Pathogenesis of Fetal Hypertrophic Cardiomyopathy in Insulin-Dependent Diabetes Mellitus

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The development of fetuses and their hearts (24th-37th week of pregnancy) in mothers with insulin-dependent diabetes mellitus of various severity was studied by M-echocardiography, dopplerometry, and fetometry. A relationship is demonstrated between the early formation of macrosomia and cardiomyopathy, on the one hand, and the severity of diabetes, on the other. Along with metabolic disorders, hemodynamic disturbances in the mother-placenta-fetus system, which depend on the disease severity, play a role in the pathogenesis of fetal cardiomyopathy.

Key Words: *fetus; diabetes mellitus; fetal cardiomyopathy; utero-placental circulation*

The infants of mothers suffering from insulin-dependent diabetes mellitus (IDDM) often develop hypertrophic cardiomyopathy (HCM) characterized by hypercontractility of the myocardium and by thickening of the ventricular wall and, to a greater extent, of the interventricular septum. Hypertrophic cardiomyopathy is sometimes revealed accidentally during M-echocardiography; otherwise newborns exhibit severe symptoms of cardiac disorder [2,8]. HCM differs from other cardiomyopathies in tnat it spontaneously regresses during the first months of life and in its fairly early manifestation during prenatal development [9]. However, the pathogenesis of diabetic HCM and the times of its development *in utero* remain obscure. The aim of this study was to evaluate the significance of hemodynamic factors in the development of fetal HCM and to determine the time of its onset in fetuses developing in mothers suffering from IDDM of various severity.

MATERIALS AND METHODS

Sixty-seven women (18-34 years, 24th-37th week of pregnancy) were enrolled in the study. Forty-two women had IDDM and 25 were healthy (control). The fetuses of IDDM mothers were retrospectively divided into 3 groups depending on the severity of HCM diagnosed after birth. Group 1 consisted of 14 fetuses without clinical anifestations of HCM after birth, group 2 fetuses (n=17) had moderate HCM, and group 3 fetuses (n=11) had obstructive HCM. All IDDM patients were under the care of endocrinologists, and the disease was appropriately corrected. The mothers of group 3 newborns had developed the most severe IDDM (the disease had started at a younger age and led to a higher frequency and severity of vascular complications).

Final diastolic and systolic sizes of the left ventricle were calculated from the standard M-echocardiogram [13] recorded in an Aloka-SSD-280 apparatus; the period of ejections was determined by the movements of the posterior wall of the left ventricle. Final diastolic and final systolic volumes were calculated as described elsewhere [12]. Stroke volume and stroke and cardiac indexes of the left ventricle were calculated. The index of asymmetry (IA), which is used to characterize HCM in children and adults [3] and to assess heart growth in fetuses [6,10], was used to diagnose HCM. This index was calculated as the ratio between the thickness of the interventricular septum and the thickness of the relaxed wall of the left ventricle. Circulation in the umbili-

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cal and middle cerebral arteries, in the descending aorta, and in the uterine arteries was studied by dopplerometry [4]. The blood flow rate curves were analyzed qualitatively, and the following slope angle-independent parameters were calculated from the standard formula [4]: the systolic-diastolic ratio and the resistance index. These indexes characterize vascular resistance in the bed which is peripheral relative to the blood vessel of interest. All calculations were performed after recording the flow rate curves on thermosensitive paper. Fetal mass was calculated and fetal growth assessed by determining biparietal size, anteroposterior and transverse diameter, and circumference of the stomach with the aid of a built-in computer.

RESULTS

There were no significant differences between M-echocardiographic data in fetuses of groups 1, 2, and 3 and the controls in the early stages of pregnancy (24-27 weeks). However, both in control and IDDM fetuses the thickness of the interventricular septum was greater than that of the relaxed wall of the left ventricle, which is typical of the early stages of ontogenesis. In normally developing fetuses the ratio between these parameters is reported to be >1.3 [6,10]. It constantly decreases during pregnancy and remains at this level only in 10% of full-term infants. As seen from Fig. 1, in control fetuses IA gradually decreased during pregnancy, dropping to 1.1±0.05 in most fetuses by the 33rd-37th week. By contrast, in fetuses of groups 1, 2, and 3 IA significantly increased, the increase being greater in group 3 (severe IDDM). The number of fetuses in which IA was higher than that in normal fetuses of the same age became greater as the severity of IDDM increased.

