First-Trimester Screening

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All patients have a 2% to 3% risk of birth defects, regardless of their prior history, family history, maternal age, or lifestyle [1]. Chromosome abnormalities account for approximately 10% of birth defects, but are important because of their high mortality and morbidity. Trisomy 21 (Down syndrome) is the most common serious chromosome abnormality at birth, occurring in approximately 1 of 500 pregnancies in the United States. The actual risk varies with maternal and gestational age and whether there is a history of previous pregnancies affected by chromosomal abnormality, although, as with other birth defects, all patients are at risk for fetal Down syndrome.

A detailed fetal anatomic survey performed at 18 to 22 weeks remains the primary means for detecting the majority of serious “structural” birth defects; however, first-trimester screening at 11 to 14 weeks has developed into the initial screening test for many patients. A wealth of information can be obtained at this time, including detection of many structural defects, as well as screening for fetal aneuploidy, including Down syndrome. The major advantage of first-trimester screening is the earlier gestational age of detection so that diagnostic testing (chorionic villous sampling [CVS] or genetic amniocentesis) can be made available for patients considered at highest risk for chromosome abnormalities. First-trimester screening can also help identify patients at increased risk for a variety of other abnormalities, including cardiac defects, that may be seen later. In this way, first-trimester screening can help triage patients for subsequent testing.

Older screening methods relied on clinical risk factors, particularly maternal age, to determine which patients might benefit from a diagnostic invasive test for fetal aneuploidy; however, maternal age alone is a poor screening method for determining who is at risk for chromosome abnormalities. First-trimester screening has proved to be very effective in screening for fetal aneuploidy. The accuracy of both first-trimester and second-trimester ultrasound can be improved by also considering various
biochemical markers. As a result, there are currently four main components to screening for fetal aneuploidy and other birth defects: (1) first-trimester ultrasound, (2) first-trimester biochemistry, (3) second-trimester ultrasound, and (4) second-trimester biochemistry. These four components of contemporary screening can be used in isolation or can be combined with one another for greater accuracy.

This article focuses on first-trimester ultrasound screening, but also describes related screening protocols that can be used.

**First-trimester aneuploidy screening**

It is now well-known that increased fluid or thickening beneath the skin at the back of the neck is associated with a higher risk for fetal aneuploidy and other birth defects. This sonographic observation mirrors the clinical description of Down syndrome made more than 100 years ago by Dr. Langdon Down, who reported that the skin of affected individuals is “too large for their bodies” [2].

During the 1980s, many ultrasound studies described the typical appearance of cystic hygromas in the second trimester, and their association with aneuploidy, particularly Turner’s syndrome [2–12]. At the same time, it was observed that cystic hygromas seen during the first trimester may have different appearances (nonseptated), and different associations (trisomies) than those seen during the second trimester. It was also observed that “cystic hygromas” seen during the first trimester can resolve to nuchal thickening alone, or even normal nuchal thickness, and still be associated with aneuploidy [13,14]. In a related observation, Benacerraf and colleagues [15,16] noted that second-trimester nuchal thickening was associated with an increased risk of Down syndrome.

In 1992, Nicolaides and colleagues [17] proposed the term “nuchal translucency (NT)” for the sonographic appearance of fluid under the skin at the back of the fetal neck observed in all fetuses during the first trimester [Fig. 1]. They further reported an association between the thickness of the translucency and the risk of fetal aneuploidy, especially trisomies. This concept of measuring NT in all fetuses formed the basis for first-trimester screening by ultrasound. By 1995, the first large study of NT was published [18]. Subsequent studies have confirmed that NT thickness can be reliably measured at 11 to 14 weeks gestation and, combined with maternal age, can produce an effective means of screening for trisomy 21 [19].

The mechanism for increased NT may vary with the underlying condition. The most likely causes include heart strain or failure [20,21] and abnormalities of lymphatic drainage [22]. Evidence for heart strain includes the finding of increased levels of atrial and brain natriuretic peptide mRNA in fetal hearts among trisomic fetuses [23]. Also, some Doppler ultrasound studies of the ductus venosus at 11 to 14 weeks in fetuses who have increased NT have reported absent or reversed flow during atrial contraction in the majority of chromosomally abnormal fetuses and in chromosomally normal fetuses who have cardiac defects [24,25].

