In recent years, improvement in the management of diabetic pregnant women has been observed, with a reduction in maternal-fetal morbidity and mortality 1,2. Nevertheless, currently, up to 25% of the newborn babies of diabetic mothers have neonatal complications 2.

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 hyper trophy of myocardial cells, because of the increase in protein and fat synthesis 3-6.

Fetal myocardial hypertrophy is the most frequently found abnormality in maternal diabetes mellitus, being observed in up to 35% of those babies 7-10 (fig. 1).

The ventricular septum seems to be particularly rich in insulin receptors 11, which could explain the more accentuated hypertrophy of that structure.

Alterations in left ventricular filling, depending or not on myocardial hypertrophy, have been reported between the 20th and 36th gestational weeks 12. The studies aimed to assess fetal diastolic function have used analysis of the E/A ratio of mitral and tricuspid flows 12,13.

Ductus venosus flow plays a fundamental role in fetal hemodynamics, and its analysis has been the object of study in several pathological situations 14-19.

Because the flow of highly saturated blood to the foramen ovale depends directly on the velocity of ductus venosus flow 20, it is rational to study that velocity in different phases of the cardiac cycle in fetuses of diabetic mothers with and without myocardial hypertrophy, and to compare it with that of control fetuses of nondiabetic mothers.

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whose gestational ages ranged from 20 weeks to term was carried out from October 2001 to December 2002. The sample was divided into the following 3 groups: group I – 20 fetuses of diabetic mothers with septal hypertrophy (FDM with MH); group II – 36 fetuses of diabetic mothers without septal hypertrophy (FDM without MH); group III – 53 control fetuses of nondiabetic mothers.

In the ultrasound assessment prior to cardiological evaluation, the fetal anatomy was analyzed to rule out malformations, as was fetal biometry to define gestational age. In fetal echocardiographic examinations were performed in a sequential and segmentary manner. Cardiac and vascular structures were studied in 4-chamber, longitudinal, transverse, and sagittal views.

At fetal Doppler echocardiography and color-flow mapping, special attention was given to the characteristics of the ductus venosus flow, as well as to the presence of myocardial hypertrophy and to mitral and tricuspid valve flows.

Myocardial hypertrophy was 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. 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.

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. Special attention was given to cases in which the ductus venosus was extremely altered with reverse flow during atrial contraction, because the placement of the sample volume in the intra-abdominal umbilical vein could simulate an abnormal ductus venosus. The venous pulsatility index (VPI), electronically calculated by the equipment after manual tracing of the velocities of the curve of the ductus venosus, was obtained with the following ratio: (maximum systolic velocity minus the presystolic velocity) divided by the mean velocity between the systolic, diastolic, and pre-systolic velocities (fig.2).

For comparison with the assessment of the ductus venosus flow, atrioventricular 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. For obtaining the maximum velocities, only the fetuses in whom 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.

An echocardiographic device capable of 2-dimensional imaging, M mode, pulsed and continuous Doppler, and color mapping equipped with phased array and convex transducers from 2.0 to 7.0 MHZ was used in the study.

The studies were recorded for documentation and review. All pregnant women signed a written informed consent. The research was assessed and approved by the Committee on Ethics in Medical Research of the Instituto de Cardiologia of the Rio Grande do Sul/ Fundação Universitária de Cardiologia.

The quantitative data were reported as mean and standard deviation. The analysis of variance (ANOVA) was used for comparing the ductus venosus pulsatility index and the mitral and tricuspid flows in the 3 groups. The Tukey test was used for analysis of multiple comparisons. The ventricular septum was analyzed by using the Student t test for comparison between groups I and II. The gestational age was controlled by analysis of covariance. The discriminating statistical significance level adopted was 0.05. Data were analyzed using the SPSS statistical program, version 11.0.