In IDDM, the acceleration of fetal growth and weight gain (fetometry data) occurred in the 28th week of pregnancy and was more pronounced in groups 1 and 2 than in controls (Fig. 2).

Echocardiographic parameters were altered in group 2 and, to a greater extent, in group 3 fetuses in comparison with the control. In group 3 fetuses, these changes were observed in the 28th-30th week and manifested themselves as a decrease in stroke (0.52±0.03 ml/kg) and cardiac (73.66±2.3 ml/min/kg) indexes compared with the control (0.638±0.04 ml/kg and 84.4±3.12 ml/min/kg, $p<0.05$). During this period a tendency towards a decrease in stroke volume was observed in group 3 fetuses, and by the 33rd-37th week this decrease became statistically significant in comparison with the control (1.7±0.186 ml/min *vs.* 2.113±1.076 ml/min, $p<0.05$). In group

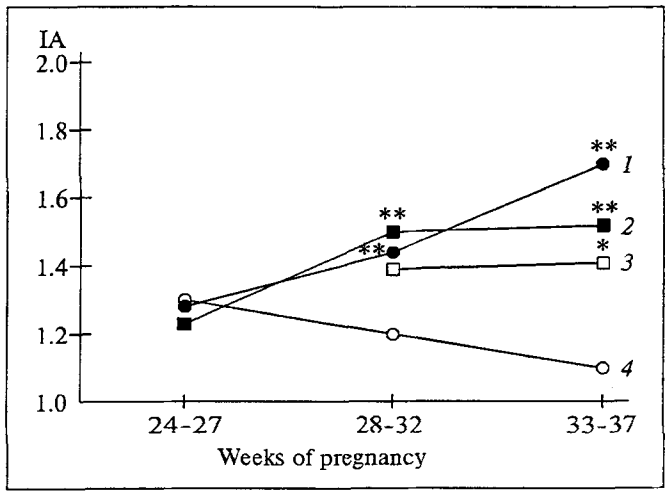

Fig. 1. Changes in the index of asymmetry (IA) recorded in fetuses developing in healthy women (*4*) and in women with IDDM: group 1 (*1*), group 2 (*2*), and group 3 (*3*).

Here and in Figs. 2–3: $^{*}p<0.05$, $^{**}p<0.01$ compared with the controls.

2 fetuses changes in cardiac function occurred later (33rd-37th week): stroke (0.523±0.03 ml/kg) and cardiac (75±6.5 ml/min/kg, $p<0.05$) indexes decreased, the decrease being smaller than in group 3 fetuses.

Correlation analysis showed a significant positive correlation between stroke volume and calculated fetal mass. This correlation was the strongest in normal and group 1 fetuses ($r=0.847$ and $r=0.8$, respectively). In group 3, the correlation coefficient was equal to 0.6, indicating impairment of cardiac function with fetal growth. The most pronounced cardiovascular disorders occurring in groups 2 and 3 fetuses after delivery are probably associated with the early development of HCM and its marked severity in the prenatal period.

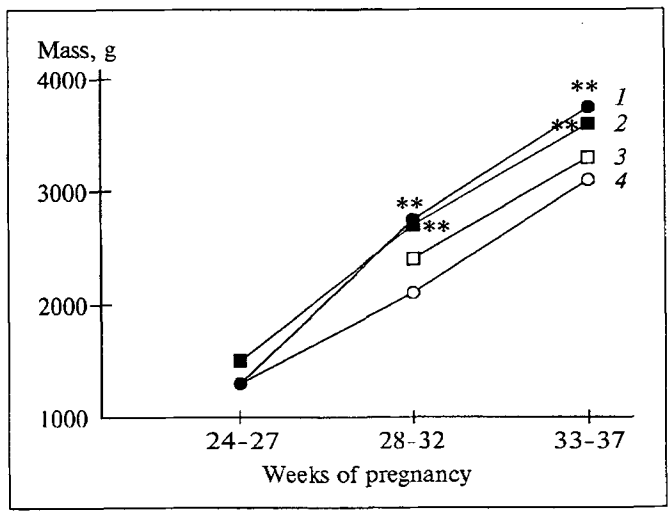

Fig. 2. Dynamics of fetal mass in healthy women (*4*) and in women witn IDDM: group 1 (*1*), group 2 (*2*), and group 3 (*3*).

