CLINICAL CASE

COARCTATION OF THE AORTA IN A FETUS WITH 46, XY, INV (9)(P12,Q13) KARYOTYPE FOLLOWING IN VITRO FERTILIZATION

Liana Pleş[1,2], Anca Ricu[1], Romina-Marina Sima[1,2], C.A. Ionescu[2,3]
[1]„St. John" Hospital, „Bucur" Maternity, Bucharest, Romania
[2]The University of Medicine and Pharmacy „Carol Davila", Bucharest, Romania
[3]„St. Pantelimon" Hospital, Bucharest, Romania

Corresponding author: Romina-Marina Sima
Phone no. 0040741071243
E-mail: romina.sima@yahoo.es

Abstract

The first pregnancy after the fertilization of a human egg in vitro and the first birth from an in vitro-fertilized embryo were reported in 1976 and 1978. Since then, more than five million pregnancies have been achieved worldwide by assisted reproductive technologies (ARTs). With ART improvement the questions about neonatal outcome and genetic implications are rising.The patient SM, 47 years of age, referred to our clinic for pregnancy prenatal care. Due to poor ovarian reserve related to her biological age she obtained this pregnancy using ART procedures. The second trimester anomaly ultrasound scan revealed coarctation of the aorta.The genetic examination of the amniotic fluid observed a male fetus with 46, XY,inv (9)(p12,q13) karyotype. The outcome of the pregnancy was favorable without hemodynamic changes in the fetus until birth. The patient delivered by cesarian section a 3200 g baby-boy with 9 Apgar Score. The cardiologic consult confirmed the mild coarctation of the aorta. The question that rises is: which is the cause, the IVF, the chromosome inversion or other environmental factors?

Keywords*: aortic coarctation, in vitro fertilization, assisted reproductive technologies*

Introduction

Coarctation of the aorta represents 4 to 6 percent of all congenital heart defects and the reported prevalence is about 4 per 10,000 live births [1,2]. It occurs more frequently in males rather than females (59 versus 41 percent) and the majority of the cases are sporadic [3].

Chromosome 9 contains non-coding heterochromatin regions which form the inv (9) breakpoints, that are called "gene deserts." According to Francis Collins, a leader in the original Human Genome Projects and director of the National Institute of Health they are "like the seat of the soul of the genome". Nature presents a study in which these gene deserts as hotspots in diseases [4].

Case presentation

The patient SM, 47 years of age, referred to our clinic for pregnancy prenatal care. She had no other pregnancy or abortion before.

She delayed to conceive because of personal reasons (professional). Due to poor ovarian reserve (Antimullerian Hormone 0.02) related to her biological age she obtained this pregnancy using ART procedures (egg donor, FIV and ICSI). According to her history, the patient had two previous unsuccesfull IVF.

The patient underwent in vitro fertilization using oocyte donation. The procedure was without complication. The patient followed our national program of prenatal care. The biological findings were normal in the first trimester of pregnancy (red blood count, hemoglobin level, renal and hepatic function evaluation, blood sugar level, urinary evaluation, etc.). The first trimester ultrasound examination revealed no abnormal findings. The first trimester evaluation for trisomy 21, 13 and 18 was negative (combined test NT 2,4 mm and present nasal bone, no tricuspid valve regurgitation). The patient didn't have a free fetal DNA test and she was not offered chorionic biopsy (considering the donor's age of 26).

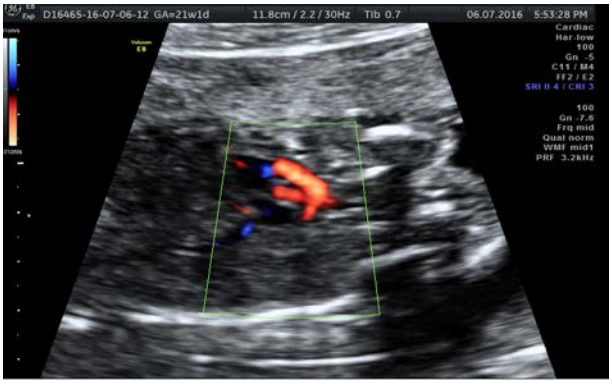

Figure 1 - Longitudinal section of the fetal thorax - narrow ascending aorta Doppler color

