Case report - **CHD and ECM**

JACOBSEN SYNDROME - PRENATAL AND POSTNATAL PHENOTYPIC CHANGES - CASE REPORT AND REVIEW

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Abstract

11 deletion syndrome, Jacobsen syndrome (JBS), is a rare genetic abnormality associated with a wide variety of phenotypes. There are only a few case reports of JBS diagnosed prenatally, however majority resulting in termination of pregnancy. We present for the first time a prenatal diagnosis of JBS with congenital heart defect common arterial trunk type I (CAT) and the changing phenotype during fetal and postnatal life.

Key words: *11q deletion syndrome, fetal and neonatal phenotype, common arterial trunk, genetic disorder*

INTRODUCTION

Jacobsen syndrome (JBS; 11q deletion syndrome) is a contiguous gene syndrome due to a partial deletion of the long arm of chromosome 11. It was first described in 1973 by Petra Jacobsen in a family with an unbalanced 11;21 translocation1. The incidence is estimated at 1:100000, with female to male ratio 2:1. More than 200 cases have been reported[2,3], with only a few diagnosed prenatally (table 1)4-13, and none of them covered a long-term observation. Congenital heart disease affects approximately 56% of JBS patients[2].

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We report a case of Jacobsen syndrome with common arterial trunk (CAT) type I monitored during fetal life and infancy, paying attention to changes in the phenotype over time.

CASE

A 35-year-old woman, gravida 2, para 1, was evaluated 8 months after delivery of a healthy child. The family history was unremarkable. The patient admitted flu-like symptoms and vaginal discharge in the 1st trimester. The ultrasound screening scan at 12 weeks showed a NT of 2,2 mm for CRL 61,0 mm. The mother's serum screening test showed a positive result for Down syndrome, with a DSR of 1/8. Genetic amniocentesis performed at 15 weeks' gestation revealed a karyotype of 46,XY,del(11)(q23)(Genetic Department in Wroclaw Medical University). The patient was informed about the availability of termination of pregnancy and the indications for fetal echocardiography if continued; she declined termination. At 20 wks, obstetric ultrasound scan showed lemon sign of the fetal calvarium and low-set ears. Heart defect was suspected. The woman was referred to our tertiary center for further evaluation of

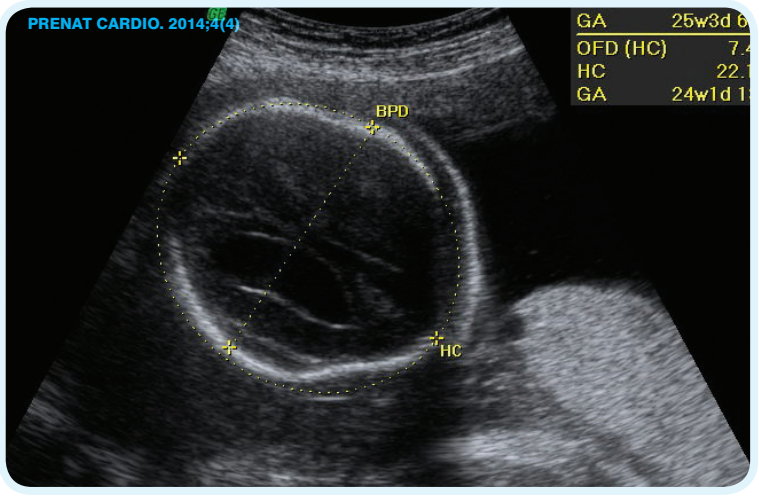

Figure 1. Fetal head at 24th week of gestation with unilateral ventriculomegaly and trigonocephaly

