ORIGINAL STUDY

FETAL CARDIOMYOPATHIES

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ABSTRACT

Fetal cardiomyopathies (CM) are rare diseases with an incidence of about 6-11% of all fetal cardiac diseases. Although the prenatal diagnosis of most fetal structural heart defects and dysrhythmias has been described previously, there is a paucity of information about CM in prenatal life (1). There are few evidences and very few information about the natural history before, during and after the birth of the fetuses affected by these diseases.Fetal cardiomyopathies can be analysed by studying atrial and ventricular contraction using B and M-mode echocardiography. A haemodynamic evaluation can be performed by Doppler mode. In this review we reported the typical findings of dilatative cardiomiopathy, of hypertrophic cardiomiopathy and of restrictive cardiomiopathy in fetuses. The prognosis is poor, except for the Hypertrophic cardiomiopathy associated with hyperglycaemia.

KEYWORDS: *Dilated cardiomiopathy, hypertrophic cardiomiopathy, restrictive cardiomyopathy, foetuses*

Introduction

Fetal cardiomyopathies (CM) are rare diseases with an incidence of about 6-11% of all fetal cardiac diseases. Although the prenatal diagnosis of most fetal structural heart defects and dysrhythmias has been described previously, there is a paucity of information about CM in prenatal life [1]. There are few evidences and very few information about the natural history before, during and after the birth of the fetuses affected by these diseases.

Fetal echocardiography plays a leading role in the fetus with congenital heart disease in many important ways. Advances in fetal echocardiography have allowed more accurate and earlier detection of cardiac abnormalities [2].

Fetal CM in utero: instrumental diagnosis

CM may develop during fetal life and may be diagnosed by prenatal echocardiography even if a normal cardiac finding in a midtrimester fetus does not exclude a subsequent CM development. Detailed prenatal sonographic examination may aid to determine the neonatal outcome.

Cardiac malformations are the most frequent and serious fetal malformations. Fetal

echocardiography is the main diagnostic tool and it is useful for the therapeutic orientation.

Today, echocardiography is a part of fetal medicine which includes the different specialties dealing with the fetus.

Fetal cardiomyopathies can be analysed by studying atrial and ventricular contraction using B and M-mode echocardiography. A haemodynamic evaluation can be performed by Doppler mode.

Fetal cardiomyopathies can be isolated or associated with other cardiac and non cardiac malformations, such as congenital cardiomiopathy or hydrops [3].

Dilated cardiomyopathy

Dilated cardiomyopathy is a very rare disease in fetuses. Only isolated case reports and small case series were reported. Our study suggests a very poor outcome for affected fetuses.

We define an adult patient as affected by DCM when he has dilatation of the cardiac chambers and systolic dysfunction, but also the fetuses with systolic univentricular or biventricular dysfunction were defined as affected by dilated cardiomiopathy, with or without chambers dilatations and without increased wall thickness.

Schmidt et al. established in 1986 the diagnosis of DCM in 6 out of 625 fetuses studied by echocardiography. In all fetuses cardiac structural abnormalities were excluded. Abnormal findings included reduced fractional shortening index in 5 patients, 3 were affected by atrioventricular valve regurgitation, 3 were with abnormal chamber dimensions and 4 with non-immune hydrops.

In 2 fetuses, with a positive family history (dilated cardiomyopathy), echocardiographical abnormalities were absent on a first examination performed during 20 weeks of gestation, and were present at 30 weeks of gestation. This suggested that

a normal fetal echocardiogram in a midtrimester fetus does not always rule out the subsequent development of dilated cardiomyopathy.

About the natural history, only 2 infants (33%) survived, 1 of whom required heart transplantation during infancy. Death from cardiac failure occurred in 1 fetus and 3 newborns.

This study has showed, for the first time, that DCM may develop during fetal life and, if serial studies are performed, it might be diagnosed by echocardiography. [4]

In order to determine the pathogenic mechanisms, hemodynamic findings, and outcome of fetal DCM, Pedra et al. reviewed the fetal echocardiograms and perinatal histories of 22 affected fetuses from 1990 to 1999 in Canada. Among the fetuses studied 2 had Cytomegalovirus congenital infection, 5 were with familial cases, 6 with endocardial fibroelastosis (EFE) related to maternal anti-Ro/La antibodies, while 9 were idiopathic cases. Systolic dysfunction was present in all cases of dilated CM and it was the unique diagnostic criterion.

In this report a broad spectrum of bad prognostic findings were identified, such as the presence of systolic dysfunction and significant atrioventricular valve regurgitation.

