LONGITUDINAL ECHO MONITORING IN FETUS WITH PHENOTYPICAL MARFAN SYNDROME, HELPFULL FOR PERINATAL MANAGEMENT - CASE PRESENTATION AND LITERATURE REVIEW

Authors:
Katarzyna Zych - Krekora[1,2], Anna Wójtowicz[3], Michał Krekora[4], Maciej Słodki[1,7], Hugues Gentillon[6], Maria Respondek - Liberska[1,5]

1. Prenatal Cardiology Department ,Research Institute Polish Mother's Memorial Hospital in Łódź, Poland 2. Pediatrics, Immunology and Nephrology Department, Research Institute Polish Mother's Memorial Hospital in Łódź, Poland 3. Department of Clinical Obstetrics and Perinatology ,University Hospital in Krakow 4. Obstetrics and Gynecology Department, Research Institute Polish Mother's Memorial Hospital in Łódź, Poland 5. Fetal Malformations Department, Medical University of Lodz 6. Department of Radiology and Diagnostic Imaging, Barlicki University Hospital, Medical University of Łódź, Łódź, Poland 7. Faculty of Health Sciences. The State University of Applied Sciences in Plock, Poland

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Abstract

It was the second pregnancy of an otherwise healthy married couple. The fetus (male) had detailed echocardiography monitoring in the second half of the pregnancy due to progression of cardiomegaly, and echocardiographic features of congestive heart failure. Marfan syndrome was suspected based on cardiac anomalies. For the first time, the rupture of aneurysm of aortic sinus Valsalva was documented. Despite transplacental treatment with digoxin there was fetal demise at the 34th week of gestation and postmortem newborn phenotype confirmed prenatal diagnosis.

Marfan Syndrome is a rare genetic anomaly which can be diagnosed prenatally by detailed echocardiography, usually with bad prognosis (just opposite to "benign"case diagnosed later on in life span). The most common prenatal cardiac manifestations are cardiomegaly with signs of cardiac insufficiency. We present the case with new echocardiographic features.

Key words: *prenatal, Marfan, cardiomegaly*

CASE REPORT

34-year-old pregnant woman was referred to our Department for detailed echocardiography due to suspicion of cardiac defect at 25th week of gestation.

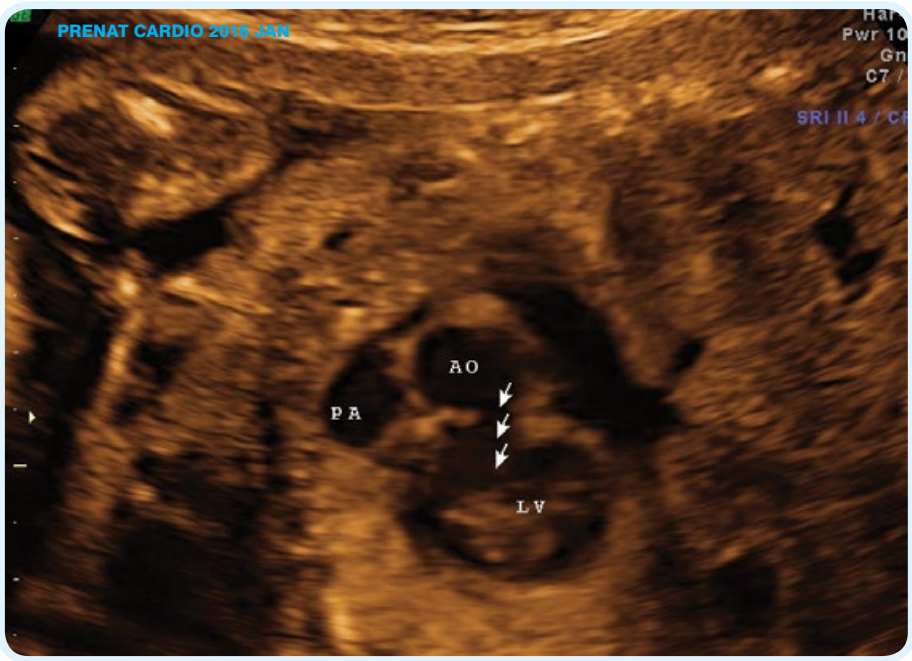

Fig. 1. Connection between aortic valsalva and left ventricle at 25,5 week

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Six years ago she gave birth to a healthy son (vaginal delivery). In the family of both the patient and her husband there was no history of genetic diseases and congenital anomalies. As a child, the patient was diagnosed with bilateral