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Author, year	Gestation of amniocentesis (wks)	Karyotype	Course of pregnancy	Delivery/ termination of pregnancy (wks)	Postnatal outcome
McClelland et al., 1998	20	46,XX,del(11)(q23)	20 wks NT	24 TOP	-
Porter et al., 1999	15	46,XY,del(11)(q24.2)/46,XY	11 wks NT	TOP	-
Chao et al., 2001	19	46,XX,der(11)t(11;18)(q24;q21.3)		23 TOP	-
Chen et al., 2001	20	46,XX,del(11)(q23)	20 wks right duplex renal system, pyelectasis, bilateral cleft lip and palate	TOP	-
Baena et al., 2003	20	del(11q)	Diaphragmatic hernia	TOP	-
Baena et al., 2003	20	del(11q)	HLHS		Neonatal death
Chen et al., 2004 *Case 1*	20	46,XY,del(11)(q24.2)	18 wks serum-screening test positive for neural tube defects 1/225 22 wks short femurs, short humeri, overlapping of the toes	24 TOP	
Chen et al., 2004 *Case 2*	18	46,XX,del(11)(q24.1)	No evident abnormalities on US	20 TOP	-
Boehm et al., 2006	17	46,XX,del(11)(q23)	17 wks oligohydramnios, reduced movements of the fetus 20 wks cerebral ventricular dilatation, IUGR	20 TOP	
Sanz-Cortes et al., 2007	20	46,XX,del(11)(q23)	20 wks calyceal and pelvic dilatation in the left kidney, facial dysmorphism 3D	21 TOP	-
Vaduga et al., 2007	21	46,XY[16]/46,XY,del(11)(q23)[3]	21 wks serum-screening test positive for Down syndrome 1/78 25 wks polyhydramnios, macrocephaly, facial dysmorphism, bilateral pyelectasis, small stomach size Umbilical cord blood sampling: Paris-Trousseau syndrome	32 TOP	-
Kato et al., 2014	after 29	46,XX,del(11)(q24)	27 wks IUGR 29 wks cleft lip	38 CS 2282g Apgar 8/9	Spina bifida, Limb dystonia, Hydronephrosis, Cleft lip, Anemia, Low platelets, AV insuff., Ear ossicle anomaly

Table 1. Literature data on prenatal diagnostics of JBS4-13

congenital malformations. Genetic ultrasound and fetal echocardiography were performed 5 times: at the 25, 31, 36 and twice at 39 weeks' gestation.

Atypical skull and CNS were difficult to interpret in every examination including retrospective evaluation, possibly due to microcephaly (Fig.1, 2, 3). Neonatal brain MRI scan showed a small right hemisphere with severe hypoplasia of the parietal and occipital lobes, unilateral lissencephaly and an assymetrical undilated ventricular system (Fig.4).

Despite the known genetic syndrome there were no evidence of prenatal facial dysmorphism on 3D surface rendering (Fig5/6). Abnormal features of the fetal face were also not evident in the immediate neonatal period (Fig.7).

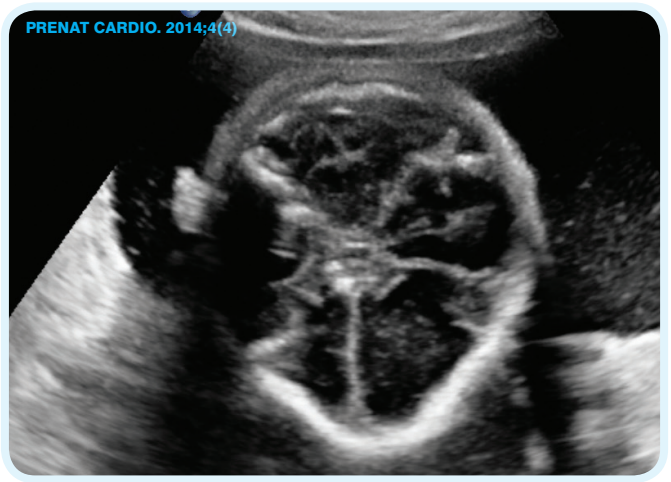


Figure 2. Fetal head at 31st week of gestation. Trigonocephaly

Wks Gestation	24	31	36	38	Neonate
Biometry	Normal	Normal	SGA	SGA	
Central Nervous System	Trigonocephaly Mild unilateral ventriculomegaly Partial agenesis of the corpus callosum	Trigonocephaly No unilateral ventriculomegaly Microcephaly	Trigonocephaly Mild unilateral ventriculomegaly	Trigonocephaly Mild unilateral ventriculomegaly Mild hemispheric asymmetry	Small right hemisphere, lissencephaly Ventricular system not dilated, assymetrical
Face in 3D	No anomalies		No anomalies, prominent ears	No evident anomalies	Thickened frontal suture, narrow BPD, broad nasal bridge, deep set eyes
Heart anatomy	TAC A:V 1:1 VSD 5mm	TAC A:V 1:1 VSD 5mm	TAC A:V relations normal VSD 5mm	TAC relations normal 1: 2 VSD 5mm	TAC type I
Functional anomalies	Tricuspid regurgitation	Tricuspid regurgitation	No TR Septum hypertrophy,	No TR Septum hypertrophy, Insufficieny of the common valve	Common valve insuff
CVPS	8	8	10	10	-
Thymus	Not seen	Difficult to assess	L-9cm, 26 x 15x 12mm	L-9cm, 26 x 15 x 12mm	Normal size
Umbilical cord (3 vessels)	Normal flows	Normal flows	Normal flows, Long cord, Peripheral umbilical cord insertion	Normal flows, Long cord, Peripheral umbilical cord insertion	-
AFI	21	24	20	20	-

