Nuchal Translucency in Multiple Pregnancies

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Aim. To evaluate the prevalence of increased nuchal translucency (NT) in multiple pregnancies and its relation to fetal karyotype and pregnancy outcome.

Methods. We measured fetal nuchal translucency (NT) in 6,338 women pregnant from 10+3 to 13+6 weeks by ultrasound, and evaluated the prevalence of NT≥95th centile in 115 multiple pregnancies, including 100 pairs of twins (70 dichorionic and 30 monochorionic placentas), 9 triplets, 5 quadruplets, and one quintuplet. Chorionicity, fetal karyotype, and pregnancy outcome were also evaluated in 400 singleton pregnancies.

Results. NT≥95th centile in a single fetus was found in 10/70 cases of dichorionic twin pregnancies (14%), in two quadruplets, in 7/30 monochorionic twin pregnancies (23.3%), and in both fetuses in one dichorionic twin pregnancy. In the control group, NT≥95th centile was found in 17/400 (4.2%) cases. In multiple pregnancies, two cases of trisomy 21 and one of 47, XXY were found. NT≥95th centile was found in 2/2 fetuses with trisomy 21 (one dichorionic twin pregnancy and one tetrachorionic pregnancy), but not in the 47, XXY trisomy (trichorionic triplet pregnancy). A skeletal dysplasia and a Goldenhar syndrome were found among the 10 dichorionic pregnancies with increased NT. Three intrauterine deaths of both fetuses, one congenital heart disease, and a case of twin-to-twin transfusion occurred in 7 monochorionic pregnancies with increased NT.

Conclusion. Increased NT in multiple pregnancies indicates fetuses at risk for chromosomal abnormalities and fetal malformation, and monochorionic twin pregnancies at higher risk for adverse outcome.

Key words: chromosome abnormalities; congenital defects; neck, ultrasonography; pregnancy, multiple; pregnancy, outcome

The ultrasound measurement of the soft tissues behind the fetal neck (nuchal translucency thickness) is a valid screening test for identification of the fetuses at highest risk for chromosomal abnormalities and congenital malformations (1-7). The fluid collection in the fetal nucha, causing increased nuchal translucency, can be elicited by cardiac failure, abnormal or delayed development of the lymphatic system, altered composition of the skin connective tissue, and venous congestion due to an increased thoracal pressure (8,9). Screening for chromosomal abnormalities by nuchal translucency has been shown as feasible and powerful approach in twin and multiple pregnancies as in singles (10-12). In this study, we evaluated the significance of increased nuchal translucency in multiple pregnancies in relation to the fetal karyotype and pregnancy outcome.

Patients and Methods

Since May 1996, we have offered to measure nuchal translucency to the patients in the first trimester of pregnancy who came to our center for prenatal diagnosis of genetic diseases and congenital malformations, maternal illnesses, exposure to teratogenic agents, maternal anxiety, and general fetal risks.

Patients were informed of the test during non-directive counseling and were given an informative leaflet. When consent was given, the test was carried out during an ultrasound examination. We used Nicolaides technique (2) for nuchal translucency measurement, which included: transabdominal approach, sagittal section of the fetus, magnification of the fetus so that it occupied at least 75% of the screen, care to distinguish between fetal skin and amnion, and the measurement of the maximum thickness of the translucent space between the skin and the soft tissues overlying the cervical spine. Five operators were involved.

Nuchal translucency measurement was recorded and the risk for trisomy 21 was calculated from the maternal age, gestational age, and nuchal translucency measurement. We used the Fetal Medicine Foundation First Trimester Scan Database (Version 1 from 1996 to 1998 and Version 3.32 since 1998) (2). Patients were immediately informed about the ultrasound results, nuchal translucency measurement, and personal risk, expressed as 1 in X.

Each woman was also given a form on the outcome of the pregnancy to fill in and return when the time comes.