A poor outcome was also observed in many affected fetuses with only a few therapeutic options available as the use of maternal corticosteroids, intravenous immunoglobulin (IVIG) and sympathomimetic therapy.

Excluding 5 cases with elective termination of pregnancy, the overall rate of mortality in the DCM group was 82.3% (14 of 17), with 8 intrauterine deaths and 6 early neonatal deaths. [5]

Three years later Pedra et al performed a prenatal and postnatal study in patients with family history of nonhypertrophic CM. This study demonstrated a high familial recurrence rate of CM.

Twenty-six cases from 16 families with a family history of CM were studied. Postnatal clinical evaluation, electrocardiogram, and echocardiogram were performed within the first 3 months, with serial revaluation for those affected by CM.

Abnormal cardiac function was observed in 8 cases (30%). Six had a previously affected sibling, 1 had other family members who were affected, and 1 had both antecedents.

Four had a prenatal diagnosis of dilated CM, of these 1 recovered, 2 died in uterus, and 1 died soon after birth. The remaining 4 had normal fetal echoes and were diagnosed to have CM in the first 3 months of life. Three had dilated CM with recovery, and 1 had restrictive CM requiring cardiac transplantation. [6]

Between 1983 and 2003 Sivasankaran et al. described the echocardiographical features, underlying causes, and outcome of fetuses with DCM. They included fetuses with dilation and reduced systolic function of either the right ventricle, left ventricle, or both. They excluded fetuses with abnormal cardiac connections, arrhythmias, or stenosis of the aortic or pulmonary valves. They identified 50 fetuses, born of 46 mothers. Among these fetuses, 24 had biventricular cardiomyopathy, 17 had isolated right ventricular cardiomyopathy, and 9 had isolated left ventricular cardiomyopathy. Two-thirds of the fetuses were hydropic at some point during gestation. There was a high rate of spontaneous intra-uterine and early neonatal death.

A cause of cardiomyopathy was identified in 37 cases. Cardiomyopathy was genetic or metabolic in 11 fetuses; infective in 11; fetal anaemia, without proven parvovirus infection, was diagnosed in 5 fetuses; fetal anaemia of cardiac origin in 5; and it was associated with renal disease in 5. In 10 cases, the pregnancy was terminated.

The survival of the fetus was very poor. The overall survival of non-hydropic fetuses was 9 out of 18, compared to 6 out of 32 hydropic fetuses.

Genetic, metabolic, infective, and cardiac diseases may present with dilated cardiomyopathy during fetal life. [7]

In our fetal echocardiographical experience, from 1982 to 2005, we have reviewed more than 13,000 examinations and we have reported 12 affected fetuses (Figure 1).
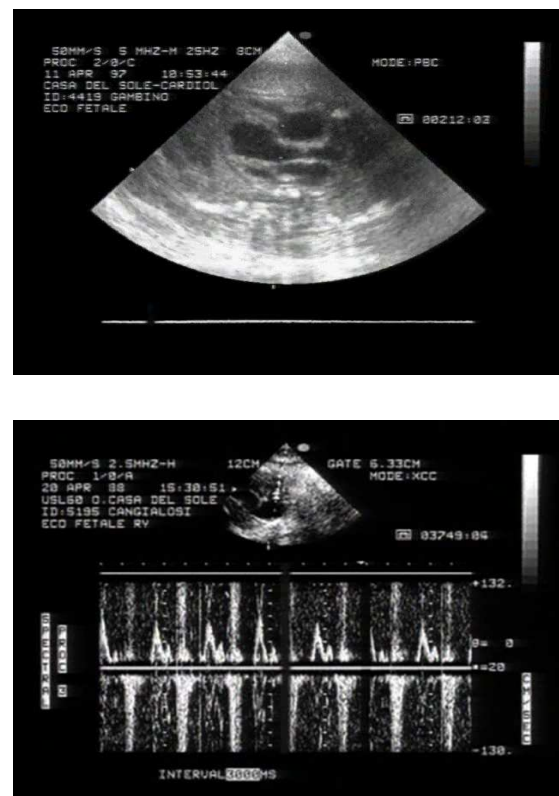

Figure 1: *B mode and Doppler view of a fetus affected by dilatative cardiomiopathy: in the A panel an enlargement of the left ventricular chamber can be observed. A mitral incompetence was showed in B panel.*

Our data confirm the bad prognostic value of hydrops, severe transvalve regurgitation and diastolic dysfunction.

