Impact of Maternal Diabetes Mellitus on Fetal Echocardiographic Parameters

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Abstract: Objectives: The present study aimed to evaluate the impedance to the ductus venosus (DV) flow and the pulmonary vein pulsatility index (PVPI) in fetuses of diabetic mothers with and without myocardial hypertrophy (MH) in comparison to control fetuses of non-diabetic mothers. Patients & Methods: The study included 100 pregnant women; 50 diabetics and 50 non-diabetics of the same gestational age. Prior to cardiological evaluation, the fetal anatomy was analyzed using ultrasound assessment to rule out malformations and fetal biometry. Fetal echocardiographic examinations were conducted for assessment of ventricular septum thickness (VST), ductus venosus pulsatility index (DVPI), mitral and tricuspid atrioventricular flows and pulmonary vein flow studies were also conducted. Results: Mean VST was significantly increased in fetuses of diabetic mother (FDM) compared to its thickness in non-diabetic group and 19 fetuses had VS hypertrophy (VSH) with significantly thicker VS compared to FDM free of VSH. FDM showed significant increase of DVPI compared to fetuses of non-diabetic mothers (FNDM) with significantly higher index in those had VSH. Mean mitral and tricuspid E wave peak flow was significantly higher in FDM compared to FNDM. Pulmonary vein pre-systolic flow showed a significant decrease and PVPI was significantly higher in FDB compared to FNDM. Conclusion: Maternal hyperglycemia induces ventricular hypertrophy that increases impedance to blood flow through cardiac chambers manifested as increased ductus venosus and pulmonary vein pulsatility indices. [Mohamed A. El-Nory **Impact of Maternal Diabetes Mellitus on Fetal Echocardiographic Parameters** Journal of American Science 2011; 7(10): 517-522].(ISSN: 1545-1003). http://www.americanscience.org.

Keywords: Pregnancy, Diabetes mellitus, Fetal echocardiography, ductus venosus flow

1. Introduction

The fetal circulation has four major communications between the systemic and pulmonary pathway: the foramen ovale, the ductus arteriosus, the ductus venosus, and the placenta. The saturated blood from the umbilical vein reaches the heart through a triphasic high velocity flow in the ductus venosus, which goes directly to the left heart across the oval fossa, stretching the septum primum towards the left atrial cavity in late diastole. The low volume flow from the pulmonary veins to the left atrium occurs throughout the cardiac cycle, with a systolic peak, a diastolic peak, and presystolic flow during atrial contraction (**Sivan *et al.*, 2004**).

Ventricular diastole is a very complex phenomenon whose main components are relaxation, compliance, myocardial rigidity, and elastic recoil. Relaxation is an active process occurring with energy consumption in the early ventricular filling, when the myocardial fibers return to their original state after ventricular contraction. Compliance is a passive process occurring during late ventricular filling and atrial contraction, and is related to fiber distensibility. Myocardial rigidity is the contrary of ventricular compliance and elastic recoil is a continuing decrease in ventricular pressure in early diastole (**Zielinsky *et al.*, 2004**).

Maternal hyperglycemia is responsible for many fetal adverse outcomes with an increased risk of a hypertrophic cardiomyopathy and congenital heart defects among newborns of diabetic mothers (**Nizard and Ville, 2009**).

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 (**Menezes *et al.*, 2001**). The ventricular septum seems to be particularly rich in insulin receptors (**Thorson and Hintz, 1977**) which could explain the more accentuated hypertrophy of that structure (**Rizzo *et al.*, 1988**). Alterations in left ventricular filling, depending or not on myocardial hypertrophy, have been reported between the 20th and 36th gestational weeks (**Tsyvian *et al.*, 1998**).

Fetal Doppler echocardiography has increased the knowledge about the cardio-circulatory changes in the prenatal period. Significant changes in the cardiovascular flow of fetuses from diabetic mothers, especially in pregnancies with inadequate glycemic control were reported. Congenital heart defects vary in appearance at different stages of pregnancy and may evolve in utero with advancing gestational age and early fetal echocardiography is feasible and allows the detection of most congenital heart defects. Therefore, early fetal echocardiography should always be followed by echocardiography at mid gestation (**Mitkowska-Wozniak & Brazert, 2005**).