Table 2. Phenotypic changes in JBS patient during fetal (25, 31, 36 and 38 weeks' gestation) and neonatal period

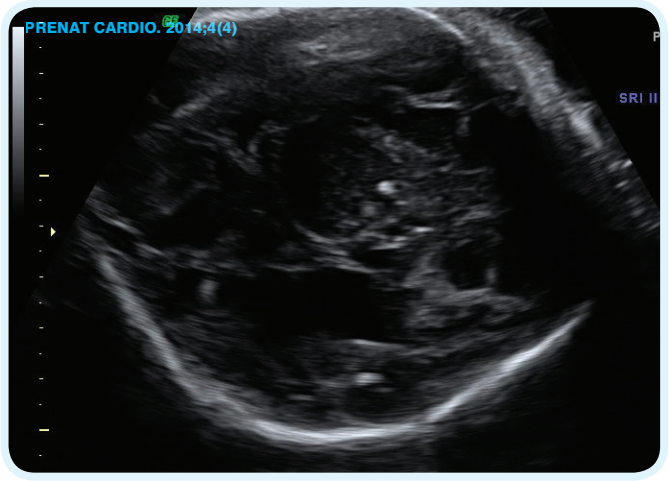


Figure 3. Fetal head at 38th week of gestation with asymmetrical ventriculomegaly and trigonocephaly

On the 3rd day of postnatal life neurologic examination revealed dysphagia. Muscle tone was normal. Over the following weeks the newborn developed a thickened frontal suture, narrow BPD, broad nasal bridge and deep set eyes (Fig 8).

The prenatal four chamber view of the heart showed a normal interatrial septum with a long FO valve flap. At 24 wks the atrium to ventricle size ratio was 1:1. There was a mild functional tricuspid insufficiency (Fig.9). Left and right diastolic dysfunction and pericardial effusion of 3 mm were observed. A 5 mm outlet type VSD was

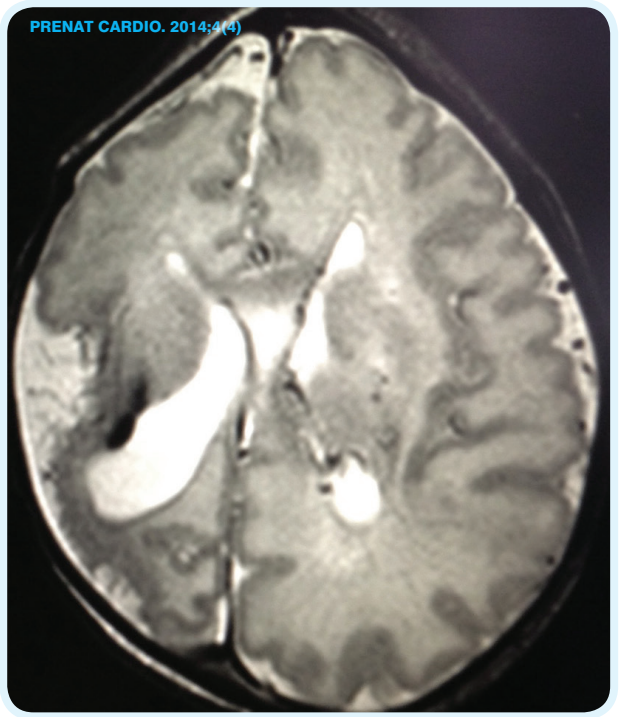


Figure 4. Neonatal MRI 10 days later

detected. There was a single arterial vessel arising above it, bifurcating. One branch, after giving 3 cranial vessels, formed the descending aorta. The other branch split in two, in the shape of a "Y", and the diagnosis of common