Corresponding author: zychkrekora@gmail.com

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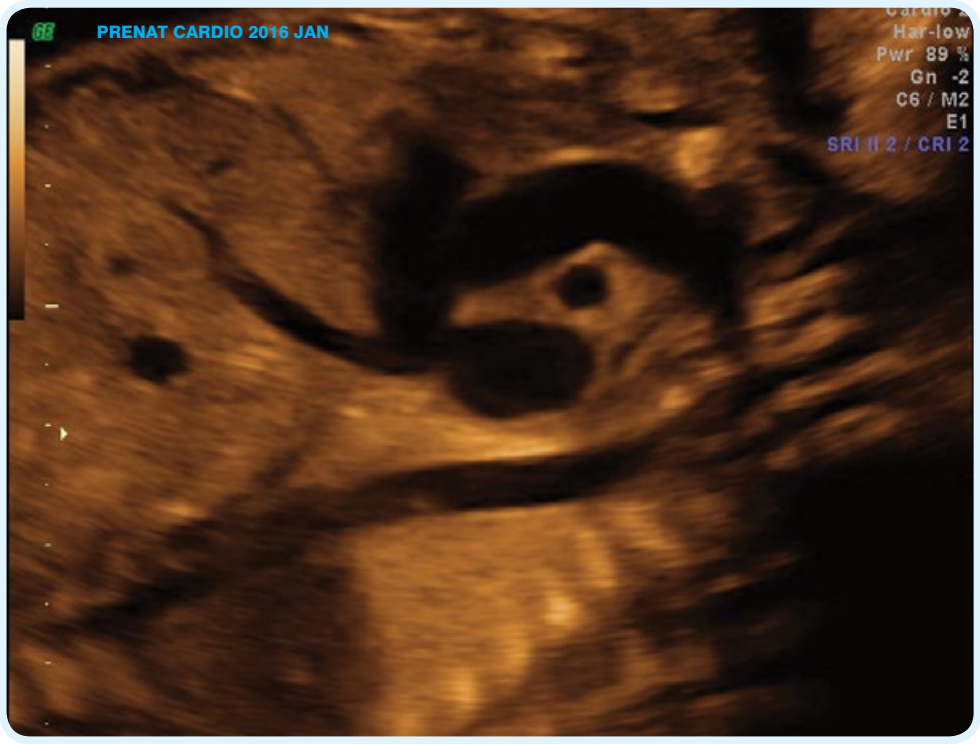


