DUCTUS VENOSUS FLOW, DIASTOLIC DYSFUNCTION AND MYOCARDIAL HYPERTROPHY IN FETUSES OF DIABETIC MOTHERS

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ABSTRACT

Infants of diabetic mothers have an established risk of developing myocardial hypertrophy even with adequate maternal metabolic control. The pulsatility index of ductus venosus flow may be a useful parameter for assessing the role of myocardial hypertrophy due to maternal diabetes in fetal diastolic ventricular function.

Aim of the work: To test the hypothesis that the pulsatility index of ductus venosus (PIDV) is higher and the mitral & tricuspid early diastolic/atrial systole velocity ratios (E/A ratios) are lower in the fetuses of diabetic mothers (FDM) with myocardial hypertrophy (MH) than in the FDM with no MH and in the control fetuses of non-diabetic mothers (FNDM).

Subjects and methods: Cross-sectional study included fetuses with gestational ages ranging from 20 to 36 weeks, divided into the following 3 groups: 10 FDM with MH (group I), 20 FDM with no MH (group II), and 30 FNDM (group III, control). The Doppler echocardiogram assessed the PIDV through the ratio (systolic velocity – pre-systolic velocity)/mean velocity. The mitral and tricuspid E/A ratios were also assessed.

Results: The mean PIDV in groups I, II, and III were 1.28 ± 0.5, 0.73 ± 0.09, and 0.59±0.09, respectively. Using ANOVA test, the mean pulsatility index was significantly higher in group I than in group II and III (P 0.001). Comparing the pulsatility index of ductus venosus in group II with that in group III, a statistically significant difference (P=0.02) was observed. The mean mitral E/A ratios in groups I, II and III were 0.68 ± 0.04, 0.73 ± 0.06 and 0.68 ± 0.1, respectively. When applying the ANOVA, the mitral E/A ratios were non significant between the three groups (P = 0.17). The mean tricuspid E/A ratios in groups I, II and III were 0.69 ± 0.05, 0.71 ± 0.03 and 0.68 ± 0.07, respectively. When applying the ANOVA, the tricuspid E/A ratios were non significant between the three groups (P = 0.19).

Conclusion: DV PI is significantly greater in FDM with MH than in FDM with no MH and in FNDM. It is a useful parameter than E/A ratios of the mitral and the tricuspid valves for assessing fetal diastolic function.

Key words: Ductus venosus, maternal diabetes; fetal myocardial hypertrophy, diastolic dysfunction.

1. INTRODUCTION

Diabetes in pregnancy is associated with risks to the woman and to the developing fetus **(1, 2)**.

Women with type 1 and type 2 diabetes have an increased risk of adverse pregnancy outcomes, including miscarriage, fetal congenital anomalies and perinatal death **(3)**.

Level I evidence shows that the rate of congenital malformations doubles or triples among diabetic women over the rate in the general population and that the rate is inversely proportional to first-trimester glycemic control **(4-6)**.

The alterations resulting from maternal diabetes are due to fetal hyperinsulinemia associated with an increase in the number of insulin receptors in the heart, leading to hyperplasia and hypertrophy of myocardial cells, because of the increase in protein and fat synthesis **(7-10)**.

Fetal myocardial hypertrophy is the most frequently found abnormality in maternal diabetes mellitus, being observed in up to 35% of those babies **(11-14)**. The ventricular septum seems to be particularly rich in insulin receptors **(15)**, which could explain the more accentuated hypertrophy of that structure.

In addition to myocardial hypertrophy in fetuses of diabetic mothers, an alteration in left ventricular filling occurs between the 20th and 36th gestational weeks **(16)**.

Doppler echocardiography is an adequate method for studying diastolic function in a noninvasive manner, using curves that relate time and velocity of ventricular filling **(17, 18)**.

A reduced ventricular compliance in fetuses of diabetic mothers could be secondary to wall thickening or to other factors, such as metabolic alterations in the uterine environment associated with qualitative changes in collagen (an increase in the fluorescent collagen in the myocardium) **(16)**.

Ductus venosus flow plays a fundamental role in fetal hemodynamics, and its analysis has been the object of study in several pathological situations **(19-24)**. Because the pulsatility index of ductus venosus flow reflects its impedance during the cardiac cycle, which is influenced by ventricular filling capacity, it may be a useful parameter for assessing the role of myocardial hypertrophy and of maternal diabetes in fetal diastolic ventricular function.

2. SUBJECTS AND METHODS

This cross-sectional observational study was carried out at Fetal Medicine Unit, Obstetrics & Gynecology department, Faculty of Medicine, Cairo University and Ultrasound unit, Obstetrics &Gynecology department, Faculty of Medicine, Zagazig University between November 2011 and November 2013.

