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**What is already known on this topic?**

- Deletion of the 7q11.23 region causes the Williams Beuren syndrome (WBS). The reciprocal duplication is responsible for a distinctive although less severe neurodevelopmental disorder
- Diagnosis of WBS is usually suspected postnatally in infants but its prenatal presentation remains challenging

**What does this study add?**

- Largest series of fetuses with a 7q11.23 deletion or a 7q11.23 duplication
- Antenatal ultrasound findings of prenatal 7q11.23 copy number variations

**Abstract**

Objective: We aimed to gather fetal cases carrying a 7q11.23 copy number variation (CNV) and collect precise clinical data to broaden knowledge of antenatal features in these syndromes.

Methods: We retrospectively recruited unrelated cases with 7q11.23 deletion, known as Williams-Beuren syndrome (WBS), or 7q11.23 duplication who had prenatal ultrasound findings. We collected laboratory and clinical data, fetal ultrasound, cardiac ultrasound and fetal autopsy reports from 18 prenatal diagnostic centers throughout France.

Results: 40 fetuses with WBS were collected and the most common features were intra-uterine growth retardation (IUGR) (70,0%, 28/40), cardiovascular defects (30,0%, 12/40), polyhydramnios (17,5%, 7/40) and protruding tongue (15,0%, 6/40). Fetal autopsy reports were available for 11 cases and were compared with ultrasound prenatal features. Four cases of fetuses with 7q11.23 microduplication were collected and prenatal ultrasound signs were variable and often isolated.

Conclusion: This work strengthens the fact that 7q11.23 CNVs are associated with a broad spectrum of antenatal presentations. IUGR and cardiovascular defects were the most frequent ultrasound signs. By reporting the biggest series of antenatal WBS, we aim to better delineate distinctive signs in fetuses with 7q11.23 CNVs.

Keywords: Williams syndrome, 7q11.23 microduplication, prenatal diagnosis

**Acknowledgment**

None

**Main text**

**Introduction**

Williams-Beuren syndrome (WBS) is a well-known genetic disorder that occurs in about 1/7500 – 1/20000 births, caused by a heterozygous recurrent deletion of WBS region at 7q11.23

ranging from 1.55 to 1.84 Mb [1–3]. In its typical form, patients display dysmorphic features, intellectual deficiency with a singular behavioral profile, cardiovascular and endocrine defects. Mean age at diagnosis is 5.38 years according to Ferrero *et al*[1]. Prenatal diagnosis of WBS remains challenging because no specific ultrasound (US) signs have emerged with only 30 cases described with antenatal manifestations to date [4–11]. The most relevant features reported in WBS fetuses were intra-uterine growth retardation (IUGR), cardiovascular defects including elastin aortopathy (narrowing of the aorta, right aortic arch and persistent left superior vena cava) and ventricular septal defect (VSD) [4,5]. One case with premature closure of the ductus arteriosus (PCDA) was reported by Srinivasan et al[12]. About 80% of WBS patients suffer from cardiovascular defects, which is the main cause of morbidity and mortality in WBS[1,13–16]. These patients require early diagnosis and treatment. The Elastin (*ELN)* gene, included in WBS critical region (WBSCR), encodes a component of elastic fibers and plays a critical role in arterial morphogenesis[17]. It has been established that *ELN* is responsible for cardiovascular and connective tissue defects in WBS patients, as heterozygous nucleotide variants were also described in patients with non-syndromic supravalvular aortic stenosis (SVAS)[18,19]. The most common cardiovascular features of *ELN* haploinsufficiency include (in order of frequency): SVAS, peripheral pulmonary artery stenosis, pulmonary valve stenosis, supravalvular pulmonary stenosis, aortic stenosis, coarctation of the aorta, bicuspid aortic valve, mitral valve anomaly and renal artery stenosis[17–19].

Duplication of the WBSCR is known to cause the 7q11.23 duplication syndrome associated with developmental delay, hypotonia, seizures, anxiety, craniofacial features and aortic dilation[20]. It occurs less frequently than WBS, and its lack of intrauterine phenotype explain that only three cases of 7q11.23 duplication with prenatal signs have been reported[5,8].

Here, we report 40 cases of WBS and 4 cases of reciprocal 7q11.23 microduplication with prenatal manifestations. To the best of our knowledge, this is the largest series of WBS prenatal phenotyping with contribution of fetopathology. The aim of the study was to possibly better delineate distinctive signs and derive a recognizable more precise phenotype in fetuses

with copy number variations (CNVs) in 7q11.23 by collecting medical record from a large series.



