Severe micrognathia in the first trimester in complete trisomy 9 – a case report and literature review

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Abstract
Trisomy 9 is a rare chromosomal abnormality with a very poor prognosis depending mostly on the amount and exact location of the duplicated genetic material. Most of the fetuses with complete trisomy 9 are spontaneously aborted in the early first trimester and therefore it is uncommonly seen at the time of 11-14 weeks’ scan. The diagnosis is usually made after fetal karyotyping performed for routine indications. We present a case of complete trisomy 9 diagnosed after chorionic villus sampling performed because of the detection of severe micrognathia at 13 weeks gestation.

Key words: trisomy 9, micrognathia, prenatal diagnosis, first trimester, sonography

Introduction
Trisomy 9 is a rare chromosomal abnormality that was first described in 1973 by Feingold and Atkins [1]. The clinical spectrum varies depending on the amount and exact location of the genetic material that is duplicated. The symptoms include intrauterine growth restriction, facial dysmorphism (microcephaly, low set malformed ears, bulbous nose, micrognathia, cleft palate) and abnormalities involving all organs – congenital heart defects (ventricular septal defect, atrial septal defect, patent ductus arteriosus, double outlet right ventricle), central nervous system malformations (Dandy-Walker malformation, ventriculomegaly, spina bifida, myelomeningocele), skeletal deformities (club hand, rocker bottom feet, camptodactyly), genitourinary defects (genital hypoplasia, horseshoe kidney), diaphragmatic hernia and other abnormalities [2-8].

A complete (non-mosaic) trisomy 9 has a prevalence of 1:1000 recognized conceptions but it is a lethal condition and the majority of pregnancies progress into spontaneous abortion in the first trimester. Rarely do the fetuses survive to the time when characteristic sonographic findings can be seen [4, 5, 9-11]. Recent advances in prenatal testing have led to detection of more cases in the first trimester of pregnancy. However, most of them are found incidentally by fetal karyotyping performed for routine indications such as maternal age or abnormal serum screen [12, 13]. There are 40 cases of prenatal diagnosis of complete trisomy 9 reported up to date in English literature but only 8 of them have been detected in the first trimester [12-15]. Due to different clinical manifestations of the syndrome, a characteristic morphology is still not complete. We present a case of trisomy 9 that was detected in the first trimester of pregnancy by chorionic villus sampling conducted because of an abnormal first trimester scan with a post mortem examination and a literature review.

Case report
A 39 year old gravida 2 was referred to our center at the 13th week of gestation for Ist trimester scan, which was performed according to Fetal Medicine Foundation (FMF) standards by an experienced FMF-certified doctor. Her medical history was unremarkable. The scan revealed a fetus of 66 mm with nuchal translucency of 1.3 mm. The fHR was 153’ and the ductus venosus flow was normal. An individual risk for trisomy 21 was 1:421; trisomy 18 – 1:641 and trisomy 13 – 1:11215. The anatomy scan revealed severe micrognathia (Fig. 1) and an abnormal four chamber view. A transabdominal chorionic villus sampling was performed and karyotyping showed trisomy 9 (47,XY,+9 in 18 metaphases) without evidence of mosaicism. A fetal ultrasound at 17 weeks’ gestation identified a severe micrognathia (Fig. 2),

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absence of one orbit, cardiac anomaly (double outlet right ventricle – DORV) and hand and foot anomalies (fixed fingers and toes – Fig. 3, 4).

Fig. 1. Severe micrognathia on the first trimester scan

Fig. 2. Severe micrognathia on the second trimester scan

Fig. 3. Abnormal hand with fixed fingers on the second trimester scan

The pregnancy was terminated at 19 weeks of gestation and a stillborn male fetus of 100 g (below 5th percentile) was delivered. A postmortem examination revealed multiple anomalies: a large fontanelle, severe facial dysmorphism (low set malformed ears, small palpebral fissures, prominent nose with a bulbous tip, severe micrognathia – Fig. 5);

Fig. 4. Abnormal foot with fixed toes on the second trimester scan

Fig. 5. Post mortem examination of the fetus: severe micrognathia, low set ears, abnormal hand, short and webbed neck, absence of intergluteal fold, short penis, skeletal malformations, ulnar deviation of the wrist and laterally deviated overlapping fingers with a gap between the thumb, index and the three remaining fingers. An autopsy and a cytogenetic confirmation from fetal tissue was declined by the patient.

