REVIEW ARTICLE

Nuchal translucency and other first-trimester sonographic markers of chromosomal abnormalities

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Nuchal translucency
Absent nasal bone
Serum PAPP-A
Serum free–β-hCG
Screening for trisomy 21

Abstract: There is extensive evidence that effective screening for major chromosomal abnormalities can be provided in the first trimester of pregnancy. Prospective studies in a total of 200,868 pregnancies, including 871 fetuses with trisomy 21, have demonstrated that increased nuchal translucency can identify 76.8% of fetuses with trisomy 21, which represents a false-positive rate of 4.2%. When fetal nuchal translucency was combined with maternal serum free–β-human chorionic gonadotropin and pregnancy-associated plasma protein-A in prospective studies in a total of 44,613 pregnancies, including 215 fetuses with trisomy 21, the detection rate was 87.0% for a false-positive rate of 5.0%. Studies from specialist centers with 15,822 pregnancies, which included 397 fetuses with trisomy 21, have demonstrated that the absence of the nasal bone can identify 69.0% of trisomy 21 fetuses, which represents a false-positive rate of 1.4%. It has been estimated that first-trimester screening by a combination of sonography and maternal serum testing can identify 97% of trisomy 21 fetuses, which represents a false-positive rate of 5%, or that the detection rate can be 91%, which represents a false-positive rate of 0.5%. In addition to increased nuchal translucency, important sonographic markers for chromosomal abnormalities, include fetal growth restriction, tachycardia, abnormal flow in the ductus venosus, megacystis, exomphalos and single umbilical artery. Most pregnant women prefer screening in the first, rather than in the second, trimester. As with all aspects of good clinical practice, those care givers who perform first-trimester screening should be trained appropriately, and their results should be subjected to external quality assurance.

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In 1866, Down1 reported that, in individuals with trisomy 21 (the condition that came to bear his name), the skin appears to be too large for the body, the nose is small, and the face is flat. In the last decade, it has become possible to observe these features by ultrasound examination in the third month of intrauterine life.

Approximately 75% of trisomy 21 fetuses have increased nuchal translucency (NT) thickness, and 70% of the fetuses have absent nasal bone.

During the last 30 years, extensive research has aimed at developing a noninvasive method for prenatal diagnosis of chromosomal and other abnormalities through the isolation and examination of fetal cells that are found in the maternal circulation. However, on the basis of currently available data,2,3 there is no realistic prospect that, in the foreseeable future, noninvasive diagnosis will replace the need for invasive testing.

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Prenatal diagnosis requires either amniocentesis from 16 weeks of gestation or chorionic villous sampling from 11 weeks of gestation. Randomized studies have demonstrated that the procedure-related risk of miscarriage is the same (approximately 1%). Consequently, invasive testing is carried out only in pregnancies that are considered to be at high risk for chromosomal abnormalities. The traditional method of screening is maternal age, with which invasive testing in 5% of the population identifies approximately 30% of the fetuses with trisomy 21. There is now extensive evidence that ultrasound examination, combined with maternal serum biochemical testing at 11 to 13 weeks of gestation, can identify 95% of the fetuses with major chromosomal abnormalities.

This article reviews the evidence on the association between chromosomal abnormalities and increased NT and other sonographic markers in the first trimester of pregnancy.

### Methods

Searches of PubMed were made to identify all articles that have been published since 1990 on first trimester sonographic markers of chromosomal abnormalities. Most publications were on fetal NT, which were grouped into series that reported on the association between increased NT and chromosomal abnormalities, into series that reported on prospective screening studies with NT alone or NT in combination with first or second trimester maternal serum biochemical testing, and into series that reported on observational screening studies.

<table>
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<th>Trisomy 21 Trisomy 18 Maternal age (y)</th>
<th>Trisomy 21 Trisomy 18 Maternal age (y)</th>
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<td>42</td>
<td>38 43 46 55</td>
<td>89 128 175 644</td>
<td>280 395 524 1516</td>
</tr>
</tbody>
</table>

### Patient-specific risk for chromosomal abnormalities

Every woman has a risk that her fetus/baby has a chromosomal defect. To calculate the individual risk, it is necessary to take into account the a priori risk, which depends on maternal age and gestational age, and to multiply this by a likelihood ratio, which depends on the results of ultrasound findings and/or maternal serum biochemical tests that were performed during the course of the pregnancy to determine the patient-specific risk.

Every time a test is carried out, the a priori risk is multiplied by the likelihood ratio that is derived from that test to calculate a new risk, which then becomes the a priori risk for the next test. This process of sequential screening necessitates that the different tests are independent of each other. If the tests are not independent of each other, then more sophisticated techniques that involve multivariate statistics can be used to calculate the combined likelihood ratio.

### Maternal age and gestation

The risk for many of the chromosomal abnormalities increases with maternal age. Additionally, because fetuses with chromosomal abnormalities are more likely to die in utero than normal fetuses, the risk decreases with advancing gestation (Table I). Estimates of the maternal age-related risk for trisomy 21 at birth are based on surveys with almost complete ascertainment of the affected patients. During the last decade, with the introduction of maternal serum biochemistry and ultrasound screening for chromosomal abnormalities at
different stages of pregnancy, it has become necessary to establish maternal age and gestational age-specific risks for chromosomal abnormalities. Such estimates were derived by a comparison of the birth prevalence of trisomy 21 to the prevalence in women who undergo second-trimester amniocentesis or first-trimester chorionic villus sampling.

The rates of fetal death in trisomy 21 between 12 weeks of gestation (when NT screening is performed) and 40 weeks of gestation is approximately 30% and between 16 weeks of gestation (when second trimester serum biochemistry is performed) and 40 weeks of gestation is approximately 20%. In trisomies 18 and 13, the rate of fetal death between 12 and 40 weeks of gestation is approximately 80% (Table 1). The frequency of conception of 45,X embryos, unlike that of trisomies, is unrelated to maternal age; and the prevalence is approximately 1 per 1500 fetuses at 12 weeks of gestation, 1 per 3000 fetuses at 20 weeks of gestation, and 1 per 4000 fetuses at 40 weeks of gestation. Polyploidy affects approximately 2% of recognized conceptions, but it is highly lethal and thus rarely observed in live births; the prevalence at 12 and 20 weeks of gestation is approximately 1 per 2000 fetuses and 1 per 250,000 fetuses, respectively.

Fetal NT thickness

Cystic hygomas, nuchal edema, and NT

During the second and third trimesters of pregnancy, abnormal accumulation of fluid behind the fetal neck can be classified as nuchal cystic hygroma or nuchal edema. In approximately 75% of fetuses with cystic hygomas, there is a chromosomal abnormality; in approximately 95% of cases, the abnormality is Turner syndrome. Nuchal edema has a diverse cause; chromosomal abnormalities are found in approximately one third of the fetuses, and in approximately 75% of these cases, the abnormality is trisomy 21 or 18. Nuchal edema is associated with fetal cardiovascular and pulmonary defects, skeletal dysplasias, congenital infection, and metabolic and hematologic disorders; consequently, the prognosis for chromosomally normal fetuses with nuchal edema is poor.

In the first trimester, the term translucency is used, irrespective of whether the collection of fluid is septated and whether it is confined to the neck or envelopes the whole fetus. Cullen et al examined 29 fetuses with abnormal nuchal fluid at 10 to 13 weeks of gestation and reported that neither the incidence of chromosomal abnormalities nor the prognosis could be predicted by the ultrasonographic appearance of the lesion. Increased NT is associated with trisomy 21, Turner syndrome, and other chromosomal abnormalities as well as many fetal malformations and genetic syndromes. The prevalence of these abnormalities is related to the thickness, rather than the appearance, of NT. Furthermore, it is possible to standardize and audit the results of a measurement but not those of a subjective appearance.

Pathophysiologic evidence of increased NT

Increased fetal NT is associated with a wide range of chromosomal and other abnormalities. The heterogeneity of conditions suggests that there may not be a single underlying mechanism for the collection of fluid in the skin of the fetal neck. Possible mechanisms include cardiac failure in association with abnormalities of the heart and great arteries; venous congestion in the head and neck caused by constriction of the fetal body in amnion rupture sequence or superior mediastinal compression found in diaphragmatic hernia or the narrow chest in skeletal dysplasia; altered composition of the extracellular matrix that may be attributed to gene dosage effects; abnormal or delayed development of the lymphatic system; failure of lymphatic drainage because of impaired fetal movements in various neuromuscular disorders; fetal anemia or hypoproteinemia; or congenital infection that acts through anemia or cardiac dysfunction.

In fetuses with increased NT, the risk of an adverse outcome, which includes chromosomal and other abnormalities and fetal and postnatal death, increases with NT thickness from approximately 5% for NT between the 95th percentile and 3.4 mm to 30% for NT of 3.5 to 4.4 mm to 50% for NT of 4.5 to 5.4 mm and 80% for NT of ≥ 5.5 mm. In most cases with increased fetal NT, a series of antenatal investigations that includes fetal karyotyping, detailed scans, fetal echocardiography, and genetic testing and infection screening can be completed by 20 weeks of gestation and will distinguish between the pregnancies that are destined to result in adverse outcome and the pregnancies that are destined to the delivery of infants without major defects.

Measurement of NT

The ability to achieve a reliable measurement of NT is dependent on appropriate training and adherence to a standard technique to achieve uniformity of results among different operators.