**Material and methods**

Study Population

We retrospectively recruited 44 unrelated fetuses affected by 7q11.23 deletion or duplication showing prenatal ultrasound findings and diagnosed either prenatally or postnatally between 1996 and 2022. This work was conducted thanks to the AchroPuce network (https://acpa-achropuce.com/) and the network of French cytogenetics laboratories (www.eaclf.org). A total of 18 French centers (university and regional hospitals) contributed to this work. Demographic data, obstetrical history, intrauterine phenotype, pregnancy outcome and genotypes were collected from local geneticists and obstetricians. US fetal examination and autopsy reports were collected, when available, to provide a precise description of the phenotype. Pregnant women were systematically referred to a fetal cardiologist when abnormal cardiac features were suspected during US follow up, or after 7q11.23 CNVs was identified. All cases had prenatal abnormalities detected by routine ultrasound examination and 21 fetuses underwent specific echocardiography. Post-natal evaluation and follow-up were also retrieved from pediatricians. Ethical approval was not required for this retrospective study.

In France, all the pregnant women (735196 live births in 2020) were offered a trisomy 21 screening by first-trimester biochemical serum markers, then a non-invasive prenatal testing was offered if the trisomy 21 combined risk is >1/1000. About 2% of pregnant women underwent an invasive prenatal diagnosis in France in 2020. All the chorionic villi samples (CVS)/amniocenteses performed for US fetal anomalies are analyzed by chromosomal microarray (CMA). Medical termination of pregnancy (TOP) can be requested at any time during pregnancy if an incurable and severe disease is diagnosed by genetic testing or antenatal imaging. In case of twin pregnancy, selective TOP can be performed in the affected fetus. Fetal autopsy was proposed to all pregnant women who chose medical TOP.

Cytogenetic analysis

After informed consent of parents for genetic testing, amniotic fluid or CVS were obtained by obstetricians using their standard clinical procedures in the context of prenatal chromosomal diagnosis. In case of CVS before cytogenetic examinations (FISH, conventional karyotyping, and CMA), a double enzymatic digestion (trypsin then collagenase) was applied to the CVS in order to ensure adequate cell dissociation and avoid any possible cytogenetic discrepancy associated with the presence of cytotrophoblast cells. Blood samples were collected in post-natal diagnosis and from parents. Different cytogenetic techniques were then performed according to local laboratory's routine namely CMA (array comparative genomic hybridization (aCGH) or Single Nucleotide Polymorphism array (SNPa)), specific WBS FISH or prenatal BACs-on-BEADS™ (BoB's). There is no consensus on the cytogenetic methodology for CNVs detection but all are related to standard of care over the time period of the study.

**Results**

The median maternal age was 31 years, ranging from 20 to 42. No relevant familial history was noted. Mean weeks of gestation (WG) at diagnosis was 28.2±6.3. Two patients (case#2 and #6) had post-natal diagnosis but were included because antenatal signs were detected during pregnancy. Indications for genetic investigations included IUGR (47,8%, 21/44), cardiovascular defects (25%, 11/44), polyhydramnios (11,4%, 5/44), short long bones (SLB) and/or short fetal femur length (SFFL) (9,1%, 4/44) and increased nuchal translucency (6,8%, 3/44). Fetal autopsy was performed in 11 cases (Table 1, Table 2).

Cytogenetics

Among the 44 fetuses, 38 thirty-nine genetic analyses were performed after amniocentesis, 4 were done after choriocentesis, 1 on fetal cordonal blood sampling and 1 was done postnatally on blood sampling. In 34 cases, deletions detected by aCGH encompassed the WBSCR, sizes ranged from 1.37 to 1.7 Mb, whereas 2 deletions were identified by BoB's, 2 by FISH using specific WBS probes and 2 by SNPa (size 1.4 and 1.87 Mb) (Table 1). All duplications were detected by aCGH and also encompassed the WBSCR with sizes ranging from 1.41 to 1.8 Mb (Table 2). All fetuses had isolated 7q11.23 CNVs.

Parental analysis of 7q11.23 deletion showed that deletions occurred *de novo* in 24 cases. In 16 cases the segregation couldn't be provided due to missing data or unavailable parents' samples. Parental analysis of 7q11.23 duplication showed that two CNVs occurred *de novo* (case#42 and #44), and two were inherited (parental phenotype not available).

