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FETAL ULTRASOUND FINDINGS IN TRISOMY 18 AT MIDPREGNANCY

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Trisomy 18 (Edwards’ syndrome), a lethal chromosomal aberration, is the second most common autosomal trisomy with an incidence 1: 8000. The aim of this study is to evaluate the sonographic findings in fetuses with trisomy 18. In ten years period (2002-2012) we analyzed fetal blood samples for chromosome abnormalities. Samples were taken by cordocentesis and processed using standard techniques. Sixteen metaphase cells were analyzed for chromosomal constitution in each sample after tripsin-Giemsa banding. A retrospective review of the cytogenetic laboratory database identified all cases of trisomy 18 in ten years period. The prenatal sonographic studies in fetuses at 16 to 22 weeks’ gestation, done before invasive testing for the karyotype were reviewed for anatomic findings. From 2100 samples of fetal blood analyzed for chromosomal abnormalities, there were 16 (0,8%) with complete trisomy 18. We found no mosaicism, or partial trisomy 18. The women that carried fetuses with trisomy 18 were 17 to 42 years of age. Four of them were above 35. From 16 fetuses with trisomy 18, 14 (87,5%) had some anomaly detected by ultrasound, and other two were tested because of advanced maternal age. The most common findings in trisomy 18 were intrauterine growth retardation, polyhidramnios and anomalies of central nervous system, in 29% respectively. Multiple anomalies, including central nervous system, heart and gastrointestinal system anomalies, were also frequent (21%). Therapeutic termination of pregnancy was done in all cases after genetic counseling. Screening for chromosomal abnormalities using ultrasound is at utmost importance in cases of nonhereditary aberrations. Detailed ultrasonographic examinations of fetuses will enable health care providers to form the appropriate management plan for each patient.

Key words: trisomy 18, fetal ultrasound, cordocentesis

INTRODUCTION

Chromosomal abnormalities are a major cause of perinatal death and childhood disabilities. Consequently the diagnosis of chromosomal disorders constitutes most important
indication of invasive prenatal diagnosis. However these invasive tests of amniocentesis, chorionic villous sampling or cordocentesis are associated with a risk of miscarriage of 1%. Therefore these tests are carried out in pregnancies at high risk for chromosomal defects. Screening using ultrasound is based on the fact that most fetuses with chromosomal abnormalities have major structural malformations or minor abnormalities that can be detected on ultrasound (Virmani, 2006).

Advances in ultrasound prenatal diagnostics have significantly improved the option of early detection of congenital anomalies, leading to improvement of perinatal care and giving the opportunity for pregnancy termination in the cases of lethal disorders (Patau, 1960, Nikolaides et al., 1992, Devore, 2000). Trisomy 18 (Edwards' syndrome), a lethal chromosomal aberration, is the second most common autosomal trisomy with an incidence 1: 8000.

Different severe congenital malformations, profound neurological dysfunction, intense mental retardation, as well as high rate of infant mortality are typical features of trisomy 18. The condition is incompatible with long term survival, and the singular cases that do survive have an extremely low quality of life. The mortality in utero is high and death in those fetuses which are live born occurs within the first few weeks of life, with a median survival period of < 1 month (Rasmussen et al., 2003).

As experience with ultrasound has grown, more and more sonographic findings have been found to be characteristic of trisomy 18. In the second or third trimester of pregnancy a wide range of associated ultrasonographic features have been described, including strawberry-shaped head, ventriculomegaly, posterior fossa cysts, choroid plexus cysts, facial cleft, micrognatia, nuchal edema, esophageal atresia, diaphragmatic hernia, cardiac defects, exomphalos, renal defects, short limbs, talipes, overlapping fingers, polyhydramnios and intrauterine growth retardation (Snijders et al., 1996).

The aim of this study is to evaluate the sonographic findings in fetuses with trisomy 18.