The present study aimed to evaluate the impedance to the ductus venosus flow and the pulmonary vein pulsatility index in fetuses of

diabetic mothers with and without myocardial hypertrophy in comparison to control fetuses of non-diabetic mothers.

2. Patients and Methods

This prospective comparative study was conducted at Obstetrics & Gynecology Department in conjunction with Radiodiagnosis department, Benha University Hospital through a period of 18 months and comprised 50 fetuses of diabetic mothers and 50 control fetuses of non-diabetic mothers. Prior to cardiological evaluation, the fetal anatomy was analyzed using ultrasound assessment to rule out malformations and fetal biometry was used to define gestational age (**Sabbagha and Hughey, 1978**).

Fetal echocardiographic examinations were performed using an Acuson ASPEN echocardiography system with a convex transducer 4 to 7MHz or a 2.25 to 4MHz *phased array* transducer, with the capacity to perform bidimensional imaging, M-mode, continuous Doppler and color mapping. Fetal echocardiographic examinations were comprehensive, following the segmental sequential approach, starting in the maternal umbilical region and searching as anatomical referential the dorsal spine, the liver, and the fetal *septum primum.* Determination of the atrial *situs*, the position of the heart in the thorax, the type and mode of atrioventricular and ventriculo-arterial connections, the aortic arch, and any associated defects was then performed.

At fetal Doppler echocardiography and color-flow mapping, the following data are collected:

1. Myocardial hypertrophy characterized by a ventricular septum thickness at the end of diastole greater than 2 standard deviations according to gestational age, using a previously described technique and as a reference the nomogram proposed by **Allan *et al.* (2000)**. The cursor was perpendicularly directed to the ventricular septum in a position distal to the leaflets of the atrioventricular valves, with 2-dimensional imaging in 4-chamber view.
2. The ductus venosus was identified by using a transversal view of the fetal abdomen at the level of the insertion of the umbilical cord. The pulsatility index for veins 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 were found based on the local nomogram (**Bahlmann *et al.*, 2000**). The venous pulsatility index, electronically calculated by the equipment after manual tracing of the velocities of the curve of the ductus venosus (DVPI), was obtained with the following ratio: (maximum systolic velocity minus the presystolic velocity) divided by the mean velocity between the systolic, diastolic, and presystolic velocities (**Hecher *et al.*,2003**).
3. Atrioventricular flows were analyzed by pulsed Doppler; 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. For obtaining the maximum velocities, only the fetuses in which the ultrasound beam could be aligned with the blood flow in parallel or at an angle lower than 20° were included in the study. The variables measured were the A wave peak and E wave peak in m/s corresponding to the mitral and tricuspid flows. The E/A ratio was calculated for each beat.
4. The pulmonary vein flow has systolic, diastolic, and presystolic phases; pulmonary vein pulsatility index was obtained by placing the pulsed Doppler sample volume over the right superior pulmonary vein, as near as possible to its junction with the left atrium, applying the formula (systolic velocity - presystolic velocity)/mean velocity. To obtain adequate flow velocity curves, 0-2m/s scales and 50 to 100MHZ filters were used. The measures performed in fetal apnea and those corresponding to the average of 3 assessments were considered (**Hong and Choi, 1999**).
5. Moreover, Doppler ultrasound studies, including RI, S/S ratio and PI for the uterine, umbilical arteries, fetal middle cerebral artery and aorta were done, to examine whether the compromised fetus of a diabetic pregnancy demonstrates features of circulatory redistribution.

3. Results

The current study included 100 pregnant women; 50 diabetics and 50 non-diabetics (Control group) with a mean gestational age at time of inclusion in the study was of 30.6±1.4 and 30.4±1.3 weeks, respectively. There was non-significant difference between both study groups as regards the gestational age. Impedance to flow in the uterine and umbilical arteries and the PI or mean velocity in the middle cerebral artery or descending thoracic aorta were not significantly different among studied groups.

