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Ductus Venosus Doppler Ultrasound in Diabetic Pregnancies

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Abstract
Background: *With the increased prevalence of diabetic pregnancies, it is necessary to develop a simple reliable method for screening of the fetal cardiovascular system, which is a potential site for adverse effects due to maternal hyperglycemia. Being an easy tool, the ductus venosus Doppler velocities might be an appropriate method.* ***Patients and Methods:*** *the study included 40 diabetic pregnant women during their third trimester (cases) and 40 women with normal pregnancy as control. Each patient was submitted to detailed history taking, clinical examination, laboratory evaluation of HbA1c and Doppler ultrasonographic assessment of ductus venosus.* ***Results:*** *The diabetic mothers had higher BMI, infants with larger birth weight and low 5-minute Apgar score. Regarding ductus venosus (DV) Doppler assessment. There was a significant elevation of all DV indices among cases than controls including pulsatility index, preload index and peak velocity index for the vien. Poor control of diabetes was associated with elevated all DV indices among diabetic cases of the study. Also, pre-gestational DM was associated with significantly higher pulsatility index and preload index. Newborns with low 5-min Apgar score had significantly higher pulsatility index and preload index than newborns with normal 5-min Apgar score.* ***Conclusion:*** *Diabetic pregnancies demonstrated significant difference of ductus venosus Doppler parameters compared with non-diabetic controls, possibly indicating a fetal cardiac effect.*

Keywords: *Diabetes mellitus, ductus venosus*

Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (ADA, 2015). It is one of the most common non-communicable diseases, with serious consequences (Ahmed et al., 2015). DM may be classified as type 1 diabetes, associated with pancreatic failure and insulin deficiency; type 2 diabetes, associated with ineffective insulin utilization; or gestational diabetes mellitus (GDM), which is diabetes first diagnosed or recognized in pregnancy (Lyons, 2015). Diabetes in pregnancy is associated with frequent adverse perinatal outcomes including congenital malformations, perinatal mortality, preterm delivery and large for gestational age (LGA) infants (McCance, 2015). Fetal anomalies predominantly involve cardiovascular anomalies, which comprises the highest proportion and are the greatest contributor to perinatal mortality (Miller et al., 2013). The ductus venosus (DV) is a blood vessel, unique to the fetal circulation that originates from the umbilical vein (UV) and enters the inferior vena cava at the inlet to the right atrium (Dahlback et al., 2015). Abnormal DV waveforms could be a consequence of delayed maturation of the cardiovascular system, fetal chromosomal abnormalities without cardiac malformations, cardiac dysfunction from congenital cardiac anomalies, or fetal growth restriction (Suksai et al., 2015). The DV waveform reflects the pressure–volume changes in the heart. Despite the limited specificity of the DV waveform, its correlation with cardiac forward function makes it of central importance in assessing the overall severity of fetal cardiovascular pathology (Seravalli et al., 2015). In recent years, DV Doppler velocities, DV velocity ratios, and diastolic time intervals have been used to evaluate fetal cardiac function and well-being in complicated pregnancies, including gestational diabetes (Avcı et al., 2015). Diabetic pregnancies might exhibit abnormal DV hemodynamics, hence it may indicates modified fetal cardiac function (Stuart et al., 2010).