Gestation and crown-rump length

The optimal gestational age for the measurement of fetal NT is 11 weeks of gestation to 13 weeks 6 days of gestation. The minimum fetal crown-rump length should be 45 mm, and the maximum length should be 84 mm.

The reasons for selecting 13 weeks 6 days of gestation as the upper limit are (1) to provide women who have
affected fetuses the option of an earlier and safer form of
termination; (2) the incidence of abnormal accumulation
of nuchal fluid in chromosomally abnormal fetuses is
lower at 14 to 18 weeks of gestation than at 14 weeks
of gestation, 17,19,20,43 and (3) the success rate for taking
a measurement at 10 to 13 weeks of gestation is 98% to
100%, which falls to 90% at 14 weeks of gestation
because the fetus is often in a vertical position, which
makes it more difficult to obtain the appropriate im-
age.44,45

The reason for selecting 10 weeks of gestation as the
earliest gestation was that screening necessitates the
availability of a diagnostic test, and in the early 1990s it
was appreciated that chorionic villous sampling before
10 weeks of gestation was associated with transverse
limb reduction defects.46,47 It was realized subsequently
that many major fetal abnormalities could be diagnosed
at the NT scan, if the minimum gestation is 11 weeks.
For example, diagnosis or exclusion of acrania and
therefore anencephaly cannot be made before 11 weeks
of gestation because sonographic assessment of ossifi-
cation of the fetal skull is not reliable before this
gestation.48 An examination of the 4-chamber view of
the heart and main arteries is possible only after 10
weeks of gestation.49-52 At 8 to 10 weeks of gestation, all
fetuses demonstrate herniation of the mid gut that is
visualized as a hyperechogenic mass in the base of the
umbilical cord; therefore, it is unsafe to diagnose or
exclude exomphalos at this gestation.53-55 The fetal
bladder can be visualized in only 50% of fetuses at 10
weeks of gestation but in all cases by 12 weeks of
gestation.52,56,57

In women who did not have a previous scan to date
the pregnancy, it would be better to schedule the NT
scan at 12 to 13 weeks of gestation, rather than at 11
weeks of gestation, because at this gestation some
fetuses would be found to be too small; and a further
scan would be necessary.45

Image and measurement

In the assessment of fetal NT, the ultrasound machine
should be of high resolution with a video-loop function
and calipers that provide measurements to 1 decimal
point. Fetal NT can be measured successfully by trans-
abdominal ultrasound examination in approximately
95% of cases; in the others, it is necessary to perform
transvaginal sonography. The results from transab-
dominal and transvaginal scanning are similar.58

Only the fetal head and upper thorax should be
included in the image for measurement of NT (Figures 1
and 2). The magnification should be as large as possible
and always such that each slight movement of the
calipers produces only a 0.1-mm change in the measure-
ment. In the magnification of the image, either before or
after the freeze zoom, it is important to turn the gain
down. This avoids the mistake of placing the caliper on
the fuzzy edge of the line, which causes an underestimate
of the nuchal measurement.59 A study in which rat heart
ventricles were measured initially by ultrasound and
then by dissection demonstrated that ultrasound meas-
urements can be accurate to the nearest 0.1 to 0.2 mm.60

A good sagittal section of the fetus, as for measure-
ment of fetal crown-rump length, should be obtained;
and the NT should be measured with the fetus in the
neutral position.55 Hyperextension of the fetal neck
can increase the NT measurement artificially by 0.6 mm, and
flexion can decrease the measurement by 0.4 mm.61

Care must be taken to distinguish between fetal skin
and amnion, because at this gestation both structures
appear as thin membranes (Figure 1). This is achieved by waiting for spontaneous fetal movement away from the amniotic membrane; alternatively, the fetus is bounced off the amnion by asking the mother to cough and/or by tapping the maternal abdomen.

The maximum thickness of the subcutaneous translucency between the skin and the soft tissue overlying the cervical spine should be measured. The calipers should be placed on the lines that define the NT thickness; the crossbar of the caliper should be such that it is hardly visible as it merges with the white line of the border and not in the nuchal fluid. During the scan, >1 measurement must be taken, and the maximum measurement should be used for the risk assessment.

The umbilical cord may be around the fetal neck in 5% to 10% of cases, which may produce a falsely increased NT and add approximately 0.8 mm to the measurement. In such cases, the measurements of NT above and below the cord are different, and in the calculation of risk, it is more appropriate to use the average of the 2 measurements.

There are no clinically relevant effects on NT measurements by ethnic origin, parity or gravidity, cigarette smoking, diabetic control, conception by assisted reproduction techniques, bleeding in early pregnancy or fetal gender.

The intraobserver and interobserver differences in measurements of fetal NT are <0.5 mm in 95% of cases.

### Deviation in measurement from normal

Fetal NT increases with crown-rump length; therefore, it is essential to take gestation into account when a determination is made about whether a given NT thickness is increased. In a study that involved 96,127 pregnancies, the median and 95th percentile at a crown-rump length of 45 mm were 1.2 and 2.1 mm; the respective values at a crown-rump length of 84 mm were 1.9 and 2.7 mm. The 99th percentile did not change with crown-rump length and was approximately 3.5 mm.

In a screening for chromosomal abnormalities, patient-specific risks are derived by the multiplication of the a priori maternal age and gestation-related risk by a likelihood ratio, which depends on the difference in fetal NT measurement from the expected normal median for the same crown-rump length (Delta value).

In screening that uses maternal serum biochemical markers, a different approach has been used to take into account the gestational age-related change in marker levels. This method involves the conversion of the measured concentration into a multiple of the median (MoM) of unaffected pregnancies at the same gestation. Essentially, the Gaussian distributions of log10 (MoM) in trisomy 21 and unaffected pregnancies are derived, and the heights of the distributions at a particular MoM, which is the likelihood ratio for trisomy 21, is used to modify the a priori maternal age-related risk to derive the patient-specific risk.

A study that involved the analysis of data of NT and crown-rump length from 128,030 unaffected and 428 trisomy 21 pregnancies demonstrated that the Delta NT approach provides accurate patient-specific risks. In contrast, the MoM approach was found to be inappropriate for this purpose, because none of the 3 basic assumptions that underpin this method are valid. First, in the unaffected population, the distributions of NT MoM and log10 (NT MoM) were not Gaussian; second, the standard deviations did not remain constant with gestation; and third, the median MoM in the trisomy 21 pregnancies was not a constant proportion of the median for unaffected pregnancies. The MoM approach resulted in women being given an overestimate of risk for trisomy at 11 weeks of gestation and a considerable underestimate of risk at 13 weeks of gestation.

### Training and quality assessment in the measurement of NT

Appropriate training of sonographers and adherence to a standard technique for the measurement of NT are essential prerequisites for good clinical practice. Furthermore, the success of a screening program necessitates the presence of a system for regular audit of results and continuous assessment of the quality of images. In 1997, a study group of the Royal College of Obstetricians and Gynaecologists in the United Kingdom recommended that NT screening should only be conducted by highly competent sonographers who are certified by an external agency and subject to external quality assurance and ongoing audit.

All sonographers who perform fetal scans should be capable of reliably measuring the crown-rump length and obtaining a proper sagittal view of the fetal spine. For such sonographers, it is easy to acquire the skill to measure NT thickness within a few hours. However, the ability to measure NT and to obtain reproducible results improves with training. Good results are achieved after 80 scans for the transabdominal route and after 100 scans transvaginally.

The Fetal Medicine Foundation (FMF), which is a UK registered charity, has established a process of training and quality assurance for the appropriate introduction of NT screening into clinical practice. Training is based on a theoretic course and practical instruction on how to obtain the appropriate image and make the correct measurement of NT. The trainee is required subsequently to submit a logbook of images, which are examined to determine whether the magnification...
is adequate, whether the section of the fetus is truly sagittal, whether the head is in the neutral position, whether the amnion is seen separately from the nuchal membrane and the calipers are placed appropriately. Ongoing quality assurance is based on an assessment of the distribution of fetal NT measurements and an examination of a sample of images that are obtained by each sonographer who is involved in screening. The distribution of measurements from each sonographer and each center is compared with those that were established by a major multicenter study co-ordinated by the FMF.82 The services of the FMF, including certification, software for calculation of risk, and quality assurance are provided free-of charge.

Three studies have demonstrated that an ongoing regular audit of images and the distribution of measurements of NT are essential for the assessment of the quality of a center and are useful in the identification of individual sonographers whose results deviate from the mean performance.88-90 The variation in measurements is reduced considerably after an initial learning phase and after feedback to the sonographers.

Additional evidence in favor of appropriate training of sonographers and adherence to a standard technique for the measurement of NT is provided by Monni et al,91 who reported that, by modifying their technique of measuring NT in accordance with the guidelines that were established by the FMF, their detection rate of trisomy 21 improved from 30% to 84%.

The process of training, certification, and quality assurance in NT measurement, as introduced by the FMF, has been endorsed and is now being carried out by the national societies of obstetricians and gynecologists in Australia, Austria, Cyprus, Germany, and Italy. Similar systems are being developed in many other countries, which includes the United States, in collaborations between the FMF and local professional organizations.

### NT thickness and risk for chromosomal abnormalities

In the early 1990s, several reports demonstrated that increased fetal NT thickness is associated with a high incidence of trisomy 21 and other chromosomal abnormalities (Table II).20,21,92-106 In the combined data from 17 series that involved a total of 1690 patients, the incidence of chromosomal abnormalities was 28.7%. However, there were large differences between the studies in the incidence of chromosomal abnormalities, which ranged from 11% to 88%, because of differences in the maternal age distributions of the populations that were examined and the definition of the minimum abnormal NT thickness, which ranged from 2 to 10 mm.

