Contribution of ductus venosus doppler in first-trimester screening for major cardiac defects

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Abstract

Ductus venosus (DV) is a very essential regulator of oxygenated blood in fetal life and play an essential role in evaluation the umbilical portal venous abnormalities. This study aimed to demonstrate the relation between DV and fetal abnormalities. A total of 422 parturient women singleton pregnancy between 11weeks - 13weeks +6days gestation were subjected to scan for detection of congenital anomalies by measuring different parameters. Using trans-abdominal and trans-vaginal Doppler ultrasound (at11weeks-13weeks+6days) and the following parameters: fetal heart rate (FHR), Nuchal tranlucency (NT), Nasal bone, TR, DV waveform: On Doppler imaging, the observation of absent or reversed A-wave in the ductus venosus was recorded, Detailed fetal echocardiography for detection of any cardiac anomalies. Another trans-abdominal ultrasound was performed at 18-24 weeks for measuring of ductus venosus and detection of congenital heart diseases, by using 2D ultrasound for anomaly scan and complementary by 3D. Also post natal assessment of heart was done to confirm diagnosis. 96.2 % of study population has Nuchal tranlucency10-19mm, the other population it ranged from 30-0.7%. Also nasal bone abnormalities appeared in 1 % of patient. Tricus valve-regurgitation and reversed wave of ductus venosus were clear in 1.3 % and 6 % of population respectively. Regarding to heart anomalies, 2 % had abnormal heart scan in addition to 2 % had postnatal echocardiograpgy. It was concluded that a significant relationship was detected between fetal abnormalities and the mentioned parameters particularly the ductus venosus doppler

1. Introduction

Approximately 20% of all stillbirths and 30% of newborn fatalities due to congenital anomalies are caused by cardiac and major artery abnormalities, making them the most common congenital disorders. As pointed out by Tegnander et al. [1], routine prenatal US screening does not detect the majority of affected fetuses as successfully as specialist fetal echocardiography does when it comes to diagnosing major cardiac defects during the prenatal period. Approximately 8 out of every 1000 live infants are affected by cardiac problems, which are also called congenital heart defects (CHD) [2]. Among these cases, 50% are categorized as serious heart abnormalities, which highlight the profound effect they may have on those afflicted. According to the analysis by Levey et al. [3], CHD are the leading causes of death and morbidity among infants and pregnant women. Tongprasert et al. [4] found encouraging results from fetal ductus venosus (DV) examinations in identifying fetuses at risk for CHD. Approximately 10% of fetuses with cardiac defects are detected by the conventional method of screening, which involves evaluating the presence of CHD, the maternal

history of DM, and maternal exposure to teratogens [5]. According to the different results shown by Kagan et al. [6] evaluating CHD in the first trimester of pregnancy is still challenging. DV is essential for the proper flow of oxygen-rich umbilical venous blood to the heart. Changes in volume and pressure inside the heart's atriums have a profound effect on the shape of the fetal atrial pressure waveform. This makes it an essential tool for monitoring fetal health, especially in situations where there can be problems with the forward cardiac function [7]. The preload on the right ventricle and general hemodynamics are greatly affected by the blood flow via the DV. When assessing fetal cardiac activity during pregnancy, it is crucial to look at the DV. According to Wald et al. [8], this technology is very valuable for fetal CHD screenings and diagnostics since it can identify the condition and any chromosomal abnormalities that may be present. A powerful tool for better early identification and prediction of CHD may be made available with the integration of DV Doppler technology into first-trimester nuchal translucency (NT) screening. The DV a-wave's absence or reversal during the first trimester might help identify fetuses at risk for CHD

