Fetal heart rate and umbilico-placental Doppler flow velocity waveforms in early pregnancies with a chromosomal abnormality and/or an increased nuchal translucency thickness

Eric Jauniaux¹, Panagiotis Gavrilí, Peter Khun, Wessam Kurdi, Jon Hyett and Kypros H.Nicolaides

The Harris Birthright Research Centre for Fetal Medicine, King's College Hospital Medical School, London, UK

¹To whom correspondence should be addressed at: Academic Department of Obstetrics and Gynaecology, University College London Medical School, 86-96 Chenes Mews, London WC1E 6HX, UK

Fetal heart rate, umbilical artery pulsatility index, end-diastolic flow, nuchal translucency thickness and placental thickness were recorded in 250 women with a viable singleton pregnancy undergoing chorionic villous sampling for fetal karyotyping at 11–14 weeks of gestation. The fetal karyotype was normal in 210 cases and abnormal in 40, including 21 with trisomy 21, 13 with trisomy 18, three with triploidy, two with monosomy X and one with trisomy 13. A total of 52 fetuses with a normal karyotype had a nuchal translucency thickness ≥ 3 mm and were considered separately. There was a stable and significant increase in the mean fetal heart rate in trisomy 21 pregnancies compared to controls. No significant difference was found for the other variables between the groups. In chromosomally normal fetuses with an increased nuchal thickness, the development of fetal heart rate and compliance of the umbilico-placental circulation were within the normal ranges. Some fetuses with trisomy 18 or triploidy had an increased resistance to blood flow in the umbilical artery, which was probably due to abnormal placental development.

Key words: Doppler velocimetry/first trimester/heart rate/pregnancy/trisomy

Introduction

Fetal cardiac activity can be observed by sonography as early as 6 weeks of gestation, approximately at the time when the heart tube starts to beat (Levi et al., 1990; Goldstein, 1992). Between 6 and 9 weeks, there is a rapid increase in the mean heart rate from 125 to 175 beats per min (bpm), followed by a gradual decrease to around 160 bpm at 14 weeks (Schats et al., 1990a; Wisser and Dirschedl, 1994). The rise in the heart rate parallels the increase in crown–rump length and is maximal when the morphological development of the embryonic heart is completed (Wisser and Dirschedl, 1994).

In the first 12 weeks of gestation, umbilical arteries show a high degree of vascular resistance to blood flow expressed by narrow systolic waveforms, absence of end-diastolic flow (EDF) and high pulsatility index (PI) values (Jauniaux et al., 1991; Wladimiroff et al., 1991; Jauniaux et al., 1995). EDF appears in the umbilical arteries between 12 and 14 weeks. The mechanism for the establishment of diastolic flow is not fully explored. The results of our previous studies suggest that the changes in umbilical circulation resistance to flow are mainly influenced by changes in the utero-placental circulation rather than changes in villous angiogenesis (Jauniaux et al., 1991, 1992).

Abnormal fetal heart rate patterns have been observed in pregnancies which subsequently abort (May and Sturtevant 1991; Merchiers et al., 1991; Wisser and Dirschedl, 1994). A single observation of an abnormally slow heart rate does not necessarily indicate subsequent fetal death but a continuous decline in heart activity is inevitably associated with abortion (Merchiers et al., 1991). Abnormally slow fetal heart rates have also been reported in ongoing first trimester pregnancy complicated by Down’s syndrome (Laboda et al., 1989; Schats et al., 1990b). Several investigators have shown an association between high resistance to flow in umbilical artery and chromosomal abnormality during the second half of pregnancy (Wenstrom et al., 1991; Harrington et al., 1995).

To investigate further the possible association between an abnormal fetal karyotype and abnormal fetal heart rate and umbilical artery flow velocity waveforms, we have investigated a series of pregnant women who were referred for prenatal diagnosis at 11–14 weeks of gestation.

Materials and methods

A total of 250 women with a viable singleton pregnancy undergoing chorionic villous sampling (CVS) for fetal karyotyping at 11–14 weeks of gestation were investigated in this study. The indications for CVS were advanced maternal age (n = 148), increased (>3 mm) fetal nuchal translucency thickness (n = 85) or parental anxiety (n = 17). Gestational age was calculated from the maternal menstrual history (available in all cases) and confirmed by ultrasound measurements of the fetal crown–rump length (CRL).

In each case, ultrasound examination was performed before CVS using a 5 MHz curvilinear transabdominal transducer with pulsed and colour Doppler facilities (Toshiba, Toshiba Co., Tokyo, Japan). In all cases the nuchal translucency thickness was measured as previously described (Nicolaides et al., 1994). In 130 cases, placental thickness was also measured as the distance between the placental cord insertion and the decidual interface.