### Estimate of risk for trisomy 21 by maternal age and fetal NT

Studies in the mid 1990s demonstrated that (1) the risk of chromosomal abnormalities increases with both maternal age and fetal NT thickness and (2) in pregnancies with low fetal NT, the maternal age-related risk is decreased.20,100,107,108 A study of 1015 pregnancies with increased fetal NT reported that the observed numbers of trisomies 21, 18, and 13 in fetuses with NT

### Table II

<table>
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<th>Study/year</th>
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<th>Abnormal karyotype (n)</th>
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<th>Trisomy 18</th>
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<td>—</td>
<td>—</td>
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<td>25</td>
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<td>39</td>
<td></td>
</tr>
</tbody>
</table>
Implementation of NT screening in routine practice

Several prospective interventional studies have examined the implementation of NT screening in routine practice; the results are summarized in Tables III and IV. In some of the studies, the screen-positive group was defined by a cut-off in fetal NT (Table III) or a combined risk that was derived from the maternal age and the deviation in fetal NT from the normal median for fetal crown-rump length (Table IV).

The important findings of these studies are that (1) fetal NT was measured successfully in >99% of cases; (2) there were inevitable variations in false-positive and detection rates between the studies because of differences in the maternal age distribution of their populations and in the fetal NT or risk cut-offs that were used; and (3) in the combined data on >200,000 pregnancies, which included >900 fetuses with trisomy 21, fetal NT screening identified >75% of fetuses with trisomy 21 and other major chromosomal abnormalities, which represents a false-positive rate of 5%, or the detection rate was approximately 60%, which represents a false-positive rate of 1% (Tables III and IV).

In the study that was co-ordinated by the FMF, 100,311 singleton pregnancies were examined by 306 appropriately trained sonographers in 22 UK centers. In all cases, the fetal NT and crown-rump length were measured, and individual patient-specific risks that were based on maternal age, gestational age, and fetal NT were calculated. Follow-up was obtained from 96,127 cases, which included 326 cases with trisomy 21 and 325 cases with other chromosomal abnormalities (Table V). The median gestation at the time of screening was 12 weeks (range, 10-14 weeks of gestation), and the median

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Gestation (wk)</th>
<th>N</th>
<th>Successful measurement (%)</th>
<th>NT cut-off</th>
<th>False-positive rate (%)</th>
<th>Detection rate of trisomy 21 (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pandya et al/1995</td>
<td>10-13</td>
<td>1,763</td>
<td>100.0</td>
<td>2.5 mm</td>
<td>3.4</td>
<td>3/4 (75.0%)</td>
</tr>
<tr>
<td>Schwarzer et al/1996</td>
<td>10-13</td>
<td>4,523</td>
<td>100.0</td>
<td>2.5 mm</td>
<td>2.7</td>
<td>8/12 (66.7%)</td>
</tr>
<tr>
<td>Schuchter et al/2001</td>
<td>10-12</td>
<td>9,342</td>
<td>100.0</td>
<td>2.5 mm</td>
<td>2.1</td>
<td>11/19 (57.9%)</td>
</tr>
<tr>
<td>Wayda et al/2001</td>
<td>10-13</td>
<td>6,841</td>
<td>100.0</td>
<td>2.5 mm</td>
<td>4.1</td>
<td>17/17 (100.0%)</td>
</tr>
<tr>
<td>Panburana et al/2001</td>
<td>10-13</td>
<td>2,067</td>
<td>100.0</td>
<td>2.5 mm</td>
<td>2.9</td>
<td>2/2 (100.0%)</td>
</tr>
<tr>
<td>Snijders et al/1998</td>
<td>10-13</td>
<td>96,127</td>
<td>100.0</td>
<td>95th percentile</td>
<td>4.4</td>
<td>234/326 (71.8%)</td>
</tr>
<tr>
<td>Theodoropoulos et al/1998</td>
<td>10-13</td>
<td>3,550</td>
<td>100.0</td>
<td>95th percentile</td>
<td>2.3</td>
<td>10/11 (90.9%)</td>
</tr>
<tr>
<td>Zoppi et al/2001</td>
<td>10-13</td>
<td>10,111</td>
<td>100.0</td>
<td>95th percentile</td>
<td>5.1</td>
<td>52/64 (81.3%)</td>
</tr>
<tr>
<td>Gasiorek-Wiens et al/2001</td>
<td>10-13</td>
<td>21,959</td>
<td>100.0</td>
<td>95th percentile</td>
<td>8.0</td>
<td>174/210 (82.9%)</td>
</tr>
<tr>
<td>Brizot et al/2001</td>
<td>10-13</td>
<td>2,492</td>
<td>100.0</td>
<td>95th percentile</td>
<td>6.4</td>
<td>7/10 (70.0%)</td>
</tr>
<tr>
<td>Comas et al/2002</td>
<td>10-13</td>
<td>7,345</td>
<td>100.0</td>
<td>95th percentile</td>
<td>4.9</td>
<td>38/38 (100.0%)</td>
</tr>
<tr>
<td>Chasen et al/2003</td>
<td>11-13</td>
<td>2,248</td>
<td>100.0</td>
<td>95th percentile</td>
<td>3.4</td>
<td>9/12 (75.0%)</td>
</tr>
<tr>
<td>Szabo et al/1995</td>
<td>9-12</td>
<td>3,380</td>
<td>100.0</td>
<td>3.0 mm</td>
<td>1.6</td>
<td>27/30 (90.0%)</td>
</tr>
<tr>
<td>Taipale et al/1997</td>
<td>10-13</td>
<td>6,939</td>
<td>98.6</td>
<td>3.0 mm</td>
<td>0.7</td>
<td>4/6 (66.7%)</td>
</tr>
<tr>
<td>Pajkrt et al/1998</td>
<td>10-13</td>
<td>3,614</td>
<td>100.0</td>
<td>3.0 mm</td>
<td>0.7</td>
<td>32/46 (69.6%)</td>
</tr>
<tr>
<td>Audibert et al/2001</td>
<td>10-13</td>
<td>4,130</td>
<td>95.5</td>
<td>3.0 mm</td>
<td>1.7</td>
<td>7/12 (58.3%)</td>
</tr>
<tr>
<td>Rosenberg et al/2002</td>
<td>12-14</td>
<td>6,234</td>
<td>98.6</td>
<td>3.0 mm</td>
<td>2.8</td>
<td>13/21 (61.9%)</td>
</tr>
<tr>
<td>Economides et al/1998</td>
<td>11-14</td>
<td>2,256</td>
<td>100.0</td>
<td>99th percentile</td>
<td>0.4</td>
<td>6/8 (75.0%)</td>
</tr>
<tr>
<td>Whitting et al/1999</td>
<td>11-14</td>
<td>5,947</td>
<td>100.0</td>
<td>99th percentile</td>
<td>0.7</td>
<td>15/23 (65.2%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>200,868</td>
<td>99.8</td>
<td></td>
<td></td>
<td>669/871 (76.8%)</td>
</tr>
</tbody>
</table>
maternal age was 31 years. The estimated risk for trisomy 21 was 1 in 300 cases in 7907 (8.3%) of the normal pregnancies, in 268 cases (82.2%) of those with trisomy 21, and in 253 cases (77.8%) with other chromosomal abnormalities. For a screen-positive rate of 5%, the detection rate was 77% (95% CI, 72%-82%).

The issue of fetal lethality

Screening for chromosomal abnormalities in the first, rather than the second, trimester has the advantage of earlier prenatal diagnosis and consequently less traumatic termination of pregnancy for those couples who choose this option. A potential disadvantage is that earlier screening preferentially identifies those chromosomally abnormal pregnancies that are destined to miscarry. Approximately 30% of affected fetuses die between 12 weeks of gestation and term. This issue of preferential intrauterine lethality of chromosomal abnormalities is, of course, a potential criticism of all methods of antenatal screening, which include second-trimester maternal serum biochemistry, because the rate of intrauterine lethality between 16 weeks of gestation and term is approximately 20%. In a study of 109 fetuses with trisomy 21 that were diagnosed in the first trimester because of increased fetal NT, the parents chose to continue with the pregnancy in 6 cases, whereas in 103 cases the parents opted for termination. In 5 of the 6 fetuses, the translucency resolved, and at the second-trimester scan, the nuchal-fold thickness was normal. All 6 trisomy 21 babies were born alive, but 1 baby had a major atrioventricular septal defect and died at the age of 6 months. These data suggest that increased NT does not identify necessarily those trisomic fetuses who are destined to die in utero.

In prenatal screening studies, it is impossible to know how many of the trisomy 21 pregnancies that were terminated would have resulted in live births. However, it is possible to estimate the impact of prenatal screening on the prevalence of trisomy 21 in live births. This can be done by a comparison of the number of affected live births with the number that are estimated on the basis of the maternal age-related prevalence of trisomy 21 in live births and the maternal age distribution of the population that was screened. In the FMF screening study, by a combination of maternal age and fetal NT, a risk cut-off of 1 in 300 was associated with a false-positive rate of 8.3% and a detection rate of 82.2.