Fig. 2.Dilatation of ascending aorta at 25,5 week

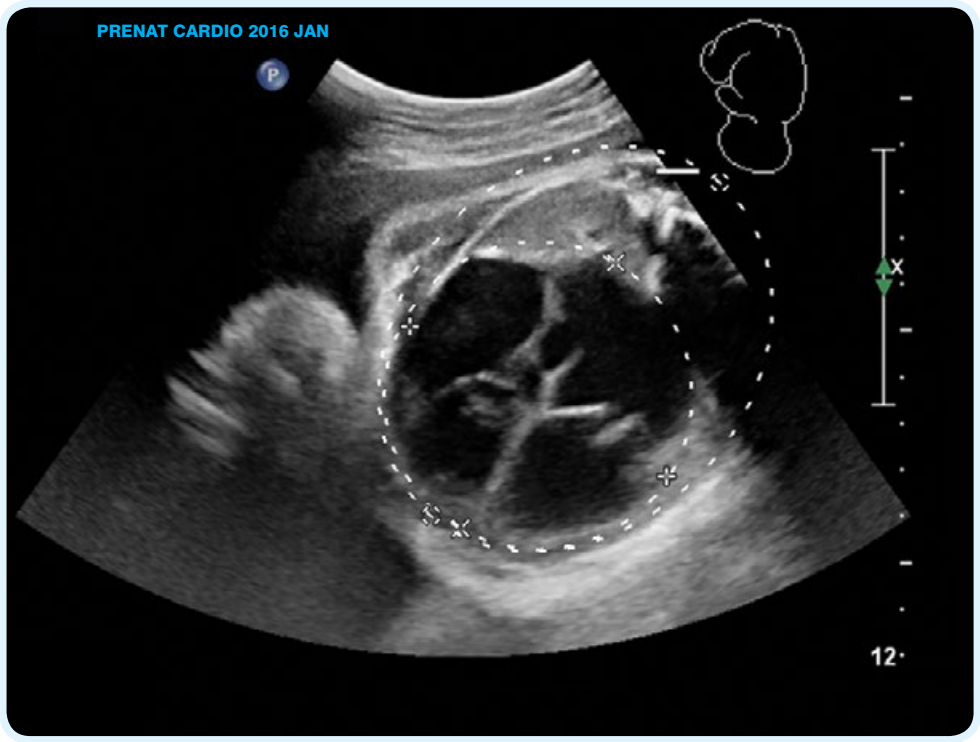


Fig. 3. Cardiomegaly at 34th week

reflux and urinary bladder-sided double pelvicalyceal system. In early school age years, reflux spontaneously regressed.

In early gestation due to upper respiratory tract infections, the patient accepted second-generation cephalosporin (Zinnat) and twice herpes labialis was treated with Acyclovirum (Heviran). The patient was under the care of an obstetrician and cardiologist due to chronic hypertension, which was treated from 2014, and by an endocrinologist for the treatment of hypothyroidism (Letrox, Potazek).

The initial ultrasound in the first trimester of pregnancy showed no abnormalities. The screening test was taken 12,6hbd - as the NT was 1.7 mm, also no deviations was found from flows in both DV and TR. The subsequent US conducted at the 19th and 20th week of pregnancy: normal AFI and normal biometry were observed; unilateral pyelectasis of the right kidney and protosystolic tricuspid valve regurgitation.

At the 24th week of pregnancy there was widening of the left atrium and aorto-pulmonary window was suspected (by obstetrician with Basic Fetal Heart Examination Certificate). This was the reason for referral fetus for our tertiary center.

In our Department at the 25,5 th week, the fetal heart size was at the upper limit (HA/CA 0, 4, AP diameter 35 mm and there was enlargement of asceding aorta and dilatation of sinus Valsalva of the aorta with communication with left ventricle. (Fig.1, 2). Cardiovascular profile score was assessed as 7 out of 10, due to the presence of cardiomegaly (minus 1) and regurgitation of the mitral, tricuspid and aortic valve (minus 2)

Between the 25,5th and 28, 2 weeks there was a similar haemodynamic situation but with further progress of cardiomegaly and Marfan syndrome was suspected. Fetal profile and hand -with long fingers and contractures of the joints. (Fig. 5, 6, 7).

In 32,4 weeks by LMM and 34,1 weeks by biometry ratio Ha / Ca was 0.66 and the AP - 49mm and as cardiac function deteriorated the transplacental therapy with digoxin therapy was initiated (standard protocol in our

Table 1 Selected echocardiography data of the fetus with Marfan syndrome

	Zinnat						**Digoxin**	
	12,6hbd	19,6hbd	24,4hbd	25,5hbd	28,2hbd	30,4hbd	32,4hbd	34,4hbd
Biometry	12,6hbd	20,5hbd	25,5hbd	26,2hbd	30,5hbd	32,4hbd	34,1hbd	35,6hbd
AFI	N	11	14	15	15	15	13	21
Ha/Ca		0,3		0,4	0,37	0,4	0,66	0,66
AP				35mm		46mm	49mm	60mm
CVPS score				7/10	7/10	7/10	6/10	3/10
Others	NT 1,7	TR, pyelectasis, choroid cysts weaves **HL - 22,4hbd from usg**	TR, MR, asymetry of left	TR, MR, AoR, PR Aneurysm of Valsalva sinus	+ aneurysm of the ascending aorta	AV Valle prolapse	enlargement of the ascending aorta aneurysm	
MCA (PI)			1,65	1,33	1,75	2,15	2,37 (early diastolic notch)	
UMB-A (PI)			1,2	1,1	1,35		1,7	