Patients and methods

The present case control study was conducted at Obstetrics and Gynecology department of AL-Azhar University hospital (New Damietta) during the period from February 2015 to the February 2016. It included 40 diabetic pregnant women during their third trimester (cases) and 40 women with normal pregnancy as control. Fetuses with IUGR or suspected chromosomal anomalies were excluded from the study. Mothers with disorders affecting cardiovascular system as hypertension, collagen and renal diseases were also excluded. Follow up: each patient was followed until delivery and the following data regarding newborns were obtained: Apgar score at 1 and 5 minutes, birth weight. Large for gestational age (LGA) are those with birth weight > the 90th percentile for gestational age. Appropriate for gestational age (AGA) are newborns with birth weight between 10th and 90th percentiles. According to Wong et al. (2010), adverse perinatal outcome was defined as1-min Apgar score < 4 or 5-min Apgar score < 7. Routine examination of newborns revealed that there were no apparent congenital anomalies. Ultrasound scan: Ultrasound scan was performed using a Voluson 730 Pro machine (USA) equipped. Amniotic fluid index (AFI) was calculated according to Phelan et al. (1993). Polyhydramnios was defined as an amniotic fluid index (AFI) of > 24 cm or a vertical pocket of at least 8 cm, while oligohydramnios was defined as an AFI of < 5 cm or a vertical pocket of < 2 cm (Idris et al., 2010). Umbilical artery blood velocities were recorded from the mid-portion of the umbilical cord. The umbilical artery PI was calculated automatically by the ultrasound systems according to the method of Gosling et al. (1971). The DV study was performed as described by Kiserud et al. (1991). The DV was identified in a midsagittal section or in an oblique transverse section of the fetal abdomen. The angle of insonation was determined by color Doppler, and pulsed Doppler signals were recorded from the isthmic portion of the DV. The following waveforms were recorded using a maximum insonation angle of 30°: peak forward velocity during ventricular systole (S-wave), peak forward velocity during early diastole (D-wave), and lowest forward velocity during atrial contraction in late diastole (a-wave). For each waveform, the mean value of three consecutive high-quality measurements was used for analysis. In addition, the time-averaged maximum velocity (Tamx) was calculated and the following DV ratios and indices were determined: pulsatility index for the vein (PIV), calculated as (S–a)/Tamx; peak velocity index for the vein (PVIV) was calculated automatically according to the formula (S–A)/D. Preload index (PLI), calculated as (S–a)/S; D/a ratio, S/a ratio; and S/D ratio (Suksai et al., 2015). Only signals obtained during fetal quiescence were included for analysis. In the event of repeated examination, only the last set of recordings before birth was included in the statistics.

Statistical analysis

The collected data were organized, tabulated and statistically analyzed using statistical package for social sciences (SPSS) version 19 (SPSS Inc, Chicago, USA), running on IBM compatible computer . Quantitative data were expressed as the mean ± standard deviation (SD). Qualitative data were presented as relative frequency and percent distribution. For comparison between two groups, the independent samples (t) test or Mann-Whitney tests were used. For comparison between categorical groups, the Chi square (X2) or Fisher's exact tests were used. Pearson correlation co-efficient (r-test) was used for correlating different variables. For all tests, P values < 0.05 were considered significant. For all tests, P values > 0.05 were considered insignificant.

Results

The study was a case control study conducted at Obstetrics and Gynecology department of AL-Azhar University hospital (New Damietta). It included 40 diabetic pregnant women during their third trimester (cases) and 40 women with normal pregnancy as control. Newborns with low 5-min Apgar score had significantly higher pulsatility index (P=0.035) and preload index (P=0.027) than newborns with normal 5-min Apgar score. Regarding general characteristics, there was no significant difference between cases and control as regard age, parity and gestational age. Diabetic mothers had higher BMI (P=0.013), infants with larger birth weight (p=0.001) and low 5-minute Apgar score (p=0.039). The majority of diabetic mothers had gestational diabetes (70%) and had poor control of diabetes (57%) (Table I). Regarding ductus venosus Doppler assessment, there was no significant difference between cases and controls as regard all DV waves except the a-wave (P=0.023). Regarding DV ratios, we found that there was significant elevation of (S/D) and (S/a) ratios (P=0.003 and 0.001) among cases than controls. Regarding DV indices, we found that there was significant elevation of all DV indices among cases than controls including pulsatility index (P=<0.001), preload index (P=0.024) and peak velocity index for the vien (P=<0.001) (Table II) . Assessment of relation between Doppler assessment of ductus venosus indices and different variables revealed that poor control of diabetes was associated with elevated all DV indices among diabetic cases of the study. Also, pre-gestational DM was associated with significantly higher pulsatility index (p=0.026) and preload index (p=0.036); also, PVIV was elevated, but without significant difference (p=0.26). Newborns with low 5-min Apgar score had significantly higher pulsatility index (p=0.035) and preload index (p=0.027) than newborns with normal 5-min Apgar score; also, PVIV was elevated with low Apgar score, but without significant difference (p=0.13). There was significant positive correlation between DV-PI with both HbA1c and Apgar score. In contrast, there was no significant correlation between DV-PI with neither birth weight nor maternal age (Table III) and (Table VI).