Mean VST was 6.57±1.41; range: 3.87-8.76 mm in control group but 9.58±3.46; range: 4.95-18.72 mm in diabetics. VST was significantly ($Z=4.759$, $p<0.001$) increased in fetuses of diabetic mother compared to its thickness in non-diabetic group, (Fig. 1).

Considering a cutoff point for VST at mean±2SD of the thickness in non-diabetic fetuses (=0.941 mm), there were 19 fetuses with VSH with mean VST=13.04±3.23; range 9.43-18.72 mm and 31 fetuses free of VSH with mean VST=7.46±1.08; range: 4.95-8.79 mm with a significantly (3.823,

p<0.001) increased VST in fetuses with VSH compared to those free of VSH, but with a non-significant (Z=1.514, p>0.05) increase of VST in fetuses without VSH compared fetuses of non-diabetic group (Fig. 2).

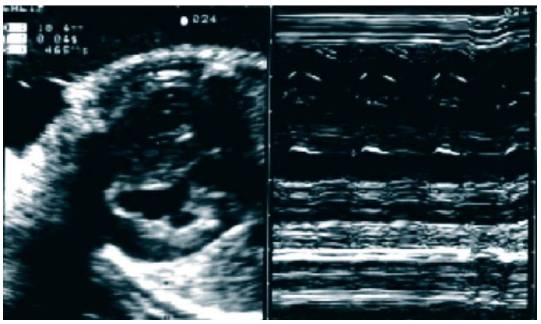

Fig. (1): Real-time and M-mode tracing of a fetus of an insulin-dependent diabetic mother at 36 weeks of gestation showing increased inter-ventricular wall septal thickness is; 10 mm, compared to the expected mean of 5 mm for this gestation age.

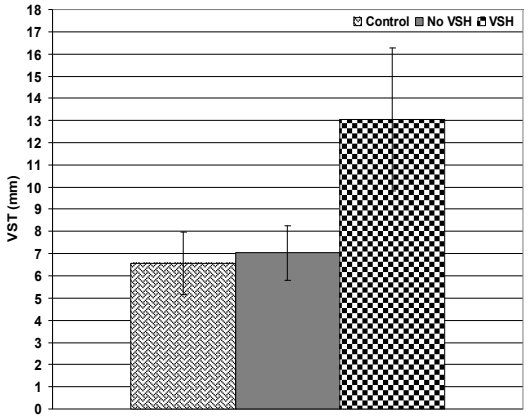

Fig. (2): Mean (±SD) VST estimated in fetuses of diabetic mothers categorized according to proposed cutoff point and compared to control VST

Mean DVPI in non-diabetic group was 0.313±0.034; range: 0.265-0.394, while was 0.355±0.053; range: 0.247-0.471 in diabetic group with a significant (Z=4.123, p<0.001) increase of DVPI in diabetic versus non-diabetic groups. Moreover, among fetuses of diabetic mothers, there was a significant (Z=3.1, p=0.002) increase of DVPI in fetuses with VSH (0.392±0.044; range: 0.321-0.471) compared to those free of VSH (0.331±0.044; range: 0.247-0.416) with a non-significant (Z=0.665, p>0.05) increase of DVPI in fetuses without VSH compared to that recorded in fetuses of non-diabetic group (Fig. 3).