Discussion
A complete trisomy 9 regarding its diverse clinical manifestation is considered to be lethal. The longest reported survival of a neonate with a complete trisomy 9 was 3.5 months but the majority of neonates die within hours after birth [16]. An early prenatal diagnosis and accurate genetic counseling is crucial to the management of ongoing and subsequent pregnancies and helps avoiding unnecessary maternal and fetal interventions.
Table 1. Cases of complete trisomy 9 detected in the first trimester

<table>
<thead>
<tr>
<th>Case</th>
<th>Author, year</th>
<th>Maternal age (years)</th>
<th>Gestational age (weeks)</th>
<th>Indication for karyotyping</th>
<th>Sonographic findings in the first trimester scan</th>
<th>Sonographic findings in repeated scan (GA)</th>
<th>Procedure</th>
<th>Karyotype (cells counted)</th>
<th>Outcome</th>
<th>Post mortem examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Martinez, 1997</td>
<td>–</td>
<td>12</td>
<td>Abnormal scan</td>
<td>NT – 4 mm</td>
<td>–</td>
<td>CVS</td>
<td>Trisomy 9</td>
<td>TOP</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Murta, 2000</td>
<td>30</td>
<td>12</td>
<td>Abnormal scan</td>
<td>NT – 9.1 mm, rDVF, rUVF VSD, bilateral pylecetasias, hyperechoic bowel, echoic intracardiac focus</td>
<td>–</td>
<td>CVS</td>
<td>Trisomy 9</td>
<td>IUFD 14 Hbd</td>
<td>+</td>
</tr>
<tr>
<td>4.</td>
<td>Sepulveda, 2003</td>
<td>42</td>
<td>11</td>
<td>Previous trisomy 13</td>
<td>none</td>
<td>(14) nuchal edema (16) IUGR, ventriculomegaly, pleural effusions, mild ascites, bilateral hydronephrosis</td>
<td>CVS AC</td>
<td>47,XX,+9(40) 47,XX,+9(118)</td>
<td>TOP 17 Hbd</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Sepulveda, 2003</td>
<td>38</td>
<td>12</td>
<td>Abnormal scan</td>
<td>NT – 4.5 mm</td>
<td>(16) ventriculomegaly, absent cerebellar vermis, nuchal edema, hypoplastic left heart, bilateral polydactyly, rocker-bottom feet, short femora</td>
<td>CVS</td>
<td>47,XY,+9(30)</td>
<td>TOP 17 Hbd</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td></td>
<td>41</td>
<td>12</td>
<td>MA</td>
<td>none</td>
<td>–</td>
<td>CVS</td>
<td>47,XY,+9(32)</td>
<td>IUFD 17 Hbd</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td></td>
<td>40</td>
<td>12</td>
<td>Abnormal scan</td>
<td>NT – 3 mm, rDVF</td>
<td>(24) IUGR, brachycephaly, diaphragmatic hernia, mediastinal shift, bilateral hydronephrosis</td>
<td>CVS</td>
<td>47,XX,+9(22)</td>
<td>IUFD 31 Hbd</td>
<td></td>
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<td>8.</td>
<td>Schwenndemann, 2009</td>
<td>–</td>
<td>11</td>
<td>Increased risk for T18 on serum screen</td>
<td>none (NT – 1.8 mm; 48th percentile growth)</td>
<td>–</td>
<td>AC</td>
<td>47,XY,+9</td>
<td>TOP</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>Present case</td>
<td>38</td>
<td>13</td>
<td>Abnormal scan</td>
<td>Micrognathia</td>
<td>(17) retromicrognathia, absent orbit, DORV, hand and foot anomalies</td>
<td>CVS</td>
<td>47,XY,+9(18)</td>
<td>TOP 18 Hbd</td>
<td></td>
</tr>
</tbody>
</table>

MA – maternal age; GA – gestational age in weeks; NT – nuchal translucency; rDVF – reversed ductus venosus flow; rUVF – reversed umbilical vein flow; IUGR – intrauterine growth restriction; DORV – double outlet right ventricle; CVS – chorionic villus sampling; AC – amniocentesis; TOP – termination of pregnancy; IUFD – intrauterine fetal demise
We have performed a literature review on complete trisomy 9. We have searched Pubmed database since 1973 using terms “trisomy 9” combined with “complete”, “non-mosaic”, “prenatal”, “ultrasound” and “sonographic”.