Fetal heart rate was determined during a period of absent fetal movements by simultaneous M-mode and real time B-mode imaging. Three individual measurements were recorded at 1 min intervals from M-mode tracing using electronic callipers. Differences in heart rate between the first and second and between the first and third measurements were calculated (variability 1 and 2 respectively).
was significantly increased in the trisomy 21 group compared to controls. Fetal heart rate showed little change with time and no significant difference was found for the other variables between the groups. No correlation was found between nuchal translucency thickness and fetal heart rate in the different groups.

In the normal group, the nuchal translucency measurement \((r = 0.40, n = 158, F = 25, P < 0.0001)\) and the placental thickness \((r = 0.28, n = 83, F = 7, P < 0.01)\) increased significantly with advancing gestational age, whereas fetal heart rate \((r = -0.47, n = 158, F = 35, P < 0.0001)\) and umbilical PI \((r = -0.56, n = 127, F = 57, P < 0.0001)\) decreased significantly. Similar correlations were found for the placental thickness, fetal heart rate and umbilical PI in the chromosomally normal group with a nuchal translucency thickness \(\geq 3\) mm and in the trisomy 21 group.

Individual measurements of fetal heart rate, umbilical PI and placental thickness obtained in the complicated cases are displayed in Figure 1, together with the mean and the corresponding range (1.96 SD) for gestational weeks 11–13. These normograms were established from the data of the normal group. It was noted that the heart rate of all but four fetuses with trisomy 21 was above the normal mean for gestational age, including three above the 95th centile. Two fetuses with trisomy 18 presented with a heart rate below the 5th centile. An increased heart rate was also found in four of the 52 chromosomally normal fetuses with a nuchal translucency\(\geq 3\) mm. The umbilical artery PI was above the 95th centile in three fetuses with a trisomy 18 and in two triploid fetuses. In the same cases, the placental thickness was found to be abnormal, below the 5th centile for the trisomy 18 cases and above the 95th centile for the triploids. An increased placental thickness was observed in three cases in the chromosomally normal group with a nuchal translucency \(\geq 3\) mm. In

### Results

The fetal karyotype was normal in 210 cases and abnormal in 40, including 21 with trisomy 21, 13 with trisomy 18, three with triploidy, two with monosomy X and one with trisomy 13. In 33 of the 40 cases of fetal chromosomal abnormalities, the nuchal translucency thickness was \(\geq 3\) mm (six trisomy 21 fetuses and one triploidy fetus had a nuchal thickness <3 mm). In the group with normal karyotype, there were 52 cases with a nuchal translucency \(\geq 3\) mm. Generalized fetal hydrops was found in four cases of trisomy 21 and in three cases of the chromosomally normal group with nuchal translucency \(\geq 3\) mm. The data on fetal heart rate, umbilical artery Doppler and placental thickness of the different groups are summarized in Tables I and II. The mean fetal heart rate was significantly increased in the trisomy 21 group compared to controls. Fetal heart rate showed little change with time and no significant difference was found for the other variables between the groups. No correlation was found between nuchal translucency thickness and fetal heart rate in the different groups.

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### Table I. Fetal heart rate, umbilical Doppler features and placental thickness in pregnancies with normal and abnormal karyotypes, and with nuchal thickness \(\geq 3\) mm. Data are presented as mean ± SD.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal karyotype</th>
<th>Abnormal karyotype</th>
<th>Nuchal thickness (\geq 3) mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>162.8 ± 8 (n = 158)</td>
<td>165 ± 12 (n = 40)</td>
<td>161 ± 10 (n = 52)</td>
</tr>
<tr>
<td>Variability 1 (bpm)</td>
<td>2.6 ± 2.1 (n = 158)</td>
<td>2.4 ± 1.6 (n = 40)</td>
<td>2 ± 1.9 (n = 52)</td>
</tr>
<tr>
<td>Variability 2 (bpm)</td>
<td>2.1 ± 1.8 (n = 158)</td>
<td>1.7 ± 1.3 (n = 40)</td>
<td>1.9 ± 1.6 (n = 52)</td>
</tr>
<tr>
<td>UPI</td>
<td>2.36 ± 0.42 (n = 127)</td>
<td>2.31 ± 0.49 (n = 23)</td>
<td>2.13 ± 0.47 (n = 24)</td>
</tr>
<tr>
<td>Placental thickness (mm)</td>
<td>15 ± 4 (n = 83)</td>
<td>15 ± 8 (n = 23)</td>
<td>15 ± 4 (n = 24)</td>
</tr>
</tbody>
</table>

bpm = beats per min; UPI = umbilical pulsatility index.