Results

Of the 118 fetuses studied, 9 were excluded (3 due to an inadequate acoustic window, 2 due to maternal hypertension, 1 due to omphalocele, and 2 due to fetal structural heart disease), which left 109 pregnancies between the 20th gestational week and term, of which 56 were diabetic and 53 nondiabetic. Of the diabetic women, 8 (7.3%) had previous diabetes mellitus and 48 (44%) had gestational diabetes.

The patients were divided into 3 groups: group I, comprising
20 (18.3%) fetuses of diabetic mothers with septal hypertrophy; group II, comprising 36 (33%) fetuses of diabetic mothers without septal hypertrophy; and group III, comprising 53 (48.6%) healthy fetuses of nondiabetic mothers. Maternal age, parity, and gesta-
tional age are shown in table I. No difference in glycemic levels was observed between groups I and II.

The means and medians of the glycemas and of the septal thicknesses are shown in table II. When applying the Student t test, the ventricular septum was significantly thicker in group I than in group II (P < 0.001).

The pulsatility index of ductus venosus in the group of fetuses of diabetic mothers with septal hypertrophy (group I) ranged from 0.29 to 2.56 (mean = 1.13 ± 0.64; median = 1.01). The pulsatility index of ductus venosus in group II ranged from 0.25 to 1.82 (mean = 0.83 ± 0.38; median = 0.73). The pulsatility index of ductus venosus in the control group ranged from 0.35 to 0.9 (mean = 0.61 ± 0.17; median = 0.6) (fig. 3 and 4).

When applying the Tukey test and ANOVA, the mean and median pulsatility index were significantly higher in group I than in group II (P=0.015) and group III (P < 0.001). Comparing the pulsatility index of ductus venosus in group II with that in group III, a statistically significant difference (P=0.017) was observed. The significant difference between the groups was maintained even when controlling the gestational age with the covariance test.

Table III shows the values of the E and A waves of the mitral and tricuspid flows.

The mitral E wave peak flow was significantly higher (P=0.024) in group I than in groups II and III (P=0.023) (fig. 5).

The tricuspid E wave peak flow was significantly higher in group I than in group III (P=0.031) (fig. 6); no difference was found between groups I and II (P=0.68).

**Discussion**

Infants of diabetic mothers have an established risk of developing myocardial hypertrophy even with adequate maternal metabolic control 26,27. The manifestation of myocardial hypertrophy in the newborn ranges from the lack of symptoms to severe heart failure due to diastolic dysfunction 28. The severity of the situation is related to the control of diabetes 29. Microscopic alterations of the hypertrophic myocardium of the infants of diabetic mothers include, in addition to hyperplasia and hypertrophy, a disorganization of the normal pattern of the myofibrils, similar to that found in the cardiomyopathy of the adult 30.

Diastole comprises the time period between closure of the semilunar valves and closure of the atrioventricular valves. It is divided into the following 4 phases: isovolumetric relaxation; rapid filling (related to ventricular relaxation); slow filling; and atrial contraction (related to compliance).

Doppler echocardiography is an adequate method for studying diastolic function in a noninvasive manner, using curves that relate time and velocity of ventricular filling 31,32. Measurement of mitral and tricuspid flow velocities allows assessment of the volume of ventricular inflow during diastole, which, in turn, depends on the atrioventricular pressure gradient. Although this measurement does not allow a direct determination of diastolic function, it allows inferring information on ventricular relaxation and compliance 33.

Studies confirming the value of Doppler echocardiography for assessing diastolic function used mainly Doppler recordings of the mitral valve 34. During intrauterine life, systemic and pulmonary circulations act in parallel. Until the present time, assessing diastolic function of the fetal heart implied in the study of mitral and tricuspid flows.