in cases where there is an elevated NT, a condition typically linked to chromosomal abnormalities [9]. Venous flow blockage and concomitant cardiac dysfunction are two possible causes of the variety of DV Doppler anomalies that may be seen in congenital heart disease. During prenatal evaluations, a large percentage of fetuses identified with CHD have abnormal Doppler waveforms in the DV. Reversed DV a-wave flow at baseline is significantly more common in CHD affecting the right side of the heart and involving obstructive lesions, such as tricuspid or pulmonary valve stenosis/atresia, as reported by Arya et al. [10]. The DV diameter in human babies throughout gestation may now be studied, thanks to recent advances in imaging resolution methods [11]. In previous research, increases in ductus venosus width (DVW) have been shown to be significantly associated with abnormal DV. Because the DV sphincter relaxes with DVW dilatation, central venous pressure rises [12]. Fetal hemodynamics may be effectively assessed with the use of the frequently used technique of Doppler US. Qualitative results and quantitative factors are both included in US. The qualitative results shed light on the blood flow patterns that were seen, including whether reverse flow was present, absent, or happened. Furthermore, the hemodynamic features are evaluated using quantitative measures called Doppler indices. The pulsatility index (PI) and systolic-to-diastolic ratio (S/D) are two of these measures, as Surachai et al. [13] explained. Note that doing fetal echocardiography requires substantial expertise, despite the fact that standards have been published for the technique. This method entails assessing numerous elements, including the atria, ventricles, pulmonary venous return, and the ductal and aortic arches. Expertise, time, and specialized equipment are required for fetal echocardiography. An easier way to diagnose CHD during pregnancy might be with the use of a DV Doppler or another simple screening plane [14]. This research aims to evaluate the possibility of atypical DV readings taken with Doppler US to improve the accuracy of prenatal CHD predictions.

2. Patients and methods

Our study was carried out at Beni-Suef University Hospital from July 2020 to May 2021. There were 384 participants in the present study. We add around 10% loss follow up, so the total sample size was 422. Age of the studied patients ranged between 22—41 years with mean ± SD 31.1 + 4.4. Inclusion criteria were Singleton pregnancy between 11weeks - 13weeks +6 day's gestation. Patients with these criteria were excluded if there were one or more of the exclusion criteria: Fetal chromosome abnormalities or fetal extra-cardiac structural anomalies in previous pregnancy, maternal complications in the present pregnancy, uncertain gestational age (GA), women with gestational diabetes, and maternal systemic disease, women on antihypertensive agents, and women who were absent during the patient follow-up process. Following obtaining the written informed consent, all patients were studied between 11weeks - 13weeks + 6 days gestation, then second assessment was done between 18weeks -24weeks (during routine scan in second trimester) to confirm if there is major CHD. The GA of the fetuses was calculated from the date of the last menstrual period and it will be confirmed by US measurement of the crown-rump length, using trans-abdominal and trans-vaginal Doppler US (at11weeks-

13weeks+6days). And the following parameters : fetal heart rate (FHR) , NT, Nasal bone , TR , DV waveform: On Doppler imaging, the observation of absent or reversed A-wave in the DV was recorded, Detailed fetal echocardiography for detection of any cardiac anomalies. Another trans-abdominal US was performed at 18-24 weeks for measuring of DV and detection of congenital heart diseases, by using 2D-US for anomaly scan and complementary by 3D. Also post natal assessment of heart was performed to confirm diagnosis. Primary outcome: to assess the relation between DV waveform and CHD. Secondary outcome: To find correlation between DV waveform and other parameters assessed in first trimesteric scan.

2.1 Statistical and data analysis
2.1.1. Sample size

Sample size was calculated based on online openepi calculator. The required sample was calculated at 95% two sided confidence Level (CL), 80% power and based on overall Population size. The required sample will be 384 participants in the present study. We add around 10% loss follow up ,so the total sample size will be 422. Results from OpenEpi, Version 3, open source calculator—SSCC.
Statistical tests: The collected data will be tabled, coded and analyzed using SPSS program.
- ✓ Description of qualitative variables will be by frequency and percentage.
- ✓ Description of quantitative variables will be in the form of mean and standard deviation (mean ± SD).
- ✓ Chi-square (χ^2) test will be used for comparison of qualitative variables with each other.
- ✓ For more statistical analysis; suitable statistical tests of significance will be used.
- ✓ *P*-values < 0.05 will be considered as statistically significant.