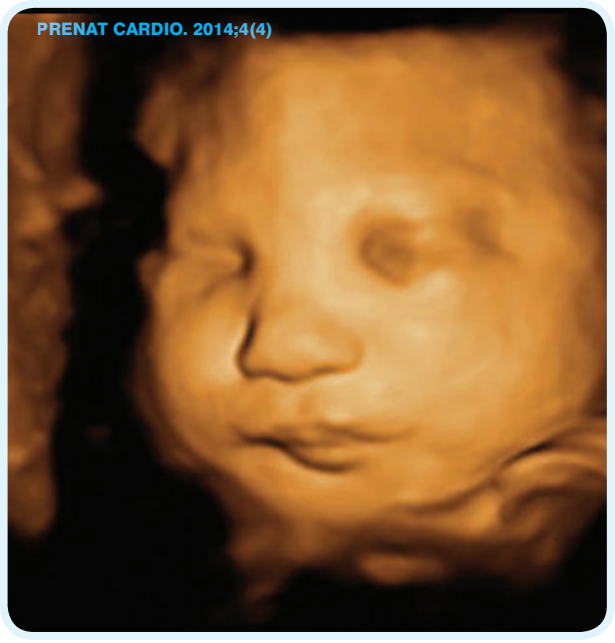


Figure 5. Fetal face at 38th week of gestation

Figure 6. Neonate during the 1st day of life (photo with parents permission)

arterial trunk (CAT) type I was made (Fig.10). The fetus was given 8 points on the cardiovascular performance score (CVPS).

At 36 weeks' gestation a spontaneous hemodynamic improvement occurred. Ventricular contractility was 37% and 50% for the right and left ventricle, respectively. Tricuspid insufficiency, pericardial effusion and AV disproportion subsided. A mild insufficiency of common semilunar valve appeared. Cardiac hypertrophy - interventricular septum thickness 6 mm - was diagnosed, and the CVPS increased to 10 points (table 2). The AFI remained mildly increased at the level of 20-24 cm. The umbilical cord had a marginal attachment and was looping, which was described as 'garter on the inferior limb' and 'tie on the belly'.

At 39 weeks' gestation, cesarean section was performed due to abnormal CTG. A baby boy, Apgar 7 (pH 7.3), weighing 2670g was breathing on his own. Due to coagulopathy (PLT 34-42 000/μl) he was given FFP.

Neonatal echocardiography and angioCT confirmed prenatal diagnosis of TAC type I (Fig. 11). Pulmonary artery banding was performed on the 26th day of life. The boy was extubated 3 days after the procedure. At the age of 5 weeks the infant was stable gaining weight (3600) and discharged home.

DISCUSSION

Case reports in literature mainly present JBS patients diagnosed late in childhood due to neurological symptoms. Psychomotor retardation is observed in 97%[14]. Brain MRI scanning shows abnormalities in 51%[2]. The most common are agenesis of the corpus callosum, cerebellar hypoplasia, pachygyria, and ventricular dilation[15,16]. White matter abnormalities, interpreted as delay of myelinization[19], are also common[17,18]. Coexistence of 11q deletion and periventricular nodular heterotopia has been described[20]. JBS is associated with ADHD, schizophrenia and bipolar affective disorder[21,22]. About 2/3 of cardiac defects in JBS are VSD and left-sided obstructive lesions: valvular, HLHS, Shone's syndrome[2]. Conotruncal anomalies, which are relatively rare in this condition, are probably caused by deletion of ADAMTS8, which is involved in regulation of angiogenesis[23,24]. 11q23 qter contains approximately 342 genes. The majority (85%) of JBS cases are caused by a *de novo* deletion. Other common causes are translocation and ring chormosome[1,15,26]. About 10% are due to extensive expansion of CGG repeats at the FRA11B[27]. With a broad spectrum of phenotypic features (table 3), only half of patients are diagnosed before the age of 1[14]. Table 4 presents candidate genes for phenotypic characters in JBS.

Usual postnatal features include ocular hypertelorism, downslanting palpebral fissures, strabismus, palpebral ptosis, flat nasal bridge, thin upper lip, trigonocephaly, small low set ears and retrognathia. So far evolution in prenatal and postnatal phenotype has been described only in Apert syndrome[43].

The haemodynamic mild changes in the fetal heart (tricuspid insufficiency, pericardial effusion) with spontaneous regression were not significant and might have been related to maternal viral infection in the first half of pregnancy.