From the 10th gestational week onwards, E and A waves may be identified 34. The profile of diastolic filling through the atrioventricular valves shows a higher diastolic velocity in the atrial contraction phase (A wave) than in the beginning of diastole (E wave) 35,36. The E/A ratio is < 1 during the entire fetal life. According to Tsyvian et al. 34, in addition to myocardial hypertrophy in fetuses of diabetic mothers, an alteration in left ventricular filling occurs between the 20th and 36th gestational weeks. Left ventricular filling depends on myocardial diastole and is modified by several factors. An influence of the deterioration of the active force of afterload and compliance of the ventricular wall is observed. The ratio between early (E) and late (A) ventricular filling at the level of mitral and tricuspid valves (E/A ratio) at echocardiography

<table>
<thead>
<tr>
<th>Table I - Characteristics of the groups studied</th>
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<tbody>
<tr>
<td>Group I</td>
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<td>-----------------</td>
</tr>
<tr>
<td>MA (years)</td>
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<tr>
<td>Number of gestations</td>
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<tr>
<td>Number of previous abortions</td>
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<td>GA (weeks)</td>
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</tbody>
</table>

FDM - fetuses of diabetic mothers; MH - myocardial hypertrophy; MA - maternal age; GA - gestational age. * P < 0.001 for comparisons between groups I and II and III.

<table>
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<tr>
<th>Table II - Means of the ventricular septum (VS) of fetuses of diabetic mothers (FDM) with and without myocardial hypertrophy (MH)</th>
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<tbody>
<tr>
<td>Group I</td>
</tr>
<tr>
<td>-----------------</td>
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<tr>
<td>VS (median)</td>
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</table>

* P < 0.001 in the comparison of group I with groups II and III.
Ductus Venosus Flow and Myocardial Hypertrophy in Fetuses of Diabetic Mothers

is used to establish the contribution of atrial contraction to total transmural flow. As already mentioned, these indices have been the major indirect measurements of diastolic function. Rizzo et al. reported a reduction in diastolic function in fetuses of diabetic mothers expressed by this ratio. 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). The higher E wave velocity in mitral and tricuspid valves in the group of fetuses of diabetic mothers with myocardial hypertrophy found in this study could reflect an altered pattern of relaxation. Tsyvian et al., in a study including fetuses of insulin-dependent diabetic mothers, showed a reduction in diastolic function, using the E/A ratio. Macklon et al., studying the cardiac function of fetuses of diabetic mothers between the 18th and 20th gestational weeks, found no difference comparing to the control group, contrary to results of previous studies reporting a reduction in E/A ratio in the atrioventricular valves and high values of peak velocity in the outflow tracts between the 20th and 36th gestational weeks. These findings may merely reflect the early phase in which these fetuses were examined, indicating that functional changes become

<table>
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<th>Table III - Doppler-echocardiographic parameters of the mitral and tricuspid E wave in the fetuses of diabetic mothers (FDM) with and without myocardial hypertrophy (MH) and healthy fetuses</th>
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<tbody>
<tr>
<td>Doppler-echocardiographic parameters (m/s)</td>
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<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Mitral A wave</td>
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<tr>
<td>Mitral E wave</td>
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<tr>
<td>Tricuspid A wave</td>
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<tr>
<td>Tricuspid E wave</td>
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</tbody>
</table>

* P = 0.024 in the comparison between groups I and II, and P = 0.023 between groups I and III; † P = 0.031 in the comparison between groups I and III.
venosus flows did not disagree. Therefore, we chose to report the

It is worth stressing that the difference found between groups II

Although the pulse index of the ductus venosus did not have a

In conclusion, fetuses of diabetic mothers with myocardial

1. Montenegro JR, Paccala G, Faria C et al. Evolução materno-fetal de gestantes dia-
2. Hod M, Dye TD. Perinatal complications following gestational diabetes mellitus -
4. Zielinski P, Hagemann L. Estudo pré-natal da miocardiopatia hipertrófica e sua asso-
6. Menezes HS, Barra M, Belló A, Martins CB, Zielinski P. Fetal myocardial hypertro-
10. Sardesai M, Gray A, McGrath M. Fatal hypertrophic cardiomyopathy in the fetus of a

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