The second trimester ultrasound scan revealed a normal fetal anatomy except for the heart. The transverse section at the four chamber view revealed a discrepancy between the right ventricle and left ventricle size in favor of the right ventricle. At a more superior section in order to obtain the 3 vessels image it was obvious the bigger main pulmonary and the small aorta, discrepancy that was more important at the two ducts view. Color Doppler depicted also a tiny left ventricle with patent mitral valve, present but reduced flux in the left outflow tract and very reduced flow on the aortic arch (Figures 1-6). The only extracardiac abnormality observed was a single umbilical cord artery.

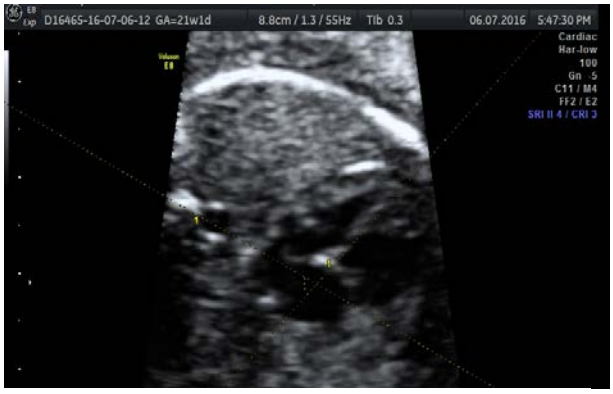

Figure 2 - Transverse section of the fetal thorax at the level of 4 chamber view - discrepancy between the RV/LV with left heart axe deviation