Subject:

The study included three groups:

Group I – 10 fetuses of diabetic mothers with interventricular septal hypertrophy (FDM with MH)

Inclusion criteria:

- Singleton
- Gestational age 20 – 36 weeks
- Diabetics (gestational – pre-gestational)
- Septal hypertrophy > 2 SD for gestational age according to **Allan (25)**

Exclusion criteria:

- Twins
- Other medical disorders

Group II – 20 fetuses of diabetic mothers without septal hypertrophy (FDM without MH);

Inclusion criteria:

- Singleton
- Gestational age 20 – 36 weeks
- Diabetics (gestational – pre-gestational)
- Septal thickness < 2 SD

Exclusion criteria:

- Twins
- Other medical disorders

Group III – 30 fetuses of non-diabetic mothers (control).

Inclusion criteria:

- Singleton
- Gestational age 20 – 36 weeks

Exclusion criteria:

- Twins
- Diabetics (gestational – pre-gestational) or other medical disorders

Methods:

For each patient, the following was done:

(A) Consent

All pregnant women signed a written informed consent.

(B) History

Maternal age, gestational age, gravidity and parity, type of diabetes were obtained.

(C) Investigations

Laboratory:

Screening by 50 g oral glucose challenge test for the control subjects was done (Normal values < 140 mg/dl).

Imaging:

Ultrasound machines: **Voluson** 730 **ProV** GE serial No. A41062 and **Voluson** 730 **ProV** GE serial No. A37004

- Ultrasound assessment: According to ISUOG (International Society of Ultrasound in Obstetrics and Gynecology guideline) **(26)**
  - The fetal anatomy (to rule out malformations)
  - Fetal biometry (femur length, biparietal diameter, head circumference and abdominal circumference)
  - Amniotic fluid index.
- Fetal echocardiography:
  - Gray scale parameters: atrial arrangement (situs), four-chamber view, left ventricular outflow tract view, right ventricular outflow tract view and three vessels view were obtained
  - Cardiac biometry: ventricular septum thickness, free ventricular wall thickness (Right and Left) and C/T cardio-thoracic circumference ratio. Myocardial hypertrophy was characterized by a ventricular septum thickness at the end of diastole greater than 2 standard deviations for gestational age according to **Allan (25)**. The cursor was perpendicularly directed to the ventricular septum in a position distal to the leaflets of the atrioventricular valves.
  - Doppler sonography: The ductus venosus was identified by using a transversal view of the fetal abdomen at the level of the insertion of the umbilical cord or a longitudinal view (Color Doppler). The pulsatility index was used in the analysis of the ductus venosus, and its result was considered abnormal when values greater than the 95th percentile of the curve of normality for the corresponding gestational age according to **Kessler J et el (27)**.
  - Atrio-ventricular flows were analyzed by pulsed Doppler. The curves corresponding to the flow through the atrioventricular valves were obtained based on a 4-chamber view. The sample volume was placed immediately distal to the valvular leaflets, inside the ventricles. The variables measured were the early diastole (E wave) peak, atrial systole (A wave) peak in m/s and early diastolic/atrial systole velocity ratios (E/A ratios) corresponding to the mitral and tricuspid flows.

3. RESULTS:

Of the 60 fetuses studied, between the 20th and 34th gestational week, 30 were diabetic and 30 non-diabetic. Of the diabetic women, 12 (40%) had previous diabetes mellitus and 18 (60%) had gestational diabetes.

The patients were divided into 3 groups: group I, comprising 10 (16.7%) fetuses of diabetic mothers with septal hypertrophy; group II, comprising 20 (33.3%) fetuses of diabetic mothers without septal hypertrophy; and group III, comprising 30 (50%) healthy fetuses of non-diabetic mothers.

Maternal age, gravidity, number of previous abortions and gestational age showed no significant difference between three groups.

Fetal biometry: femur length in group I was significantly higher than group II an III (P=0.006), no difference in biparietal diameter between three groups (P=0.07), head circumference was significantly higher in group I than group II and III (P=0.014), abdominal circumference was significantly higher in group I than group II and III (P=0.002), AFI significantly higher in group I than group II and III (P=0.001).

The pulsatility index of ductus venosus in the group of fetuses of diabetic mothers with septal hypertrophy (group I) ranged from 0.9 to 2.64 (mean = 1.28 ± 0.5) **Fig 1**. The pulsatility index of ductus venosus in group II ranged from 0.59 to 0.83 (mean = 0.73 ± 0.09). The pulsatility index of ductus venosus in the control group ranged from 0.45 to 0.88 (mean = 0.59 ± 0.09).