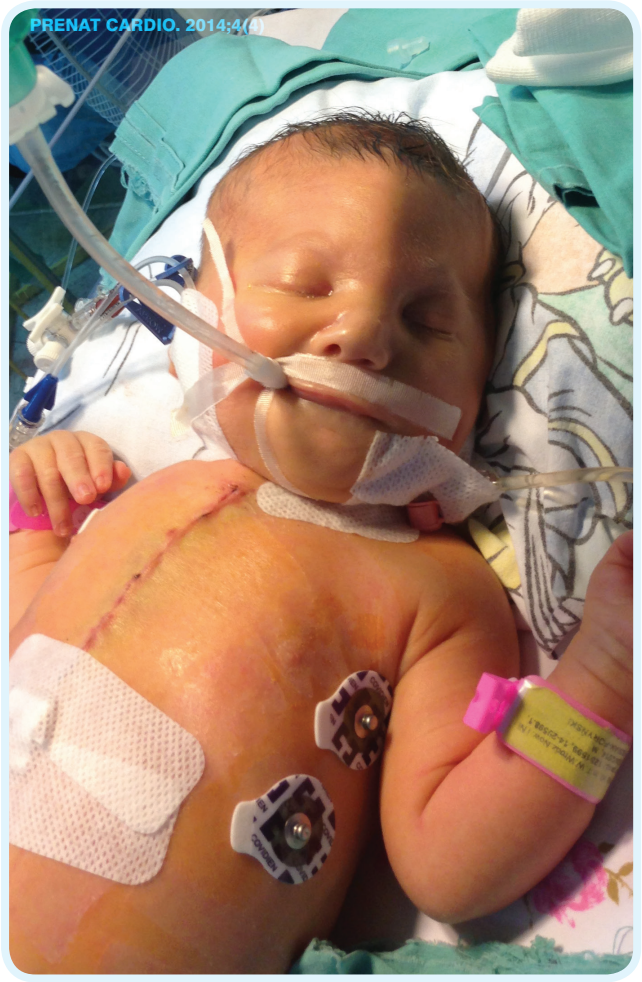
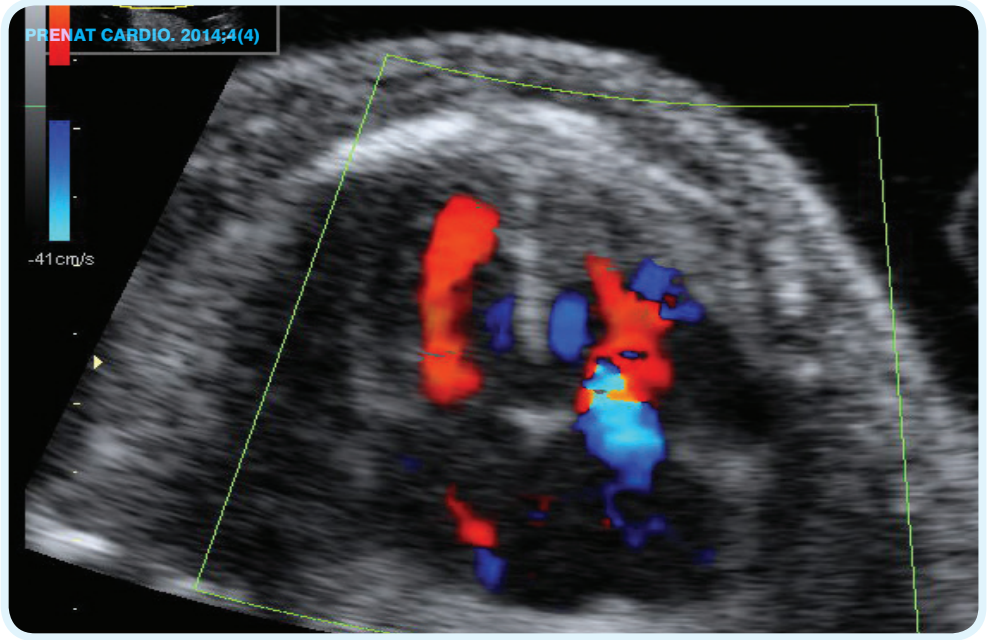


Figure 7. Infant on 37th day (after cardiac surgery – banding of the pulmonaryartery). Photo with parents' permission; Cardio SurgeryDepartment Polish Mother's Research Institute, Chief: Prof. J. Moll

Figure 8. Fetal heart at 24th week of gestation: the 4 chamber view with tricuspid valve regurgitation and atria: ventricles relations 1:1



Group of symptoms	Common symptoms
Neurologic [14,15,16,17,18,20]	Psychomotor retardation, corpus callosum agenesis, cerebellar hypoplasia, pachygiria, ventricular dilatation, abnormalities of the white matter, periventricular nodular heterotopia
Psychiatric[21,22]	ADHD, schizophrenia, bipolar affective disorder
Cardiac[14]	VSD, left heart defects
Haematologic[28,29,30,31,32]	Thrombocytopenia/ Paris-Trousseau syndrome
Ophthalmologic [33]	Hypertelorism, epicanthal fold, ptosis, down-slanting fissures, strabismus, ocular coloboma, retinal vascular tortuosity, refractive error
Otolaryngologic[14]	Hearing deficits
Endocrine[34]	IGF-1, TSH deficiency
Orthopedic[2,20,35,36]	Transverse limb reduction defect, hand and foot abnormalities
Gastrointestinal[14]	Pyloric stenosis
Genitourinary and renal[14]	Structural kidney defects, undescended testes