2.1.2 Ethical Consideration

Administrative approvals were sought from the head of selected facilities. Ethical approval was sought from Beni-Suef University Ethical Committee. Informed consents were signed from the participants. They were assured that data are confidential and anonymous. Sociodemographic questions were for identifying the characteristics not identity. Respondents were aware of the aim and steps of the study. They were allowed to express their opinion and comments. The participants themselves were not obliged to participate.

3. Results

In table (1): the maternal age ranged from 22—41 years with Mean ± SD 31.1 + 4.4. BMI; Mean ± SD 29 + 2.7. The mean parity was 2.3 (± 1.3 SD). In table (2): CRL ranged from 50 – 90 mm in the study population with mean 71.15 ± 12.2 SD. FHR ranged from 155 – 180 bpm in the study population with mean 168.34 ± 7.87 SD. NT ranged from 1 – 4.7 mm in the study population with mean 1.38 ± 0.39 SD. Nuchal translucency ranged from 1.0 – 1.9 mm in 96.2% of the study population, from 2.0 – 2.9 mm in 2.5%, 3.0-5.9 mm in 1.3%.(99%) of the study population had normal length nasal bone, 0.3% had hypoplastic nasal bone and 0.7% had an absent nasal bone. (98.7%) of the study, the population had normal tricuspid valve waveform, and 1.3 % had tricuspid valve - regurgitation. (94.0%) of the study, the population had

normal ductus venosus, and 6.0% had reserved A waveform. (98.2.0%) of the study, the population had normal fetal scan, and 1.8% had abnormal fetal scan. 0.3 % had ventriculomegaly, 0.3% had cleft palate, and 0.3% had talipus, 0.3 % had omphalocele , 0.7% cystic hygroma, 0.3% had meningocele and 0.3% had micromelia. In the 1st trimester; (98%) of the study, the population had normal heart scan, and 2% had an abnormal heart scan, of these 0.3% had ventricular septal defect (VSD),0.8% had AVSD , 0.5% had left Hypoplastic, and 0.3% had Ebstein anomaly and 0.3% had Fallot Tetralogy. In the 2nd trimester fetal echocardiography, (97.2%) of the study, the population had normal heart scan, and 2% had an abnormal heart scan, of these 0.8% had ventricular septal defect (VSD),0.8% had AVSD , 0.5% had left Hypoplastic, and 0.3% had Ebstein anomaly and 0.3% had Fallot Tetralogy and 0.3% TGA. In postnatal fetal echocardiography, (97.2%) of the study population had normal heart scan, and 2% had an abnormal heart scan, of these 0.8% had ventricular septal defect (VSD),0.8% had AVSD , 0.5% had left Hypoplastic, and 0.3% had Ebstein anomaly and 0.3% had Fallot Tetralogy and 0.3% TGA. Table (3) shows significant relationship between maternal age and Nuchal translucency. While no significant relationship between maternal age and measured parameters (nasal bone, tricuspid regurgitation, and ductus venosus). Table (4) shows a highly significant relationship between measured parameters (Nuchal translucency, nasal bone, tricuspid regurgitation, and ductus venosus). *The results proved that all measured parameters were positive in all cases of abnormal ductus venosus. In table (5), major cardiac defect was observed in 11(2.8%) fetuses and 9 (81.8 %) of these had abnormal Doppler waveforms in the ductus venosus, there was highly significant relation between abnormal ductus venosus waveforms and cardiac defects.