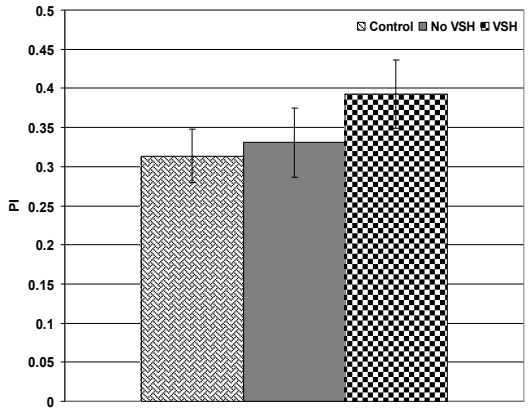

Fig. (3): Mean (±SD) DVPI estimated in fetuses of diabetic mothers categorized according to proposed cutoff point and compared to control VST

Mean mitral E wave peak flow estimated in fetuses of diabetic mothers (0.365±0.055; range: 0.276-0.493) was significantly (Z=3.497, p<0.001) higher compared to flow estimated in fetuses of control mothers (0.326±0.043; range: 0.23-0.405). Moreover, mean mitral E wave peak flow in fetuses with VSH (0.410±0.038; 0.34-0.493) was significantly higher compared both to control group (Z=3.824, p<0.001) and to fetuses free of VSH of diabetic mothers, (Z=3.702, p<0.001). However, fetuses of diabetic mothers and free of VSH (0.335±0.043; range: 0.276-0.416) showed non-significantly (Z=0.805, p>0.05) higher mean mitral E wave peak flow compared to those of non-diabetic mothers (Fig. 4).

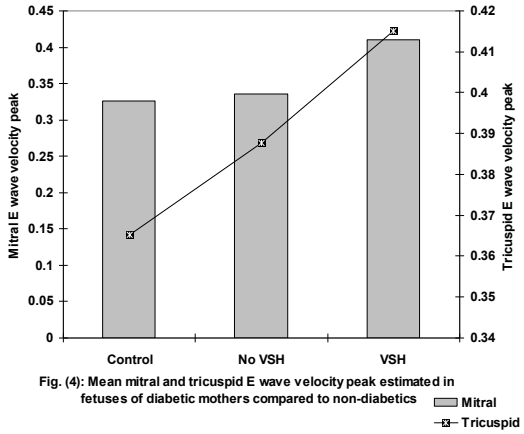

Fig. (4): Mean mitral and tricuspid E wave velocity peak estimated in fetuses of diabetic mothers compared to non-diabetics

Mean tricuspid E wave peak flow estimated in fetuses of diabetic mothers (0.398±0.053; range: 0.309-0.514) was significantly (Z=3.109, p=0.002) higher compared to flow estimated in fetuses of controls (0.365±0.055; range: 0.287-0.450). Moreover, mean tricuspid E wave peak flow in fetuses with VSH (0.415±0.049; 0.342-0.514) was significantly higher compared both to control group (Z=3.662, p<0.001) and to fetuses free of VSH of diabetic mothers, (Z=3.340, p=0.001). Similarly, fetuses of diabetic mothers and free of VSH (0.388±0.054; range: 0.309-0.492) showed

significantly (Z=2.717, p=0.007) higher mean tricuspid E wave peak flow compared to those of non-diabetic mothers (Figs. 4, 5).

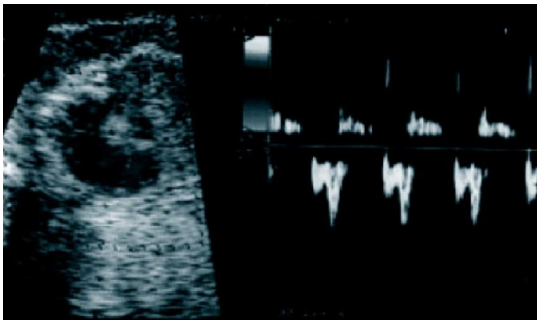

Fig. (5): Flow velocity waveforms across the tricuspid valve in a fetus of an insulin-dependent diabetic mother at 32 weeks of gestation. The E/A ratio is decreased (0.48 compared to expected mean of 0.77 for this gestational age).

Pulmonary vein flow studies showed a non-significant (p>0.05) difference between both groups as regards the systolic and diastolic flow, but the pre-systolic flow showed a significant (Z=6.154, p<0.001) decrease in diabetic group compared to that reported in control group. Pulmonary vein pulsatility index (PVPI) was significantly (Z=4.165, p<0.001) higher in diabetic compared to controls, (Table 1, Figs. 6 & 7).