Table 3. Clinical symptoms of JBS

Genes	Phenotype
KIRREL3[37]	Neurocognitive delay
KCNJ5[37]	Long QT syndrome 13
B3GAT1[38]	Affective bipolar disorder
BSX[39]	Cognitive impairment
NRGN[39]	Auditory attention deficit
ADAMTS8[23]	Conotruncal heart defect
FEZ1, RICS[23]	Abnormalities of the white matter
KCNJ1[23]	Antenatal Bartter syndrome type 2
TECTA[40]	Neurosensorial deafness
FLI-1[41]	Paris-Trousseau Syndrome
BARX-2[42]	Facial dysmorphism, craniosynostosis
ETS1[20]	Transverse limb reduction defect

Table 4. Candidate genes for JBS features

In this report we document the value of prenatal longitudinal ultrasound monitoring as an additional diagnostic tool, as compared with single cross sectional evaluation (Fig. 12, 13). We also stress that 3D of ultrasound of the fetal face may have less diagnostic value in comparison with echocardiographic findings in confirming structural defects in a genetic syndrome.

Postnatal JBS phenotype may resemble Noonan, Turner or Kabuki syndrome and neonatal thrombocytopenia is often attributed to sepsis. Making a diagnosis of JBS requires a cytogenetic test[2].