Clinical findings

7q11.23 microdeletion

Routine US follow up was collected for all 40 cases and specific fetal echocardiography was available for 21 fetuses. The most frequent abnormal features were IUGR (70,0%, 28/40), cardiovascular defects (30,0%, 12/40), SLB and/or SFFL (25,0%, 10/40), polyhydramnios (17,5%, 7/40) and protruding tongue (15,0%, 6/40) (Table 3, Fig1). The latter was noted after 32 WG in all fetuses. Acute estimation of fetal weight and its follow up was available for 16 cases. Of note, growth restriction began at 2$^{nd}$ trimester in 81,3% (13/16) fetuses and at 3$^{rd}$ trimester in 18,8% (3/16) fetuses. Upon the 16 cases with documented estimated fetal weight (EFW), 56,3% (9/16) had EFW below the 10$^{th}$ percentile, 31,3% (5/16) had EFW below the 3$^{rd}$ percentile and 12,5% (2/16) had EFW below the 1$^{st}$ percentile. Of note, IUGR could not be definitely assessed in three fetuses (case#1 #11 and #26) with a gestational age below 18 WG. Other signs were less frequent and are summarized in Table 3. The most common cardiovascular defects were left-sided obstructive lesions of various severity, observed in

11/14 (78,6%) fetuses. Severe hypoplastic aortic arch was the most prevalent cardiovascular defect (42.9%, 6/14). SVAS was diagnosed postnatally in 2 cases (case#5 and #36) but detected on prenatal echocardiography solely in one fetus (case#34). One fetus (case#5) presented with PCDA complicated by severe biventricular failure, hydrops fetalis, fetal distress necessitating emergency delivery by caesarian section. Two fetuses (case#12 and #29) with complex cardiopathy were also reported (Table 4). Prenatal cardiovascular defects were found isolated in two cases, but most of the time it was associated with extra-cardiac features (83,3%, 10/12) such as IUGR (50%, 6/12) or protruding tongue (16,7%, 2/12).

Thirty pregnancies ended by a medical TOP and fetal autopsy reports were available for 11 cases (Table 1). The most recurrent pathology features were facial dysmorphism (long philtrum, infra-orbital crease, flat midface, depressed nasal bridge, anteverted nares, macrostomia, low-set ears), cardiovascular defects and fetal hypotrophy.

7q11.23 microduplication

Four cases of 7q11.23 microduplication were also collected (Table 2). US signs were moderate and nonspecific. Notably, each feature was isolated except in one fetus (case#44) who harbored hyperechogenic kidneys, confirmed in postnatal follow up, and transitory echogenic fetal bowel. No fetal autopsy was performed.

**Discussion**

In this work we report prenatal manifestations of 40 cases with 7q11.23 microdeletion (WBS) and 4 cases with 7q11.23 microduplication. It appears that WBS is associated with a broad range of US signs with IUGR (70,0%), cardiovascular defects (30,0%), short long bone and/or short fetal femur length (25,0%) and polyhydramnios (17,5%) being the most frequent. In most cases (72,5%), more than two US features were identified. It is relevant to note that IUGR, that remains the major WBS US sign, generally occurs early in our series, from the 2nd trimester, with various severity. It is difficult to obtain universal criteria for IUGR as its definition can be

different among countries, but we have retained EFW at 10th percentile as threshold, following French guidelines and experience[21–23]. We observed unusual features as protruding tongue (15,0%) and buried penis (5,0%)[4,5,11]. Protruding tongue could be an emerging WBS specific US sign thanks to the improved quality of ultrasound evaluation; indeed, all the cases were recently diagnosed, from 2017 to 2020. It could correspond to a premature sign of future WBS neonate's hypotonia. Macroglossia, which can be assessed by tongue circumference measurement[24], is commonly associated with protrusion of the tongue. However, it was not reported in our fetuses. Fetal autopsy provided supplemental features that were not detected by US, notably facial dysmorphism (case#16, #25, #28, #29 and #36) or cardiovascular defects (case#10 and #36). Conversely, US features were confirmed by autopsy in most cases (90,9%), suggesting the presence of a 'good' correlation of ultrasound images resolution to macroscopic pathology exam. Only 4 fetuses with a 7q11.23 duplication could be gathered and showed heterogeneous and isolated US signs.