(1) AFI - amniotic fluid index- to determine the AFI we used a four-quadranttechnique
(2) HA/ CA-area surface of the heart/area surface of the chest
(3) AP - heart distance in mm.
(4) CVPS- cardiovascularprofile score
(5) MCA - The fetalmiddlecerebralartery (MCA) pulsalityindex (PI)
(6) UMB-A - UmbilicalArerial Doppler Pulsality index (PI)

institution). Two weeks later there was no improvement in cardiac function and progression of cardiomegaly was present: AP-60mm, Ha / Ca-0.6 (Fig 8). The relation between both atria and ventricles was 1:1, along with progression of atrioventricular valves regurgitation. Cardiovascular profile score was at that time 4 (minus 2 for heart size, minus 2 for regurgitations, minus 2 for umbilical vein pulsation).

In anticipation of fetal death or neonatal death, there was discussion about cesarean section and prematurity or conservative approach (just monitoring) or an attempt to administer digoxiny directly to the fetus. The third option was accepted by the patient and the day before the scheduled procedure the fetus was pronounced dead. Two days later, the pregnant woman gave birth vaginally to a dead newborn with morphological features of Marfan syndrome such as: elongated lower limbs, long fingers, and joint contractures and also crumpled ear. The genetic analysis is under evaluation. The summery of prenatal evaluation in this case is presented in Table 1.

DISCUSSION

Marfan Syndrome (MS) is rare 1 to 3/10 000 autosomal disorder based on mutation in gene located on chromosome 15q21.1 causing a fibrillinopathy which affects mainly the cardiovascular, skeletal and ocular system[1,2] but also the skin and nervous system[3,4].

Most of the prenatal cases are sporadic (25 %) – the de novo mutation appears to cluster in a certain region of the gene composed of exons 23 to 32[9]. The greatest contributors to disease morbidity and mortality are cardiac anomalies including: aorting root dilation (60%), aortic dissection, valvular prolapses (91% mitral valve prolapse) or insufficiency[5,10]. There is only one case in literature which describes neonatal MS with aneurysmal

