Sonographic screening for trisomy 13 at 11 to 13 +6 weeks of gestation

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Objective: The purpose of this study was to examine the sonographic features of trisomy 13 at 11 to 13 +6 weeks of gestation.

Study design: This was a retrospective study that examined the features of trisomy 13 at the ultrasound scan at 11 to 13 +6 weeks of gestation, which in our center is performed for the measurement of crown-rump length, nuchal translucency thickness, and fetal heart rate and the examination for major defects.

Results: In the 181 fetuses with trisomy 13, there were holoprosencephaly, exomphalos, and/or megacystis in 92 fetuses (50.2%), fetal heart rate above the 95th percentile in 129 fetuses (71.3%), and nuchal translucency above the 95th percentile in 141 fetuses (77.9%). There was no significant association between nuchal translucency and fetal heart rate, and it was estimated that inclusion of fetal heart rate in nuchal translucency screening can improve the detection rate of trisomy 13 by approximately 5%.

Conclusion: At the 11 to 13 +6 -week scan, the measurement of fetal nuchal translucency and fetal heart rate and fetal examination for holoprosencephaly, exomphalos, and megacystis can identify >90% of fetuses with trisomy 13.

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Trisomy 13, which was first described by Patau et al1 in 1960, is the third most common trisomy, after trisomies 21 and 18. The condition is lethal, and the rate of miscarriage or fetal death between 12 and 40 weeks of gestation is approximately 80%.2 The median survival time for children who are born with this disorder is 7 days, and only 5% of infants survive to the end of the first year.3

Prenatal screening for trisomy 21, by a combination of maternal age and fetal nuchal translucency (NT) thickness at 11 to 13 +6 weeks of gestation, also identifies a high proportion of fetuses with trisomy 13. Thus, in a multicenter study that involved 96,127 pregnancies,
which included 326 pregnancies with trisomy 21 and 46 with trisomy 13, the estimated risk for trisomy 21 was 1 in ≥300 in 8% of the normal pregnancies, in 82% of pregnancies with trisomy 21, and in 80% of pregnancies with trisomy 13. In addition to increased NT, trisomy 13 is associated with fetal tachycardia and major defects (such as holoprosencephaly, exomphalos and megacystis) that can be detected at the 11 to 13-week scan.

The aim of the study was to examine the potential value of combining fetal NT, fetal heart rate (FHR), and major defects in early screening for trisomy 13.

Material and methods

This was a retrospective study that examined the features of trisomy 13 in the first trimester. Some of the patients included in this study have been included in previous publications. In our center, an ultrasound examination is performed routinely at 11 to 13 weeks of gestation for pregnancy dating, the detection of major structural defects, and the assessment of risk for chromosomal abnormalities by the measurement of fetal NT thickness. During this examination, the FHR is also measured. Pulsed-wave Doppler imaging is used to obtain 6 to 10 cardiac cycles during fetal quiescence, and the FHR is calculated by the ultrasound machine software. All ultrasound findings are entered into a database at the time of the examination. Fetal karyotype and outcome are entered into the same database when they become available. We performed a search of the database to identify all live fetuses that were examined at 11 to 13 weeks of gestation and that were found subsequently to be affected with trisomy 13. We then examined these records to obtain the data on fetal crown-rump length (CRL), NT, FHR, and the presence or absence of holoprosencephaly, exomphalos, and megacystis.

Statistical analysis

In the trisomy 13 fetuses, the difference between the measured NT and FHR from the appropriate normal regressed mean for CRL was calculated (delta values). The previously published normal range of FHR for CRL was derived from the data of 25,000 pregnancies that resulted in the birth of healthy and phenotypically normal babies, and the normal range for NT with CRL was based on the data from 96,127 pregnancies in the UK multicenter study. Normal Q-Q plots were used to determine the normality of the distribution of delta FHR and delta NT in the trisomy 13 fetuses, and correlation analysis was used to determine the significance of the association between delta NT and delta FHR. The unpaired t-test was used to examine whether there were significant differences in delta FHR between the trisomy 13 fetuses with and without holoprosencephaly, exomphalos, or megacystis.

Assessment of the performance of a combined risk algorithm for trisomy 13 that incorporated delta FHR and delta NT as a potential screening tool was examined with standard statistical modeling techniques. From within the observed distributions of delta FHR and for delta NT for unaffected pregnancies and those with trisomy 13, we randomly simulated delta NT and delta FHR measurements for a population of 50,000 unaffected and 50,000 trisomy 13 fetuses. Using the individual values and the likelihood ratio (LR) as determined in this study for delta NT and that for delta FHR, we calculated a combined LR that was based on the multiplication of the 2 LRs.