4. Discussion

Cardiac and major arterial abnormalities are the predominant congenital problems, accounting for roughly 20% of all instances of stillbirth and 30% of newborn mortality associated with congenital malformations. According to Tegnander et al. [1], whereas specialized fetal echocardiography is very effective in discovering the majority of significant cardiac problems prenatally, it is crucial to acknowledge that standard ultrasound screening throughout pregnancy is less successful in identifying most afflicted babies. The DV serves a crucial function in the effective distribution of highly oxygenated umbilical venous blood to the cardiovascular system. The waveform of fetal atrial pressure exhibits a complex relationship with changes in pressure and volume inside the cardiac atria. Therefore, it plays a vital role in monitoring any fetal condition that may possibly affect the effectiveness of cardiac function in the future [7]. The integration of DV Doppler technology into the first assessment of first-trimester NT has been seen to considerably enhance the capacity to forecast CHD during the early stages. Papatheodorou et al. [9] found that in babies with an elevated NT but no chromosomal abnormalities, the identification or reversal of the DV a-wave in the first trimester may serve as a means to classify fetuses that may be at risk for CHD. This study is carried out on 422 patients, age of the studied patients ranged between 22—41 years (mean of 31.4 years ±4.4). BMI of all patients ranged between 19 and 39 (mean of 29 ±2.7). Parity ranged between 1 and 6 (mean of 2.3 times ±1.3). NT ranged from 1.0 – 1.9 mm in 96.2% of the study population, from 2.0 – 2.9 mm in 2.5%, 3.0-5.9 mm in 1.3%. (99%) of the study population had normal nasal bone (NB), 0.3% had hypoplastic NB and 0.7% had an absent NB. (98.7%) of the study population had normal Tricuspid valve (TV) waveform, and (1.3%) had TV - regurgitation. Regarding the heart anomalies; (98%) of the study, the population had normal heart scan, and 2% had an abnormal heart scan, of these 0.3% had VSD,0.8% had AVSD , 0.5% had left Hypoplastic, and 0.3% had Ebstein anomaly and 0.3% had FT. (94.0%) of the study population had (Normal A wave) normal DV, and 6.0% had reserved A wave. According to our study there is highly significant relationship between measured parameters (NT, nasal bone, TR, and DV) and presence of CHD. The results proved that all measured parameters were positive in all cases of abnormal DV. There is also highly significant relationship between DV waveforms and cardiac defects by echocardiography. Major cardiac defect was observed in 11(2.8%) fetuses and 9 (81.8 %) of these had abnormal Doppler waveforms in the DV, there was highly significant relation between abnormal DV waveforms and cardiac defects.

Table 1: Patients' demographic characters of study population

	Min – Max	Mean ± SD.	Median (IQR)
Age(year)	22 – 41	31.4 ± 4.4	33 (6)
BMI	19 – 39	29 ± 2.7	29(3)
Parity	1 – 6	2.3 ± 1.3	2 (2)

IQR: Inter Quartile Range,   SD: Standard deviation

Table 2: 1st Trimester 2nd trimester and postnatal fetal Scan data in study participants

Parameters/ Participants (n= 396)	1st Trimester Scan	2nd Trimester Scan	Post natal scan
Crown Rumple length (mm) (CRL) (Mean ± SD)	71.15 ± 12.2	-	-
Fetal Heart Rate (bpm) (FHR) (Mean ± SD)	168.34 ± 7.87	-	-
Nuchal translucency(mm) (NT) (Mean ± SD)	1.38 ± 0.39	-	-
Nuchal Translucency (N, %)			
1.0 – 1.9 mm	381 (96.2%)	-	-
2.0 – 2.9 mm	10 (2.5%)	-	-
3.0 – 5.9 mm	5 (1.3 %)	-	-
Nasal bone (N, %)			
Normal	392 (99 %)	-	-
Hypoplastic	1 (0.3 %)	-	-
Absent	3 (0.7 %)	-	-
Tricuspid valve (N, %)			
Normal	391 (98.7 %)	-	-
Regurgitation	5 (1.3 %)	-	-
Ductus venosus (N, %)			
Normal	385 (97.2 %)	-	-
Abnormal A- wave (Reversed Or absent)	11 (2.8 %)	-	-
Echocardiography			
Normal	388 (98%)	385 (97.2%)	385 (97.2%)
VSD	1 (0.3%)	3 (0.8%)	3 (0.8%)
AVSD	3 (0.8%)	3 (0.8%)	3 (0.8%)
LT hypoplastic heart	2 (0.5%)	2 (0.5%)	2 (0.5%)
Ebstein Anomaly	1 (0.3%)	1 (0.3%)	1 (0.3%)
Fallot Tetralogy	1 (0.3%)	1 (0.3%)	1 (0.3%)
TGA	0	1 (0.3%)	1 (0.3%)
Associated congenital Anomalies			
Normal	-	389 (98.2%)	-
Ventriculomegaly	-	1 (0.3%)	-
Cleft lip	-	1 (0.3%)	-
Cystic hygroma	-	1 (0.3%)	-
Talips	-	1 (0.3%)	-
Omphalocele	-	1 (0.3%)	-
Meningiocele	-	1 (0.3%)	-
Micromelia	-	1 (0.3%)	-