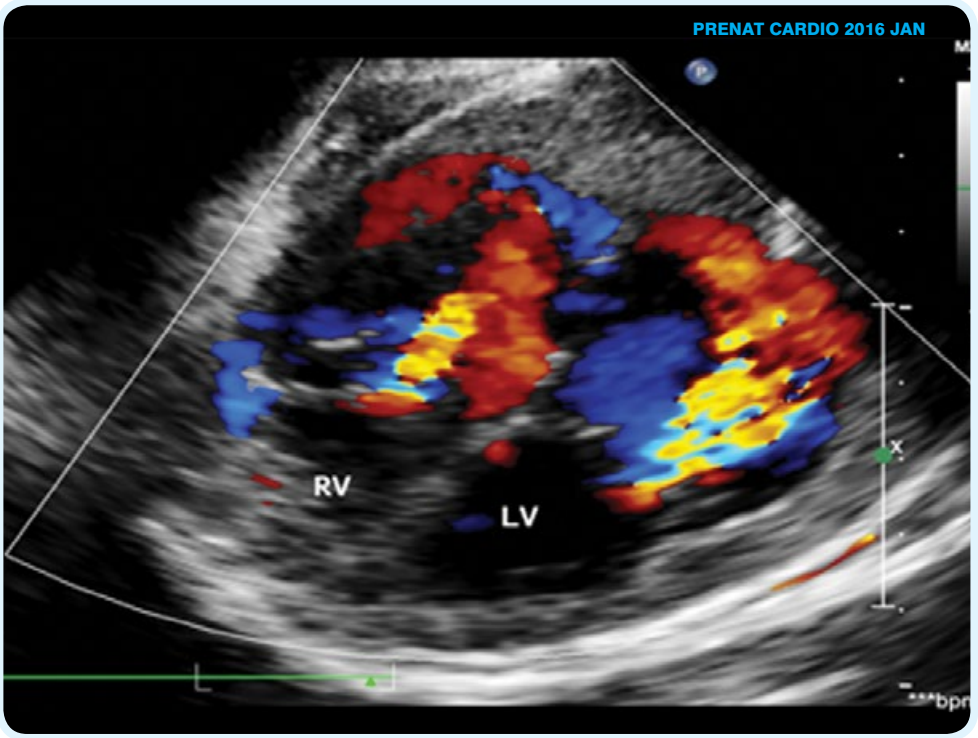


Fig. 4. Mitral and tricupid valve regurgitations at 34 th wk

Table 2. Sonographicand echocardiographic features of prenatal MS and current case

Author & year of publication	GA of initial ultrasound findings	Cardiomegaly	Dilatation of LVOT and/or other structures	Intracardiac flows	Prolaps	Other US findings	Termination	Intrauterine demise
Koenigsberg et al. -1981[13]	24					Long limb	YES	
Chaouiet al.- 1994[14]	37	YES	YES	AV insufficiency				
Lopeset al.- 1995[9]	34	YES	Dilation of aortic and pulmonary roots,	Mild TR, severe MR, Mild AoR and mild PR	AV	IUGR		
Ng et al.-1999[15]	29	YES	Dilated RA and RV , displastic TV	Severe TR		Slender Finders and toes		
Lopeset al.-2006[8]	33	YES	Aortic & pulmonary root dilation	Pulmonary atresia, dysplastic MV & TV		(Arachnodactyly, arthrogryposis, lung hypoplasia)		39 wks
Ramaswamy et al.-2006[16]	29	YES	Aortic &Pulmonary Root dilation,		AV			
Stadie et al.-2007[10]	22	YES	Aortic Root dilation	Mild TR, MR, AoR and PR		Long femur lenght Bilateral CPC		
Stadieet al.-2006[17]	28	YES	Aortic & Pulmonary Root dilation,		AV	Absent DV		
Anuwutnavin et al.-2014[2]	21		Aortic root dilation, Left heart disproportion, Left axis deviation, enlarging left side, mild right ventricular hypoplasia,	Mild TR,PR,	MV			
Zych-Krekora et.al current case	28	YES	Aortic and pulmonary root dilation,Left heart disproportion, Left axis	TR, AoR, PR	AV	choroid cysts, kidney pyelectasis		37
Total	Mean gest age: Min: 21 Max 37	9/10	9/10	MR=4 TR=7 PR=4 AoR=4	5/10	Long bones 2/10	1	2

TR - tricuspid valve regurgitation, MR- mitral valve regurgitation, AoR - aortic valve regurgitation, PR - pulmonary valve regurgittaion, A_ aortic valve, TV - tricuspid valve, DV- ductus venosus, IUGR- intrauterine growth retardation

pulmonary trunk with functional pulmonary atresia[2]. The main symptoms within the optical system are: bilateral ectopialentis, myopia, or retinal detachment. Symptoms within the skeletal system include: bone overgrowth, dolichostenomelia, scoliosis, or flexion contractures[5].

There are two kinds of MS, perinatal or neonatal and adult (classical). While most patients with the classical form of MS have an almost normal lifespan, the neonatal form is associated with a very bad prognosis – most die from cardiac failure in first two years of life[1,3,6]. The diagnosis of Marfan congenital syndrome relies on a set of defined clinical criteria "Ghent criteria" developed to facilitate recognition of the syndrome and improve patient management. Although both forms are autosomal dominant, the adult form has less severe symptoms within the cardiovascular system. While the primary cause of death in the classical form is due to aortic root disease, in neonatal presentation cardiac failure secondary to severe mitral regurgitation is a principal mechanism[7].

The first reported case of prenatal diagnosis based on the cardiovascular system was diagnosed in 1993 (and published by Chaoui In 1994), then in 2006 2 cases were diagnosed, and by 2014 there were 10[2,8,11]. Also, there is insensitive in detecting manifestations of MS in the first two trimesters[10].