Table (I): Demographic characteristics of studied cases

Variables		Cases (n=40)	Control (n=40)	P
Maternal				
Age (years)		29.3±4.7	28.9±5.13	0.66
BMI (kg/m^2)		34.6±10.5	29.04±9.2	0.013*
Parity	Multiparous	16 (40%)	11 (27%)	0.34
	Primiparous	24 (60%)	29 (73%)	
Gestational age (weeks)		29.4±2.7	30.3±3.07	0.17
Amniotic fluid index		19.31±6.25	14.43±4.7	<0.001*
Umbilical artery PI		1.24±0.32	1.18±0.24	0.45
Neonatal				
Birth weight (g)		3546±814	3117±398	0.005*
Birth weight	Appropriate for GA (AGA)	26 (65%)	38 (95%)	0.001*
	Large for GA (LGA)	14 (35%)	2 (5%)	
5-min Apgar	< 7	6 (12.5%)	0 (0%)	0.039*
	≥ 7	34 (85%)	40 (100%)	
Characters of diabetic pregnancies				
Type of DM	Pregestational		12 (30%)	
	Gestational		28 (70%)	
HbA1c (%)	Good control (< 7%)		17 (42.5%)	
	Poor control (> 7%)		23 (57.5%)	

: significant

Table (II): Comparison between ductus venosus parameters in diabetic and non-diabetic pregnancies

	Cases (n=40)	Control (n=40)	P
S-wave (cm/s)	70.2±12.6	65.4±11.3	0.1
D-wave (cm/s)	44.2±9.8	47.6±8.7	0.11
a-wave (cm/s)	28.6±7.7	32.4±6.9	0.023*
Tamx (cm/s)	52.1±10.3	53.9±12.4	0.48
D/a ratio	1.92±0.42	1.79±0.34	0.13
S/D ratio	1.42±0.19	1.28±0.14	0.003*
S/a ratio	2.43±0.49	2.09±0.42	0.001*
DV-PI	0.623±0.04	0.589±0.035	<0.001*
PLI	0.504±0.043	0.481±0.05	0.024*
DV-PVIV	0.348±0.054	0.312±0.042	<0.001*

**: significant*

Table (III): Comparison between ductus venosus doppler indices of diabetic cases in relation to various parameters

	DV-PI	P	PLI	P	DV-PVIV	P
HbA1c		0.001*		0.003*		0.046*
≥ 7% (n=23)	0.651±0.046		0.528±0.047		0.367±0.058	
< 7% (n=17)	0.603±0.042		0.486±0.038		0.331±0.052	
Type of DM		0.026*		0.036*		0.26
Pre-gestational (12)	0.647±0.04		0.527±0.042		0.361±0.044	
Gestational (28)	0.615±0.04		0.496±0.041		0.342±0.05	
5- min Apgar score		0.035*		0.027*		0.13
< 7 (n=6)	0.646±0.04		0.528±0.034		0.369±0.042	
≥ 7 (n=34)	0.617±0.04		0.502±0.041		0.334±0.053	
Birth weight		0.12		0.44		0.53
LGA (n=14)	0.638±0.04		0.509±0.043		0.357±0.054	
AGA (n=26)	0.617±0.04		0.498±0.043		0.346±0.053	

**: significant*

Table (VI): Correlation between ductus venosus -pulsatility index and some parameters

Variable	DV-PI	
	r	**P**
HbA1c*	0.52	0.001
Birth weight	0.19	0.25
Apgar score	0.43	0.005
Maternal age	0.11	0.504

Discussion

Diabetes is the most common metabolic disorder to affect pregnancy and is associated with increased maternal and neonatal morbidity (Sutton et al., 2015). Fetal cardiovascular development in women with diabetes mellitus can be affected by maternal hyperglycemia (Kulkarni et al., 2015). Ductus venosus blood flow plays an important role in right ventricular preload and hemodynamics (Chiu et al., 2015). Ductus venosus assessment is a crucial part of a prenatal fetal heart activity assessment; it is a valuable initial diagnostic and screening tool for many fetal cardiovascular abnormalities (Peixoto et al., 2015).

Examination of ductus venosus Doppler parameters among our cases resulted in variable figures between the simple waves and the more complex ratios and indices. Most of the studied parameters of our cases were within the normal reference ranges for DV flow velocities and waveform indices (Kessler et al., 2006 and Turan et al., 2014). These studies obtained their results from limited heterogeneous pregnancies; in addition, there is no local reference ranges for DV velocities. The choice of case control design aimed at eliminating the expected bias if a non-documented reference ranges was used. However, this design represented some limitation because of the inaccuracy in defining abnormal results.This study aimed to evaluate the parameters of ductus venosus Doppler ultrasound among diabetic pregnant women and its neonatal effect.

In the present study, there was no significant difference between diabetic pregnancies and controls regarding DV waves except for end-diastolic velocity (a-wave). Despite the lack of reported DV waves among the majority of researches related to diabetic pregnancies, these findings reflect the known fetal cardiac effects of decreased myocardial diastolic function caused by maternal diabetes (Turan et al., 2011).