VSD: Ventricular septal defect- TGA: Transposition of great arteries

Table 3: correlation between measured parameters and maternal age

	Test	p- value
Nuchal translucency	Pearson correlation	0. 038
Nasal bone	Chi-square	0. 74
Tricuspid regurgitation	Chi-square	0. 85
Ductus venosus	Chi-square	0. 42

Table 4: Correlation between measured parameters and fetal cardiac anomalies

Parameters	p –value
Ductus venosus	<0.001
Maternal age	0. 65
Nuchal translucency	<0.001
Nasal bone	<0.001
Tricuspid regurgitation	<0.001

Table 5: Relationship between ductus venosus waveforms and cardiac defects by echocardiography

		Echocardiography			
		Normal	*Cardiac Defects*	χ^2	*P-Value*
Ductus Venosus	*Normal*	383 (99.5%)	2 (18.2%)	*261.73*	*<0.001*
	Abnormal (Reversed A wave Or absent)	2 (0.5%)	9 (81.8%)		

While bearing some differences from the results of previous research, the current study's conclusions show a positive agreement with other studies. The average mother age was found to be 31.9 years, ranging from 16 to 46 years, in research done by Favre et al. [15]. With a range of 11–14 weeks, the average GA was 12.7 weeks. Also, there was a range of 40–91 mm for the crown–rump length, with an average of 69 mm. A total of 482 cases underwent fetal karyotyping, with 42 cases resulting in abnormalities and 440 cases showing normal results. The karyotypes showed a range of abnormalities, including 34 occurrences of trisomy (23 occurrences of trisomy 21, 8 occurrences of trisomy 18, and 3 occurrences of trisomy 13), 5 occurrences of sex chromosomal abnormalities, 2 occurrences of triploidy, and 1 occurrence of structural abnormality. One hundred thirty-five fetuses, or 12.9% of the total, had an increased NT thickness. For 105 fetuses, abnormal DV blood flow velocimetry was found. Out of the total number of patients, 45 had aberrant DV blood flow on its own, whereas 60 had an association with thicker NT. Along with a normal prenatal cytogenetic study; twenty-nine instances were found to have abnormally elevated NT thickness and aberrant DV velocimetry. There was a total of 25 CHD found, including 24 major

abnormalities and 1 little one, a VSD. Ten cases (40%) were determined to have a normal karyotype through antenatal or postmortem cytogenetic analysis, or assumed based on postnatal medical examination, while fifteen cases (60%) showed an abnormal karyotype in the cohort of patients with cardiac anomalies. Out of the 10 instances with CHD and normal karyotypes, nine (or 90%) showed unusually high NT thickness in addition to aberrant blood flow velocimetry in the DV.

This patient had a unique case of VSD, but there were no out-of-the-ordinary findings in terms of NT thickness or DV blood flow velocimetry . Researchers Favre et al. [15] found that measuring the DV blood flow velocity during the first trimester improved the accuracy of detecting major CHD. This was true even in cases where the karyotype was normal and the NT was thicker than usual. It is recommended to schedule a thorough echocardiogram for the patient between 14 and 16 weeks of gestation once prenatal cytogenetic information has successfully eliminated the possibility of aneuploidy. It is advised to do another scan later in the pregnancy to evaluate the heart's architecture in particular if the findings show normal cardiac activity . Previous studies that have investigated the DV waveform's