### Table II. Comparison of fetal heart rate and umbilical Doppler features between trisomy 21 and trisomy 18 fetuses and controls matched for gestational age.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Trisomy 21</th>
<th>Controls</th>
<th>t</th>
<th>P</th>
<th>Trisomy 18</th>
<th>Controls</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>170 ± 11 (n = 21)</td>
<td>162 ± 8 (n = 63)</td>
<td>10.1</td>
<td>&lt;0.005</td>
<td>160 ± 10 (n = 13)</td>
<td>163 ± 8 (n = 39)</td>
<td>1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Variability 1 (bpm)</td>
<td>2.9 ± 2.4 (n = 21)</td>
<td>3.3 ± 2.5 (n = 63)</td>
<td>0.1</td>
<td>NS</td>
<td>2.0 ± 1.7 (n = 13)</td>
<td>3.0 ± 2.8 (n = 39)</td>
<td>2.0</td>
<td>NS</td>
</tr>
<tr>
<td>Variability 2 (bpm)</td>
<td>1.7 ± 1.5 (n = 21)</td>
<td>2.5 ± 1.9 (n = 63)</td>
<td>0.06</td>
<td>NS</td>
<td>1.8 ± 1.1 (n = 13)</td>
<td>2.3 ± 1.6 (n = 39)</td>
<td>0.41</td>
<td>NS</td>
</tr>
<tr>
<td>UPI</td>
<td>2.03 ± 0.43 (n = 11)</td>
<td>2.29 ± 0.43 (n = 33)</td>
<td>1.7</td>
<td>NS</td>
<td>2.58 ± 0.45 (n = 10)</td>
<td>2.32 ± 0.46 (n = 30)</td>
<td>2.0</td>
<td>NS</td>
</tr>
<tr>
<td>Placental thickness (mm)</td>
<td>16 ± 3 (n = 11)</td>
<td>14 ± 4 (n = 33)</td>
<td>1.9</td>
<td>NS</td>
<td>11 ± 5 (n = 10)</td>
<td>15 ± 4 (n = 30)</td>
<td>3.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. t = rank test. bpm = beats per min; UPI = umbilical pulsatility index; NS = not significant.
two of these cases, the fetus was also hydropic and presented with an increased heart rate.

In normal pregnancies at 11 weeks of gestation, umbilical artery EDF was absent or incomplete in 59.7% and 40.3% of the cases respectively. Complete EDF started to appear at 12 weeks of gestation, and at 13 weeks a complete EDF was found in the umbilical artery of 68.2% of the normal fetuses (Table III). The development pattern of umbilical artery EDF was similar in chromosomally normal fetuses with a nuchal translucency ≥3 mm, whereas it was delayed in fetuses with a chromosomal abnormality.

Discussion
Heart action is the earliest proof of a viable fetus and any pregnancy ultimately ending in a normal outcome has cardiac
activity present in the early embryonic stages (Goldstein, 1992). Sporadic cases of a fetus with Down's syndrome presenting with an abnormally low heart rate in the first trimester of pregnancy have been previously reported (Laboda et al., 1989; Schats et al., 1990b). However, Van Lith et al. (1992), in a study of 10 chromosomally abnormal fetuses between 6 and 16 weeks, including five with trisomy 21, found no difference in the fetal heart rate compared to normal fetuses. In the present series, the mean fetal heart rate was significantly increased in the trisomy 21 group compared to the normal karyotype group. Of the fetuses with trisomy 21, 17 had a heart rate above the normal mean and three were above the 95th centile of the normal range, suggesting that this chromosomal disorder can be associated with fetal tachycardia between 11 and 13 weeks of gestation. Conversely, two fetuses with trisomy 18 presented with a heart rate below the 5th centile, which may indicate that these fetuses were compromised and would have died if the parents had decided to continue with the pregnancy.

In chromosomally abnormal fetuses there is often evidence of early developmental defects. Nuchal translucency thickness ≥3 mm is found in 86% of trisomic fetuses between 10 and 13 weeks of gestation (Nicolaides et al., 1994). The incidence of ventricular and atrioventricular cardiac septal defects is higher in fetuses with both trisomy 21 and increased nuchal translucency at 10–13 weeks of gestation than in live-born infants with only this chromosomal abnormality (Hyett et al., 1995). Fetuses with Down's syndrome are not known to have an increased heart rate in the second half of pregnancy or at delivery, suggesting that the abnormally high fetal heart rate observed earlier in pregnancy is a temporary phenomenon. The factors which control the first trimester fetal heart rate are uncertain. Cardiac septal defects found in fetuses with Down's syndrome could be associated with a delay in the development of the conductive pathways between the upper and lower halves of the heart. Major cardiac defects may lead to progressive heart failure with generalized fetal hydrops and eventually to fetal death before the end of the second trimester (Jauniaux et al., 1990). The relationship in early pregnancy between congenital heart defects, fetal tachycardia and fetal hydrops needs further exploration.