MATERIALS AND METHODS
Since January 2002 till January 2012, in the Department for cytogenetics, Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, we have analyzed fetal blood samples for chromosome abnormalities. Samples were taken by cordocentesis and processed using standard techniques. All specimens were G-banded using trypsin-Giemsa. Sixteen metaphase cells were analyzed for chromosomal constitution in each sample.

A retrospective review of the cytogenetic laboratory database identified all cases of trisomy 18 detected in ten years period (2002.-2012.) All ultrasound findings were identified at the time of the routine midpregnancy scanning, at 16 to 22 weeks' gestation, before knowledge of cytogenetic diagnosis. Ultrasonographic examinations were performed transabdominally by one of experienced maternal-fetal medicine physician sonographers. On parents demand, after genetic counseling and ethics committee approval, pregnancies were terminated.

RESULTS
From 2100 samples of fetal blood analyzed for chromosomal abnormalities in ten years period, there were 16 (0.8%) with trisomy 18. In all cases trisomy 18 was complete. We found no mosaicism or partial trisomy 18. In 10 cases (62.5%) fetuses were female and in 6 cases (37.5%) fetuses were male. The women that carried fetuses with trisomy 18 were 17 to 42 years of age. Four of them were above 35.
From 16 fetuses with trisomy 18, 14 (87.5%) had some anomaly detected by ultrasound. Two of them were examined because of the advanced maternal age. Mean gestational age when abnormalities were detected was 19 (16-22) weeks, and mean gestational age at diagnosis was 26 (22-30) weeks.

Table 1. Ultrasonographic findings in fetuses with trisomy 18

<table>
<thead>
<tr>
<th>Mothers age</th>
<th>Ultrasonographic findings</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>polihydramnion, heart defect</td>
<td>47,XY+18</td>
</tr>
<tr>
<td>2</td>
<td>IUGR</td>
<td>47,XX+18</td>
</tr>
<tr>
<td>3</td>
<td>oligohydramnion</td>
<td>47,XY+18</td>
</tr>
<tr>
<td>4</td>
<td>heart defect</td>
<td>47,XY+18</td>
</tr>
<tr>
<td>5</td>
<td>oligohydramnion</td>
<td>47,XY+18</td>
</tr>
<tr>
<td>6</td>
<td>omphalocele</td>
<td>47,XX+18</td>
</tr>
<tr>
<td>7</td>
<td>choroid plexus cyst</td>
<td>47,XY+18</td>
</tr>
<tr>
<td>8</td>
<td>multiple anomalies</td>
<td>47,XX+18</td>
</tr>
<tr>
<td>9</td>
<td>choroid plexus cyst, IUGR</td>
<td>47,XX+18</td>
</tr>
<tr>
<td>10</td>
<td>polyhydramnion</td>
<td>47,XX+18</td>
</tr>
<tr>
<td>11</td>
<td>IUGR, polyhydramnion</td>
<td>47,XX+18</td>
</tr>
<tr>
<td>12</td>
<td>multiple anomalies</td>
<td>47,XY+18</td>
</tr>
<tr>
<td>13</td>
<td>ventriculomegalias, polyhydramnion</td>
<td>47,XX+18</td>
</tr>
<tr>
<td>14</td>
<td>IUGR, multiple anomalies</td>
<td>47,XX+18</td>
</tr>
</tbody>
</table>

The most common findings in trisomy 18 were IUGR (intrauterine growth retardation), polyhydramnios and anomalies of central nervous system (CNS), in 29% respectively. Multiple anomalies, including CNS, heart and gastrointestinal system anomalies, were also frequent (21%).

Therapeutic termination of pregnancy was done in all cases after genetic counseling, and mean gestational age at termination was 28 (24-32) weeks.
Trisomy 18 (Edwards’ syndrome) is a chromosomal aberration that results from the presence of an extra copy of chromosome 18. The etiologies of the trisomy 18 are known as maternal meiotic nondisjunction (over 90%), paternal meiotic nondisjunction (5%) and paternal dislocation. Every organ system can be affected by trisomy 18 (Gedikbası et al., 2008). Many studies done during the past years showed different sensitivity of sonographic screening for trisomy 18 as well as different frequency of findings.