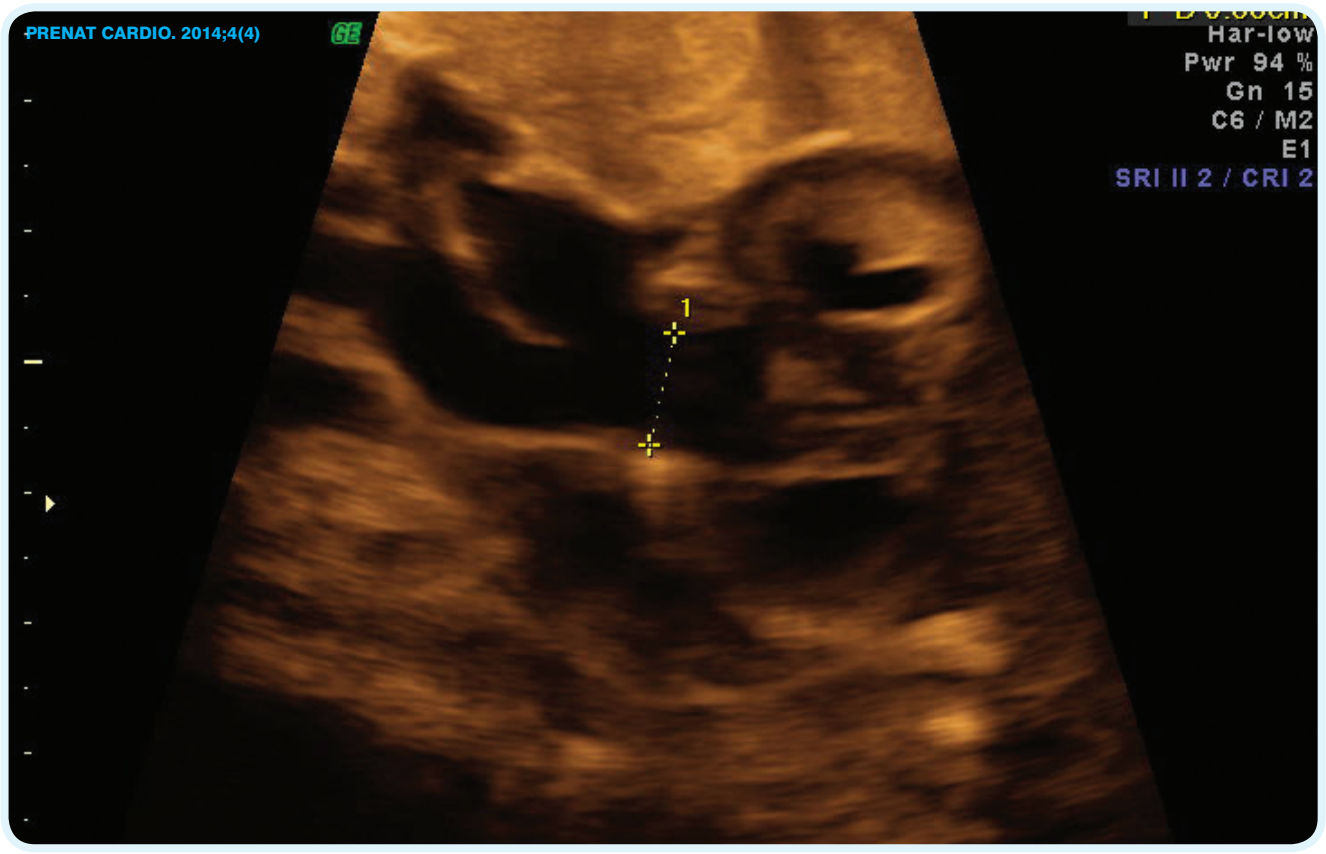


Figure 9. Fetal heart in long axis view with truncus arteriosus

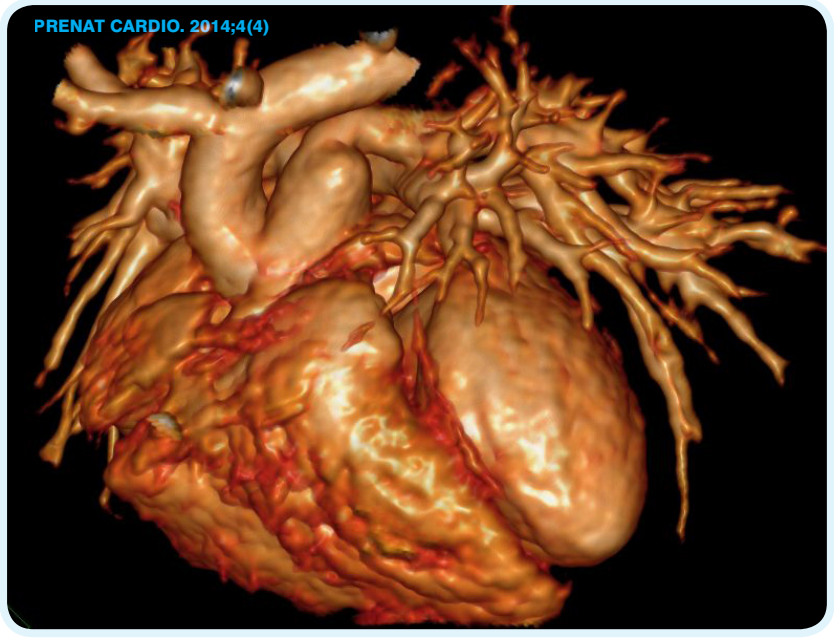


Figure 10. Neonatal angio CT before cardiac surgery (kindess of support from Radiology Department of our Institute)

CONCLUSION

We report the first case of Jacobsen syndrome describing, in addition to prenatal cytogenetic diagnostics, longitudinal observation in the second half of pregnancy and the early neonatal period: the fetal head, face, heart, biometry and postnatal observations demonstrate the changes in CNS and craniofacial phenotype.

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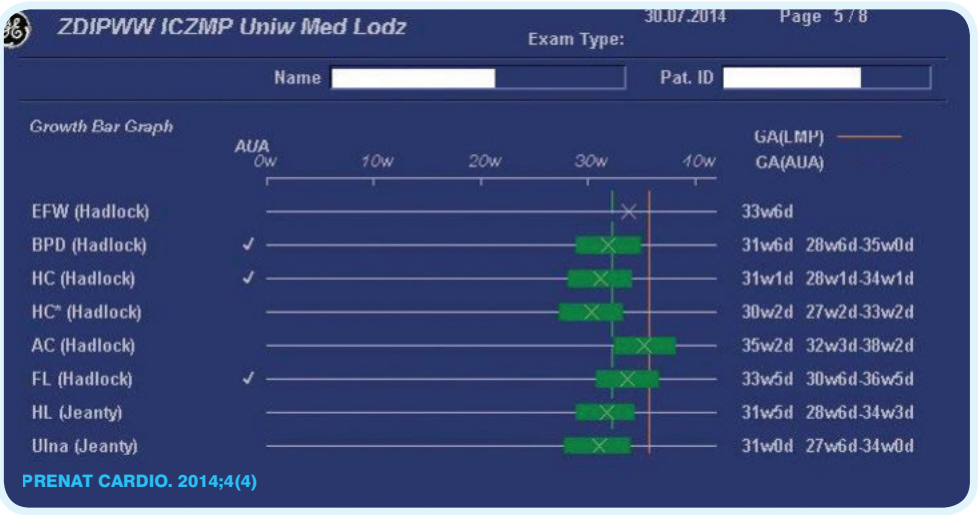