Abnormal lymphatic drainage may occur because of developmental delay in the connection with the venous system, or a primary abnormal dilatation or proliferation of the lymphatic channels. Fetuses who have Turner’s syndrome are known to have hypoplasia of lymphatic vessels [26,27]. Lymphatic drainage could also be impaired by lack of fetal movements in various neuromuscular disorders, such as fetal akinesia deformation sequence [28].

An alternative explanation for increased NT is abnormal composition of the extracellular matrix. Many of the component proteins of the extracellular matrix are encoded on chromosomes 21, 18, or 13. Immunohistochemical studies of the skin of chromosomally abnormal fetuses have demonstrated specific alterations of the extracellular matrix that may be attributed to gene dosage effects [29,30]. Altered composition of the extracellular matrix may also be the underlying mechanism for increased fetal NT in certain genetic syndromes that are associated with alterations in collagen metabolism (such as achondrogenesis Type II), abnormalities of fibroblast growth factor receptors (such as achondroplasia and thanatophoric dysplasia), or disturbed metabolism of peroxisome biogenesis factor (such as Zellweger syndrome).

All studies indicate that proper training is required to obtain reproducible, accurate data from
Box 1: Criteria for what constitutes an adequate NT measurement include

1. Crown–rump length between 45 mm and 84 mm
2. Sagittal view that shows the nuchal measurement and face with the fetus in neutral position
3. Magnification so that only the upper two thirds of the fetus is included on the image
4. Distinguishing nuchal membrane from the amnion
5. Measuring maximal subcutaneous translucency overlying the neck
6. Identifying causes of falsely increased nuchal translucency measurements, including fetal extension, and nuchal cord

NT measurements [31–33]. The Fetal Medicine Foundation (www.fetalmedicine.org) has outlined guidelines that have become the standard for measurement of NT throughout the world. These are listed in Box 1. They also offer a certificate of competency for those sonographers who successfully show they can adhere to them. Virtually identical guidelines have now been proposed by the Society for Maternal Fetal Medicine in the United States, and they also offer a certificate of competency.

Use of the guidelines proposed by the Fetal Medicine Foundation have resulted in a high consistency in results [Table 1]. Monni and coworkers [34] reported that after modifying their technique of measuring NT, by following the guidelines established by The Fetal Medicine Foundation, their detection rate of trisomy 21 improved from 30% to 84%.

The ability to measure NT and obtain reproducible results improves with training; good results are achieved after 80 and 100 scans for the transabdominal and the transvaginal routes, respectively [35]. The intraobserver and interobserver differences in measurements are less than 0.5 mm in 95% of cases [36]. NT is usually measured using a transabdominal approach; transvaginal scanning may be necessary in 5% to 10% of pregnancies when transabdominal scans are technically limited.

The normal range for NT measurements is gestational age dependent. Pandya and colleagues [36] reported that the median NT increases from 1.3 mm at a crown–rump length (CRL) of 38 mm to 1.9 mm at a CRL of 84 mm. The 95th percentile increases from 2.2 mm at a crown rump length of 38 mm to 2.8 mm at a CRL of 84 mm. Sonographers should recognize that technical factors influence NT measurements. For example, extension of the neck increases NT thickness, whereas flexion reduces the measurement.

The criteria for a positive NT scan have evolved since its first description. Initially a categorical cutoff measurement (usually 2.5 or 3 mm) was used by most centers; however, as noted above, NT increases with gestational age, and the degree of risk was found to vary with NT measurements. Therefore, it is more appropriate to express NT measurements relative to gestational age or CRL as a delta value or multiple of the median. Use of multiple of median data and derived likelihood ratios can then estimate the patient-specific risk. This also permits integration of risk based on NT with biochemical data to generate a combined risk. It should be noted that the median NT measurement for Down syndrome is about two multiples of the median. This is equivalent to about 2.5 mm at 12 weeks.

The effectiveness of NT screening for detection of fetal Down syndrome has now been confirmed by a number of studies [see Table 1]. In the largest multicenter study published [19], 96,127 singleton pregnancies were examined, including 326 af-

Table 1: Studies examining the implementation of fetal nuchal translucency measurement at 10–14 weeks of gestation in screening for trisomy 21

