

## INCREASED NUCHAL TRANSLUCENCY AS A MARKER FOR FETAL CHROMOSOMAL DEFECTS

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### ABSTRACT

**Background** Screening for trisomy 21 (Down's syndrome) by measuring maternal serum alpha-fetoprotein, chorionic gonadotropin, and estriol concentrations and then performing chorionic-villus sampling or amniocentesis identifies approximately 60 percent of fetuses with this disorder. We used ultrasonography to detect increased nuchal translucency and cystic hygroma, which are characteristic features of fetuses with chromosomal defects.

**Methods** We performed transvaginal ultrasonography in 10,010 unselected adolescents and women less than 40 years of age with live singleton fetuses at 10 to 15.9 weeks of gestation. Increased fetal nuchal translucency was defined as an area of translucency at least 3 mm in width, and cystic hygromas were defined as septated, fluid-filled sacs in the nuchal region. Subjects whose fetuses had these findings were offered fetal karyotyping. Information on pregnancies, deliveries, and neonates was subsequently obtained from hospital records and national birth and malformation registries.

**Results** Nuchal translucency or cystic hygroma was seen in 76 fetuses (0.8 percent), of which 18 (24 percent) had an abnormal karyotype. The sensitivity for trisomies 21, 18, and 13 combined was 62 percent (13 of 21 fetuses), and the sensitivity for trisomy 21 alone was 54 percent (7 of 13 fetuses).

**Conclusions** The use of transvaginal ultrasonography to detect increased nuchal translucency and cystic hygroma is a sensitive test for fetal aneuploidy. It can be done earlier in pregnancy than serum screening, and it decreases the subsequent need for chorionic-villus sampling or amniocentesis. (N Engl J Med 1997;337:1654-8.)

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**M**ATERNAL serum screening for fetal trisomy 21 (Down's syndrome) at 15 to 16 weeks of gestation is an established practice in many countries. The biochemical basis for this approach is that in the presence of fetal trisomy 21, the average maternal serum concentrations of chorionic gonadotropin are higher than normal and those of alpha-fetoprotein and estriol are lower than normal. When the values for screening tests are set at levels that will identify approximately 60 percent of the cases of trisomy 21, about 5 percent of pregnant women will have a positive test and may then undergo chorionic-villus sampling or amniocentesis.<sup>1-5</sup>

Fetal chromosomal abnormalities can also result in abnormalities detectable by ultrasonography. In-

creased nuchal translucency, which is caused by the subcutaneous accumulation of fluid in the neck of a fetus, and cystic hygroma of the neck are characteristic ultrasonographic findings in fetuses with trisomies, Turner's syndrome, and certain other chromosomal abnormalities.<sup>6-12</sup> Most ultrasound studies have been performed on mothers who are at elevated risk for fetal trisomy, because of advanced age or positive serum screening tests for trisomy 21,<sup>12,13</sup> and data on the usefulness of increased nuchal translucency as a primary screening method for fetal chromosomal abnormalities in unselected women are limited.<sup>14,15</sup>

The aim of our study was to define the frequency of increased fetal nuchal translucency in an unselected population of pregnant adolescents and women and to assess its usefulness in identifying fetuses at risk for chromosomal abnormalities.

### METHODS

#### Study Subjects

From January 1993 to December 1995, all newly pregnant adolescents and women residing in a defined area of the western part of greater Helsinki, Finland, were invited to undergo transvaginal ultrasonography at 13 to 14 weeks of gestation to determine gestational age and to identify major fetal congenital anomalies. The invitations were extended during the first antenatal visit to the local maternity-welfare centers, at which care is free and which are attended by over 99 percent of pregnant women in Finland. The subjects were advised of the possible findings, and they gave oral informed consent for the procedure.

The final study group consisted of 10,010 subjects with viable singleton pregnancies. Ninety-nine percent were white. The mean gestational age at the time of ultrasonography was 13.5 weeks (range, 10.0 to 15.9). Gestational age was based on the length from crown to rump for a gestational age of up to 13 weeks 2 days and on the biparietal diameter or femoral length for older fetuses.<sup>16-18</sup> We excluded 294 adolescents and women who were more than 15 weeks and 6 days pregnant, as well as 91 women who were 40 years of age or older (because they were offered chorionic-villus sampling at 10 to 12 weeks of gestation at the expense of the national health care system). The median maternal age was 29 years (range, 16 to 39) in the group as a whole and 29 years (range, 17 to 39) in the 76 subjects whose fetuses had increased nuchal translucency or cystic hygroma. Maternal serum screening for trisomy 21 was not systematically offered but was performed in some subjects.