### Table IV

Prospective screening studies for trisomy 21 at 10 to 14 weeks of gestation with the use of the FMF software to estimate patient-specific risks that were based on maternal age, gestational age and fetal NT thickness

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Mean maternal age (y)</th>
<th>1/300</th>
<th>7,907/95,476 (8.3%)</th>
<th>268/326 (82.2%)*</th>
<th>253/325 (77.8%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snijders et al/199882</td>
<td>31</td>
<td>1/300</td>
<td>151/3,528 (4.3%)</td>
<td>10/11 (90.9%)</td>
<td>11/11 (100.0%)</td>
</tr>
<tr>
<td>Theodoropoulos et al/1998114</td>
<td>29</td>
<td>1/300</td>
<td>762/9,753 (7.8%)</td>
<td>17/21 (81.0%)*</td>
<td>25/28 (89.3%)</td>
</tr>
<tr>
<td>Thilaganathan et al/1999127</td>
<td>29</td>
<td>1/270</td>
<td>121/5,450 (7.4%)</td>
<td>10/12 (83.3%)</td>
<td>8/11 (72.7%)</td>
</tr>
<tr>
<td>Schwarzler et al/1999110</td>
<td>32</td>
<td>1/300</td>
<td>50/989 (6.0%)</td>
<td>6/8 (75.0%)</td>
<td>3/3 (100.0%)</td>
</tr>
<tr>
<td>O’Callaghan et al/2000128</td>
<td>28</td>
<td>1/300</td>
<td>183/2,470 (7.4%)</td>
<td>9/10 (90.0%)</td>
<td>9/12 (75.0%)</td>
</tr>
<tr>
<td>Brizet et al/2001117</td>
<td>33</td>
<td>1/300</td>
<td>2800/21,475 (13.0%)</td>
<td>184/210 (87.6%)</td>
<td>239/274 (88.2%)</td>
</tr>
<tr>
<td>Gasiorek-Wiens et al/2001116</td>
<td>33</td>
<td>1/100</td>
<td>61/2,600 (2.3%)</td>
<td>8/8 (100%)</td>
<td>5/7 (71.4%)</td>
</tr>
<tr>
<td>Sau et al/2001129</td>
<td>28</td>
<td>1/300</td>
<td>887/10,001 (8.9%)</td>
<td>58/64 (90.6%)</td>
<td>39/46 (84.8%)</td>
</tr>
<tr>
<td>Zoppiti et al/2001115</td>
<td>31</td>
<td>1/300</td>
<td>565/11,820 (4.8%)</td>
<td>22/27 (81.5%)</td>
<td>—</td>
</tr>
<tr>
<td>Prefumo and Thilaganathan/2002130</td>
<td>31</td>
<td>1/300</td>
<td>169/2,216 (7.5%)</td>
<td>10/12 (83.3%)*</td>
<td>15/20 (75.0%)</td>
</tr>
<tr>
<td>Chasen et al/2003118</td>
<td>33</td>
<td>1/300</td>
<td>95,476 4209 (4.4%)</td>
<td>7907 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>13,756/164,828 (8.3%)</td>
<td>602/709 (84.9%)</td>
<td>607/737 (82.4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* In 3 studies, the detection rate at a fixed 5% false-positive rate was estimated. In the combined data on a total of 359 cases of trisomy 21, it was estimated that 278 cases (78.4%) would have been detected.

### Table V

A multicenter study that was co-ordinated by the FMF

<table>
<thead>
<tr>
<th>Fetal karyotype</th>
<th>N</th>
<th>NT &gt; 95th percentile</th>
<th>Risk ≥ 1 in 300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>95,476</td>
<td>4209 (4.4%)</td>
<td>7907 (8.3%)</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>326</td>
<td>234 (71.2%)</td>
<td>268 (82.2%)</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>119</td>
<td>89 (74.8%)</td>
<td>97 (81.5%)</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>46</td>
<td>33 (71.7%)</td>
<td>37 (80.4%)</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>54</td>
<td>47 (87.0%)</td>
<td>48 (88.9%)</td>
</tr>
<tr>
<td>Triploidy</td>
<td>32</td>
<td>19 (59.4%)</td>
<td>20 (62.5%)</td>
</tr>
<tr>
<td>Other*</td>
<td>64</td>
<td>41 (64.1%)</td>
<td>51 (79.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>96,127</td>
<td>4767 (5.0%)</td>
<td>8428 (8.8%)</td>
</tr>
</tbody>
</table>

* Deletions, partial trisomies, unbalanced translocations, sex chromosome aneuploidies.

maternal age was 31 years. The estimated risk for trisomy 21 was >1 in 300 cases in 7907 (8.3%) of the normal pregnancies, in 268 cases (82.2%) of those with trisomy 21, and in 253 cases (77.8%) with other chromosomal abnormalities. For a screen-positive rate of 5%, the detection rate was 77% (95% CI, 72%-82%).

### The issue of fetal lethality

Screening for chromosomal abnormalities in the first, rather than the second, trimester has the advantage of earlier prenatal diagnosis and consequently less traumatic termination of pregnancy for those couples who choose this option. A potential disadvantage is that...
that prenatal screening followed by invasive diagnostic testing and selective termination of affected fetuses would have reduced the potential live birth prevalence of trisomy 21 by 78% to 82%.82

Observational studies

The ability to achieve a reliable measurement of NT is dependent on appropriate training, adherence to a standard technique, and motivation of the sonographer. All 3 components are well illustrated by the differences in results between interventional (Tables III and IV) and observational studies, in which the sonographers were asked to record the fetal NT measurements but not act on the results (Table VI).132-137 Thus, successful measurement of NT was achieved in >99% of cases in the interventional studies (Table III), but in only 75% of cases in the observational studies (Table VI). Furthermore, in the interventional studies, there was increased NT in 76.8% of the trisomy 21 and 4.2% of the chromosomally normal fetuses, compared with the respective rates of 38.4% and 5.0% in the observational studies.

In the observational studies, the scans often were carried out at inappropriate gestations, and the sonographers were either not trained adequately or were not motivated sufficiently to measure NT. In the first study, the sonographers were instructed to take no extra scanning time other than that that was necessary for the measurement of the crown-rump length.132 Fetal NT was measured successfully in only 66% of cases. In the second study, the fetal crown-rump length was <33 mm in 54% of cases, and the sonographers who were instructed to measure fetal NT within 3 minutes were unable to do so in 42% of cases.134 In the third study in 16 centers, the sonographers did not receive any training but were given written instructions on how to measure NT.135 Inevitably, there were large variations between centers in the ability to measure NT (median, 83%; range, 61%-100%), the median value of NT (median, 1.5 mm; range, 1.0-4.0 mm), and the percentage of trisomy 21 fetuses with NT at >95th percentile (median, 31%; range, 0-100%). The authors concluded that it is necessary that the measurement of NT should be standardized and subjected to ongoing quality assurance.

These methods problems are further highlighted by a study of 47,053 singleton pregnancies that were examined at 6 to 16 weeks of gestation.137 In 11,025 of the patients (23.4%), no valid NT measurement was taken because the scans were carried out at inappropriate gestations (n = 4228 pregnancies) or the sonographers were unable to obtain a measurement (n = 3416 pregnancies) or none of the images were deemed to be of an acceptable quality (n = 3881 pregnancies).137

Further evidence on the difference between observational and interventional studies is provided by Crossley et al.136 In this observational study, 17,229 pregnancies were recruited, and fetal NT was measured successfully in 72.9% of cases. In a subsequent study of >2000 pregnancies in which the results of the scan were given to the women, fetal NT was measured successfully in 99.8% of cases.136

Fetal NT and maternal serum biochemistry

Trisomic pregnancies are associated with altered maternal serum concentrations of various fetoplacental products, which included a-fetoprotein (AFP), free β-human choric gonadotropin (β-hCG), inhibin A, and unconjugated estriol.138-142 Screening by maternal age and various combinations of these fetoplacental products can identify 60% to 75% of trisomy 21 pregnancies, which represents a false-positive rate of 5%.143 However, an essential component of biochemical screening is the accurate dating of the pregnancy by ultrasound, otherwise the detection rate is reduced by approximately 10%.

**Table VI** Results of observational studies on the effectiveness of NT providing data about gestation at screening, the number of patients who were recruited, and the number of women with satisfactory measurements of NT, false-positive rate, and detection rate of trisomy 21

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Gestation (wk)</th>
<th>N</th>
<th>Successful measurement (%)</th>
<th>NT cut-off</th>
<th>False-positive rate (%)</th>
<th>Detection rate (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roberts et al/1995</td>
<td>8-13</td>
<td>1,704</td>
<td>66.1</td>
<td>3.0 mm</td>
<td>6.2</td>
<td>1/3 (33.3%)</td>
</tr>
<tr>
<td>Bewley et al/1995</td>
<td>8-13</td>
<td>923</td>
<td>58.2</td>
<td>3.0 mm</td>
<td>6.3</td>
<td>2/4 (50.0%)</td>
</tr>
<tr>
<td>Kornman et al/1996</td>
<td>8-13</td>
<td>4,049</td>
<td>83.0</td>
<td>95th percentile</td>
<td>5.0</td>
<td>18/58 (31.0%)</td>
</tr>
<tr>
<td>Haddow et al/1998</td>
<td>9-15</td>
<td>17,229</td>
<td>72.9</td>
<td>95th percentile</td>
<td>5.0</td>
<td>18/37 (48.6%)</td>
</tr>
<tr>
<td>Crossley et al/2002</td>
<td>10-14</td>
<td>47,053</td>
<td>76.6*</td>
<td>95th percentile</td>
<td>5.0</td>
<td>29/75 (38.7%)</td>
</tr>
<tr>
<td>Wald et al/2003</td>
<td>6-16</td>
<td>70,958</td>
<td>75.1</td>
<td></td>
<td>5.0</td>
<td>68/177 (38.4%)</td>
</tr>
</tbody>
</table>
* Satisfactory images at 10 to 14 weeks of gestation.
Table VII  Prospective first-trimester screening studies by fetal NT and maternal serum free β-hCG and PAPP-A that provided data on the detection rate for trisomy 21 at a 5% false-positive rate