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Screening cutoff</th>
<th>FPR</th>
<th>DR</th>
</tr>
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<tbody>
<tr>
<td>Pandya et al, 1995 [37]</td>
<td>1763</td>
<td>NT &gt;2.5 mm</td>
<td>3.6%</td>
<td>3 of 4 (75%)</td>
</tr>
<tr>
<td>Szabo et al, 1995 [38]</td>
<td>3380</td>
<td>NT &gt;3.0 mm</td>
<td>1.6%</td>
<td>28 of 31 (90%)</td>
</tr>
<tr>
<td>Taiplae et al, 1997 [39]</td>
<td>6939</td>
<td>NT &gt;3.0 mm</td>
<td>0.8%</td>
<td>4 of 6 (67%)</td>
</tr>
<tr>
<td>Hafner et al, 1998 [40]</td>
<td>4233</td>
<td>NT &gt;2.5 mm</td>
<td>1.7%</td>
<td>3 of 7 (43%)</td>
</tr>
<tr>
<td>Pajkrt et al, 1998 [41]</td>
<td>1473</td>
<td>NT &gt;3.0 mm</td>
<td>2.2%</td>
<td>6 of 9 (67%)</td>
</tr>
<tr>
<td>Economides et al, 1998 [42]</td>
<td>2281</td>
<td>NT &gt;99th centile</td>
<td>0.4%</td>
<td>6 of 8 (75%)</td>
</tr>
<tr>
<td>Zoppi et al, 2000 [43]</td>
<td>5210</td>
<td>Risk &gt;1 in 100</td>
<td>4.2%</td>
<td>33 of 47 (70%)</td>
</tr>
<tr>
<td>Thilaganathan et al, 1999 [44]</td>
<td>11,398</td>
<td>Risk &gt;1 in 200</td>
<td>4.7%</td>
<td>16 of 21 (76%)</td>
</tr>
<tr>
<td>Schwarzler et al, 1999 [45]</td>
<td>4523</td>
<td>Risk &gt;1 in 270</td>
<td>4.7%</td>
<td>10 of 12 (83%)</td>
</tr>
<tr>
<td>Theodoropoulos et al, 1998 [46]</td>
<td>3550</td>
<td>Risk &gt;1 in 300</td>
<td>4.9%</td>
<td>10 of 11 (91%)</td>
</tr>
<tr>
<td>Total</td>
<td>44,750</td>
<td></td>
<td>3.0%</td>
<td>119 of 156 (76%)</td>
</tr>
</tbody>
</table>

Abbreviations: DR, detection rate; FPR, false-positive rate; N, number.
affected by trisomy 21 and 325 who had other chromosomal abnormalities. The median gestation at the time of screening was 12 weeks (range 10–14 weeks), and the median maternal age was 31 years (range 14–45 years). The fetal NT was above the 95th percentile for crown-rump length in 72% of the trisomy 21 pregnancies [Figs. 2, 3].

The estimated risk for trisomy 21 based on maternal age and fetal NT was above 1 in 300 in 8.3% of normal pregnancies and 82% of those affected by trisomy 21. There does not appear to any correlation between the rise in free β-hCG and fall in PAPP-A seen in trisomy 21 pregnancies, so these markers may be combined for screening purposes [47]. Similarly, these biochemical markers are independent of fetal NT thickness, allowing combination of biochemical and ultrasound tests [48,49].

Some authorities believe it is important to distinguish cystic hygromas from increased NT [50], whereas others do not. Malone and coworkers [50] reported 132 cases of cystic hygroma with follow-up among 38,167 screened patients (1 in 289). Chromosomal abnormalities were diagnosed in 67 (51%), including 25 who had Down syndrome, 19 who had Turner’s syndrome, 13 who had trisomy 18, and 10 who had other types of chromosome abnormalities. Major structural fetal malformations, primarily cardiac and skeletal abnormalities, were diagnosed in 22 of the remaining 65 cases (34%). Of the remaining cases, 20 resulted in spontaneous fetal death (n = 5) or elective pregnancy termination (15). One of 23 normal survi-

The effectiveness of screening for fetal aneuploidy is further increased when nuchal translucency thickness is combined with biochemical markers [Table 2]. The two most effective maternal serum markers currently used in the first trimester are pregnancy-associated plasma protein A (PAPP-A) and free β-human chorionic gonadotrophin (B-hCG). Maternal serum free β-human chorionic gonadotropin (β-hCG) normally decreases with gestation after 10 weeks and maternal serum PAPP-A levels normally increase. Levels of these two proteins tend to be increased and decreased, respectively, in pregnancies affected by trisomy 21.