Prenatal invasive analysis of fetal karyotype was offered if case fell within the two categories eligible under the decrees of the Italian Ministry of Health (1995 and 1998): "the
presence of a priori procreative risk (maternal age 35 and over; one parent a carrier of chromosomal abnormalities) and “a fetal risk manifested during the pregnancy (malformations visualized by ultrasound or positive results from biochemical tests for chromosomal abnormalities”).

For the purpose of this study, we conducted a computer search of the center’s database to identify the cases of twin and multiple pregnancies with known fetal karyotype and pregnancy outcome.

The prevalence of nuchal translucency greater than or equal to the 95th centile for crown-rump length (13) was determined in multiple and dichorionic or monochorionic twin pregnancies.

The measurements of the study group were compared with those of the first 400 spontaneous single pregnancies taken from the 1999 database.

### Results

Fetal nuchal translucency was measured by ultrasound in 6,338 pregnancies, including 153 multiple pregnancies, from 10+3 to 13+6 weeks of gestation. We excluded 23 multiple pregnancies with estimated delivery date after January 2000 and lost 15 cases during the follow-up. This left 115 multiple pregnancies with 252 fetuses for analysis. There were 100 pairs of twins (70 pairs with dichorionic placentas and 30 pairs with monochorionic placentas, all diamniotic), 9 sets of triplets, 5 sets of quadruplets, and 1 set of quintuplets. Median maternal age was 33 years (range, 20-33). The median gestational age at measurement was 11+4 weeks (range, 10+3-13+6).

Forty-seven pregnancies resulted from assisted reproductive techniques (9 sets of triplets, 5 sets of quadruplets, 1 set of quintuplets, and 32 sets of dichorionic twins). Karyotype analysis was performed in 53 pregnancies.

All 5 quadruplet pregnancies, the single case of quintuplet pregnancy, and 4 out of 9 triplet pregnancies underwent the first trimester multifetal pregnancy reduction to twins after nuchal translucency measurement. In two cases of reduction from quadruplets to twins, the presence of a thick nuchal translucency in one of the fetuses was used as a principal criterion for choosing which of the fetuses to reduce, and the karyotypes of reduced fetuses were determined from the cardiac blood cells. We found a fetus with trisomy 21 by chorion villus sampling in a spontaneous dichorionic twin pregnancy (maternal age 39, spontaneous intrauterine death at 13 weeks of pregnancy), a trisomy 21 by fetal blood sampling in a reduced fetus in a set of quadruplets (maternal age 33), and a fetus with 47, XXY by amniocentesis in a triplet pregnancy (maternal age 37).

Among the remaining 5 triplet pregnancies, intrauterine death of the 47, XXY fetus spontaneously occurred in one case after amniocentesis at 19 weeks. These pregnancies resulted in the birth of 14 babies (median gestational age 33 weeks, range 31-35; median weight at birth 1,890 grams, range 1,610-2,170).

In the dichorionic twin pregnancies, one case of skeletal dysplasia was diagnosed by ultrasound in the first trimester. This fetus was chosen for selective fetal reduction at 13 weeks. Then, a case of Goldenhar syndrome with interventricular septal defect was diagnosed after birth. In one of the pregnancies, one twin was stillbirth due to intra-partum asphyxia. There was also a case when both fetuses from one pregnancy died after amniocentesis at 18 weeks. The median gestational age at delivery in dichorionic twin pregnancies and in 10 cases of multiple pregnancies reduced to twins was 36 weeks (range 32-39), with median weight at birth 2,155 grams (range 1,520-3,260), and the mean inter-twin difference was 223.0 grams.

In the monochorionic pregnancies, 3 intrauterine deaths of both fetuses with normal karyotype occurred at 13, 25, and 35 weeks of pregnancy. There was also a case of congenital heart defect, and a case of mild twin-to-twin transfusion (presenting polyhydramnios and megacystis in the fetus with increased nuchal translucency, and oligohydramnios in the other sac, which resolved spontaneously around the 22 week). One case of monochorionic twin pregnancy underwent therapeutic abortion after prenatal diagnosis of homozgyous β-thalassemia by chorionic villi sampling. Median gestational age at delivery in the monochorionic twin pregnancies was 33 weeks (range, 28 to 37), with median weight at birth 2,075 grams (range, 910 to 2,520). The mean inter-twin difference was 352.5 grams.