Present series on the largest number of unrelated fetuses with CNVs in 7q11.23 confirms the diagnosis features already reported (IUGR, cardiac defects, polyhydramnios)[4, 5, 11] but underlines distinctive and so far unreported presentation. Indeed, some US features are more prevalent in our series compared to the literature, namely IUGR (70,0% VS 53,3%), and polyhydramnios (17,5% VS 3,3%)[4,5,11]. On the other hand, cardiovascular defects are less frequent in our series than in the literature (30,0% VS 56,7%)[4,5,11]. This could be explained by the following factors. First, the limited number of patients per series could reach to an inaccurate estimation of the prevalence of an anomaly (our prenatal WBS series being the largest ever published). Also, some TOP were decided on the basis of the genetic results, available earlier and earlier, whatever cardiovascular defects. Finally, the presence of cardiovascular defects cannot be strictly excluded in the fetuses that did not have echocardiography or autopsy. However, we expect that no cardiovascular defects have been missed in these fetuses as they all had US examination by a fetal referent practitioner. The main cardiovascular defects of WBS fetuses described so far included, in order of frequency:

SVAS, ventricular septal defects, aortic coarctation, pulmonary artery stenosis and right aortic arch [4–12]. Most of our WBS fetuses' cardiac features were left-sided obstructive lesions (79% of cardiac defects). Only one fetus was prenatally diagnosed with SVAS and no case with peripheral pulmonary stenosis, whereas these two features are the most frequent cardiac lesions described postnatally in WBS (50% and 22% respectively)[16]. The common aspect of the hourglass-shaped lesion described postnatally could be difficult to detect in a fetus whose ascending aorta is smaller.

In our series, the four fetuses harboring a 7q11.23 duplication had a milder phenotype than the three previously reported antenatal presentations, those cases were associated with choroid plexus cyst, ventriculomegaly and lissencephaly[5,8]. More cases would be needed to draw a precise phenotype. The high variability of these prenatal phenotypes increases the importance of genetic testing by CMA. Before the edge of routine CMA, targeted FISH required US specific signs for the diagnosis of microdeletion syndromes, hence prenatal diagnosis of WBS was unusual. On the other hand, variants of unknown significance newly identified by prenatal CMA has become an important issue[25].

It has been hypothesized that *ELN* haploinsufficiency leads to the increase of proliferation of arterial smooth muscular cells, explaining arterial occlusion[17,26]. A more recent work raised the implication of a vascular deficient circumferential growth in aortic obstruction associated with elastin deficiency[27]. Interestingly we reported a case of PCDA that was associated with severe biventricular dysfunction. It is worth noting that PCDA is not a common finding in WBS. The DA takes part to the parallel circulation pattern by bypassing the non-compliant lungs during the *in utero* life[28,29]. After birth, inflation of the lungs and the consequent increase of oxygen levels lead to DA closure. PCDA, can occur secondary to maternal drug exposure or be idiopathic, most of time[30]. Only four cases of genetic PCDA were previously reported by Srinivasan et al[12]. They described 4 patients with a history of PCDA, one of them was diagnosed with WBS and the three other cases were diagnosed with Alagille syndrome. In several patients with 7q11.23 duplication, patent DA have been described[31,32]. We can

hypothesize that the *ELN* gene could be involved in DA physiology, as duplication leads to patent DA and deletion leads to PCDA. Clinicians following patients with point mutations in *ELN* should be aware of their potential effect on premature fetal DA closure during their future pregnancies.

To conclude, we bring additional data on 7q11.23 CNVs prenatal phenotype with the biggest series described so far. We confirmed that WBS often associates early IUGR and cardiovascular defect, with left-sided obstructive lesions being the most frequent. Technical improvement of prenatal imaging allowed to identify more abnormal features with strong postnatal findings correlation. Therefore, considering systematic reference to fetal cardiology in these cases could be relevant to predict postnatal morbidity. Few specific features have emerged including protruding tongue and DA abnormalities. DA should be monitored carefully in fetuses with 7q11.23 deletion or duplication. Further studies are needed to explore the possible implication of *ELN* gene in DA closure.

**Figure legends**

**Figure 1: Ultrasound examination of fetus 4 at 33 weeks and 2 days of gestation**. Front view of 3D ultrasonography (A) and side view (B) showed typical WBS facial dysmorphia with protruding tongue, short upturned nose, large mouth, thick lips and long prominent philtrum. All features persisted at 35 weeks of gestation. Short long bone was also noticed.