Non –compaction and dilated cardiomyopathy

Some cases of dilated cardiomyopathy in patients affected by non compaction have been described previously. Isolated non-compaction of the ventricular myocardium (INVM) is a rare cardiomyopathy characterized by the persistence of numerous marked ventricular trabeculations and deep intertrabecular recesses with direct vascular supply by the ventricular cavities. There are conflicting opinions about the diagnosis of fetal echocardiography in the literature.

Ozkutlu S. et al. in their study diagnosed six cases of fetal INVM (Isolated Non-compaction of the Ventricular Myocardium). Diagnosis of the disease is based on the 2-D echocardiography features. Ozkutlu affirms that the examiner should be aware of the existence of this rare anomaly. When the echocardiography examination shows recesses in ventricle walls the diagnosis can be made. [8]

An example of heart failure were reported by Aras et al., when a case of IVNC and myocardial bridging were misdiagnosed and confused with apical Hypertrophic cardiomyopathy. [9]

Kitao et al. in their study described a case of INVM that developed in a pregnant woman and her neonate. Maternal echocardiography demonstrated INVM with characteristic findings of prominent and excessive ventricular trabeculations and deep intertrabecular recesses in the left ventricle. An M-mode echocardiography suggested depressed left ventricular systolic function. A fetal echocardiography at 24 weeks' gestation demonstrated cardiomegaly, but morphologic findings were not definitive for INVM. The neonate died of heart failure on the second day of life. [10]

The prognosis of the fetus with a post- non compaction dilated cardiomyopathy was poor.

In our experience the diagnosis of non compaction was made in 2 fetuses without ventricular dilatation, but with ventricular dysfunction detected at echocardiogram during the 30th and the 31st week of life. Today both patients are alive and in good health conditions.

Hypertrophic cardiomiopathy in the fetus

CMI in infants is a well-known disease. Etiologically primary fetal CM is a heterogeneous condition that can be the result of intrinsic fetal pathology as well as of extrinsic factors. It can be concentric or asymmetric.

Prognosis of infants with hypertrophic cardiomyopathy (CMI) associated with maternal diabetes [11-13] is good.

CMI has been well documented in infants of diabetic mothers.

Many studies have been published which indicated a good prognosis [14,15] of fetuses affected by hyperglycaemia, while a bad prognosis has been reported in fetuses without diabetic mother.

From March 1987 to April 1991, Zielinsky et al. have been reviewed prenatal echocardiography of 283 fetuses and in 39 of whom a diagnosis of disproportionate septal hypertrophy was made (mean septal thickness 7.12 +/- 1.6 mm), at an average of 32 weeks of gestational age. Diabetes mellitus was present in 36 of these pregnancies (92.3%). In ten cases, a spontaneous regression of the septal hypertrophy was shown. There were three neonatal deaths, unrelated to the myocardial disease. This form of cardiomiopathy, even if it is benign, can be associated with a hydrops fetalis, and when it occurs it is generally benign and transient. [16]

The asymmetric septal enlargement is an anabolic result of fetal hyperinsulinemia triggered by maternal hyperglycemia during the third trimester.

Rizzo et al. suggest that strict maternal diabetes control does not rule out accelerated fetal cardiac growth and abnormal development of cardiac function.

Serial M-mode and Doppler echocardiographical recordings were made at 4-weeks intervals in

14 fetuses of well-controlled type I insulin-dependent diabetic mothers, and they showed significant differences in the slope and intercept values for the function describing the growth of the interventricular septum (P less than or equal to .001) and the right and left ventricular wall thickness (P less than or equal to .01), resulting in accelerated cardiac growth.

For this reason an echocardiographical evaluation of the CMI may be observed in fetuses of diabetic mothers every 3 months, with an accurate evaluation of the thickness of the interventricular septum.

A systolic anterior motion of the mitral valve can be present, but only one have shown a gradient across the left ventricular outflow tract.

In the absence of diabetes other causes can determine cardiac hypertrophy.

Four cases of early severe and transient CMI are reported by Vaillant et al. in 1997. [17]

They believe it is a consequence of myocardial ischemia due to acute fetal distress. In all cases electrocardiographical and biologic signs of myocardial ischemia were present. The first echocardiogram showed abnormalities in systolic or diastolic left ventricular function, without hypertrophy of the walls. CMI occurred between 2 and 7 days of life and affected first the interventricular septum and the free wall of the right ventricle. The left ventricular posterior wall subsequently became abnormal, resulting in severe overall myocardial hypertrophy, which finally

disappeared in all three cases between 1 and 5 months of life.

Noonan' s syndrome, a well-known syndrome of multiple congenital anomalies, is frequently accompanied by cardiovascular diseases including CMI.