Prenatal diagnosis for pregnancies at increased risk for MS is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15 to 18 weeks gestation or chorionic villus sampling CVS at approximately 10 to 12th weeks of gestation[10]. Unfortunately, it is not possible to diagnose the form, whether the neonatal or classical[7]. At this time, there is limited application for molecular testing and comprehensive clinical evaluation remains the most effective way to make a detection and diagnosis of MS, and still no possibility to find the MS caused by de novo mutation.

The diagnosis of Marfan syndrome in adults can be difficult, as many of the features are also identified within the normal population. Features appear in an age-dependent manner and there is substantial phenotypic variability between diseased individuals. There is also considerable overlap with other connective-tissue disorders such as congenital contractural arachnodactyly (CCA), Loeys-Dietz syndrome (LDS), Ehlers-Danlos syndrome type 4 (vascular type), arterial tortuosity syndrome and Shprintzen-Goldberg syndrome, which are covered by the Marfan Panel. If the patient has an isolated aortic aneurysm with no other Marfan-like organ manifestations, there is recommend to use the Blueprint Genetics Aorta Panel, which covers all syndromic and non-syndromic forms of aortic aneurysm disease[12].

While performing an ultrasound of the fetus with suspected MS, one must remember other similar rare syndromes - such as Archard syndrome or Beals-Hecht syndrome, but in which abnormal cardiac features are uncommon (15%)2. Beals-Hecht syndrome (congenital contractual arachnodactyly - CCA) - caused by mutation in the gene encoding fibrillin-2. Cardiac involvement is less frequent, mainly characterized by congenital heart defects such as- atrial or ventricular septal defect, aortic hypoplasia, interrupted aortic arch and absent postanatally ductus arteriosus[2]. Similarly, aortic root aneurysmatic dilation may be also seen in a patient with Loeys-Dietz syndrome[7]. A method of treating cardiovascular symptoms has changed significantly in recent years