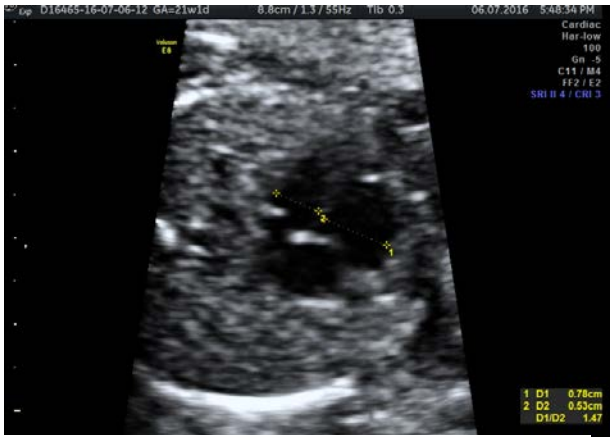

Figure 3 - Measurement of the ventricular width

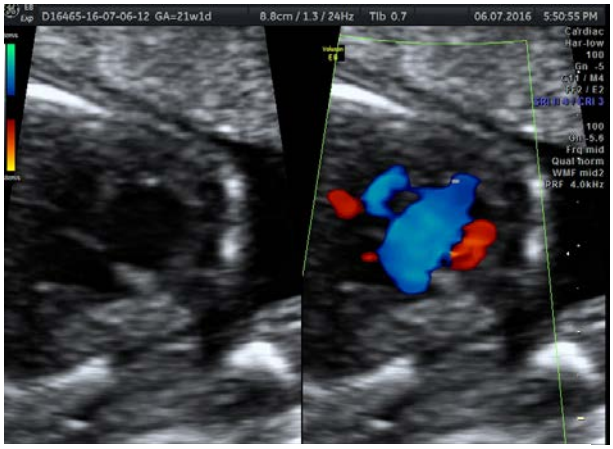

Figure 4 - color Doppler effects depicting ventricular discrepancy

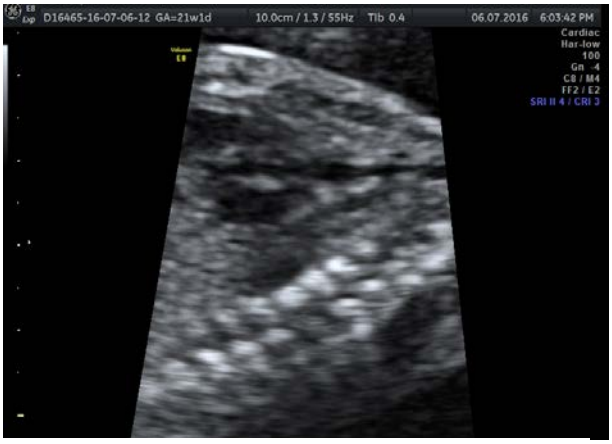

Figure 5 - Narow ascending aorta simulating interrupted aortic arch

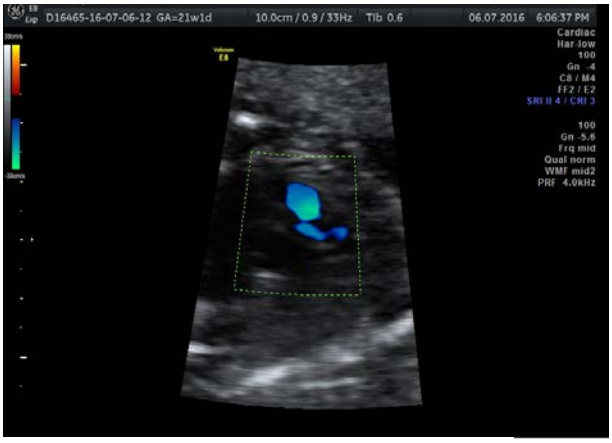

Figure 6 - Narrow ascending aorta color

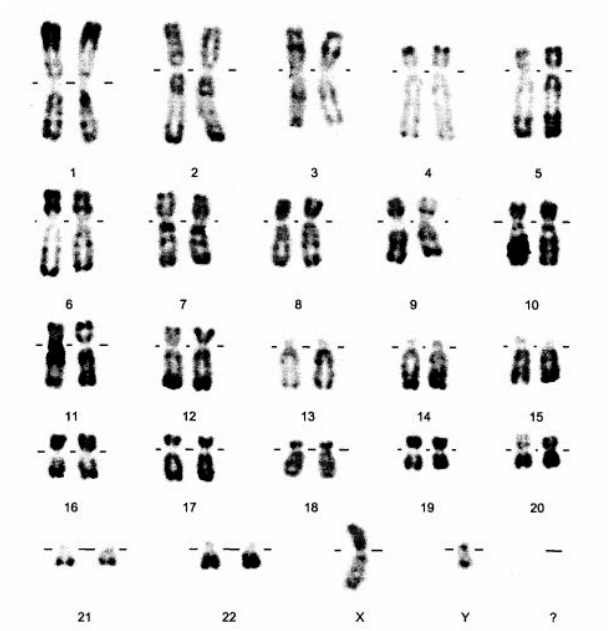

Figure 7 - Fetal karyotype

Considering the association between the CoA and chromosomal abnormalities a genetic diagnosis was proposed. The patient agreed and signed the informed consent for diagnosis amniocentesis wich was performed at 21 weeks of gestation. The procedure was without any maternal of fetal complications. The genetic examination of amniotic fluid revealed a male fetus with 46, XY,inv (9)(p12,q13) karyotype (Figure 7). After the genetic counselling the couple decided to keep the pregnancy. The outcome of the pregnancy was favorable without hemodynamic changes in the fetus until birth. The patient delivered by cesarian section a 3200 g baby-boy with 9 Apgar Score. The cardiologic consult confirmed the mild coarctation of the aorta without hemodynamic response and recommended monitoring in the first 6 months after birth.

Discussions

In 1760 Morgagni was the first one who described coarctation of the aorta [5], and in its simplest type referring to the congenital narrowing of the proximal thoracic aorta. Aortic coarctation is most often described as a little stenosis in the juxtaductal position but it may be associated with hypoplasia of the transverse aortic arch, long segment narrowing, or stenosis of the abdominal aorta [6]. Other studies report that coarctation of the aorta accounts for 5%-7% of all congenital heart diseases [7] with an incidence of 3 cases per 10000 births [8]. Coarctation may be seen in isolation or with other cardiac defects such as ventricular septal defect, bicuspid aortic valve transposition of the great arteries, atrioventricular canal defects, patent ductus arteriosus, or left-sided obstructive heart defects, including hypoplastic left heart syndrome [9].