40 cases of complete trisomy 9 diagnosed prenatally have been found. Mean maternal age was 33 years, mean gestational age at the ultrasound scan was 20 weeks. The most common abnormalities found sonographically were genitourinary (62.5%; mostly genital hypoplasia) and central nervous system malformations (60%; mostly posterior fossa abnormalities).

Micrognathia was the most common facial manifestation described in 7 cases (17.5%; 43.75% of all facial anomalies). In 5 cases there were no sonographic features present and the karyotyping was performed for routine indications.

Among 40 cases diagnosed prenatally, there were 8 detected in the first trimester but only one of them showed structural anomalies in the ultrasound scan. The most common indication for karyotyping was increased nuchal translucency (NT), which was present in five cases. Abnormal Doppler flow was seen in two cases. In three cases there were no anomalies found in the first trimester scan. Four of the pregnancies were terminated, another four progressed into intrauterine fetal demise (see Table 1).

In 1993 Bromley and Benacerraf analysed the association of fetal micrognathia with chromosomal anomalies and fetal outcome. Interestingly, 25% of the cases showed chromosomal aberrations (trisomy 9 in one case) and only four of 20 reported fetuses survived [17]. This poor prognosis was confirmed by Luedders et al. last year [18]. These reports indicate a necessity of karyotyping when micrognathia is encountered prenatally. To our knowledge it is the first report of a micrognathia seen in the first trimester scan leading to a diagnosis of a complete trisomy 9. Until this report the earliest case of micrognathia seen in trisomy 9 was at 16 weeks’ ultrasound scan performed because of abnormal MSAFP level. As the morphology and sonographic findings of trisomy 9 are similar to trisomy 18 and 13 due to IUGR, micrognathia and elevated MSAFP it can be easily mistaken with those more common aberrations and should be taken into consideration, when observing these anomalies [19-23].

Some authors reported increased nuchal translucency and abnormal ductus venosus flow in fetuses with trisomy 9 [12, 14, 15]. Interestingly, both NT and ductus venosus flow were normal in our case. The individual risk for chromosomal aberrations (based on maternal age, nuchal translucency, fetal heart rate) was not increased and but for the detection of micrognathia and abnormal four chamber view in the first trimester, the CVS procedure would probably not have been performed.

The most common cardiac manifestation of the syndrome is ventricular septal defect. We report a double outlet right ventricle (DORV) which up to date has only been seen twice in trisomy 9 prenatally [20, 24]. Most of other structural anomalies described in previous reports were seen at the post mortem examination in our case (facial dismorphism, genital hypoplasia, skeletal abnormalities). There was no posterior fossa manifestation, which is the most common central nervous system anomaly seen in trisomy 9, but this alteration can not be diagnosed in the first and early second trimester.

The diagnosis of complete trisomy 9 after chorionic villus sampling should be confirmed by other tissue sampling (amniotic fluid, fetal blood, placenta, skin) to minimize the risk of mosaicism or placental pseudomosaicism [12, 25, 26]. In this case there were 18 cells counted from a standard culture and there was no sign of mosaicism. Further testing and an autopsy were declined by the patient. There remains a risk of a mosaicism but the clinical manifestation was consistent with complete trisomy 9.

To conclude, we present a first case of complete trisomy 9 diagnosed in the first trimester based on abnormal ultrasound scan at 13 weeks gestation which showed a severe micrognathia. Regarding the poor prognosis of the syndrome, an early diagnosis is important for further management of the ongoing pregnancy.

References
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