Childbirths in this area of Finland (about 3600 per year) take place in two clinics, Jorvi Hospital and Helsinki University Central Hospital. The study protocol was approved by the ethics committees of both hospitals.

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### Measurement of Nuchal Translucency

Transvaginal ultrasonography was performed with a 6.5-MHz transducer (model EUB-415, Hitachi Medical, Tokyo, Japan). The fetus was imaged sagittally — that is, in the same plane used to measure the crown–rump length (Fig. 1). Eleven subjects who refused to undergo transvaginal ultrasonography were scanned transabdominally.

If the fetal neck was not clearly seen, the subject's uterus was gently manipulated with the probe or the examiner's hand, which was placed above the symphysis pubis. If this maneuver did not help, the subject was rescanned after a 30-minute walk. We found that it was important to wait until the fetus bounced off the uterine wall in order to see a clear distinction between the amnion and the skin covering the fetal neck. The neck was seen poorly in 138 fetuses (1.4 percent); the results for these fetuses were considered negative.

The extent of nuchal translucency was measured as the maximal thickness of the sonolucent zone between the inner aspect of the fetal skin and the outer aspect of the soft tissue overlying the cervical spine or the occipital bone (Fig. 1B). Increased nuchal translucency was defined a priori as the presence of a zone of at least 3 mm of translucency because this value had earlier been suggested as one that could be used to differentiate between fetuses at low risk for chromosomal abnormalities and those at high risk.<sup>19</sup>

The ultrasonography was performed by one obstetrician in 11 percent of the women and by a group of five specially trained midwives in the remainder. Every suggestion of an abnormality was checked at the time of the procedure by the obstetrician (who also resolved any disagreements in the diagnosis) or by another experienced obstetrician.

The fetuses with nuchal translucency of 3 mm or more were examined by at least two observers, but those with translucency of less than 3 mm were examined by only one observer. We tested the reproducibility of the measurements in the first 40 fetuses with translucency of 3 mm or more as identified by one observer; in 80 percent of these fetuses, the intraobserver and interobserver differences were 0 to 0.25 mm and 0 to 0.3 mm, respectively. The maximal intraobserver and interobserver differences were 0.5 mm and 0.6 mm, respectively. In one prospective study, measurements made by the same or different persons varied 95 percent of the time by less than 0.54 mm and 0.62 mm, respectively.<sup>20</sup>

We also looked for cystic hygromas, defined as large fluid-filled sacs, mostly septated, in the posterior occipital region of the fetus (Fig. 1C). The presence or absence of generalized hydrops was documented. We did not measure the nuchal fold, another marker for fetal aneuploidy used from 14 to 21 weeks of pregnancy.<sup>21</sup>

### Karyotyping and Outcome of Pregnancies

When fetal nuchal translucency was increased, the parents were counseled about the increased risk of fetal aneuploidy and were offered fetal karyotyping by chorionic-villus sampling or amniocentesis. The fetus was examined if the pregnancy was terminated. All live newborns were examined by a neonatologist, and karyotyping was performed in all newborns suspected of having any chromosomal abnormality.

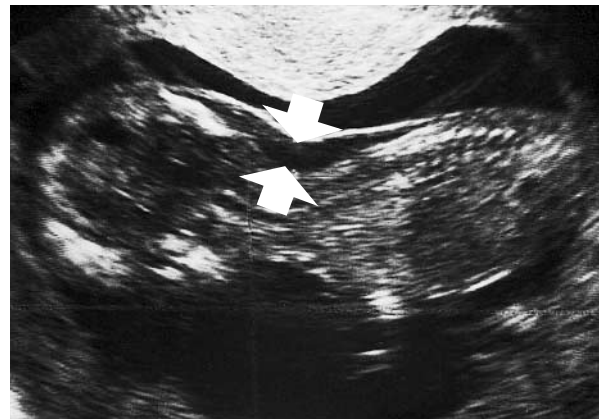
We entered information on the pregnancies, deliveries, and neonates in a data base that was later completed by entering data from the national birth registry and the national malformation registry. The latter also receives information on chromosomal abnormalities identified in neonates by the nine chromosome laboratories in the country; the reporting of these abnormalities is compulsory. In 50 subjects (0.5 percent) the outcome of the pregnancy could not be ascertained; transvaginal ultrasonography had revealed no fetal abnormalities in any of these subjects.