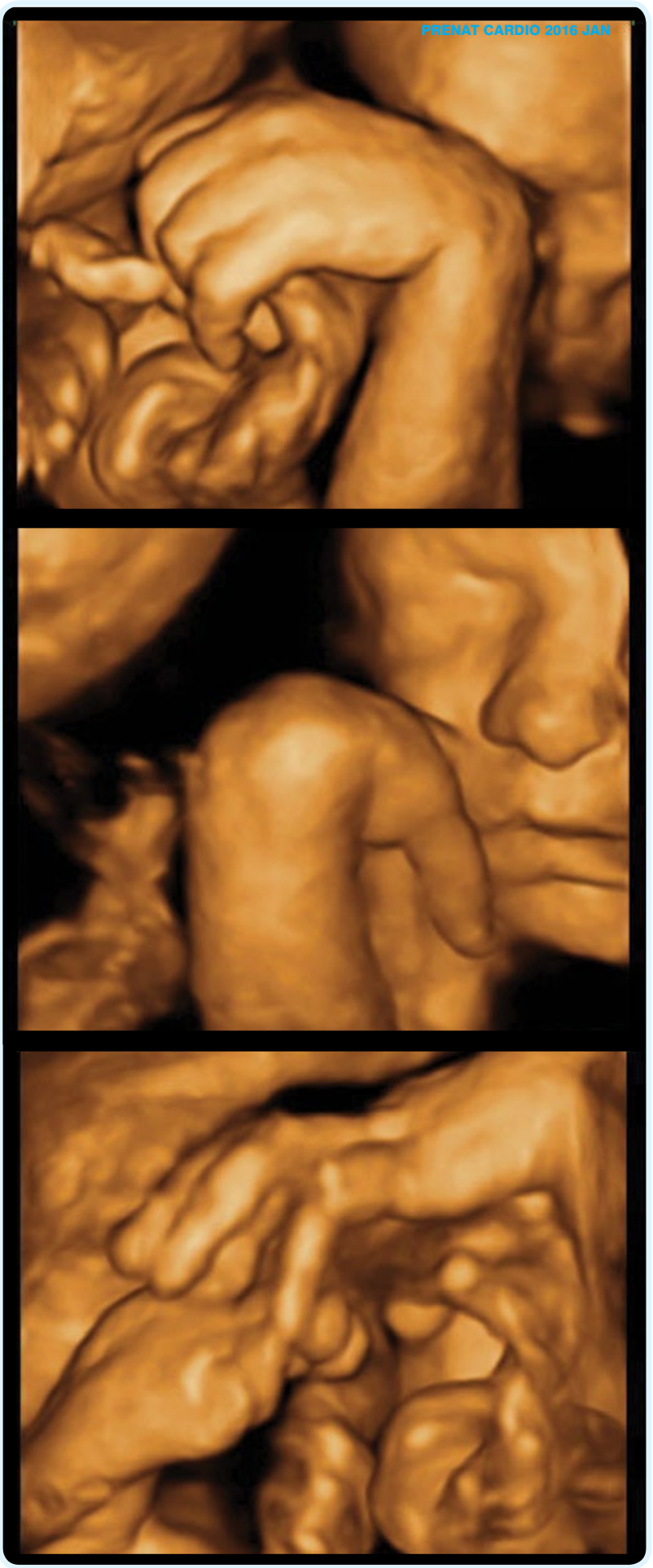


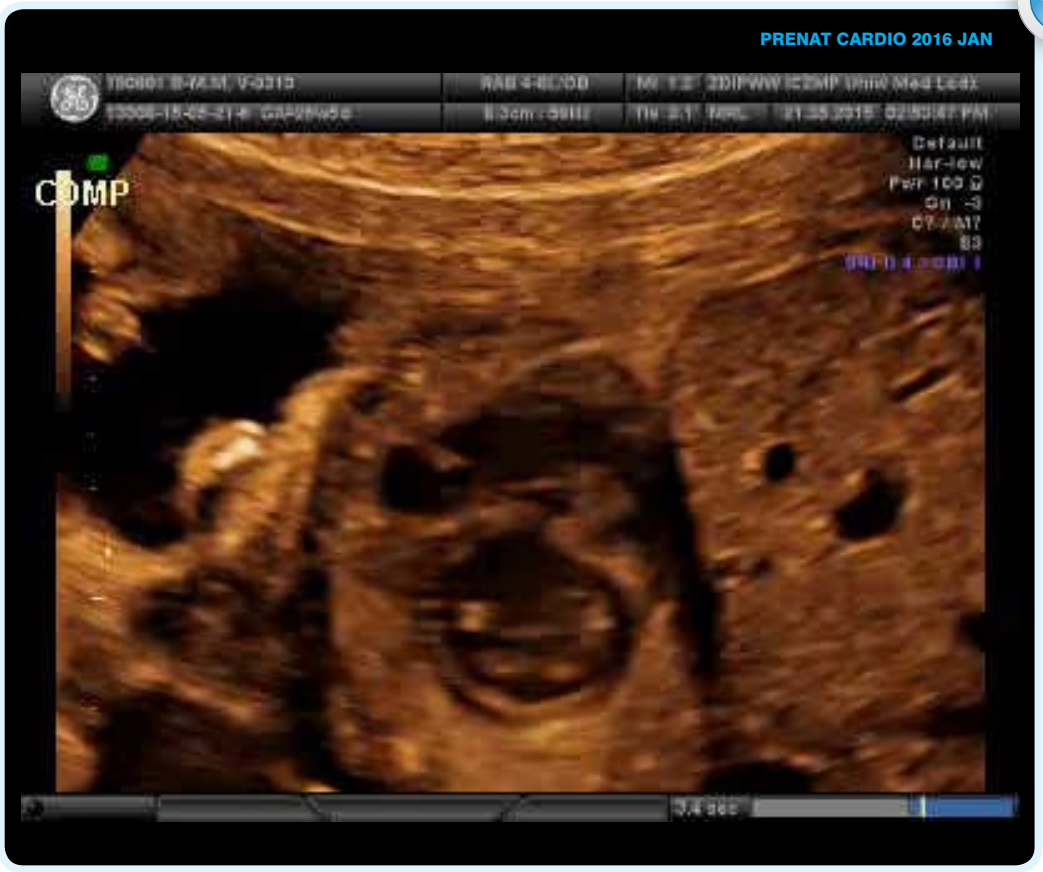
Fig.5,6,7. Joint contractures in 3d imag

due to the knowledge pathomechanism of the disease itself. The major role has TGF-beta, also losartan has been proven effective in the primary prevention of progressive aortic root dilation[5]. Perindopril therapy reduces arterial stiffness, central and peripheral pulse wave velocities and aortic root diameters[10].