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Gestation (wk)</th>
<th>N</th>
<th>Detection rate (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krantz et al/2000150</td>
<td>10-13+6</td>
<td>5,809</td>
<td>30/33 (90.9%)</td>
</tr>
<tr>
<td>Bindra et al/2002151</td>
<td>11-13+6</td>
<td>14,383</td>
<td>74/82 (90.2%)</td>
</tr>
<tr>
<td>Spencer et al/2000152;</td>
<td>10-13+6</td>
<td>11,105</td>
<td>23/25 (92.0%)</td>
</tr>
<tr>
<td>2003153</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schuchter et al/2002154</td>
<td>10-13+6</td>
<td>4,802</td>
<td>12/14 (85.7%)</td>
</tr>
<tr>
<td>Wapner et al/2003155</td>
<td>10-13+6</td>
<td>8,514</td>
<td>48/61 (78.7%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>44,613</td>
<td>187/215 (87.0%)</td>
</tr>
</tbody>
</table>

Fetal NT and maternal serum testing in the first-trimester

In trisomy 21 pregnancies at 10+3 to 13+6 weeks of gestation, the maternal serum concentration of free β-hCG is higher than in chromosomally normal fetuses, whereas pregnancy-associated plasma protein-A (PAPP-A) is lower (approximately 2 MoM and 0.5 MoM, respectively).138,144-148

There is no significant association between fetal NT and maternal serum free β-hCG or PAPP-A in either trisomy 21 or chromosomally normal pregnancies; therefore, the ultrasonographic and biochemical markers can be combined to provide more effective screening than either method individually.146-149 In a retrospective study of 210 singleton pregnancies with trisomy 21 and 946 chromosomally normal control subjects who were matched for maternal age, gestation, and sample storage time, we estimated that the detection rate for trisomy 21 by a combination of maternal age, fetal NT, and maternal serum PAPP-A and free β-hCG would be approximately 90%, which represents a screen positive rate of 5%.149

Six prospective screening studies have confirmed the feasibility and effectiveness of combining fetal NT and maternal serum free β-hCG and PAPP-A (Table VII).150-155 The study of Bindra et al151 also reported the detection rates for fixed false-positive rates between 1% and 5% (Table VIII) and the false-positive rates for fixed detection rates between 60% and 90% (Table IX) of screening for trisomy 21 by maternal age alone, maternal age and fetal NT, maternal age, and serum free β-hCG and PAPP-A and by maternal age, fetal NT, and maternal serum biochemistry. Thus, for a 5% false-positive rate, the detection rate of trisomy 21 by the first-trimester combined test was 90%, which is superior to the 30% that was achieved by maternal age and 65% that was achieved by second-trimester biochemistry. Alternatively, the detection rate of 65% that was achieved by second-trimester biochemical testing with a 5% false-positive rate can be achieved by first-trimester combined testing, with a false-positive rate of only 0.5%.151

In trisomies 18 and 13, maternal serum free β-hCG and PAPP-A are decreased.156,157 In cases of sex chromosomal anomalies, maternal serum free β-hCG is normal, and PAPP-A is low.158 In diandric triploidy, maternal serum free β-hCG is increased greatly, whereas PAPP-A is decreased mildly.159 Ditynic triploidy is associated with markedly decreased maternal serum free β-hCG and PAPP-A.159 Screening by a combination of fetal NT and maternal serum PAPP-A and free β-hCG can identify approximately 90% of all these chromosomal abnormalities, which represents a screen positive rate of 1%.

An important development in biochemical analysis is the introduction of a new technique (random access immunoassay analyzer with time-resolved amplified cryptate emission), which provides automated, precise, and reproducible measurements within 30 minutes of obtaining a blood sample. This has made it possible to combine biochemical and ultrasonographic testing and to counsel in 1-stop clinics for early assessment of fetal risk.151-153

Fetal NT and maternal serum testing in the second trimester

In women who undergo second-trimester biochemical testing after first-trimester NT screening the a priori risk must be adjusted to take into account the first-trimester screening results.9 Supportive evidence is provided by the findings of 3 prospective studies that examined the impact of first-trimester screening by NT on second-trimester biochemical testing.129,160,161 In 1 study, the proportion of affected pregnancies in the screen-positive group (positive predictive value) with the second-trimester double maternal serum test was 1 in 40 pregnancies, but after the introduction of screening by NT, 83% of trisomy 21 pregnancies were identified in the first trimester, and the positive predictive value of biochemical testing decreased to 1 in 200 pregnancies.160 In the second study, first-trimester screening by NT identified 71% of trisomy 21 pregnancies, which represents a screen-positive rate of 2%; the positive predictive value of the second-trimester quadruple maternal serum test was only 1 in 150 pregnancies.161 In the third study, 2683 women had NT screening; in 74 women (2.8%), the estimated risk for trisomy 21 was 1 in ≥100 pregnancies; this group contained all 8 cases of trisomy 21.129 In the 2609 screen-negative women, 1057 women agreed to have the second-trimester triple maternal serum test, and 1552 women (59.5%) declined further screening. In the 1057 women who had serum testing, 46 women (4.4%) had an estimated risk for trisomy 21 of 1 in ≥250 pregnancies, and these were all false positive.129
Three studies reported on prospective screening by a combination of fetal NT in the first trimester and maternal serum biochemistry in the second trimester. They classified as screen positive those women with increased fetal NT (above a cut off of 2.5 mm or 3.0 mm) and those women with a maternal serum screening-derived risk of 1 in 250 pregnancies. In 2 of the studies, most of the patients had both components of the test. For a combined screen positive rate of 6.5%, the detection rate of trisomy 21 was 93.5% (Table VIII). If screening had been only by NT, the detection rate would have been 58.1%, which represents a screen positive rate of 2.3%. In the third study of 9118 patients, 5506 women had both components of the test; 821 women had only ultrasound testing, and 2791 women had only serum biochemistry. For an invasive testing rate of 8.6%, 17 of the 21 fetuses (81.0%) with trisomy 21 were detected. In the subgroup of 6234 women who had NT screening, the fetal NT was ≥ 3 mm in 3% of cases, which included 13 of the 21 women (61.9%) with trisomy 21.

These results demonstrate that, in prospective interventional 2-stage studies for an invasive testing rate of approximately 2.5%, approximately 60% of trisomy 21 pregnancies can be detected in the first trimester because of increased fetal NT. Second-trimester serum testing will result in invasive testing in a further 4% to 5% of pregnancies to identify a further 30% of affected fetuses. The same detection rate with a lower false-positive rate can be achieved by combining fetal NT with biochemical testing in the first trimester (Table VIII).

### Integration of first and second trimester testing

A statistical model that combined first-trimester fetal NT and maternal serum PAPP-A with second-trimester free β-hCG, estriol, and inhibin A estimated that, for a false-positive rate of 5%, the detection rate of trisomy 21 could be 94%. Even if the estimates of this hypothetic test are found to be true in prospective studies, it is unlikely that the test will gain widespread clinical acceptance. This test assumes complete compliance by the pregnant women in participating in a 2-stage process that is separated by 1 month, in having an ultrasound scan without receiving information as to whether the fetus looks normal, and in accepting second- rather than first-trimester diagnosis and termination.

Some of the logistical problems in the implementation of an integrated test are highlighted by the results of a multicenter observational serum, urine, and ultrasound screening study that investigated first and second trimester screening for trisomy 21. Of the 47,053 women with singleton pregnancies who were recruited, 9691 women (20.6%) did not attend for second-trimester serum testing, and all components of the protocol were completed in only 28,434 of the women (60.4%).

### Table VIII

<table>
<thead>
<tr>
<th>Method of screening</th>
<th>Fixed false-positive rate (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1%</td>
</tr>
<tr>
<td>Maternal age</td>
<td>9 (11.0%)</td>
</tr>
<tr>
<td>β-hCG and PAPP-A</td>
<td>22 (26.8%)</td>
</tr>
<tr>
<td>NT</td>
<td>53 (64.6%)</td>
</tr>
<tr>
<td>NT and β-hCG and PAPP-A</td>
<td>63 (76.8%)</td>
</tr>
</tbody>
</table>

* In this population of 14,383 pregnancies, there were 82 cases of trisomy 21.

### Table IX

<table>
<thead>
<tr>
<th>Method of screening</th>
<th>Fixed sensitivity (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60%</td>
</tr>
<tr>
<td>Maternal age</td>
<td>1993 (14.0%)</td>
</tr>
<tr>
<td>β-hCG and PAPP-A</td>
<td>723 (5.1%)</td>
</tr>
<tr>
<td>NT</td>
<td>80 (0.6%)</td>
</tr>
<tr>
<td>NT and β-hCG and PAPP-A</td>
<td>37 (0.3%)</td>
</tr>
</tbody>
</table>

* In this population, there were 14,240 normal and 82 trisomy 21 pregnancies.
In this study, there were 101 fetuses with trisomy 21. The data from the 75 cases with satisfactory NT images were then used to develop a model that was based on the combination of fetal NT and PAPP-A at 9 to 10 weeks of gestation and maternal serum free β-hCG, inhibin-A, unconjugated estriol, and AFP at 14 to 20 weeks of gestation. According to this statistical model, for a 5% false-positive rate, 93% of trisomy 21 fetuses could be detected. However, it is likely that this model is inaccurate. For example, the predicted detection rates, for a 5% false-positive rate, were 71% for the double test, 77% for the triple test and 83% for the quadruple test, which are substantially higher than the respective rates of 61%, 66%, and 75% that were reported by the same authors in their prospective screening studies (Table XI).