PI values from the umbilical artery remain high in early pregnancy, suggesting minor changes in vascular resistance until the beginning of the second trimester (Jauniaux et al., 1995). Umbilical artery EDF starts to appear after 10 weeks of gestation but is often incomplete and/or inconsistently present in normal fetuses between 11 and 13 weeks. The rapid decrease in umbilical PI parallels the sudden increase in uterine peak systolic velocity and we have previously suggested that the establishment of the intervillous circulation could be the main factor influencing the umbilical artery's compliance. It has recently been demonstrated that abnormal development of umbilical artery EDF during the second trimester of pregnancy is an ominous sign of adverse fetal outcome (Ariyuki et al., 1993; Sherer et al., 1993; Montenegro et al., 1995). In the present study, the umbilical artery PI was abnormally high in three of the 10 fetuses investigated with trisomy 18 and in the two triploid fetuses investigated. In these cases, the EDF at 13 weeks of gestation was either incomplete or absent, suggesting abnormal development of the umbilico-placental circulation.

Placental thickness increases progressively from a mean value of 20 mm at 16 weeks of gestation to 30 mm at 28 weeks (Jauniaux et al., 1994). There is an association around mid-gestation between an increase in placental thickness and subsequent slow fetal growth and/or hypertensive disorders of pregnancy (Dombrowski et al., 1992; Jauniaux et al., 1994). It has been recently suggested that an increased placental thickness in the second trimester is a highly sensitive marker of the subsequent development of fetal hydrops related to α-thalassaemia in high risk populations (Ko et al., 1995). We found that some fetuses with trisomy 18 had a decreased placental thickness and that it was notably increased in the two fetuses with triploidy. In the former, the placenta is generally hypoplastic with a low weight for gestational age, whereas in the latter the placenta is often abnormally large if there are associated hydatidiform changes (Shepard et al., 1989). The abnormal development of the placental tissue with poor vascularization of the villous trees (Hustin and Jauniaux, 1992) can explain the increased resistance to flow observed in the umbilical artery of these cases. In chromosomally normal fetuses with generalized hydrops, the placental thickness may

### Table III. Distribution of end-diastolic flow (EDF) waveforms in pregnancies with normal and abnormal karyotypes according to gestational age

<table>
<thead>
<tr>
<th>Gestational age and karyotype</th>
<th>n</th>
<th>Absent EDF</th>
<th>Incomplete EDF</th>
<th>Present EDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>67</td>
<td>40 (59.7)</td>
<td>27 (40.3)</td>
<td>–</td>
</tr>
<tr>
<td>Abnormal</td>
<td>9</td>
<td>8 (88.8)</td>
<td>1 (12.2)</td>
<td>–</td>
</tr>
<tr>
<td>Normal with NT &gt;3 mm</td>
<td>6</td>
<td>4 (66.6)</td>
<td>2 (33.4)</td>
<td>–</td>
</tr>
<tr>
<td>12 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>38</td>
<td>5 (13.2)</td>
<td>24 (63.2)</td>
<td>9 (23.6)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>7</td>
<td>4 (57.1)</td>
<td>3 (42.9)</td>
<td>–</td>
</tr>
<tr>
<td>Normal with NT &gt;3 mm</td>
<td>7</td>
<td>–</td>
<td>5 (71.4)</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td>13 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>22</td>
<td>–</td>
<td>7 (31.8)</td>
<td>15 (68.2)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>7</td>
<td>3 (42.8)</td>
<td>2 (28.6)</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td>Normal with NT &gt;3 mm</td>
<td>11</td>
<td>–</td>
<td>3 (27.3)</td>
<td>8 (72.7)</td>
</tr>
</tbody>
</table>

NT= nuchal thickness.
Numbers in parentheses are percentages.
also be increased; however, the umbilical Doppler results remained normal and within this context placental development should not be altered.

In conclusion, our findings indicate that in chromosomally normal fetuses with an increased nuchal thickness, the development of fetal heart rate and compliance of the umbilico-placental circulation is not different from fetuses with normal nuchal thickness. In chromosomally abnormal fetuses with trisomy 21, the heart rate is increased but the Doppler features are normal. Our data also suggest that in some fetuses with trisomy 18 or triploidy, an increased resistance to blood flow in the umbilical artery can be found in early pregnancy, probably due to an abnormal development of villous vascularization.

References


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