Using the combined LR and a pregnancy population with the maternal age distribution of pregnancies in England and Wales in 2002 and the maternal age a priori risk of trisomy 13 at 12 weeks of gestation, we then estimated the detection rates of trisomy 13, at various false-positive rates.

Results

The database search identified 181 pregnancies with fetal trisomy 13 that were examined between June 30, 1994, and August 31, 2004. The median maternal age was 36 years (range, 19-48 years); the median gestation was 12 weeks (range, 11-13 weeks), and the median CRL was 58.5 mm (range, 45.0-84.0 mm). The diagnosis of trisomy 13 was made by chorionic villous sampling or amniocentesis in 179 of the cases, and the parents elected to have pregnancy termination. In 2 cases, the diagnosis was made postnatally, and the infants died in the neonatal period.

The distribution of delta FHR was adequately Gaussian because of the linear nature of the derived Q-Q plots (Figure 1). The mean and SD in delta FHR did not change significantly with CRL in either the normal (mean, 0 ± 6.0) or in the trisomy 13 fetuses (mean, 14.8 ± 10.2). In the trisomy 13 fetuses, the mean delta FHR was significantly higher than normal (mean, 15 beats/min; 95% CI, 14-16 beats/min; P < .0001; Figures 2 and 3), and the LR
for trisomy 13 increased exponentially with delta FHR: 
\[ LR(FHR) = 0.588 \times e^{-0.5 \left( \frac{\text{delta FHR} - 14.8}{10.19} \right)^2} \]

In the trisomy 13 fetuses, the FHR was above the 95th percentile and above the 99th percentile of the normal range for CRL in 129 (71.3%) and 93 (51.4%) of the cases, respectively. A delta FHR of > 20 beats/min, which is equivalent to 186 beats/min at a CRL of 45 mm and 174 beats/min at a CRL of 85 mm, was observed in 15 of the normal fetuses (0.06%) and in 57 of the trisomy 13 fetuses (31.49%; LR, 495.4; 95% CI, 285.9-858.4).

In the trisomy 13 fetuses, the mean delta NT was significantly higher than normal (mean, 3.0 mm; 95% CI, 2.7-3.4; \( P < .0001 \); Figure 4), and NT was above the 95th and 99th percentiles of the normal range for CRL in 141 (77.9%) and 108 (59.7%) of the cases, respectively (Figure 4). The LR for trisomy 13 increased with delta NT: 
\[ LR(NT) = 250 \times e^{\frac{-5}{4} \ln(\text{delta NT})} \]

There was no significant association between delta NT and delta FHR (\( r = .114; P = .12 \)). The estimated detection rates of trisomy 13 for false-positive rates of 0.05% to 1% in screening by maternal age and fetal heart rate, nuchal translucency, or the combination of the two are shown in Table I.

Major defects were observed in 92 of the 181 fetuses (50.8%; Table II). There were no significant differences in delta FHR between those fetuses with and those fetuses without holoprosencephaly (\( t = 0.42; P = .672 \),

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Table I Detection rates for trisomy 13 at different false positive rates, using screening by maternal age and either fetal heart rate, nuchal translucency, or the combination of the two.

<table>
<thead>
<tr>
<th>False positive rate (%)</th>
<th>FHR</th>
<th>NT</th>
<th>FHR + NT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>40.3</td>
<td>70.7</td>
<td>76.1</td>
</tr>
<tr>
<td>0.15</td>
<td>43.2</td>
<td>75.3</td>
<td>81.0</td>
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<tr>
<td>0.25</td>
<td>47.1</td>
<td>77.2</td>
<td>82.9</td>
</tr>
<tr>
<td>0.50</td>
<td>53.2</td>
<td>78.2</td>
<td>83.5</td>
</tr>
<tr>
<td>1.00</td>
<td>59.4</td>
<td>79.1</td>
<td>84.1</td>
</tr>
</tbody>
</table>