**Table 1: Demographic, clinical and genetic data from fetuses with 7q11.23 microdeletion**. Increased nuchal translucency measurements are underlined. IUGR: intra uterine growth retardation, LSVC: left superior vena cava. ND: not determined. NP: not performed. NT: nuchal translucency measurement. PT: protruding tongue. SLB: short long bone. SUA: single umbilical artery. TOP: termination of pregnancy. UK: unknown. VSD: ventricular septal defect.

**Table 2: Demographic, clinical and genetic data from fetuses with 7q11.23 microduplication**. NP: not performed. NT: nuchal translucency measurement. TOP: termination of pregnancy.

**Table 3: Fetal ultrasound features of fetuses with 7q11.23**. IUGR: intrauterine growth retardation. SFFL: short fetal femur length. SLB: short long bone.

**Table 4: Cardiovascular phenotype of fetuses with 7q11.23 microdeletions and microduplications**. Grey boxes indicate post-natal findings. VSD: ventricular septal defect. AV: atrioventricular.

## Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

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| Case | Maternal age (years) | Gestational age at diagnosis (weeks + days) | Indication for prenatal diagnosis | NT (mm) | Pregnancy outcome | Fetopathology | Genetic tests | Genomic coordinates (hg19) | CNVs Size |
|---|---|---|---|---|---|---|---|---|---|
| **1** | UK | 13+2 | Increased NT | 5,1 | TOP | Isolated neck oedema | Array CGH, FISH | arr[hg19]7q11.23(72726578 -74139390)x1 dn | 1,41 Mb |
| **2** | 28 | After birth | IUGR, hypoplastic nasal bone | 1,19 | Birth | NP | Karyotype, FISH | ND | ND |
| **3** | 32 | 35 | Cardiovascular defects | UK | TOP | IUGR, abnormal facial shape, aortic coarctation, cervical ribs | Array SNP, FISH | arr[hg19]7q11.23(72722981 -74138121)x1 dn | 1,4 Mb |
| **4** | 31 | 36+6 | SLB, protruding tongue | 1,3 | TOP | NP | Array CGH, FISH | arr[hg19]7q11.23(74139390 -72726578)x1 | 1,41 Mb |
| **5** | 36 | 33 | Anasarca | UK | Birth | NP | Array CGH, FISH, karyotype | arr[hg19]7q11.23(72726578 -74139390)x1 dn | 1,4 Mb |
| **6** | 26 | After birth | Polyhydramnios | 1,9 | Birth | NP | Array CGH | arr[hg19]7q11.23(72726578 -74139390)x1 | 1,41 Mb |
| **7** | 23 | 29+5 | IUGR, facial dysmorphism, gyration delay | 1,9 | TOP | NP | Array CGH, FISH | arr[hg19]7q11.23(72766313 -74133332)x1 dn | 1,37 Mb |
| **8** | 30 | 32 | SLB, polyhydramnios | 1,5 | TOP | NP | Array CGH, FISH | arr[hg19]7q11.23(72766313 -74133332)x1 dn | 1,37 Mb |
| **9** | 30 | 27+2 | IUGR | 1,7 | TOP | NP | Array CGH, FISH | arr[hg19]7q11.23(72726578 -74119570)x1 | 1,39 Mb |
| **10** | 27 | 34 | Polyhydramnios | 1,59 | TOP | Muscular VSD, LSVC, duodenal atresia, annular pancreas | Array CGH, FISH | arr[hg19]7q11.23(72726578 -74139390)x1 dn | 1,41 Mb |
| **11** | 31 | 16 | Omphalocele | 1,2 | TOP | Omphalocele, bilateral microphthalmia | SNP-array, FISH, karyotype | arr[hg19]7q11.23(72407478 -74281516)x1 dn | 1,87 Mb |
| **12** | 20 | 24+4 | Cardiovascular defects | 2,3 | Birth | NP | Array CGH | arr[hg19]7q11.23(72726578 -74139390)x1 | 1,4 Mb |
| **13** | 35 | 25 | Cardiovascular defects | 2,1 | TOP | NP | Array CGH, FISH | arr[hg19]7q11.23(72726578 -74139390)x1 dn | 1,4 Mb |
| **14** | 32 | 35 | IUGR | 1,5 | TOP | NP | Array CGH, FISH | arr[hg19]7q11.23(72726578 -74139390)x1 dn | 1,4 Mb |