### RESULTS

Among the 10,010 subjects, 7221 (72 percent) underwent transvaginal ultrasonography at 13 to 14.9 weeks of gestation, 1782 (18 percent) at 10 to



A



B



C

**Figure 1.** Sagittal Transvaginal Ultrasonographic Images.

Panel A shows a normal fetus at 13 weeks of gestation with no translucency of the neck (arrow). Panel B shows a zone of nuchal translucency of 6 mm (arrows) in a 14-week fetus with trisomy 21. Panel C shows a 12-week fetus with Turner's syndrome and a large cystic hygroma (arrows).

**TABLE 1.** GESTATIONAL AGE AND FREQUENCY OF NUCHAL TRANSLUCENCY OF  $\geq 3$  mm OR CYSTIC HYGROMA AS DETERMINED BY TRANSVAGINAL ULTRASONOGRAPHY IN 10,010 PREGNANT SUBJECTS.

| WEEKS OF GESTATION | TOTAL NO. SCREENED | NUCHAL TRANSLUCENCY OF $\geq 3$ mm OR CYSTIC HYGROMA |         |
|--------------------|--------------------|--|---------|
|                    |                    | NO. OF FETUSES                                       | PERCENT |
| 10-10.9            | 57                 | 1  | 1.8     |
| 11-11.9            | 227                | 3  | 1.3     |
| 12-12.9            | 1,498              | 17   | 1.1     |
| 13-13.9            | 5,157              | 39   | 0.8     |
| 14-14.9            | 2,064              | 15   | 0.7     |
| 15-15.9            | 1,007              | 1  | 0.1     |
| Total              | 10,010             | 76   | 0.8     |

12.9 weeks, and 1007 (10 percent) at 15 to 15.9 weeks. Nuchal translucency of 3 mm or more or cystic hygroma was detected in a total of 76 fetuses (0.8 percent); the frequency of these findings decreased from 1.8 percent at 10 to 10.9 weeks of gestation to 0.1 percent at 15 to 15.9 weeks (Table 1).

Increased nuchal translucency was detected in 7 of 13 fetuses with trisomy 21 (54 percent) (Tables 2 and 3), 13 of 21 fetuses (62 percent) with trisomy 21, 18, or 13, and 18 of 26 fetuses with any type of aneuploidy (69 percent). The positive predictive value of increased nuchal translucency was 9 percent for trisomy 21 and 17 percent for all the trisomies. The specificity for trisomy 21 and for all trisomies was 99 percent (Table 3). Of the 10,010 fetuses, 55 had increased nuchal translucency and a normal

**TABLE 2.** ABNORMAL KARYOTYPES AMONG 10,010 FETUSES AND THE WIDTH OF NUCHAL TRANSLUCENCY AT TRANSVAGINAL ULTRASONOGRAPHIC SCREENING.

