B, Nycz-Reska M, Cnota W, Jagielska A, Wloch A, Borowski D, et al. Quantitative and qualitative Ductus Venosus blood flow evaluation in the screening for Trisomy 18 and 13 - suitability study. Ginekol Pol. 2020;91(3):144-8. [Crossref] [PubMed]
13. Maiz N, Wright D, Ferreira AF, Syngelaki A, Nicolaides KH. A mixture model of ductus venosus pulsatility index in screening for aneuploidies at 11-13 weeks' gestation. Fetal Diagn Ther. 2012;31(4):221-9. [Crossref] [PubMed]

14. Bhide A, Acharya G, Bilardo CM, Brezinka C, Cafici D, Hernandez-Andrade E, et al. ISUOG practice guidelines: use of Doppler ultrasonography in obstetrics. Ultrasound Obstet Gynecol. 2013;41(2):233-9. [PubMed]
15. Yılmaz Baran Ş, Kalaycı H, Doğan Durdağ G, Yetkinel S, Arslan A, Bulgan Kılıçdağ E. Does abnormal ductus venosus pulsatility index at the first-trimester effect on adverse pregnancy outcomes? J Gynecol Obstet Hum Reprod. 2020;49(9):101851. [Crossref] [PubMed]
16. Wright D, Syngelaki A, Bradbury I, Akolekar R, Nicolaides KH. First-trimester screening for trisomies 21, 18 and 13 by ultrasound and biochemical testing. Fetal Diagn Ther. 2014;35(2):118-26. [Crossref] [PubMed]
17. Kalayci H, Yilmaz Baran Ş, Doğan Durdağ G, Yetkinel S, Alemdaroğlu S, Özdoğan S, et al. Reference values of the ductus venosus pulsatility index for pregnant women between 11 and 13+6 weeks of gestation. J Matern Fetal Neonatal Med. 2020;33(7):1134-9. [Crossref] [PubMed]
18. Peixoto AB, Caldas TM, Martins WP, Ferreira PC, Nardozza LM, Costa Fda S, et al. Reference range for the pulsatility index ductus venosus Doppler measurement between 11 and 13 + 6 weeks of gestation in a Brazilian population. J Matern Fetal Neonatal Med. 2016;29(17):2738-41. [Crossref] [PubMed]
19. Pruksanusak N, Kor-anantakul O, Suntharasaj T, Suwanrath C, Hanprasertpong T, Pranpanus S, et al. A reference for ductus venosus blood flow at 11-13+6 weeks of gestation. Gynecol Obstet Invest. 2014;78(1):22-5. [Crossref] [PubMed]
20. Antolín E, Comas C, Torrents M, Mu-oz A, Figueras F, Echevarría M, et al. The role of ductus venosus blood flow assessment in screening for chromosomal abnormalities at 10-16 weeks of gestation. Ultrasound Obstet Gynecol. 2001;17(4):295-300. [Crossref] [PubMed]
21. Wagner P, Sonek J, Eberle K, Abele H, Hoopmann M, Prodan N, et al. First trimester screening for major cardiac defects based on the ductus venosus flow in fetuses with trisomy 21. Prenat Diagn. 2018 Apr 16. [Crossref] [PubMed]
22. Burger NB, Matias A, Kok E, de Groot CJ, Christoffels VM, Bekker MN, et al. Absence of an anatomical origin for altered ductus venosus flow velocity waveforms in first-trimester human fetuses with increased nuchal translucency. Prenat Diagn. 2016;36(6):537-44. [Crossref] [PubMed]
23. Karadzov-Orlic N, Egic A, Filimonovic D, Damnjanovic-Pazin B, Milovanovic Z, Lukic R, et al. Screening performances of abnormal first-trimester ductus venosus blood flow and increased nuchal translucency thickness in detection of major heart defects. Prenat Diagn. 2015;35(13):1308-15. [Crossref] [PubMed]
24. Matias A, Montenegro N. Ductus venosus blood flow in chromosomally abnormal fetuses at 11 to 14 weeks of gestation. Semin Perinatol. 2001;25(1):32-7. [Crossref] [PubMed]
25. Abele H, Wagner P, Sonek J, Hoopmann M, Brucker S, Artunc-Ulkumen B, et al. First trimester ultrasound screening for Down syndrome based on maternal age, fetal nuchal translucency and different combinations of the additional markers nasal bone, tricuspid and ductus venosus flow. Prenat Diagn. 2015;35(12):1182-6. [Crossref] [PubMed]
26. Wagner P, Sonek J, Klein J, Hoopmann M, Abele H, Kagan KO. First-trimester ultrasound screening for trisomy 21 based on maternal age, fetal nuchal translucency, and different methods of ductus venosus assessment. Prenat Diagn. 2017;37(7):680-5. [Crossref] [PubMed]
27. Borrell A, Martinez JM, Serés A, Borobio V, Cararach V, Fortuny A. Ductus venosus assessment at the time of nuchal translucency measurement in the detection of fetal aneuploidy. Prenat Diagn. 2003;23(11):921-6. [Crossref] [PubMed]
28. Timmerman E, Oude Rengerink K, Pajkrt E, Opmeer BC, van der Post JA, Bilardo CM. Ductus venosus pulsatility index measurement reduces the false-positive rate in first-trimester screening. Ultrasound Obstet Gynecol. 2010;36(6):661-7. [Crossref] [PubMed]
29. Czuba B, Zarotyński D, Dubiel M, Borowski D, Węgrzyn P, Cnota W, et al. Screening for trisomy 21 based on maternal age, nuchal translucency measurement, first trimester biochemistry and quantitative and qualitative assessment of the flow in the DV - the assessment of efficacy. Ginekol Pol. 2017;88(9):481-5. [Crossref] [PubMed]
30. Bilardo CM, Müller MA, Zikulnig L, Schipper M, Hecher K. Ductus venosus studies in fetuses at high risk for chromosomal or heart abnormalities: relationship with nuchal translucency measurement and fetal outcome. Ultrasound Obstet Gynecol. 2001;17(4):288-94. [Crossref] [PubMed]
31. Martínez JM, Comas M, Borrell A, Bennasar M, Gómez O, Puerto B, et al. Abnormal first-trimester ductus venosus blood flow: a marker of cardiac defects in fetuses with normal karyotype and nuchal translucency. Ultrasound Obstet Gynecol. 2010;35(3):267-72. [Crossref] [PubMed]
32. Wiechec M, Nocun A, Matyszkiewicz A, Wiercinska E, Latała E. First trimester severe ductus venosus flow abnormalities in isolation or combination with other markers of aneuploidy and fetal anomalies. J Perinat Med. 2016;44(2):201-9. [Crossref] [PubMed]
33. Garcia-Delgado R, Garcia-Rodriguez R, Romero Requejo A, Armas Roca M, Obreros Zegarra L, Medina Castellano M, et al. Echographic features and perinatal outcomes in fetuses with congenital absence of ductus venosus. Acta Obstet Gynecol Scand. 2017;96(10):1205-13. [Crossref] [PubMed]
34. Staboulidou I, Pereira S, Cruz Jde J, Syngelaki A, Nicolaides KH. Prevalence and outcome of absence of ductus venosus at 11(+0) to 13(+6) weeks. Fetal Diagn Ther. 2011;30(1):35-40. [Crossref] [PubMed]
35. Timmerman E, Clur SA, Pajkrt E, Bilardo CM. First-trimester measurement of the ductus venosus pulsatility index and the prediction of congenital heart defects. Ultrasound Obstet Gynecol. 2010;36(6):668-75. [Crossref] [PubMed]