Table (1): Mean pulmonary venous flow data

Group Phase	Control	Diabetic
Mean flow during systolic phase	0.233±0.062	0.254±0.056
Mean flow during diastolic phase	0.217±0.018	0.205±0.025
Mean flow during pre-systolic phase	0.099±0.015	-0.101±0.205*
PVPI	0.817±0.051	1.585±0.242*

*: significant versus control

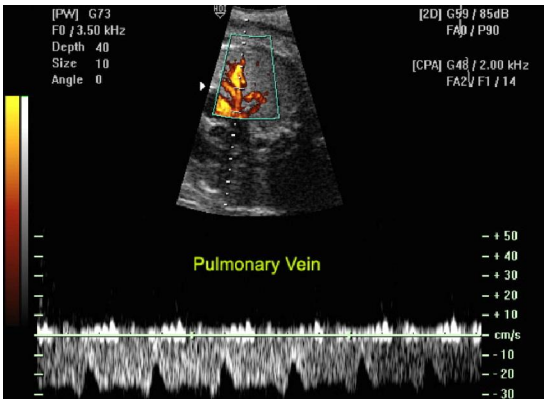

Fig. (6): Doppler echocardiogram a curve of DV and the obtainment of the pulse index of a fetus of controls

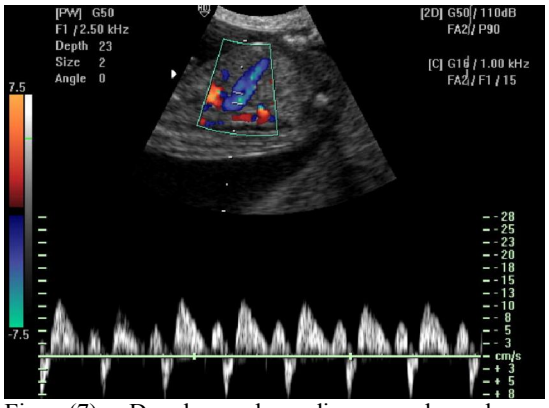

Fig. (7): Doppler echocardiogram showed a presystolic reverse DV flow in a fetus of diabetic mother.

4. Discussion

Ventricular septal hypertrophy was detected in the current study in 19 of 50 fetuses of diabetic mothers (38%) with significantly increased VST compared both to fetuses of non-diabetic mothers and to the other fetuses of diabetic mothers, this finding illustrates the effect of exposure to maternal hyperglycemia on fetal myocardium and points to individual variation in the fetal response to maternal hyperglycemia. These findings go in hand with **Ullmo *et al.* (2004)** who retrospectively reported that pregnancies of both type-1 and type-2 diabetes carry an increased risk for fetal development of pathologic ventricular hypertrophy compared with those with gestational diabetes. Also, **Russell *et al.* (2008)** and **Zielinsky *et al.* (2009)** reported significantly thicker fetal interventricular septum and the right ventricular free wall in the diabetic cohort in the third trimester.

The reported VSH could be considered as a part of fetal macrosomia associated with maternal diabetes. Multiple studies tried to explore the underlying pathogenesis for VSH in fetuses of diabetic mother and attributed this to the increased production of variant growth factors; **Roberts *et al.* (2002)** experimentally reported that systemic level of insulin growth factor-I (IGF-I) and the modulation of its bioavailability by IGF binding proteins-1 and -3 within the mother may influence placental growth and differentiation in an endocrine fashion; **Lassus *et al.* (2003)** found a developmental increase in concentrations of vascular endothelial growth factor (VEGF) and angiogenin during the last trimester of gestation in umbilical cord plasma and that the umbilical cord VEGF level was lower in term fetuses born to diabetic mothers than in those born to healthy mothers and may be associated with an aberrant fetal vascular development in diabetic pregnancies. Moreover, **Loukovaara *et al.* (2004)** found the concentrations of epidermal growth factor are higher than normal in fetuses of diabetic mothers at

term and that the rise in epidermal growth factor levels is a metabolic response of the fetoplacental unit to diabetes-related hyperglycemia. **Koklu *et al.* (2007)** found serum leptin and IGF-I concentrations in macrosomic neonates of diabetic mothers compared to macrosomic neonates of non-diabetic mothers and serum IGF-I, IGFBP-3 and leptin levels of the infants were positively correlated with mean and weight-adjusted aortic intima-media thickness measurements