| CHROMOSOMAL ABNORMALITY AND WIDTH OF TRANSLUCENCY (mm) | GENERALIZED HYDROPS | PRENATAL KARYOTYPING | WEEKS OF GESTATION | MATERNAL AGE (YR) | OUTCOME              |
|--|---------------------|----------------------|--------------------|-------------------|----------------------|
| <b>Trisomy 21</b>                                      |                     |                      |                    |                   |                      |
| <3   | No                  | No                   | 14                 | 31                | Delivery             |
| <3   | No                  | No                   | 15                 | 35                | Delivery             |
| <3   | No                  | No                   | 15                 | 36                | Delivery             |
| <3   | No                  | No                   | 13                 | 31                | Delivery             |
| <3   | No                  | Yes (1/310)*         | 14                 | 29                | Termination          |
| <3   | No                  | Yes (1/270)*         | 13                 | 28                | Termination          |
| 3.5  | No                  | Yes                  | 13                 | 27                | Delivery             |
| 4  | No                  | Yes                  | 13                 | 24                | Termination          |
| 4  | No                  | Yes                  | 14                 | 35                | Termination          |
| 6  | Yes                 | Yes                  | 14                 | 32                | Termination          |
| 7  | No                  | Yes                  | 14                 | 25                | Termination          |
| 7  | Yes                 | Yes                  | 13                 | 24                | Termination          |
| 8  | Yes                 | Yes                  | 13                 | 35                | Termination          |
| <b>Trisomy 18</b>                                      |                     |                      |                    |                   |                      |
| <3   | No                  | No                   | 13                 | 25                | Delivery             |
| 6  | No                  | Yes                  | 13                 | 33                | Termination          |
| 9  | No                  | Yes                  | 12                 | 39                | Termination          |
| 9  | Yes                 | Yes                  | 14                 | 28                | Termination          |
| 9  | Yes                 | Yes                  | 12                 | 26                | Termination          |
| 12   | Yes                 | Yes                  | 13                 | 32                | Termination          |
| <b>Trisomy 13</b>                                      |                     |                      |                    |                   |                      |
| <3   | No                  | No                   | 13                 | 25                | Delivery             |
| 5  | Yes                 | Yes                  | 12                 | 32                | Termination          |
| <b>Turner's syndrome</b>                               |                     |                      |                    |                   |                      |
| 10†  | Yes                 | Yes                  | 13                 | 33                | Termination          |
| 10†  | Yes                 | Yes                  | 14                 | 29                | Termination          |
| 15†  | Yes                 | Yes                  | 13                 | 17                | Termination          |
| 15†  | Yes                 | Yes                  | 12                 | 27                | Spontaneous abortion |
| 22†  | No                  | Yes                  | 14                 | 24                | Termination          |

\*The risk of Down's syndrome based on the results of serum screening is given in parentheses.

†Cystic hygroma was identified.

**TABLE 3.** SENSITIVITY, SPECIFICITY, AND POSITIVE AND NEGATIVE PREDICTIVE VALUES OF INCREASED NUCHAL TRANSLUCENCY OR CYSTIC HYGROMA FOR FETAL ANEUPLOIDIES.\*

| VARIABLE                  | TRISOMY 21 |                  | TRISOMIES 13, 18, AND 21 |                  | ALL ANEUPLOIDIES |                  |
|---------------------------|------------|------------------|--------------------------|------------------|------------------|------------------|
|                           | NO./TOTAL  | PERCENT (95% CI) | NO./TOTAL                | PERCENT (95% CI) | NO./TOTAL        | PERCENT (95% CI) |
| Sensitivity               | 7/13       | 54 (25–81)       | 13/21                    | 62 (38–82)       | 18/26            | 69 (48–86)       |
| Specificity               | 9928/9997  | 99 (99–100)      | 9926/9989                | 99 (99–100)      | 9926/9984        | 99 (99–100)      |
| Positive predictive value | 7/76       | 9 (4–18)         | 13/76                    | 17 (9–28)        | 18/76            | 24 (15–35)       |
| Negative predictive value | 9928/9934  | 100              | 9926/9934                | 100              | 9926/9934        | 100              |

\*CI denotes confidence interval.

karyotype and 1 had cystic hygroma with a normal karyotype.

One subject whose fetus had increased nuchal translucency chose to have her pregnancy terminated without karyotyping, and another had a spontaneous abortion before undergoing amniocentesis. The remaining 74 subjects whose fetuses had increased nuchal translucency or cystic hygroma underwent chorionic-villus sampling or amniocentesis. Among these subjects, the extent of fetal nuchal translucency ranged from 3 to 48 mm (median, 6) at a mean gestational age of 13.5 weeks (range, 10 to 15), and the fetal karyotype was abnormal in 18 (24 percent).