Nuchal translucency was above the 95th centile in one fetus in 10 out of 70 dichorionic twin pregnancies (14%) (5 dichorionic pregnancies obtained by assisted reproductive techniques and 5 spontaneously conceived dichorionic pregnancies), in one fetus in two sets of quadruplets, and in 7 out of 30 fetuses of monochorionic twin pregnancies (23.3%). Nuchal translucency was greater than the 95th centile in both fetuses in one case of dichorionic twin pregnancy (Table 1).

Nuchal translucency was over the 95th centile in 2/2 fetuses with trisomy 21, whereas it was not increased in the 47, XXY case (Table 2).

The skeletal dysplasia and the Goldenhar syndrome occurred in dichorionic twin pregnancies with nuchal translucency greater than 95th centile.

### Table 1. Distribution of nuchal translucency (NT) greater than or equal to the 95th centile in multiple pregnancies (per pregnancy) and in the control group (singles)

<table>
<thead>
<tr>
<th>Pregnancy</th>
<th>No.</th>
<th>NT≥95th centile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>Twin monochorionic</td>
<td>30 sets</td>
<td>7 (23.0)</td>
</tr>
<tr>
<td>Twin dichorionic</td>
<td>70 sets</td>
<td>10 (14.0)</td>
</tr>
<tr>
<td>Triplet</td>
<td>9 sets</td>
<td>0</td>
</tr>
<tr>
<td>Quadruplet</td>
<td>5 sets</td>
<td>2 (40.0)</td>
</tr>
<tr>
<td>Quintuplet</td>
<td>1 set</td>
<td>0</td>
</tr>
<tr>
<td>Singles</td>
<td>400</td>
<td>17 (4.2)</td>
</tr>
</tbody>
</table>

*In 1/10 dichorionic twin pregnancies, the nuchal translucency was greater than the 95th centile in both fetuses, so the number of dichorionic twins with increased nuchal translucency was 11.
Among the 7 monochorionic pregnancies with increased nuchal translucency, 3 intrauterine deaths of both fetuses, a congenital heart disease, and twin-to-twin transfusion (recipient fetus) occurred.

In the control group of single fetuses, the median maternal age was 34 years (range, 15 to 35), and median gestational age 11.4 weeks (range, 10.3 to 13.6). Nuchal translucency was greater than or equal to 95th centile in 17 out of 400 cases (4.2%). A trisomy 21 (maternal age 39), cystic hygroma, and Dandy-Walker syndrome (both with normal karyotype) were found in single fetuses with increased nuchal translucency. Among fetuses with normal nuchal translucency, there were two miscarriages, one case of tricuspid aplasia, and one case of pyloric stenosis.

### Discussion

Higher average maternal age at conception and the widespread use of assisted reproductive techniques lead to a constant increase in the rate of twin and multiple pregnancies (14), which are at higher risk of specific prenatal and perinatal problems (15). Moreover, the risk of fetal chromosomal defects is higher in multiple pregnancies because of the advanced age of the mothers (16).

As these pregnancies are highly precious to the parents, the need of invasive prenatal diagnostic procedures (17,18), which are more difficult to perform in multiple than in singleton pregnancies (19), is not unanimously accepted. Non-invasive screening test for chromosomal abnormalities in multiple pregnancies would be more advisable. However, maternal serum biochemistry in twin pregnancies during the second trimester may be difficult because there is evidence that serum marker concentration is affected by assisted reproduction techniques (20), and also because of the difficulty to establish which of the fetuses has positive test results. On the other hand, it has been shown that nuchal translucency measurements in twin and multiple pregnancies are comparable to screening in singles (10,11). Nuchal translucency measurement combined with first trimester maternal serum biochemistry allows high detection rate of affected twins and can specifically detect a test-positive twin (21).