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|---|---|---|---|---|---|---|---|---|---|
| **15** | 31 | 34 | IUGR, SUA, unilateral renal agenesis | 0,9 | TOP | NP | Array CGH, FISH | arr[hg19]7q11.23(72726578-74339040)x1 | 1,6 Mb |
| **16** | 35 | 33 | Cardiovascular defects | 1,4 | TOP | SLB, thin upper lip vermilion, broad philtrum, prominent earlobes, LSVC, asymetric large vessels and ventricles | Array CGH, FISH | arr[hg19]7q11.23(72726578-74139390)x1 | 1,4 Mb |
| **17** | 30 | 18 | IUGR | 1,4 | Selective TOP | NP | Array CGH, FISH | arr[hg19]7q11.23(72726578-74139390)x1 | 1,4 Mb |
| **18** | 30 | 28 | IUGR | 1,3 | UK | UK | Array CGH, FISH | arr[hg19]7q11.23(72726578-74139390)x1 | 1,4 Mb |
| **19** | 42 | 23+3 | Absent fetal nasal bone, fetal choroid plexus cysts | UK | UK | UK | Array CGH, FISH | arr[hg19]7q11.23(72726578-74139390)x1 dn | 1,4 Mb |
| **20** | 30 | 32+1 | IUGR | 1,2 | TOP | NP | Array CGH, FISH | arr[hg19]7q11.23(72726578-74139390)x1 | 1,4 Mb |
| **21** | 20 | 30+1 | IUGR, unilateral renal agenesis | 1,3 | Birth | NP | Array CGH, FISH | arr[hg19]7q11.23(72726378-74139390)x1 dn | 1,4 Mb |
| **22** | 22 | 26+5 | IUGR | 1,0 | TOP | NP | Array CGH | arr[hg19]7q11.23(72726578-74139390)x1 dn | 1,41 Mb |
| **23** | 37 | 28 | IUGR | 0,9 | TOP | NP | Array CGH | arr[hg19]7q11.23(72726578-74139390)x1 dn | 1,41 Mb |
| **24** | 37 | 29 | IUGR | 1,22 | Intrauterine fetal death | Ovotestis, micropenis, umbilical cord knot with stricture | Array CGH, FISH, karyotype | arr[hg19]7q11.23(72726578-74139331)x1 dn | 1.4 Mb |
| **25** | 38 | 23 | Cardiovascular defects | 2,2 | TOP | IUGR, facial dysmorphism, abnormal cerebellum, hypoplastic left heart, mitral valve atresia, aortic atresia | Array CGH, FISH, karyotype | arr[hg19]7q11.23(72726578-74139390)x1 | 1.4 Mb |
| **26** | 29 | 12+6 | Increased NT | 3,6 | TOP | UK | Array CGH, FISH | arr[hg19]7q11.23(72726518-74139450)x1 dn | 1.4 Mb |
| **27** | 33 | 30 | Cardiovascular defects | 2,3 | TOP | UK | Array CGH, FISH | arr[hg19]7q11.23(72721760-74142327)x1 dn | 1.4 Mb |