Among 33 cases of CMI, studied by Pedra et al, 7 had CMI associated with maternal diabetes, 2 had Noonan's syndrome, 2 had homozygous alpha thalassemia, 1 had a family history of CMI, and 18 were the recipient in TTTS; in 3, no pathogenesis was identified. Excluding 2 with termination of pregnancy and 2 lost to follow-up, the overall rate of mortality for the CMI group was 51.7% (15 of 29).

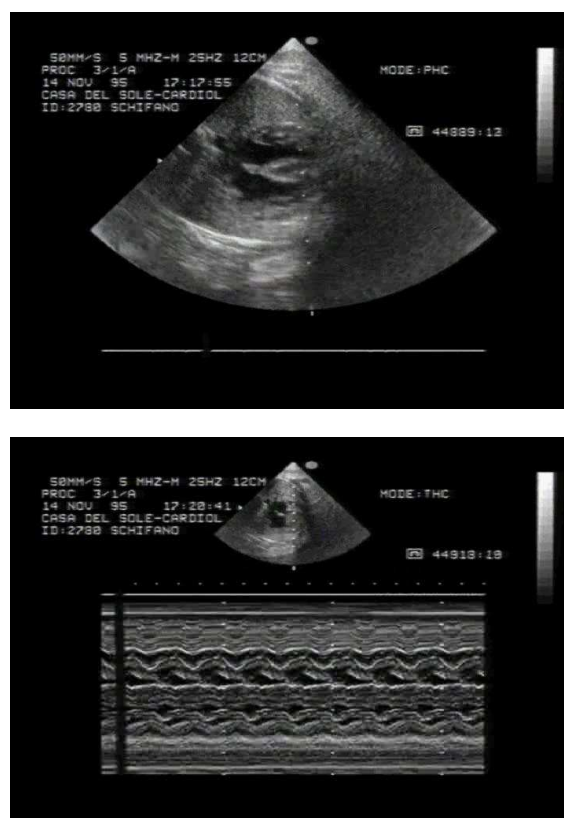The prognosis of non diabetic CMI is less positive (Figure 2). [5]

Figure 2. *Image of a fetus affected by hypertrophic cardiomiopathy: a biventricular hypertrophy can be observed in B mode (panel A) and in M mode (panel B).*

On the basis of our experience, from 1987 to 2005, in more than 13.000 examinations we have observed 16 affected fetuses with a ventricular walls thickness, more than 2 standard deviations versus the normal values normalized for the gestational age, with or without systolic or diastolic ventricular dysfunction and we defined them as affected by CMI [1; 11, 15, 18-22].

About the patients without a diabetic history, of 7 patients 2 died and 5 survived. We recognized "hydrops" as a risk factor for CMI.

Detailed prenatal ultrasound examination may aid to determine the neonatal outcome.

Restrictive cardiomyopathy

Very few reports were reported of restrictive cardiomyopathy in fetuses, and all of endocardial fibroelastosis (EFE), with a very poor prognosis. It is a congenital heart disease which causes congestive heart failure in early infancy, characterized by an abnormal thickening of the endocardium of one or both ventricles. A diagnosis of EFE in uterus using fetal echocardiography may be made on the basis of increased echo density of the endocardium and poor contractility of the ventricle.

Rustico et al. described in 1995 a case of very early diagnosis of fibroelastosis and aortic valve stenosis observed in uterus at 14 weeks' gestation by transvaginal ultrasound. [16]

Tannouri et al. reported two cases: a primary dilated form and a secondary contracted form. The dilated form was associated with an intracavitary thrombus of the left ventricle. [23]

Weiner et al. used new modalities for early prenatal diagnosis of endocardial fibroelastosis causing fetal heart failure. A mildly asymmetric four-chamber view with slightly enlarged atria and any other fetal heart abnormalities suggested EFE. [24]

Doppler studies demonstrated abnormal cardiac function with extremely low atrioventricular E/A ratio, defined as the ratio between the rapid ventricular filling (E wave) and the atrial systole (A wave), and an abnormal venous flow velocity wave forms. On the basis of these observations diagnosis was done. 2 weeks later the abnormal morphologic signs were more prominent, and pregnancy was terminated [25-33].

5. Conclusions

Fetal cardiomyopathies (CM) are rare diseases with an incidence of about 6-11% of all fetal cardiac disease. Fetal echocardiography is the main diagnostic instrument. The prognosis is poor, except for the Hypertrophic cardiomiopathy associated with hyperglycaemia.

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