![Fig. 2. Mildly increased nuchal translucency measurement associated with trisomy 21 (calibers). The nuchal measurement was 2.3 mm, which is about twice normal for gestational age. Biochemical values also indicated an increased risk for trisomy 21.](image1)

![Fig. 3. Increased nuchal translucency and trisomy 21. The nuchal translucency measurement (NT) exceeded 3 mm.](image2)

**Table 2: Studies examining the implementation of a combined first-trimester test using maternal age, fetal nuchal translucency thickness, free β-hCG and PAPP-A to screen for trisomy 21**

<table>
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<tr>
<th>Author</th>
<th>N</th>
<th>FPR</th>
<th>DR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlandi et al, 1997 [53]</td>
<td>744</td>
<td>5.0%</td>
<td>6 of 7 (86%)</td>
</tr>
<tr>
<td>Biagotti et al, 1998 [54]</td>
<td>232</td>
<td>5.0%</td>
<td>24 of 32 (75%)</td>
</tr>
<tr>
<td>Benattar et al, 1999 [55]</td>
<td>1656</td>
<td>5.0%</td>
<td>5 of 5 (100%)</td>
</tr>
<tr>
<td>De Biasio et al, 1999 [56]</td>
<td>1467</td>
<td>3.3%</td>
<td>11 of 13 (85%)</td>
</tr>
<tr>
<td>De Graff et al, 1999 [57]</td>
<td>300</td>
<td>5.0%</td>
<td>31 of 37 (84%)</td>
</tr>
<tr>
<td>Spencer et al, 1999 [47]</td>
<td>1156</td>
<td>5.0%</td>
<td>187 of 210 (89%)</td>
</tr>
<tr>
<td>Krantz et al, 2000 [58]</td>
<td>5718</td>
<td>5.0%</td>
<td>30 of 33 (90%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>11,273</strong></td>
<td><strong>4.8%</strong></td>
<td><strong>294 of 337 (87%)</strong></td>
</tr>
</tbody>
</table>
vors (4%) was diagnosed with cerebral palsy and developmental delay at birth. Overall, survival with normal pediatric outcome was confirmed in 17% of cases (22 of 132). Compared with increased nuchal translucency (>3 mm), cystic hygromas carried a fivefold, 12 fold, and sixfold increased risk of aneuploidy, cardiac malformation, and perinatal death, respectively. On the other hand, cystic hygromas were associated with larger NT measurements than those that had increased NT but did not have cystic hygromas, so it remains uncertain whether cystic hygromas are an independent risk factor. Like patients who have increased NT, the vast majority of pregnancies that have normal evaluation at the completion of the second trimester resulted in a healthy infant and a normal pediatric outcome.

Lateral neck cysts, also termed “jugular lymphatic sacs,” have been found by Bekker and coworkers [51] to be associated with larger NT measurements and thus a higher risk for fetal aneuploidy [Fig. 4]. They found that among 26 fetuses with increased NT (>95th percentile), 22 had clearly visible jugular lymphatic sacs and 16 of 26 (62%) had aneuploidy. In comparison, two fetuses in the control group also showed jugular lymphatic sacs and their NT measurements were upper normal (2.8 mm and 2.9 mm). Although one might conclude that lateral neck cysts are associated with a high risk of fetal aneuploidy, Sharony and colleagues [52] found that the outcome of lateral neck cysts is associated with both the presence of other abnormalities and the NT measurement, but not with the presence of cysts themselves. On the other hand, these authors found a relatively high incidence of lateral neck cysts (2.4%) in the general population, suggesting that some of these cysts were very small and would have escaped general detection.

Fig. 4. Distended jugular lymphatic “sacs.” (A) Increased nuchal translucency measurement of 2.5 mm is noted. (B) Transvaginal scans show small bilateral fluid collections consistent with jugular lymphatic sacs. These are associated with increased nuchal translucency measurements.
Screening strategies

First-trimester combined screen

The first-trimester combined screen uses maternal age, NT measurement, and biochemical markers (free β-hCG and PAPP-A) to estimate the risk for fetal Down syndrome and trisomy 18. This is the most popular and effective screening strategy during the first trimester. A number of studies suggest a detection rate in the range of 85% to 90% for a screen positive rate of 5% [see Table 1] [52–59].