A large collaborative study on 448 twin pregnancies, found increased nuchal translucency in 7.3% of the cases as well as in 7 out of 8 cases of trisomy 21 (11). Another study on 24 multiple pregnancies by assisted reproduction, where no chromosomal abnormalities occurred (12), suggested that nuchal translucency measurement was feasible in high order multiple pregnancies. In our series of 115 multiple pregnancies, two thirds of chromosomal abnormalities had an increased nuchal translucency, as well as both cases with trisomy 21.

However, our results could be an overestimate, first because we offered invasive prenatal diagnosis in cases of increased nuchal translucency. It was, therefore, easier to identify trisomy 21 in those fetuses than in fetuses without visibly increased nuchal translucency, which could have been present amongst those miscarried, aborted, or lost at follow-up. Also, in most reductions of multifetal pregnancy, the karyotype of reduced fetuses was not obtained and exhaustive pathological examination of the fetuses was not possible.

In two cases of multifetal pregnancy reduction, increased nuchal translucency was used as a guiding criterion in the choice of reduction, as we reported previously (22).

It has been shown that the presence of an increased nuchal translucency is associated with an increased rate of structural malformations and, in particular, cardiac defects in fetuses with normal karyotype (6,7). We can expect higher occurrence of fetal malformation per pregnancy in multifetal pregnancies than in single pregnancies. In a dizygotic twin pregnancy, the risk of a fetal malformation is slightly higher than double per pregnancy (because of the independent probabilities per fetus). In our series, there was a high rate of increased nuchal translucency in dichorionic pregnancies (14%), comparing with 4.2% in singles and 5.4% in dichorionic pregnancies in the study of Sebire et al (11). The rate of chromosomal abnormalities and structural malformations in our series of dichorionic twins cannot completely explain this difference, and further studies involving a greater number of patients are needed. No evident difference was found between the rate of increased nuchal translucency in dichorionic pregnancies assisted by reproductive technologies and spontaneous dichorionic pregnancies.

We found a higher rate of increased nuchal translucency in monochorionic pregnancies (23% versus 14% in dichorionic pregnancies). In monozygotic pregnancies, where rates of Mendelian disorders and chromosomal abnormalities are identical to those of a singleton pregnancy, there is an increased risk of structural malformations. Sebire et al (11) have also pointed out a greater prevalence of increased nuchal translucency in fetuses from

### Table 2. Chromosomal abnormalities and nuchal translucency (NT) in 115 multiple pregnancies

<table>
<thead>
<tr>
<th>Chromosomal abnormalities</th>
<th>Maternal age (years)</th>
<th>Pregnancy</th>
<th>NT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>39</td>
<td>dichorionic twin</td>
<td>≥95th</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>33</td>
<td>tetrachorionic quadruplet</td>
<td>≥95th</td>
</tr>
<tr>
<td>47, XXY</td>
<td>37</td>
<td>trichorionic triplet</td>
<td>&lt;95th</td>
</tr>
</tbody>
</table>

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monochorionic twin pregnancies (8.4%) than in fetuses from dichorionic pregnancies (5.4%), explaining this as a possible early manifestation of the heart failure due to twin-to-twin transfusion.

Increased nuchal translucency in monochorionic pregnancies in our study was frequently associated with an unfavorable outcome of the pregnancy: 3 cases of intrauterine death, the presence of congenital cardiac defect in one of twins; and a twin-to-twin transfusion, probably due to a mechanism of temporary placental circulatory imbalance (11). This should oblige us to reconsider the significance of an increased nuchal translucency when calculating the risk for chromosomal abnormalities in monochorionic pregnancies. In these cases, the cause of increased nuchal translucency could be structural malformations or placental circulation problems rather than chromosomal abnormalities present in both fetuses or the extremely rare case of heterokaryotypia (23).

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References

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