The main differential diagnosis that should be made is: left heart outflow obstruction, type A interrupted aortic arch and hypoplastic left heart syndrome.

Obstruction to the left ventricular outflow of the heart may be at the valve (74%), above the aortic valve (5%), or in the subvalvar

region (23%). These lesions represent 3 to 6% of all congenital heart defects (CHD), and they occur more frequently in males (male-female ratio of 4:1). Subvalvar and valvar stenosis may be associated with other CHD such as anomalies of the mitral valve, pulmonary stenosis (PS), patent ductus arteriosus (DAP) and, defects of the interatrial septum. A variety of defects can obstruct the subaortic outflow tract, with or without a coexisting ventricular septal defect. Obstruction can be produced by hypertrophy of the ventricular septum, as seen in hypertrophic cardiomyopathy, by excessive tissue tags derived from the membranous septum or the leaflets of the atrioventricular valves or by uncommon attachment of the tension apparatus of the atrioventricular valve [10].

Prenatal diagnosis of the coarctation of the aorta is difficult and the literature reports a high rate of false positive and false negative diagnosis [11].

An accurate diagnosis of the heart condition and ruling out chromosomal or extracardiac abnomalies allowed an adequate counseling of the couple, since the evolution and the prognosis of the other conditions are worse than in coarctation. In utero evolution of the coarctation is usually good but the birth should take place in a tertiary center. Being a duct dependent condition after birth the ductus arteriosus must remain open using prostaglandines in order to provide a reasonable oxygen level in the descending aorta. It is obvious that prenatal diagnosis of the condition allowed taking all the required measures in time and thus improving the postnatal outcome of the baby.

The patients with coarctation of the aorta have a poor outcome without any intervention. In his 1970 natural history study, Campbell examined autopsy and clinical records of 465 patients with coarctation who survived beyond one year of age. The mean age of death was 34 years, with the dominant mortality at 43 years of age (75%). The causes of death were congestive heart failure (26%), aortic rupture (21%), bacterial endocarditis (18%), and intracranial hemorrhage (12%) [12]. Nowadays several treatment options are available. There are guidelines about surgical interventions for children and adults with coarctation, related to peak-to-peak gradient $\geq$ 20 mmHg or lesser gradients and when is a significant anatomic evidence of narrowing aorta on scans with extensive collateral flow [13]. Other factors that influence the surgical intervention are elevated left ventricular end diastolic pressure, left ventricular hypertrophy, the presence of systemic hypertension and additional cardiac defects and/or single ventricle physiology [14].

Coarctation of the aorta can associate chromosomal abnormalities. According to the literature trisomies 13, 18 and Turner syndrome are the most commune [15]. In our case Turner syndrome was ruled out since the baby was a boy.

Anintrachromosomal break and subsequent rearrangement may cause an inversion of the chromosomes which is a structural aberration. The pericentric inversion of chromosome 9 or inv(9) may be seen in normal humans and its frequency is estimated to 1 to 3% in the general population. The most common inversion chromosome 9 observed in humans is inv(9)(p12q13). The disease association of inv(9)(p12q13) has been observed in various human diseases, especially families with bad obstetric history, repeated spontaneous abortions, infertility, and congenital anomalies. The abnormal phenotype was found due to unbalanced inversions at different breakpoint regions. There are very few reports to estimate the frequency and clinical impact of inv(9) in the population. Among them, one study proved a high frequency of inv(9) (p12q13) (64.9%) among patients with genetic disorders, that also infers its decisive role in disease development, more often in the case of de novo inversions [16]. There are some other few reports on the inv(9) variations in hematological malignancies. However, there are reports about inv(9) considered as a constitutional abnormality with familial inheritance [17] as well as an acquired

chromosomal abnormality in hematological malignancies. Most of the studies perceive inv(9) as a constitutional abnormality with minor implication on outcome [18].