Two large US studies have also been reported showing the effectiveness of first-trimester screening. The First-trimester Maternal Serum Biochemistry and Fetal Nuchal Translucency Screening (BUN) study found a 79% detection rate, for a 5% false-positive rate [60]. The First- and Second-Trimester Evaluation of Risk (FASTER) Research Consortium trial [61] is the largest US-based study, and the only study that has compared first-trimester screening with second-trimester screening. The FASTER data [61] clearly confirm the pioneering work of Nicolaides and colleagues [17,19], with similar results. The overall detection rate was 85%, for a false-positive rate of 5%; however, the results clearly varied with gestational age, with detection rate of 87% at 11 weeks compared with 82% at 13 weeks.

First-trimester combined screen plus other ultrasound markers

Although increased NT remains the primary ultrasound marker of fetal aneuploidy and other birth defects during the first trimester, several other ultrasound findings have been found to be helpful at this time. These include hypoplastic or absent nasal bone, and abnormal Doppler waveforms of the tricuspid valve and ductus venosus.

Hypoplastic/absent nasal bone

A small nasal bone was first noted to a common feature of patients who had trisomy 21 by Dr. Langdon Down [2]. Anthropomorphic studies in patients who have trisomy 21 have shown a small nasal bone in approximately half of affected cases. A number of ultrasound studies have now also shown an association between sonographically absent nasal bone and trisomy 21 as well as other chromosome abnormalities [62–69]. In the combined data of 15,822 fetuses, the fetal profile was successfully examined in 97.4%, and the nasal bone was absent in 1.4% of normal fetuses and in 69% of fetuses who had trisomy 21.

A minority of studies have concluded that an absent nasal bone is not a useful feature to detect fetal Down syndrome, and that reproducibility is poor during the first trimester [70,71]. This probably reflects the technical difficulty in obtaining accurate nasal bone measurements at this time. Imaging of the nasal bones requires a near-perfect midsagittal image and optimal angle of insonation with the fetal profile, whereas NT measurements can be obtained with minor variations off-center and differences in direction of imaging. Demonstrating the absence of a very small structure is even more difficult than detecting its presence, because it can be difficult to know for certain whether the nasal bones are absent or whether the images are simply suboptimal. Malone and coworkers [71] found that factors associated with an increased failure rate of nasal bone included early gestational age when the nasal bone is normally small, larger maternal body habitus, inadequate nuchal translucency sonography, and use of a transvaginal sonographic approach.

Increased impedance of flow of the ductus venosus

Abnormal Doppler flow patterns of the ductus venosus have been associated with an increased risk of fetal Down syndrome [Fig. 5] [24,25]. Matias and colleagues [24] performed ductus venosus Doppler measurements on 486 singleton fetuses, including 68 who had chromosomal abnormalities, at 10 to 14 weeks’ gestation. In 90.5% of the chromosomally abnormal fetuses there was reversed or absent flow during atrial contraction,
whereas abnormal ductus flow was only present in 3.1% of the chromosomally normal fetuses. The height of the A-wave was found to be the only significant independent factor in multivariate regression analysis. Other researchers have also found that ductus venosus Doppler studies can substantially improve Down syndrome screening efficiency [72].

Tricuspid regurgitation has also been associated with an increased risk of fetal Down syndrome. In the largest study reported, Faiola and coworkers [73] reported that the tricuspid valve was successfully examined in 718 (96.8%) cases. Tricuspid regurgitation was found in 39 (8.5%) of the 458 chromosomally normal fetuses, in 82 (65.1%) of the 126 who had trisomy 21, in 44 (53%) of the 83 who had trisomy 18 or 13, and in 11 (21.6%) of the 51 who had other chromosomal defects. In chromosomally normal fetuses, tricuspid regurgitation was associated with increased NT measurements, suggesting that Doppler studies may be particularly useful in this group of patients.

Fetuses who have abnormal flow patterns of the ductus venosus and tricuspid valve also appear to have a higher risk of cardiac defects. Among 142 chromosomally normal fetuses who had increased NT, 11 fetuses had reversed or absent flow on ductus venosus Doppler during atrial contraction, and 7 of these had major cardiac defects at subsequent echocardiography [25]. Similarly, Faiola and colleagues [73] found that in the chromosomally normal fetuses, tricuspid regurgitation was found in nearly half (46.9%) of fetuses who had cardiac defects and in 5.6% of those who did not have cardiac defects (likelihood ratio of 8.4).

Nicolaides and coworkers [74] suggest that secondary findings of absent nasal bone or abnormal Doppler studies could be particularly useful in patients found to be in the intermediate risk group by the first-trimester screen. Using these secondary signs in patients with an intermediate risk group (risk of 1 in 100 to 1 in 1000) for fetal Down syndrome, the researchers reported detection rates of 92% for absent nasal bone, 94% for increased impedance of the ductus venosus, and 91.7% for tricuspid regurgitation, with each method showing an overall false-positive rate of less than 3% [74].