Figure 11. Fetal biometry suggesting microcephaly

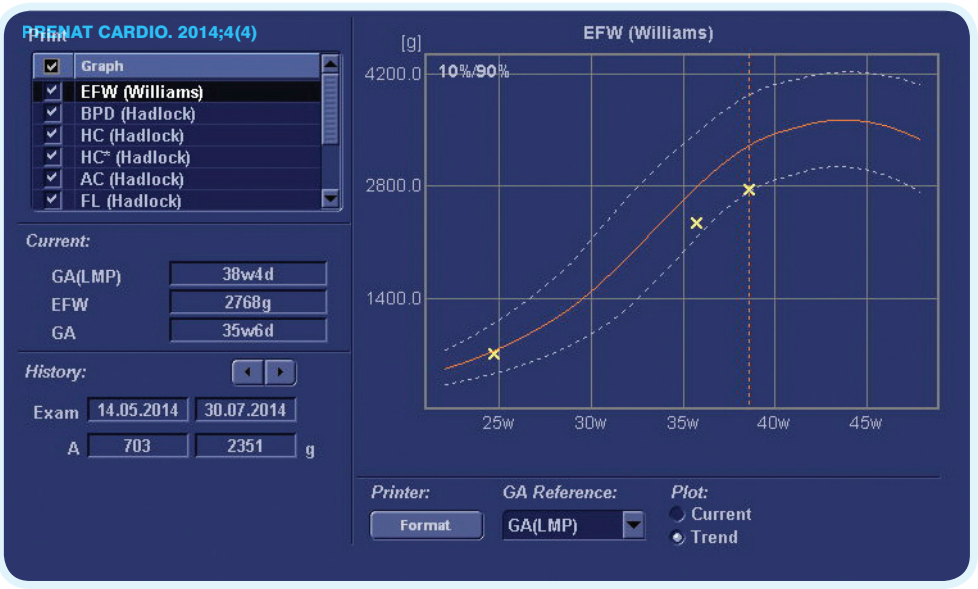

Figure 12. Fetal biometry during the second half of gestation

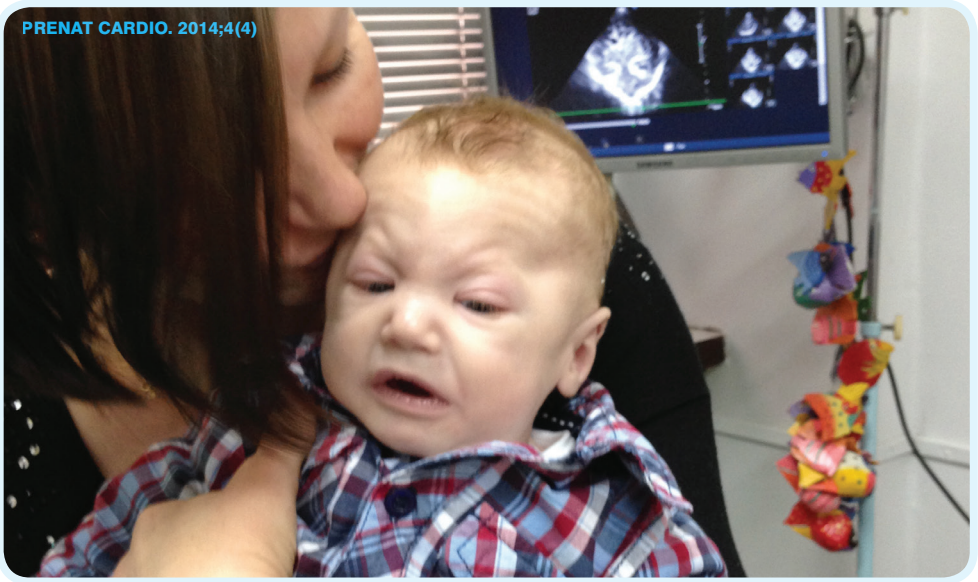

Figure 13. Our patient with his mom at 3 months of age (photo with parents permission). On the wall behind his head the last transfonatell scan on TV screen

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