A similar study in the United States (FASTER trial) reported its findings in the subgroup of 33,557 pregnancies with complete first and second trimester data, which included 84 cases of trisomy 21. It was estimated that, for a 5.4% false-positive rate, 90% of trisomy 21 fetuses could be detected. However, the prospective studies that

<table>
<thead>
<tr>
<th>Table X</th>
<th>Prospective screening by a combination of fetal NT thickness in the first trimester and maternal serum biochemistry in the second trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study/year</td>
<td>N</td>
</tr>
<tr>
<td>Schuchter et al/2001</td>
<td>9,342</td>
</tr>
<tr>
<td>Audibert et al/2001</td>
<td>4,130</td>
</tr>
<tr>
<td>Total</td>
<td>13,472</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table XI</th>
<th>Differences in false-positive and detection rates in screening for trisomy 21 by fetal NT and serum biochemical testing between prospective studies and various theoretic modeling techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study/year</td>
<td>Type of study</td>
</tr>
<tr>
<td>Wald et al/2003</td>
<td>Retrospective statistical model</td>
</tr>
<tr>
<td>Wald et al/2003</td>
<td>Prospective study</td>
</tr>
<tr>
<td>Wald et al/2003</td>
<td>Retrospective statistical model</td>
</tr>
<tr>
<td>Wald et al/2003</td>
<td>Prospective study</td>
</tr>
<tr>
<td>Wald et al/2003</td>
<td>Retrospective statistical model</td>
</tr>
<tr>
<td>Wald et al/2003</td>
<td>Prospective study</td>
</tr>
<tr>
<td>Wald et al/2003</td>
<td>Retrospective statistical model</td>
</tr>
<tr>
<td>Studies in Table III</td>
<td>Prospective studies</td>
</tr>
<tr>
<td>Wald et al/2003</td>
<td>Retrospective statistical model</td>
</tr>
<tr>
<td>Malone et al/2004</td>
<td>Retrospective statistical model</td>
</tr>
<tr>
<td>Studies in Table VII</td>
<td>Prospective studies</td>
</tr>
<tr>
<td>Wald et al/1999</td>
<td>Theoretical model</td>
</tr>
<tr>
<td>Wald et al/2003</td>
<td>Retrospective statistical model</td>
</tr>
<tr>
<td>Malone et al/2004</td>
<td>Retrospective statistical model</td>
</tr>
<tr>
<td>Bindra et al/2002</td>
<td>Prospective study</td>
</tr>
</tbody>
</table>
are summarized in Table VII have demonstrated that such results are achievable by screening with fetal NT and maternal serum free $\beta$-hCG and PAPA-A in the first trimester.

In the initial theoretic model of the integrated test, it was estimated that, for a detection rate of 85%, the false-positive rate would be 1%,\textsuperscript{162} which was revised to 1.2% after retrospective statistical modeling of the serum, urine, and ultrasound screening study results\textsuperscript{164} and further revised to 2.8% after modeling of the FASTER results (Table XI).\textsuperscript{165} In the prospective study of Bindra et al.,\textsuperscript{151} the detection rate of 85% was achieved with a false-positive rate of 3.0% by screening with fetal NT and maternal serum free $\beta$-hCG and PAPA-A in the first trimester.

**NT followed by second-trimester ultrasonography**

In the first trimester, a common feature of many chromosomal abnormalities is increased NT thickness. In the second trimester scan, each chromosomal defect has its own syndromal pattern of detectable abnormalities. For example, trisomy 21 is associated with nasal hypoplasia, increased nuchal fold thickness, cardiac defects, intracardiac echogenic foci, duodenal atresia and echogenic bowel, mild hydronephrosis, shortening of the femur and more so of the humerus, sandal gap, and clinodactyly or mid-phalanx hypoplasia of the fifth finger.

In women with second-trimester sonographic markers of chromosomal abnormalities after first-trimester screening, the a priori risk must be adjusted to take into account the first-trimester screening results. On the basis of existing data, the likelihood ratio for trisomy 21, if there is no detectable defect or marker, is 0.30. The estimated positive and negative likelihood ratios are 53.0 and 0.67 for short humerus, 7.9 and 0.62 for short femur, 6.8 and 0.85 for mild hydronephrosis, 6.4 and 0.75 for intracardiac echogenic foci, and 21.2 and 0.87 for echogenic bowel.

Additional information and references are provided on the website of the American Journal of Obstetrics and Gynecology.

**Absence of fetal nasal bone**

In 1866 Down noted that a common characteristic of patients with trisomy 21 is a small nose.\textsuperscript{1} An anthropometric study in 105 patients with Down syndrome at 7 months to 36 years of age reported that the nasal root depth was abnormally short in 49.5% of cases.\textsuperscript{166} In the combined data from 4 postmortem radiologic studies in a total of 105 aborted fetuses with trisomy 21 at 12 to 25 weeks of gestation, there was absence of ossification of the nasal bone in 32.4% of cases and nasal hypoplasia in 21.4% of cases.\textsuperscript{167,170} Sonographic studies at 15 to 24 weeks of gestation reported that approximately 65% of trisomy 21 fetuses have absent or short nasal bone.\textsuperscript{171-175}

**Sonographic assessment**

The fetal nasal bone can be visualized by sonography at 11\textsuperscript{+0} to 13\textsuperscript{+6} weeks of gestation.\textsuperscript{176} This examination requires that the image is magnified so that the head and the upper thorax only are included in the screen (Figures 1 and 2). A mid-sagittal view of the fetal profile is obtained with the ultrasound transducer being held parallel to the longitudinal axis of the nasal bone. The angle of insonation is crucial because the nasal bone will not be visible almost invariably when the longitudinal axis of the bone is perpendicular to the ultrasound transducer. In the correct view, there are 3 distinct lines. The first 2 lines, which are proximal to the forehead, are horizontal and parallel to each other, resembling an “equal sign.” The top line represents the skin and the bottom line, which is thicker and more echogenic than the overlying skin, represents the nasal bone. A third line, which is almost in continuity with the skin but at a higher level, represents the tip of the nose. When the nasal bone line appears as a thin line, less echogenic than the overlying skin, it suggests that the nasal bone is not yet ossified and is classified therefore as being absent.

A study that investigated the necessary training of 15 sonographers with experience in measuring fetal NT to become competent in examining the fetal nasal bone at 11\textsuperscript{+0} to 13\textsuperscript{+6} weeks of gestation has demonstrated that the number of supervised scans that are required is on average 80, with a range of 40 to 120 scans.\textsuperscript{177} Another study of 501 consecutively scanned fetuses by experienced sonographers reported that the fetal nasal bone can be examined successfully and measured in all cases without extension of the length of time that is required for scanning.\textsuperscript{178}

**Association with chromosomal abnormalities**

Several studies have demonstrated a high association between absent nasal bone at 11\textsuperscript{+0} to 13\textsuperscript{+6} weeks of gestation and trisomy 21 and other chromosomal abnormalities (Tables XII and XIII).\textsuperscript{176,179-186} In the combined data from these studies on a total of 15,822 fetuses, the fetal profile was examined successfully in 15,413 cases (97.4%), and the nasal bone was absent in 176 of 12,652 chromosomally normal fetuses (1.4%) and in 274 of 397 fetuses (69.0%) with trisomy 21. An important finding of these studies was that the incidence
of absent nasal bone decreased with fetal crown-rump length, increased with NT thickness, and was substantially higher in Afro-Caribbean pregnancies than in white pregnancies. Consequently, in the calculation of likelihood ratios in screening for trisomy 21, adjustments must be made for these confounding factors.\textsuperscript{185,186}

In contrast with the aforementioned studies, Malone \textit{et al.}\textsuperscript{187} reported that they were able to examine the fetal nose in only 75.9% of 6316 fetuses who were scanned at 10 to 13 weeks of gestation and that the nasal bone apparently was present in all 9 of their trisomy 21 fetuses. However, the image that they published to illustrate their technique reports the nasal bone at the tip rather than the base of the nose.\textsuperscript{188} Similarly, De Biasio and Venturini,\textsuperscript{189} who retrospectively examined the photographs that were obtained for the measurement of fetal NT reported that the nasal bone was present in all 5 fetuses with trisomy 21. However, all 5 images that they published were inappropriate, both for the measurement of fetal NT and for the examination of the nasal bone, because they were either too small or the fetus was too vertical or too oblique.

The conclusion can be drawn that, at 11\textsuperscript{+0} to 13\textsuperscript{+6} weeks of gestation, the fetal profile can be examined successfully in >95% of cases and that the nasal bone is absent in approximately 70% of trisomy 21 fetuses and in approximately 55% of trisomy 13 fetuses. In chromosomally normal fetuses, the incidence of absent nasal bone is <1% in white populations and approximately 10% in Afro-Caribbean populations. Consequently, the absence of the nasal bone is an important marker of trisomy 21. However, it is imperative that sonographers who undertake risk assessment by examination of the fetal profile receive appropriate training and certification of their competence in performing such a scan.