Avcı et al. (2015) reported non-significant differences between fetuses with intracardiac echogenic focus and controls in the S-wave (p = 0.21) and D-wave (p = 0.07) velocities, and there was statistically significant differences between the groups in the v-descent (p = 0.03) and a-wave (p = 0.04) velocities .In another cross-sectional study, a significant association between the presence of a-wave and heart related

outflow tracts and right heart diseases was found (P = 0.01), no significant association of the S and D waves with other types of heart disease (Herrera et al., 2015).
This change in the velocity of the v-descent and a-wave may be related to decreased end-systolic relaxation and increased atrial contraction. These changes in cardiac function may be related to restriction of AV valve motion owing to microcalcifications in the papillary muscles, leading to delayed atrial passive emptying, augmented atrial contraction, and a-wave depression; and restricted ventricular end-systolic relaxation owing to increased calcium deposition in the myocardium (Avcı et al., 2015).

Regarding DV ratios, we found that there was significant elevation of (S/D) and (S/a) ratios among cases than controls; while there was no significant difference as regard D/a ratio. These ratios allow quantification of waveform abnormalities during all phases of the waveform, therefore providing the possibility to determine if there are different waveform patterns that contribute to an abnormal PIV (Turan et al., 2014). In their study, Avcı et al. (2015) reported no difference between cases and controls as regard any of the studied DV ratios .Regarding DV indices, there was significant elevation of all DV indices among cases than controls including pulsatility index, preload index and peak velocity index for the vien. Stuart et al. (2010) analyzed the PI-DV retrospectively in 142 diabetic patients and compared to previously published DV-PI reference values from a non-diabetic low-risk population. DV-PI was significantly higher in pregnancies complicated by either pre-existing insulin-dependent DM or gestational diabetes when compared with normal reference values.

Wong et al. (2010) prospectively investigated DV-PVIV among pre-gestational diabetic pregnancies. They reported high frequency of abnormal PVIV (30%) among cases. However, they did not exclude cases with other morbidities affecting cardiovascular system as maternal hypertension or IUGR. On the other hand, Turan et al. (2011) demonstrated non-significant differences in UA-PI, DV-PIV and individual velocity ratios (S/v, S/D, S/a, v/D, v/a and D/a) between 63 cases with PGDM and controls during first-trimester screening at 11 to 14 weeks' gestation. Variation in timing of screening may be the corresponding cause . Also, Dahlback et al. (2015) suggested that the changes in the DV blood flow velocities during ventricular systole (S/ ES) were less frequent than alterations in ratios reflecting blood flows during atrial contraction in ventricular diastole (DV-PIV). Evaluation of multiple indices reflect the global cardiac function because semiquantitative DV Doppler indices, such as the PIV, give an incomplete reflection of cardiac function because relative changes in v- and D-wave velocities are not well reflected (Sanapo et al., 2014).

Our results are in consistent with several reports which evaluated cardiac performance in fetuses of diabetic mothers through their examination by fetal echocardiography, fetuses of poorly controlled diabetic mothers demonstrated significant differences in first-trimester diastolic myocardial function compared with non-diabetic controls (Turan et al., 2011). In a more recent study using two- dimensional speckle-tracking echocardiography, unfavorable changes occurred in the fetal myocardium in response to both maternal DM (Kulkarni et al., 2015).

Assessment of the relation between DV Doppler indices and different variables revealed that poor control of diabetes (evidenced by high HbA1c), PGDM and low 5-min Apgar score, but not birth weight. In Turan et al. (2011) study, the decrease in myocardial performance is more marked with increasing HbA1c and appears to be independent of preload and afterload. Also, Stuart et al. (2010) reported a statistically significant correlation between DV-PI SD-scores and mean HbA1c values in DM pregnancies during the last month before the last DV measurement (Pearson rho = 0.31; P = 0.02). In addition, they reported non-significant difference in absolute DV-PI was detected between the PGDM and GDM groups (P = 0.86); while Wong et al. (2010) didn't find any relation between abnormal DV-PVIV with both 5-min Apgar score and birth weight.

Conclusion
Diabetic pregnancies demonstrated significant difference of ductus venosus Doppler parameters compared with non-diabetic controls, possibly indicating a fetal cardiac effect. DV Doppler indices exhibited significant difference more than simple DV waves or ratios. Increased DV Doppler indices were linked to poor glycemic control among diabetic cases. Pre-gestational DM demonstrated significantly higher pulsatility index and preload index than GDM. Elevated DV Doppler indices were significantly associated with low 5-min Apgar score among studied cases. There was significant positive correlation between HbA1c and DV-pulsatility index.

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