FHR, Fetal heart rate; NT, nuchal translucency.
In this first-trimester study, we selected 3 easily detectable major defects, high NT thickness, and tachycardia. The common sonographic findings in fetuses with trisomy 13, during the second trimester, are holoprosencephaly, microcephaly, facial abnormalities, cardiac and renal defects, exomphalos, and post axial polydactyly.9 In this first-trimester study, we selected 3 easily detectable major defects and found that, in approximately one half of the fetuses with trisomy 13, there are holoprosencephalies, exomphalos, and/or megacystis. The prevalence of each of these conditions at 11 to 13 weeks of gestation is approximately 1 in 1000 to 3000 fetuses.9–15 All 3 defects are associated with a high incidence of chromosomal abnormalities, mainly trisomies 13 and 18, which are found in approximately 60% of fetuses with exomphalos, in approximately 20% of fetuses with megacystis, and in approximately 30% of fetuses with holoprosencephaly. There was no significant difference in NT or FHR in the trisomy 13 fetuses with or without these defects. Therefore, in the presence of these defects at the 11 to 13+6-week scan, the parents should be counseled regarding the high risk for chromosomal abnormalities and offered the option of fetal karyotyping, irrespective of the fetal NT thickness or FHR. Because the overall prevalence of holoprosencephaly, exomphalos, and megacystis is less than 0.1% and a high proportion have associated chromosomal abnormalities, a policy of karyotyping all affected fetuses would not lead to a significant increase in the invasive testing rate.

In the trisomy 13 fetuses, NT thickness was above the 95th and 99th percentiles of the normal range for CRL in 78% and 60% of cases, respectively. These findings are compatible with the findings of the multicenter screening study of 96,127 pregnancies, which included 46 cases of trisomy 13.14 Consequently, approximately 75% of trisomy 13 fetuses can be identified as part of a first-trimester screening program for trisomy 21, without the need for an increase in the invasive testing rate.

In the trisomy 13 fetuses, FHR was above the 95th and the 99th percentiles of the normal range for CRL in 71% and 51% of cases, respectively. We have suggested previously that, because trisomy 13 is associated with narrowing of the outflow tract from the left ventricle, the tachycardia may be mediated by the action of baroreceptors in the aortic arch.6 In fetal life, the heart normally performs near the peak of the Frank-Starling curve of ventricular function17; therefore, tachycardia may represent a compensatory mechanism to increase cardiac output in the phase of left heart obstruction.18

The risk for trisomy 13 at 11 to 13+6 weeks of gestation increases with the deviation in both FHR and NT. Furthermore, there is no significant association between FHR and NT; in screening for trisomy 13, the detection rate can increase, and the false-positive rate can decrease by combining the measurements of NT and FHR. At any given false-positive rate, the detection rate that is achieved by maternal age and fetal NT is improved by approximately 5% with the inclusion of FHR. When the FHR was >20 beats/min above the normal mean for CRL (approximately 185 beats/min at a CRL of 45 mm and 175 beats/min at a CRL of 85 mm), the LR for trisomy 13 was approximately 500. Such a degree of tachycardia was observed in >30% of trisomy 13 fetuses and in only 0.06% of normal fetuses.

First-trimester screening by a combination of maternal age and fetal NT is aimed primarily at the early diagnosis of trisomy 21. For a 5% false-positive rate, the detection rate of trisomy 21 is at least 75%. As demonstrated by the findings of this study, the 11 to 13+6-week scan can also detect >90% of fetuses with trisomy

<table>
<thead>
<tr>
<th>Defect</th>
<th>N</th>
<th>%</th>
<th>Nuchal translucency</th>
<th>Fetal heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any defect</td>
<td>92</td>
<td>50.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exomphalos</td>
<td>51</td>
<td>28.2</td>
<td></td>
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<tr>
<td>Holoprosencephaly</td>
<td>48</td>
<td>26.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Megacystis</td>
<td>21</td>
<td>11.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No defect</td>
<td>89</td>
<td>49.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table II: Number of structural defects in fetuses with trisomy 13. Note that the total is more than 100% as some fetuses had more than one abnormality.
13. Approximately 75% to 80% of affected fetuses can be identified by NT screening. In the remaining 20% to 25% of trisomy 13 fetuses, approximately 50% of the fetuses can be identified by the diagnosis of holoprosencephaly, exomphalos, or megacystis, which are found in approximately 0.1% of the whole population. Measurement of the FHR and the diagnosis of severe tachycardia, which is found in only 0.06% of the population, would lead to the detection of a further 30% of affected fetuses that were not identified by the previous 2 methods. Conversely, parents who are at an increased risk of having a fetus with trisomy 13, such as those with a previously affected pregnancy, can be counseled that, if at the 11 to 13+6-week scan, the fetal NT and FHR are within the normal range and there is no obvious major defect, there is a >90% reduction in the risk of recurrence of this chromosomal abnormality.

References