In the 18 fetuses with confirmed aneuploidy, the extent of nuchal translucency ranged from 4 to 22 mm (median, 9). All five fetuses with Turner's syndrome had cystic hygroma, and four also had generalized hydrops (Table 2). Three of the six fetuses with trisomy 18 had generalized hydrops. Seventeen of the 18 subjects whose fetuses had aneuploidy terminated their pregnancies; 1 subject whose fetus had trisomy 21 decided to continue her pregnancy.

Analysis of the outcome of the 10,010 pregnancies revealed that eight fetuses with chromosomal aneuploidies were not identified by transvaginal ultrasonography: one had trisomy 13, one trisomy 18, and six trisomy 21. These missed cases were randomly distributed among the six examiners. Two of the six cases of trisomy 21 were diagnosed by serum biochemical tests; in both cases the results of transvaginal ultrasonography were normal (Table 2).

Transvaginal ultrasonography was not associated with bleeding, uterine contractions, or infections.

### DISCUSSION

Our results suggest that increased nuchal translucency is an effective indicator of fetal aneuploidy in unselected pregnant women. Using routine transvaginal ultrasonography at 10 to 15 weeks of gestation, we identified 54 percent of the fetuses with trisomy 21, 62 percent of those with any trisomy, and

69 percent of those with any aneuploidy. These results extend earlier studies in high-risk populations in which the presence of increased nuchal translucency had a sensitivity of 18 to 70 percent for the detection of karyotypic abnormalities.<sup>6-10,15,22-25</sup>

In studies of first-trimester pregnancies, the proportion of fetuses with increased nuchal translucency has ranged from 1 to 6 percent.<sup>12,14,15</sup> Our lower rate (0.8 percent) may be due to a more advanced gestational age at screening and to our use of transvaginal ultrasonography, which may be better able than transabdominal ultrasonography to distinguish fetal skin from amnion.<sup>26</sup> As in our study, a thickness of 3 mm has been the most commonly used value for nuchal translucency to differentiate fetuses at high risk for chromosomal abnormalities from those at low risk,<sup>19</sup> but values ranging from 2.5 to 4 mm have also been used.<sup>12,23</sup>

On the basis of maternal serum screening set to detect 60 percent of fetuses with trisomy 21, about 5 percent of all pregnant women are found to be at risk for a fetus with the disorder.<sup>1-5</sup> The proportion at risk on the basis of transvaginal ultrasonography in our study was much smaller (0.8 percent). Yet, in terms of the number of diagnosed cases of trisomy 21, our net results are similar to those reported for serum screening,<sup>1-5</sup> including those of a study in Helsinki.<sup>5</sup> Therefore, if transvaginal ultrasonography is used as the primary screening test, fewer women will need to undergo chorionic-villus sampling or amniocentesis.

Another advantage of transvaginal ultrasonography as compared with biochemical screening is that it effectively identifies aneuploidies other than trisomy 21, in addition to providing information about gestational age and fetal anatomy. Both methods can identify other fetal anomalies such as neural-tube defects and omphalocele. Ultrasonography<sup>27</sup> and a transvaginal probe<sup>28</sup> are currently considered safe in pregnancy. No complications of pregnancy in our study were attributable to the use of the vaginal probe.

In our series, transvaginal ultrasonography missed two fetuses with trisomy 21 that were later identified by serum biochemical tests at 15 to 16 weeks of gestation. Thus, combined use of these two methods may improve the accuracy of risk assessment. The accuracy can be further increased by including maternal age in the risk calculations.<sup>1-5,12</sup>

Wide application of transvaginal ultrasonography in early pregnancy has been limited by the belief that it requires sophisticated equipment and highly trained personnel. We found, however, that a standard ultrasound machine with a 6.5-MHz transvaginal probe is sufficient for an effective large-scale screening unit run by one trained obstetrician and a few well-trained midwives. The skill needed to measure nuchal translucency is no greater than that required to obtain a reliable measurement of the crown-rump length.<sup>20,29</sup>

We conclude that transvaginal ultrasonography is effective in screening for fetal aneuploidy, but comparative studies with other currently used methods will be required to identify the most cost-effective combinations. Transvaginal ultrasonography can be done earlier in pregnancy than biochemical screening, and its rate of detection is similar, but it is associated with a lower need for subsequent chorionic-villus sampling or amniocentesis.

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