### Integrated sonographic and biochemical screening in the first trimester

A case-control study comprised of 100 trisomy 21 and 400 chromosomally normal singleton pregnancies at 11\textsuperscript{+0} to 13\textsuperscript{+6} weeks of gestation examined the potential performance of screening for trisomy 21 by a combination of sonography for the measurement of fetal NT and the assessment of the presence or absence of the fetal nasal bone and measurement of maternal serum free $\beta$-hCG and PAPP-A at 11\textsuperscript{+0} to 13\textsuperscript{+6} weeks of gestation. It was estimated that, for a false-positive rate of 5%, the detection rate of trisomy 21 would be 97% and, for a false-positive rate of 0.5%, the detection rate would be 91% (Table XIV).\textsuperscript{190}

### Other sonographic markers in the first trimester

In addition to increased NT, chromosomal abnormalities are associated with a pattern of characteristic

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**Table XII** Studies that reported about the incidence of absent nasal bone in first-trimester trisomy 21 fetuses

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Type of study</th>
<th>Gestation (wk)</th>
<th>N</th>
<th>Successful examination (%)</th>
<th>False-positive rate (%)</th>
<th>Detection rate of trisomy 21 (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cicero et al/2001\textsuperscript{172*}</td>
<td>Before chorionic villi sampling</td>
<td>11-13\textsuperscript{+6}</td>
<td>701</td>
<td>100</td>
<td>0.5</td>
<td>43/59 (72.9%)</td>
</tr>
<tr>
<td>Otano et al/2002\textsuperscript{179}</td>
<td>Before chorionic villi sampling</td>
<td>11-13\textsuperscript{+6}</td>
<td>194</td>
<td>94.3</td>
<td>0.6</td>
<td>3/5 (60.0%)</td>
</tr>
<tr>
<td>Zoppi et al/2003\textsuperscript{180}</td>
<td>Screening</td>
<td>11-13\textsuperscript{+6}</td>
<td>5,532</td>
<td>99.8</td>
<td>0.2</td>
<td>19/27 (70.0%)</td>
</tr>
<tr>
<td>Orlandi et al/2003\textsuperscript{181}</td>
<td>Screening</td>
<td>11-13\textsuperscript{+6}</td>
<td>1,089</td>
<td>94.3</td>
<td>1.0</td>
<td>10/15 (66.7%)</td>
</tr>
<tr>
<td>Viora et al/2003\textsuperscript{182}</td>
<td>Screening</td>
<td>11-13\textsuperscript{+6}</td>
<td>1,906</td>
<td>91.9</td>
<td>1.4</td>
<td>8/10 (80.0%)</td>
</tr>
<tr>
<td>Senat et al/2003\textsuperscript{183}</td>
<td>Retrospective</td>
<td>11-13\textsuperscript{+6}</td>
<td>1,040</td>
<td>91.9</td>
<td>0.4</td>
<td>3/4 (75.0%)</td>
</tr>
<tr>
<td>Wong et al/2003\textsuperscript{184}</td>
<td>Before chorionic villi sampling</td>
<td>11-13\textsuperscript{+6}</td>
<td>143</td>
<td>83.2</td>
<td>0.9</td>
<td>2/3 (66.7%)</td>
</tr>
<tr>
<td>Cicero et al/2003\textsuperscript{185*}</td>
<td>Before chorionic villi sampling</td>
<td>11-13\textsuperscript{+6}</td>
<td>3,829</td>
<td>98.9</td>
<td>2.8</td>
<td>162/242 (67.0%)</td>
</tr>
<tr>
<td>Cicero et al/2004\textsuperscript{186}</td>
<td>Before chorionic villi sampling</td>
<td>11-13\textsuperscript{+6}</td>
<td>5,918</td>
<td>98.9</td>
<td>2.5</td>
<td>229/333 (68.8%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>15,822</td>
<td>97.4</td>
<td>1.4</td>
<td>274/397 (69.0%)</td>
</tr>
</tbody>
</table>

* Included in Cicero et al 2004.\textsuperscript{186}

**Table XIII** Incidence of absent nasal bone at 11 to 13\textsuperscript{+6} weeks of gestation in chromosomally abnormal fetuses\textsuperscript{186}

<table>
<thead>
<tr>
<th>Chromosomal abnormality</th>
<th>Absent nasal bone (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>229/333 (68.8%)</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>68/124 (54.8%)</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>13/38 (34.2%)</td>
</tr>
<tr>
<td>Triploidy</td>
<td>0/19 (0)</td>
</tr>
<tr>
<td>Turner’s syndrome</td>
<td>5/46 (10.9%)</td>
</tr>
<tr>
<td>XXY, XXX, XYY</td>
<td>1/20 (5.0%)</td>
</tr>
<tr>
<td>Other</td>
<td>8/48 (16.7%)</td>
</tr>
</tbody>
</table>
sonographic findings in the first trimester. Trisomy 21 is associated with abnormal flow velocity patterns in the ductus venosus and maxillary hypoplaxia. In trisomy 18, there is early onset fetal growth restriction, bradycardia in approximately 20% of cases, exomphalos in 30% of cases, absent nasal bone in 55% of cases, and single umbilical artery in 75% of cases. Trisomy 13 is characterized by fetal tachycardia, which is observed in approximately two thirds of the cases, early onset fetal growth restriction, and megacystis, holoprosencephaly, or exomphalos in approximately 40% of the cases. Turner syndrome is characterized by fetal tachycardia, which is observed in approximately 50% of the cases, and early onset fetal growth restriction. In triploidy, there is early onset asymmetric fetal growth restriction, bradycardia in 30% of cases, holoprosencephaly, exomphalos or posterior fossa cyst in approximately 40% of cases, and molar changes in the placenta in approximately one third of cases.

The website of the American Journal of Obstetrics and Gynecology provides additional information and references on crown-rump length, fetal heart rate, maxillary length, ear length, femur and humerus length, single umbilical artery, megacystis, exomphalos, choroid plexus cysts, pyelectasis and cardiac echogenic foci, placental volume, and Doppler findings in the ductus venosus, uterine arteries, umbilical arteries and vein, jugular vein, and carotid artery.

Chromosomal abnormalities in multiple pregnancies

In multiple pregnancies that are compared with singleton pregnancies, prenatal diagnosis of chromosomal abnormalities is complicated because the techniques of invasive testing may provide uncertain results or may be associated with higher risks of miscarriage and because the fetuses may be discordant for an abnormality, in which case 1 of the options for the subsequent management of the pregnancy is selective feticide.

Selective feticide can result in spontaneous abortion or severe preterm delivery, which may occur several months after the procedure. The risk for these complications is related to the gestation at feticide. Selective feticide after 16 weeks of gestation is associated with a 3-fold increase in risk compared with reduction before 16 weeks of gestation, and there is an inverse correlation between the gestation at feticide with the gestation at delivery.

Amniocentesis in twins is effective in providing a reliable karyotype for both fetuses; the procedure-related fetal loss rate is approximately 2%. In the case of chorionic villus sampling, the procedure-related fetal loss rate is approximately 1%, but in approximately 1% of cases, there may be a diagnostic error, either because of sampling the same placenta twice or cross-contamination. The main advantage of chorionic villus sampling is that it provides results sufficiently early to allow for safer selective feticide.

Screening by maternal age

In dizygotic pregnancies, the maternal age-related risk for chromosomal abnormalities for each twin may be the same as in singleton pregnancies; therefore, the chance that at least 1 fetus is affected by a chromosomal defect is twice as high as in singleton pregnancies. Furthermore, because the rate of dizygotic twinning increases with maternal age, the proportion of twin pregnancies with chromosomal abnormalities is higher than in singleton pregnancies. In monozygotic twins, the risk for chromosomal abnormalities is the same as in singleton pregnancies; therefore, the chance that at least 1 fetus is affected by a chromosomal abnormality is approximately twice that in singleton pregnancies, and in most cases both fetuses are affected. The relative proportion of spontaneous dizygotic to monozygotic twins in white populations is approximately 2-to-1; therefore, the prevalence of chromosomal abnormalities that affect at least 1 fetus in twin pregnancies would be expected to be approximately 1.6 times that in singleton pregnancies.

Chorionicity can be determined reliably by ultrasoundography in early pregnancy. In counseling parents, it is possible to give more specific estimates of 1 and/or both fetuses who are being affected, depending on chorionicity. Thus, in monochorionic twins, the parents can be counseled that both fetuses would be affected and that this risk is similar to that in singleton pregnancies. If the pregnancy is dichorionic, then the parents can be counseled that the risk of discordancy for a chromosomal abnormality is approximately twice that in singleton pregnancies, whereas the risk that both fetuses would be affected can be derived by squaring the singleton risk ratio. This is in reality an oversimplification, because unlike monochorionic pregnancies that

<table>
<thead>
<tr>
<th>Table XIV Integrated first-trimester sonographic and biochemical screening for trisomy 21*</th>
</tr>
</thead>
<tbody>
<tr>
<td>False positive rate (%)</td>
</tr>
<tr>
<td>0.5</td>
</tr>
<tr>
<td>1.0</td>
</tr>
<tr>
<td>2.0</td>
</tr>
<tr>
<td>3.0</td>
</tr>
<tr>
<td>4.0</td>
</tr>
<tr>
<td>5.0</td>
</tr>
</tbody>
</table>

* Estimated detection rates for different fixed false-positive rates with the use of various marker combinations with maternal age.
are always monozygotic, only approximately 90% of dichorionic pregnancies are dizygotic.