Conclusion

We presented a case of a fetus obtained with ART that was diagnosed by ultrasound in the second trimester of pregnancy with coarctation of the aorta. An appropriate diagnosis of the condition, ruling out other extracardiac abnormalities and severe genetic disorders provided a solid background for the counseling the couple. In that particular situation the stakes were higher since it was a "precious" baby, obtained by ART with a mother in her late 40s. The genetic exam revealed 46, XY,inv (9)(p12,q13) karyotype of the fetus. The question that rises is: which is the cause, the IVF, the chromosome inversion or other environmental factors?

References

[1]Reller MD, Strickland MJ, Riehle-Colarusso T, et al. Prevalence of congenital heart defects in metropolitan Atlanta, 1998-2005. J Pediatr 2008; 153:807.

[2]Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol 2002; 39:1890.

[3]Report of the New England Regional Infant Cardiac Program. Pediatrics 1980; 65:375.

[4]Harismendy O, Notani D, Song X, Rahim NG, Tanasa B, Heintzman N, et al. 9p21 DNA variants associated with coronary artery disease impair interferon-gamma signalling response. Nature.2011;470(7333):264–8. doi: 10.1038/nature09753.

[5]Zani A, Cozzi DA. Giovanni Battista Morgagni and his contribution to pediatric surgery. J Pediatr Surg.2008;43:729–733.

[6]Price TP, Whisenhunt AK, Policha A, Ayad MT, Gardiner GA, Abai B, DiMuzio PJ, Salvatore DM. Middle aortic coarctation. Ann Vasc Surg. 2014;28:1314.e15–1314.e21.

[7]Pádua LM, Garcia LC, Rubira CJ, de Oliveira Carvalho PE. Stent placement versus surgery for coarctation of the thoracic aorta. Cochrane Database Syst Rev. 2012;5:CD008204.

[8]Ringel RE, Gauvreau K, Moses H, Jenkins KJ. Coarctation of the Aorta Stent Trial (COAST): study design and rationale. Am Heart J. 2012;164:7–13.

[9]Warnes CA. Bicuspid aortic valve and coarctation: two villains part of a diffuse problem. Heart.2003;89:965–966.

[10]Rayburn ST, Netherland DE, Heath BJ. Discrete membranous subaortic stenosis:improved results after resection and myectomy. Ann Thorac Surg. 1997;64:105–109.

[11]Alfred Abuhamad, Rabih Chaoui A practical Guide to Fetal Echocardiography, Wolters Kluwer Lippincot Williams &Wilkins 2010 pg 166.

[12]Campbell M. Natural history of coarctation of the aorta. Br Heart J. 1970;32:633–640.

[13]Feltes TF, Bacha E, Beekman RH, Cheatham JP, Feinstein JA, Gomes AS, Hijazi ZM, Ing FF, de Moor M, Morrow WR, et al. Indications for cardiac catheterization and intervention in pediatric cardiac disease: a scientific statement from the American Heart Association. Circulation. 2011;123:2607–2652.

[14]Vergales JE, Gangemi JJ, Rhueban KS, Lim DS. Coarctation of the aorta - the current state of surgical and transcatheter therapies. Curr Cardiol Rev. 2013;9:211–219.

[15]Paladini D, Volpe P, Russo MG, Aortic coarctation: prognostic indicators of survival in the fetus Heart 2004;90(11):1348-1349.

[16]Rao BV, Kerketta L, Korgaonkar S, Ghosh K. Pericentric inversion of chromosome 9 [inv (9)(p12q13)]: Its association with genetic diseases. Indian J Human Genetics. 2006;12(3):129.

[17]Suh B, Song J, Kim J, Park TS, Choi JR. Constitutional pericentric inversion 9 in Korean patients with chronic myelogenous leukemia. Korean J Lab Med. 2010;30(3):218–23. doi: 10.3343/kjlm.2010.30.3.218.

[18]Akgul M, Ozkinay F, Ercal D, Cogulu O, Dogan O, Altay B, et al. Cytogenetic abnormalities in 179 cases with male infertility in Western Region of Turkey: report and review. J Assist Reprod Genet. 2009;26(2-3):119–22. doi: 10.1007/s10815-009-9296-8.