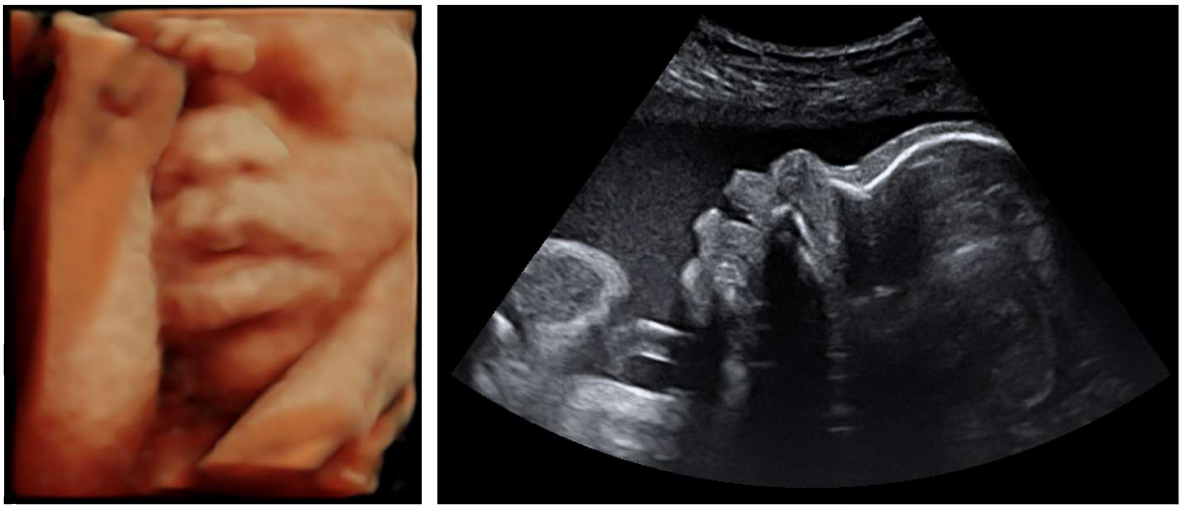
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **28** | 27 | 32+5 | Cardiovascular defects | 2,1 | TOP | IUGR, facial dysmorphism (low set ears, absent antihelix, infra-orbital crease, bulbous nose, depressed nasal bridge, anteverted nares, exaggerated cupid's bow, thick lip, PT), overlapping toes, LSVC, perimembranous VSD, valvular pulmonary stenosis, bilateral ventricular hypertrophy | Array CGH, FISH | arr[hg19]7q11.23(72726578 -74139390 )x1 dn | 1,41 Mb |
| **29** | 34 | 23+5 | Cardiovascular defects | 1 | TOP | Weight at 10th percentile, dysmorphism (microturridolichocephaly, infra-orbital crease, wide nasal bridge, macrostomia, PT, low-set ears, short neck), complex cardiopathy (right atrioventricular valve hypoplasia, large VSD with double outlet right ventricle, pulmonary aortic hypoplasia, retroesophageal right subclavian artery) | Array CGH, FISH | arr[hg19]7q11.23(72726578 -74139390)x1 | 1,41 Mb |
| **30** | 37 | 33 | IUGR, polyhydramnios | UK | TOP | IUGR, no relevant morphogenic abnormality | Karyotype, FISH | ND | ND |
| **31** | 31 | 34+3 | Short fetal femur length | UK | TOP | NP | Array CGH, FISH, karyotype | arr[hg19]7q11.23(72721760 -74233342)x1 | 1.5 Mb |
| **32** | 34 | 30+2 | IUGR | 1,4 | UK | UK | Array CGH, FISH, karyotype | arr[hg19]7q11.23(72719857 -74142327)x1 | 1.4 Mb |
| **33** | 30 | 34+2 | Cardiovascular defects, short fetal femur length | 1,2 | TOP | NP | Array CGH, FISH, karyotype | arr[hg19]7q11.23(72721760 -74361090)x1 dn | 1.6 Mb |
| **34** | 30 | 28 | IUGR | UK | Birth | NP | Array CGH, FISH | arr[hg19]7q11.23(72721760 -74172327)x1 | 1,4 Mb |
| **35** | 33 | 34+6 | Cardiovascular defects, IUGR | 0,92 | TOP | NP | Bacs-on-Beads | ND | ND |
| **36** | 31 | 32+4 | IUGR | 1 | TOP | Dysmorphism (malar hypoplasia, hypoplastic nasal bone, bulbous nose, wide mouth with thick lower lip, pointed chin, large earlobes, dolichocephalic skull, clinodactyly and brachymesophalangia of the 5$^{th}$ fingers), hematic peritoneal, pleural and pericardial effusion, bilateral ectopic calcifications under the calcaneums, supra-valvular aortic narrowing and tortuosity of the ductus arteriosus. | Bacs-on-Beads | ND | ND |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **37** | 38 | 30+2 | IUGR | 2 | Selective TOP | NP | Array CGH | arr[hg19]7q11.23(72574585-74285320)x1 dn | 1,71 Mb |
| **38** | 35 | UK | IUGR, SUA | 1,4 | TOP | NP | Array CGH | arr[hg19]7q11.23(73312582-74725057)x1 dn | 1,4 Mb |
| **39** | 24 | 30 | IUGR | 1,1 | TOP | NP | Array CGH | arr[hg19]7q11.23(72726578-74139390)x1 dn | 1,4 Mb |
| **40** | 25 | 23+5 | IUGR, abnormal corpus callosum morphology | 0,9 | TOP | NP | Array CGH, FISH | arr[hg19]7q11.23(72726578-74139390)x1 dn | 1,4 Mb |