The summary of the past cases published in literature and the current case is presented in Table 2.

CONCLUSION

Prenatal manifestations of Marfan Syndrome are usually cardiac anomalies: cardiomegaly, dilatation of aortic root sinus Valsalva rupture (first described in presented case: valvular insufficiency and heart failure).



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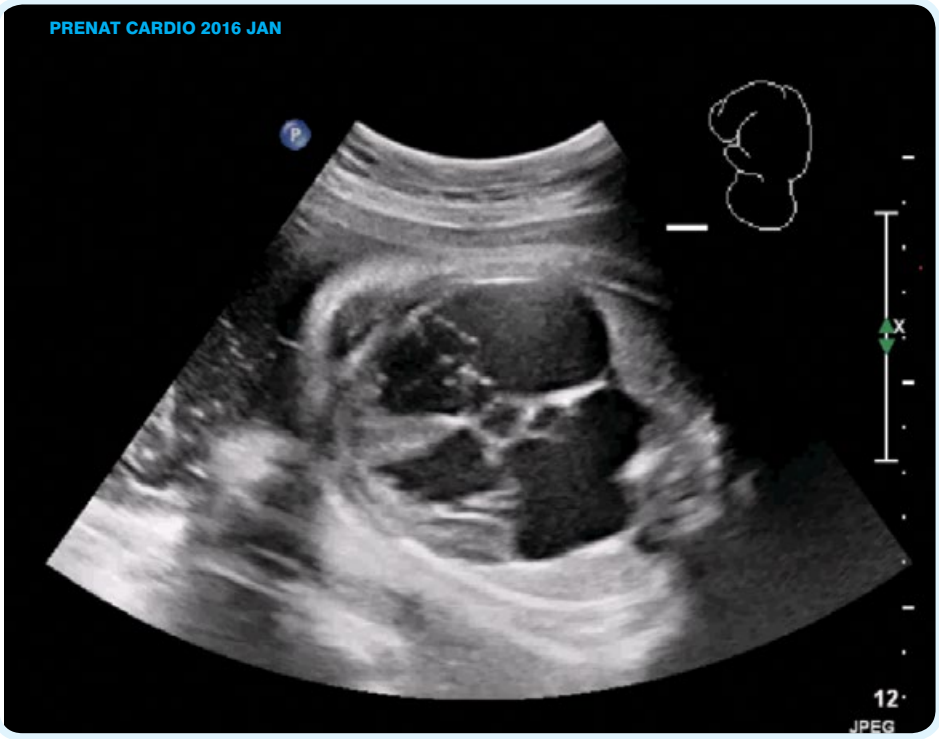

Fig.8. 34 weeks of pregnancy occupying almost the entire surface of the chest , the transversal diameter of the fetal heart was 60 mm

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Co-authors participations:

Katarzyna Zych-Krekora - first draft of manuscript, iterature search, submitting manuscript

Anna Wójtowicz - first cardiac evaluation, final diagnosis, work with the manuscript

Michał Krekora - work with manuscript, English version correction

Maciej Słodki - work with the manuscript, final version

Hughes Gentillon - work with manuscript

Maria Respondek - Liberska - author of the photos and cine, final version of the manuscript

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When this article was approved for final printing, we received information about the publication of a the same clinical case in another journal :

Anna Wójtowicz, Dagna Ochrem, Artur Dobosz, Hubert Huras, Maria Respondek-Liberska. Neonatal Marfan syndrome diagnosed prenatally. Ginekol Pol 2017, 88: 45