potential as a CHD screening tool have reached similar results as our own. The total detection rate was found to be 50% in a thorough meta-analysis done by Papatheodorou et al. [9], while the false-positive rate was discovered to be 7%. Furthermore, it was noted that the test's accuracy relied on the NT assessment. There was a 4% risk of false-positive findings in fetuses with a normal NT, but a 20% prevalence in fetuses with an elevated NT. In the largest investigation on the topic, 85 fetuses were found to have CHD, whereas almost 41,000 fetuses were found to be unaffected (20). Approximately 30% of the people with the illness under examination showed a reversal pattern in the DV a-wave, whereas just 2.1% of the general population without the disorder demonstrated this reversal, according to the researchers. Borrell et al. [2] found results that are in agreement with our study's conclusions. For this study, the researchers compared the DV-PIV method with a qualitative assessment of the a-wave, looking for signs of reversed flow. Among the fetuses identified with CHD, 39% showed a reversal pattern in the a-wave flow, compared to just 1.8% of the general population without known CHD. Researchers found that only 38% of impacted fetuses had a DV-PIV higher than the 95th percentile. When the two DV-flow characteristics were combined, the detection rate improved to 55% with a false-positive rate of 6.5%. However, it must be stressed that the authors also included the assessment of the NT thickness in the later analysis .No matter if the fetus has a big heart defect or not, the results of Martinez et al. [16] showed that fetal NT is associated with an increased risk of a reversed a-wave in the DV. Two percent of the typically developing fetuses with NT readings below the 95th percentile and four percent of those with NT readings above the 95th percentile had a-wave inversion. Major cardiac defects were detected in 18% of fetuses and 47% of those without the problem. Twenty percent of the unaffected fetuses showed abnormal flow in the DV in the combined data from the studies on fetuses with elevated NT, but 69 percent of the fetuses with significant CHD showed this same pattern of abnormal flow. These rates suggest that the prior few studies looked at a large number of pregnancies with far higher fetal NT readings. These results in severely abnormally heart-shaped babies are in line with those of an earlier screening research that included 5,925 pregnancies. A total of 12 instances (12.9%) with normal NT measures and 6 cases (46.1%) with enhanced NT measurements were found to have aberrant blood flow in the DV in this investigation. Atypical ductal blood flow and/or elevated NT measures were seen in a variety of cardiac disorders. There were no identifiable CHD in fetuses with aberrant DV flow and increased NT, according to a previous investigation that was smaller in size. On the other hand, every single anomaly that was found in fetuses with normal NT was situated on the right side. Evidence presented by Chelemen et al. [17] suggested that DV flow is aberrant in fetuses with significant heart abnormalities. This aberrant flow is seen in both normal and enhanced NT instances. Early screening for cardiac abnormalities, which includes measuring fetal NT, is therefore improved by assessing flow in the DV. There were a total of 85 euploid babies with significant heart problems and 40,905 euploid fetuses without heart defects that made up the research population. Of the fetuses identified with CHD, 30 (35.3% of the total) had NT measurements above the 95th percentile, while 18 (21.2% of the total) had NT measurements above the 99th percentile. On the other hand, out of 1,956 (4.8%) instances involving fetuses that did not have CHD, 290 (0.7%) had NT measurements that were higher than the 95th%ile. Of the fetuses identified with cardiac anomalies, 24 (28.2%) had a reversed a-wave, while 856 (2.1%) of the fetuses without cardiac abnormalities had it. If the NT value is higher than the 99th centile or the a-wave is inverted; it is suggested to do a specialist fetal echocardiogram. With a total false positive rate of just 2.7%, this particular method has been shown to identify 38.8% of severe heart abnormalities .

Conclusions

From the results of our study, we conclude that there was significant relationship between fetal abnormalities in the first trimester and measured parameters (NT, nasal bone, TR and DV). We concluded that measurement of DV blood flow at 11-13+6 weeks of pregnancy is a useful, effective method of screening for CHD.

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