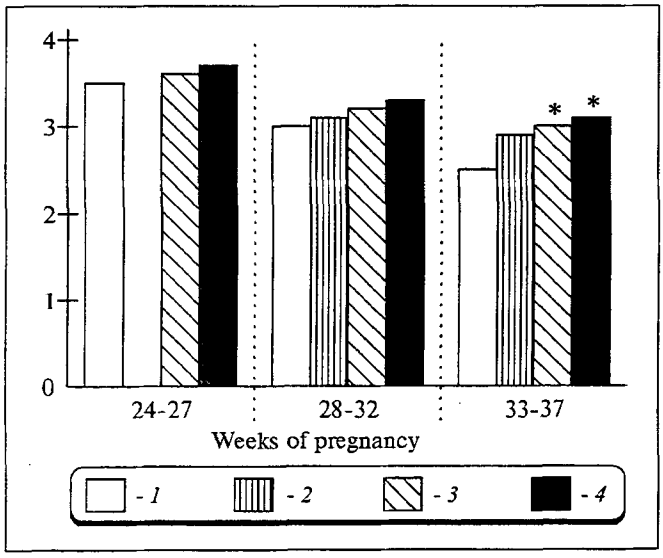

Fig. 3. Changes in systolic–diastolic ratio occurring in the umbilical artery in fetuses developing in healthy women (*4*) and in women with IDDM: group 1 (*1*), group 2 (*2*), and group 3 (*3*). Ordinate: systolic–diastolic ratio.

In the 33rd-37th week of pregnancy, hemodynamic disorders were noted in group 2 and especially in group 3. Vascular resistance of the umbilical artery increased, which was manifested in higher systolic-diastolic ratios on the blood flow rate curves as a result of a decrease in the diastolic component (Fig. 3).

At the same time, in group 3 fetuses the resistance index of the middle cerebral artery decreased: 0.7±0.027 *vs.* 0.79±0.02 in the control ($p<0.01$). The cerebroplacental ratio (the ratio between the resistance index of the middle cerebral artery to that of the umbilical artery) in group 3 fetuses was also lowered: 1.1±0.06 *vs.* 1.3±0.05 in controls, $p<0.05$). Both these parameters attest to a decrease in the vascular resistance of the fetal cerebral vessels, which is a manifestation of compensatory centralization of the fetal circulation associated with developing hypoxia due to placental insufficiency. The latter is confirmed by the increased vascular resistance of placental vessels in women with severe IDDM.

Morphological studies [5] have shown that placental maturation and vascularization are impaired in IDDM, the degree of the impairments being directly dependent on the disease severity.

Hyperinsulinism, in which the number of insulin receptors and their sensitivity to insulin increase [11], also plays a role in the development of fetal HCM. In addition to an increase in fetal mass, hyperinsulinism promotes the development of chronic hypoxia [7]. Together with placental insufficiency it aggravates fetal hypoxia and induces hemodynamic and cardiac disorders. In adequately compensated IDDM (mothers of group 1 fetuses), pronounced symptoms of HCM were observed later (33rd-37th week of pregnancy) than in severe IDDM (28th-30th week). In this group, there were no changes in fetal cardiac and central hemodynamics or clinical manifestations of HCM in infants. It can be assumed that in compensated IDDM elevated blood insulin is the major factor in the development of fetal HCM. In severe diabetes (groups 2 and 3) the development and severity of fetal HCM also depend on the time of its onset and on the severity of circulatory disorders occurring in the mother-placental-fetus system and the severity of chronic hypoxia. Activation of the renin-angiotensin-aldosterone system in the fetus-placenta complex occurring in IDDM in the 34th week of pregnancy [1] may stimulate the development of myocardial hypertrophy. Angiotensin II, an effector peptide of this system, mediates the development of hypertrophic processes in the cardiovascular system [1].

The rapid growth of the fetal mass promotes cardiac hypertrophy, which is more pronounced in severe and inadequately compensated IDDM (group 3 fetuses). All parameters characterizing cardiac function are normalized after birth and the removal from all disorders in the mother-placenta-fetus system.

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