Shields et al. (1998) detected at least one abnormality in 86% of cases. The most common abnormalities noted were persistent abnormal position of fetal fingers (89%), choroid plexus cysts (43%), abnormally shaped fetal head (43%), two-vessel umbilical cord (40%), cardiac defects (37%), IUGR (29%); omphalocele (20%), neural tube defects (9%) and cystic hygroma or lymphangiectasia (14%). Abnormalities of amniotic fluid volume (12%) and renal defects (9%) were seen less frequently. They suggested that the fetal hand appears to be abnormal in most early second trimester fetuses with trisomy 18, but the abnormality may be subtle and/or unilateral (Shields et al., 1998).

In the study of Tongsong at al. trisomy 18 fetuses had at least one abnormal sonographic finding. The common findings included IUGR, choroids plexus cyst, cardiac anomalies, clenched hand, omphalocele and cleft lip. Other less common findings were diaphragmatic hernia, abnormal head shape, polyhydramnios and single umbilical artery (Tongsong et al., 2002).

Watson et al. (2008) had sensitivity of 97% in trisomy 18 screening, and IUGR (51%), cardiac (63%) and CNS (34%) anomalies were most frequently detected. In our study ultrasonography identified abnormal fetal anatomy or abnormal biometric findings in 87.5%. The most frequent findings were IUGR (29%), polyhydramnios (29%), CNS anomalies (29%) and multiple organ anomalies (21%). Median gestational age when abnormalities were found was 19 weeks. In the study of Bronsteen et al. (2004) the percentage of fetuses with anomalies at 15-16 weeks, 17 weeks, 18 weeks, 19 weeks and 20 weeks were 67%, 88%, 93%, 100% and 100% respectively.

Yeo et al. (2003) also found sensitivity of 100% for sonography for detecting trisomy 18 performed at a median gestation age of 20 weeks. Oyelese and Vintzileos (2005) emphasized...
that excluding trisomy 18 by genetic sonography means performing a complete sonographic anatomical survey. Cases may be missed if certain structures, such as the hands, ears or heart are not visualized adequately. They also suggested that detection < 100% of some studies was the consequence of incomplete sonographic examinations.

The demonstration of an extra chromosome 18, or less commonly a partial trisomy of the long arm of chromosome 18, on the standard G-banded karyotype allows for confirmation of the clinical diagnosis. A small portion of patients (less than 5%) have mosaicism of trisomy 18; they show an extremely variable phenotype (CEREDA and CAREY, 2012).

In our study two fetuses with trisomy 18 were examined for chromosomal aberrations because of the advanced maternal age, so there were no data about sonographic findings. In order to better understand the molecular mechanisms underlying the congenital anomalies observed in trisomy 18, KOIDE et al. (2011) investigated the in utero gene expression profile of second trimester fetuses with this condition. Results showed that 352 probe sets representing 251 annotated genes were statistically significantly differentially expressed between trisomy 18 and controls. Only 7 genes were located on chromosome 18, including ROCK1, an up-regulated gene involved in valvuloseptal and endocardial cusion formation. Pathway analysis indicated disrupted regulation of genes involved in adrenal development was identified, which may explain both the abnormal maternal serum estriols and the pre and postnatal growth retardation in trisomy 18 (KOIDE et al., 2011).

**CONCLUSION**

Screening for chromosomal abnormalities using ultrasound is at utmost importance in cases of nonhereditary aberrations. Detailed ultrasonographic examinations of fetuses will enable health care providers to form the appropriate management plan for each patient.

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NALAZI ULTRAZVUČNIH PREGLEDA FETUSA SA TRIZOMIJOM 18 U DRUGOM TROMESEČJU TRUDNOĆE

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