Mitral and tricuspid wave peak flow were significantly higher in diabetic group compared to non-diabetic group with a significant increase in fetuses had VSH compared both to non-diabetic group and to those without VSH. These findings agreed with **Hat *et al.* (2008)** reported significantly higher mean myocardial velocities of the E 'and A' waves at the mural mitral annulus, in fetuses of diabetic mothers with and without myocardial hypertrophy compared to control group with statistically significant differences were in E' and A' diastolic waves at the aortic mitral annulus, as well as for the tricuspid annulus when tissue Doppler assessment was carried out in the same sample and concluded that pulsed tissue Doppler, when used in fetuses of diabetic mothers and compared with fetuses of non-diabetic mothers, shows evidence of impaired diastolic function, independently of the presence of myocardial hypertrophy

Pulmonary vein flow studies showed a significant decrease of the pre-systolic flow in diabetic group compared to non-diabetic group with a significantly increased PVPI diabetic group. This alteration is due to the involvement of fetal diastolic function secondary to maternal diabetes, with left ventricular hypertrophy, and an increase in muscle mass and a consequent decrease in ventricular compliance. The increase in left atrial pressure leads to a restriction of pulmonary venous emptying, resulting in a decrease in presystolic velocity in pulmonary vein or reverse flow in presystole. The marker of this retrograde transmission of pressure would be the increase in pulmonary vein pulsatility index, because this index reflects the correlation between systolic and presystolic velocities, and the mean pulmonary venous flow velocity. These data were in line previously reported in literature; **Zielinsky *et al.* (2004)** reported significantly greater DVPI in fetuses of diabetic mothers with myocardial hypertrophy than in fetuses of diabetic mothers without myocardial hypertrophy and concluded that because DVPI represent modifications in ventricular compliance, this index may be a more sensitive parameter for assessing fetal diastolic function. **Kozák-Bárány et al. *et al.* (2004)** found that in the infants of mothers with well-controlled pregestational or gestational diabetes, prolonged deceleration time of early left ventricular diastolic filling, probably reflecting an impaired left ventricular relaxation rather than compliance and attributed this to maternal hyperglycemia during the third trimester and subsequent fetal hyperinsulinaemia leading to neonatal cardiac hypertrophy. **Wong *et al.* (2007)** found fetuses of women with mild gestational impaired glucose tolerance lack the ventricular hypertrophy and diastolic dysfunction that is common in fetuses of diabetic mothers, and they have a decreased myocardial performance index late in gestation.

The current study reported normal Doppler indices for the uterine, umbilical arteries, the fetal middle cerebral artery and aorta; these findings are in agreement with **Tan *et al.* (2005)** who found diabetic pregnancy is not associated with a significantly higher incidence of abnormal umbilical artery resistance index on Doppler study than non-diabetic pregnancy and is not a useful single indicator by which to predict subsequent fetal outcome or the development of neonatal septal hypertrophic cardiomyopathy in diabetic pregnancies and with **Akcakus *et al.* (2007)** who reported that macrosomic neonates of diabetic mothers have significant aortic intima-media thickness and left ventricular mass indexed for body surface area and birth weight with lipid alterations and this might play a role in the pathogenesis of atherosclerosis in adult life.

It could be concluded that maternal hyperglycemia induces ventricular hypertrophy that increases impedance to blood flow through cardiac chambers manifested as increased ductus venosus and pulmonary vein pulsatility indices.

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