When applying the ANOVA, the mean pulsatility index was significantly higher in group I than in group II and III (P=0.001). Comparing the pulsatility index of ductus venosus in group II with that in group III, a statistically significant difference (P=0.02) was observed **Fig 2**.

The mitral E wave peak velocity mean in group I, II and III (38.9, 34.6 and 31.4). The mitral E wave peak velocity was significantly higher in group I than in groups II and III (P=0.001).

The mitral E/A ratio in group I range from 0.62-0.75 (mean 0.68 ± 0.04). The mitral E/A ratio in group II range from 0.61-0.84 (mean 0.73 ± 0.06). The mitral E/A ratio in group III range from 0.43-0.82 (mean 0.68 ± 0.1) **Fig 3**. When applying the ANOVA, the mitral E/A ratios were non significant between the three groups (P = 0.17).

The tricuspid E wave peak velocity mean in group I, II and III (45.3, 37.1 and 34.7). The tricuspid E wave peak velocity was significantly higher in group I than in group II and III (P=0.001).

The tricuspid E/A ratio in group I range from 0.62-0.76 (mean 0.69 ± 0.05). The tricuspid E/A ratio in group II range from 0.65-0.76 (mean 0.71 ± 0.03). The tricuspid E/A ratio in group III range from 0.49-0.78 (mean 0.68 ± 0.01). When applying the ANOVA, the tricuspid E/A ratios were non significant between the three groups (P = 0.19).

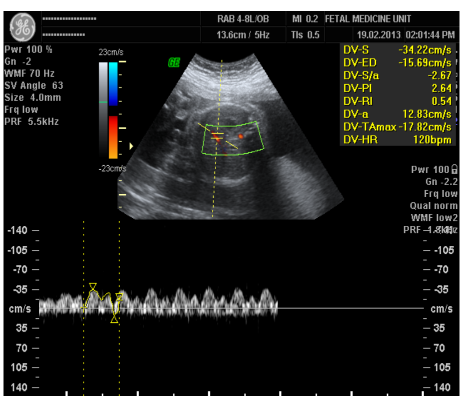

Figure (1): Ductus venosus PI in diabetic patient with myocardial hypertrophy

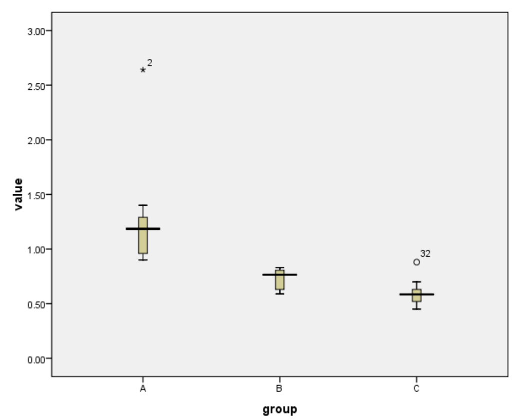

Figure (2): Ductus venosus PI

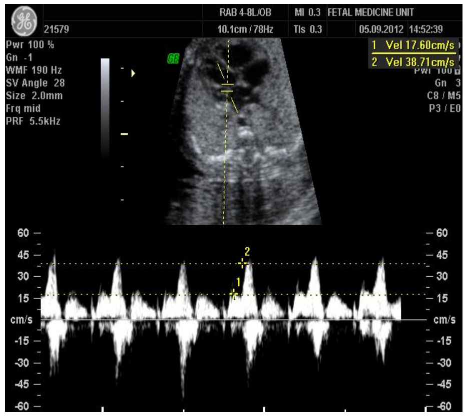

Figure (3): Mitral valve E/A ratio (normal pregnant lady)

4. DISCUSSION

This study assessed the diastolic function in fetuses of diabetic mothers with and without myocardial hypertrophy and compares it with that in healthy fetuses of non-diabetic mothers by studying the behavior of the ductus venosus blood flow and mitral and tricuspid valves blood flow.

Fetuses of diabetic mothers with septal hypertrophy (Group I) showed a significantly higher pulsatility index of the ductus venosus than fetuses of diabetic mothers without septal hypertrophy (Group II) and control fetuses (Group III).

This behavior may be attributed to changes in diastolic ventricular function in fetuses with myocardial hypertrophy, because the pulsatility index of the ductus venosus flow represents the impedance of blood flow during the cardiac cycle, which is influenced by ventricular filling capacity.