| Case | Maternal age (years) | Gestational age at diagnosis (weeks + days) | Indication for prenatal diagnosis | NT (mm) | Pregnancy outcome | Fetopathology | Genetic tests | Genomic coordinates (hg19) | CNVs Size |
|---|---|---|---|---|---|---|---|---|---|
| **41** | 31 | 13+1 | Increased NT | 3,2 | TOP | NP | Array CGH, FISH | arr[hg19]7q11.23(72476289-74285345)x3 dn | 1.8 Mb |
| **42** | 42 | 33+3 | Polyhydramnios | 1,5 | Birth | NP | Array CGH | arr[hg19]7q11.23(72726578-74139390)x3 pat | 1,41 Mb |
| **43** | 39 | 27+6 | Cardiovascular defects | 1,67 | TOP | NP | Array CGH, qPCR | arr[hg19]7q11.23(72726578-74139390)x3 dn | 1,41 Mb |
| **44** | 35 | 29 | Hyperechogenic kidneys | 1,4 | Birth | NP | Array CGH; karyotype | arr[hg19]7q11.23(72726578-74339044)x3 mat | 1,6 Mb |

| | Total (40) | |
|---|---|---|
| **IUGR** | 28 | 70,0% |
| **SFFL/SFB** | 10 | 25,0% |
| **Hypoplastic/absent nasal bone** | 3 | 7,5% |
| **Increased nuchal translucency** | 2 | 5,0% |
| **Cardiovascular defects** | 12 | 30,0% |
| **Echogenic intracardiac focus** | 1 | 2,5% |
| **Single umbilical artery** | 2 | 5,0% |
| **Polyhydramnios** | 7 | 17,5% |
| **Abnormality of skull size/shape** | 3 | 7,5% |
| **Protruding tongue** | 6 | 15,0% |
| **Duodenal atresia** | 1 | 2,5% |
| **Small stomach** | 1 | 2,5% |
| **Omphalocele** | 1 | 2,5% |
| **Urinary tract abnormalities** | 2 | 5,0% |
| **Buried penis** | 2 | 5,0% |
| **Gyration delay** | 1 | 2,5% |
| **Aplasia/Hypoplasia of the corpus callosum** | 1 | 2,5% |
| **Fetal choroid plexus cysts** | 1 | 2,5% |

| | | Deletion | | | | | | | | | | | | | | Duplication | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Case** | **3** | **5** | **10** | **12** | **13** | **16** | **25** | **27** | **28** | **29** | **33** | **34** | **35** | **36** | **44** | **45** |
| **Left-sided obstructive lesions** | Ventricle dysymmetry at the expand of left ventricle (non hypoplastic) | | | | | | + | | | + | | | | | | | |
| | Supravalvular aortic stenosis | | + | | | | | | | | | | + | | + | | |
| | Hypoplastic aortic arch | + | + | | | + | + | | + | | | | | + | | | |
| | Post natal aortic coarctation | + | + | | | | | | | | | | | | | | |
| | Aortic coarctation syndrome (VSD + coarctation) | | | | | + | | | | | | | | + | | | |
| | Interrupted aortic arch | | | | + | | | | | | | | | | | | |
| | Not detailed | | | | | | | | | | | + | | | | | |
| **Hypoplastic left heart syndrome (with mitral and aortic atresia)** | | | | | | | | + | | | | | | | | | |
| **Single ventricle** | Double oulet right ventricle, hypoplastic right AV valve, pulmonary stenosis, hypoplastic pulmonary arteries, retroesophageal right subclavian artery | | | | | | | | | | + | | | | | | |
| **Double outlet right ventricle** | Transposition of the great arteries type with hypoplastic aortic arch | | | | + | | | | onditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License | | | | | | | | |
| **Right sided obstructive lesions** | Pulmonary valve stenosis | | + | | | | | | | + | | | | | | | |
| | Premature duct closure | | + | | | | | | | | | | | | | | |
| **Atrioventricular septal defect** | | | | | | | | | | | | | | | | + | |
| **Others structural anomalies** | Left superior vena cava | | | + | | | + | | | + | | | | | | | |
| | Ascending aorta dilation | | | | | | | | | | | | | | | | + |
| **Functional anomalies** | Cardiomegaly | | + | | | | | | | | | | | | | | |
| | Severe biventricular hypertrophy | | + | | | | | | | + | | | | | | | |
| | Severe systolic dysfunction | | + | | | | | | | | | | | | | | |



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