**Screening by second-trimester maternal serum biochemistry**

In singleton pregnancies, screening for trisomy 21 by a combination of maternal age and second-trimester maternal serum biochemistry can detect 50% to 70% of trisomy 21 cases, which represents a 5% false-positive rate. In twin pregnancies, the median value for maternal serum markers (such as AFP, hCG, free β-hCG, and inhibin-A) are approximately twice those for singleton pregnancies. When this is taken into account in the mathematical modeling for calculation of risks, the estimate was that serum screening in twins may identify approximately 45% of affected fetuses, which represents a 5% false positive rate.

**Screening by fetal NT thickness**

Pandya et al reported that, in 9 twin pregnancies that were discordant for trisomies 21 or 18, fetal NT at 10 to 13 weeks of gestation was >2.5 mm in 8 of the 9 trisomic fetuses and in 1 of the 9 chromosomally normal fetuses. Maymon et al examined 174 twin pregnancies; the fetal NT was >95th percentile in 16 of the fetuses (4.6%), which included all 5 chromosomally abnormal fetuses. A study of 60 twin pregnancies, in which fetal NT was measured in the first trimester and maternal serum biochemistry testing was performed in the second trimester, reported that the false-positive rates of the 2 screening methods were 5% and 15%, respectively. There was 1 fetus with trisomy 21 that was identified by NT screening.

In a screening study for trisomy 21 in 448 twin pregnancies, NT thickness was >95th percentile of the normal range, for crown-rump length in singleton pregnancies, in 7 of the 8 pregnancies (87.5%) with trisomy 21. In the chromosomally normal group, the NT was higher in fetuses from dichorionic pregnancies (7/30 pregnancies; 23.3%) than in fetuses from dichorionic pregnancies (5.4%). The prevalence of pregnancies with increased NT in at least 1 of the fetuses in 13.7% of the monochorionic pregnancies and in 11.1% of the dichorionic pregnancies. Another study reported that the incidence of increased fetal NT in at least 1 fetus is higher in monochorionic (7/30 pregnancies; 23.3%) than in dichorionic (10/70 pregnancies; 14.3%) twin pregnancies. In a series of 303 dichorionic pregnancies, fetal NT was >95th percentile in 52 of the 606 fetuses (8.6%) and in at least 1 in 41 fetuses (13.5%) of the 303 pregnancies. There were 2 cases of both fetuses being affected by trisomy 21; in 1 case, the NT was increased in both fetuses (3.1 mm and 2.4 mm at 11 weeks of gestation), but in the second case, the NT was increased only in 1 of the fetuses (8.2 mm and 1.8 mm at 13 weeks of gestation).

These findings suggest that, in dichorionic twin pregnancies, the detection rate and false-positive rate of fetal NT in screening for trisomy 21 are similar to those in singleton pregnancies. Therefore, effective screening and diagnosis of major chromosomal abnormalities can be achieved in the first trimester, which allows the possibility of earlier and safer selective feticide for those parents who choose this option. An important advantage of screening by fetal NT in dichorionic twins is that, when there is discordancy for a chromosomal abnormality, the presence of a sonographically detectable marker helps to ensure the correct identification of the abnormal twin, should the parents choose selective termination.

In monochorionic pregnancies, the false-positive rate of NT screening is higher than in singleton pregnancies, because increased NT is an early manifestation of twin-to-twin transfusion syndrome. The number of cases that were examined is still too small to draw definite conclusions as to whether, in the calculation of risk of trisomy 21 in monochorionic pregnancies, the NT of the fetus with the largest or the smallest measurement (or the average of the 2 measurements) should be considered.

**Screening by fetal NT thickness and maternal serum biochemistry**

In a prospective screening study by fetal NT, maternal serum free β-hCG was measured in 4181 singleton and 148 twin pregnancies. In the twin pregnancies, there were 12 pregnancies with trisomy 21. In the normal twin pregnancies, compared with singleton pregnancies, the median maternal serum free β-hCG adjusted for maternal weight was 1.94 MoM. In the 12 trisomy 21 twin pregnancies, the median level of free β-hCG was significantly higher than in normal twin pregnancies. In a study of 159 twin pregnancies, the average free β-hCG was 2.1 times greater and the PAPP-A was 1.9 times greater than in 3466 singleton pregnancies. With statistical modeling techniques, the prediction was that, at a 5% false-positive rate, screening by a combination of fetal NT and maternal serum biochemistry would identify approximately 80% of trisomy 21 pregnancies.

In a prospective screening study in 206 twin pregnancies, the false-positive rate was 9.0% of pregnancies (19/206) and 6.9% of fetuses (28/412), and the detection rate of trisomy 21 was 75% (3/4 pregnancies).

**Screening in higher-order multiple pregnancies**

Fetal NT is the only reliable method of screening for chromosomal abnormality in multifetal pregnancies. In...
a study of 79 fetuses from 24 pregnancies with \( \geq 3 \) fetuses that were conceived by assisted reproduction, fetal NT was measured successfully in all cases, and the distribution of measurements was similar to that in singleton pregnancies.\(^{211}\)

**Women's attitudes to first- versus second-trimester screening**

Two studies have investigated the preference of pregnant women in terms of the methods of screening. In the first study, 43 of 224 women (19.2%) did not want to have any screening. In those who wanted screening, 177 of 181 of the women (97.8%) preferred the screening to be carried out in the first rather than in the second trimester.\(^{212}\)

In the second study, 100 women who indicated an interest in having prenatal screening for Down syndrome were interviewed at their first hospital antenatal visit to assess their attitudes to first- versus second-trimester screening.\(^{213}\) Women were told that the detection rates of the 2 methods were identical, and 74% of the women chose first-trimester NT screening rather than second-trimester serum screening. A criticism of NT screening has been that some women with increased fetal NT will face unnecessary decisions regarding invasive testing and ultimately pregnancy termination in an affected pregnancy that would otherwise have ended in spontaneous miscarriage.\(^{214}\)

In the survey of women's preferences, 69% of women stated that they would still choose NT screening, even if all the Down syndrome pregnancies that were identified by this method miscarried before the second trimester.\(^{213}\) The women wanted to know whether their fetus had Down syndrome, regardless of the pregnancy outcome; they also valued the knowledge of an underlying reason for a miscarriage if it occurred.

**Clinical importance of respect for autonomy**

Respect for autonomy is a central principle in medical ethics and law.\(^{215}\) This ethical principle obliges the physician to elicit and implement the patient's preferences. The relevance of respect for autonomy to first-trimester screening is 2-fold. First, early diagnosis of fetal abnormality and the option of early termination of pregnancy are important to many women. Second, most first-trimester screening tests provide reassurance for many women who would prefer not to have an invasive procedure if the risk is low.\(^{216,217}\) Consequently, the provision of a high-quality first-trimester screening service significantly enhances the autonomy of pregnant women.\(^{218}\)

**Comment**

Diagnosis of fetal chromosomal abnormalities requires invasive testing. Randomized studies have demonstrated that the risk of miscarriage from chorionic villus sampling in the first trimester is the same as for amniocentesis in the second trimester, provided these procedures are carried out by appropriately trained and experienced operators.

Most pregnant women prefer screening to be performed in the first rather than in the second trimester. The provision of a high-quality first-trimester screening service significantly enhances the autonomy of pregnant women.

The preference of women for first-trimester screening remains, even if they are told that all affected fetuses that are identified by first trimester screening miscarry before the second trimester. In reality, the rate of fetal death in trisomy 21 between 12 weeks of gestation and 16 weeks of gestation is <10%. There is evidence that increased NT does not necessarily identify those trisomic fetuses that are destined to die in utero and that with first-trimester screening the observed detection rate of trisomy 21 is only 2% to 3% higher than the potential rate of reducing the live birth incidence of this abnormality.

Prospective studies in >200,000 pregnancies, including >900 fetuses with trisomy 21, have demonstrated that NT screening can identify >75% of fetuses with trisomy 21 and other major chromosomal abnormalities, which represents a false-positive rate of 5%. This is superior to the 30% detection rate that is achieved by maternal age and 65% detection rate that is achieved by second trimester maternal serum biochemistry.

The recently introduced integrated test, which is claimed to be an effective method of screening, is a hypothetic test that is based on various statistical modeling techniques. It is unlikely that this test will gain widespread clinical acceptance, and it is likely that the real detection rate would be considerably lower and that the false-positive rate would be substantially higher than the original estimates.

Prospective studies, in >40,000 pregnancies, including >200 fetuses with trisomy 21, have demonstrated that first-trimester screening by a combination of fetal NT and maternal serum free \( \beta \)-hCG and PAPP-A can identify 85% to 90% of fetuses with trisomy 21, which represents a false-positive rate of 5%. This method can also identify >90% of fetuses with trisomies 18 and 13, Turner syndrome, and triploidy, which represents a screen-positive rate of 1%.

In dichorionic twin pregnancies, the measurement of NT in each fetus provides effective screening that leads to the diagnosis of major chromosomal abnormalities in the first trimester. This allows the possibility of earlier and safer selective feticide for those parents who choose...
this option. In monochorionic pregnancies, the false-
positive rate of NT screening is higher than in singleton
pregnancies, because increased NT is an early manifes-
tation of twin-to-twin transfusion syndrome and
a marker of chromosomal abnormalities.

As with all aspects of good clinical practice, those
operators who perform first-trimester scans should be
trained appropriately, and their results should be sub-
jected to external quality assurance. This process has
been well established by the FMF several years ago and
is accepted widely internationally.

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