Fetuses of diabetic mothers without septal hypertrophy showed higher DVPI than fetuses of non diabetic mothers suggests that other factors such as metabolic alterations in the uterine environment associated with qualitative changes in collagen in addition to myocardial hypertrophy interfere with fetal diastolic function in maternal diabetes.

Zielinsky et al (28) found similar results that PIDV is significantly greater in FDM with MH than in FDM with no MH and in FNDM.

Wong et al (29) show similar results but by using different index and stated that the sensitivity of DV-PVIV (Ductus venosus peak velocity index for veins) in predicting adverse perinatal outcomes in pregestational diabetic pregnancies was 53.3%, the specificity was 74.6%, the positive predictive value was 32.0% and the negative predictive value was 87.7%.

Stuart et al found similar results and stated that DV PI was significantly higher in pregnancies complicated by either pre-existing insulin-dependant (DM) or gestational diabetes when compared with normal reference values **(30)**.

Doppler echocardiography is an adequate method for studying diastolic function in a non-invasive manner, using curves that relate time and velocity of ventricular filling **(17, 18)**.

Measurement of mitral and tricuspid flow velocities allows assessment of the volume of ventricular inflow during diastole, which in turn, depends on the atrio-ventricular pressure gradient. Although this measurement does not allow a direct determination of diastolic function, it allows inferring information on ventricular relaxation and compliance **(31)**. From the 10th gestational week onwards, E and A waves may be identified (**32)**. The profile of diastolic filling through the atrio-ventricular valves shows a higher diastolic velocity in the atrial contraction phase (A wave) than in the beginning of diastole (E wave) (**33, 34)**. The E/A ratio is < 1 during the entire fetal life.

This study showed that the mitral and tricuspid E/A ratios were non significant between the three groups.

Tsyvian et al, in a study including fetuses of insulin-dependent diabetic mothers, showed a reduction in diastolic function, using the E/A ratio (**16)**.

According to **Tsyvian et al**, in addition to myocardial hypertrophy in fetuses of diabetic mothers, an alteration in left ventricular filling occurs between the 20th and 36th gestational weeks **(16)**.

E is smaller than A and the E/A ratio increases during pregnancy toward 1, to be inversed after birth **(35)**.

Balli et al (36) stated that the increase in mitral E/A and tricuspid E/A ratios were lower in fetuses of gestational diabetic mothers with advancing gestation.

Our results differ from those of **Balli et al (36)** probably because their study included cases at more advanced gestational age than this study, which made the statistical significance. Probably because functional changes become evident late in gestations influenced by diabetes

Weiner et al (37) reported that the E/A ratio of the mitral and tricuspid valves did not increase in fetuses of diabetic women during the third trimester and was significantly higher in fetuses of non diabetic women compared with fetuses of diabetic women at 34 and 38 week' gestation.

Rizzo et al (38) reported lower ratios of E/A in fetuses of pre-gestational diabetic pregnant women between 16 and 20 weeks compared with those of healthy mothers.

Our results differ from those of **Rizzo et al (38)** probably because this study comprised pregnant women at more advanced gestational ages. In addition, in the study by **Rizzo et al (38)**, fetuses of diabetic mothers were not divided into 2 groups (with and without hypertrophy), as in this study.

These findings may merely reflect the early phase in which these fetuses were examined, or suggest that the analysis of the atrio-ventricular flows may not be sensitive enough to assess diastolic function.

While **Chen et al (39)** found similar results to this study that E/A ratios did not differ significantly among the DM1, DM2 and control group ($P = > 0.05$).

Wong et al (40) reported similar values of E/A ratio of the mitral and tricuspid valves in control group fetuses versus fetuses of mothers with impaired glucose tolerance.

Russell et al (41) found that there was no difference in E/A ratio between the cohorts (pregestational diabetics and healthy control subjects) in the second or third trimester.

However, the results observed in the analysis of the ductus venosus flow suggest that ventricular compliance is impaired as a consequence of myocardial hypertrophy, indicating that the assessment of the ductus venosus may be more sensitive than the analysis of atrio-ventricular flows for detecting a decrease in ventricular compliance.

5. CONCLUSION

In conclusion, fetuses of diabetic mothers with myocardial hypertrophy have impairment in ductus venosus flow with an increase in the pulsatility index of that flow as compared with fetuses of diabetic mothers with normal myocardial thickness and normal fetuses of non-diabetic mothers. It can be used for prediction of diastolic dysfunction in fetuses of diabetic mothers.

E/A ratios of the mitral and the tricuspid valves cannot be used to assess diastolic function.

6. RECOMMENDATIONS

Further larger study to assess the diastolic dysfunction in fetuses in diabetic mothers at different gestational age sub-groups to be performed.

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