**First-trimester screening followed by second-trimester biochemistry**

Second-trimester biochemical screening can detect 70% to 80% of affected fetuses who had Down syndrome (at a false positive rate of 7%–8%). The effectiveness appears to be clearly higher for the “quad” screen (HCG, alpha-fetoprotein, estriol, and inhibit-A), than the older “triple” screen that did not include inhibit-A [50]; however, the effectiveness of second-trimester biochemical screening is more limited in a population that has already been screened, and in the authors’ experience, most patients who have undergone first-trimester screening will choose not to undergo second-trimester biochemical screening.

For those patients who would like additional reassurance by way of a second-trimester biochemical screen, it should be done in a way that accounts for the first-trimester screening results rather than treating them as independent tests. One method is the so-called “integrated screen,” which combines the elements of the first-trimester combined screen with the elements of the second-trimester “quad” screen, providing a single, low false-positive result in the second trimester [75]. This is the most accurate screening method currently available, with detection rate of 92% in the FASTER study [76]; however, a major disadvantage of integrated screening is that patients do not receive results until after completion of the second-trimester biochemistry. Thus screen-positive women do not have the option of CVS for early definitive diagnosis [77]. In addition, it is considered unethical to suppress ultrasound information obtained in the first trimester.

“Stepwise sequential” screening is an alternative approach that has been proposed; it interprets second-trimester results based on first-trimester risk assessment. A clear advantage of stepwise sequential screening is that it provides some women an earlier diagnosis while maintaining an extremely high detection rate. This method has gained rapid acceptance and it is expected to be widely adapted into clinical practice in the near future [78]. When patients in the FASTER trial underwent first-trimester combined screening at 11 weeks and the false-positive rate of each component was set at 2.5%, stepwise sequential screening provided a 95% detection of Down syndrome, for a 4.9% false-positive rate. This compares to a 4.0% false-positive rate for fully integrated screening.

Incorporation of second-trimester biochemical as part of a stepwise sequential screen would be most effective for patients considered in an intermediate risk group (risk between 1 in 100 and 1 in 1000) [79]. The intermediate group includes 15% of affected fetuses who had Down syndrome and approximately 15% of normal fetuses. In comparison, high risk patients (risk >1 in 100) should probably consider diagnostic invasive testing without additional screening; this group includes 80% of affected fetuses who have Down syndrome but only 5% of normal fetuses. Also, low-risk patients (risk <1 in 1000) probably do not require additional screening in most cases; this group of patients includes less than 5% of affected fetuses.
who have Down syndrome, but 80% of normal fetuses.

**First-trimester screening followed by second-trimester ultrasonography**

A second-trimester fetal survey remains the primary method of detecting the majority of birth defects that can be detected prenatally [80]. Because of the wide range of anomalies that can be detected at this time, this examination is unlikely to be replaced by any other screening test in the future. In addition to detection of structural defects, the presence or absence of various sonographic markers can further modify the risk for fetal aneuploidy, including Down syndrome. The estimated risk can be derived by multiplying the background risk (based on maternal age, gestational age, history of previously affected pregnancies, and, where appropriate, the results of previous screening by NT or biochemistry in the current pregnancy) by the likelihood ratio of the specific defect [81]. The most common second-trimester ultrasound markers that are systematically evaluated include nuchal thickening, echogenic intracardiac foci, absent or hypoplastic nasal bone, hyperechoic bowel, renal pyelectasis, and shortened femur and humerus lengths relative to the biparietal diameter. Nyberg and coworkers [82] and others have calculated likelihood ratios for many of these markers and have refined this for single markers [83].

In the vast majority of cases, second-trimester ultrasound markers such as echogenic intracardiac foci will be found in normal fetuses, especially when the marker is isolated. In this situation, a prior normal first-trimester screening result can be very reassuring. Because a normal first-trimester screening results permits significant reduction of risk for fetal Down syndrome, and because isolated findings such as echogenic intracardiac foci only slightly increase the risk, most patients will remain at very low risk and do not require further testing. Ultrasound findings, however, can also improve the detection rate of fetuses who have Down syndrome in patients who have borderline normal results from first-trimester screening, or fetuses who show multiple markers or major defects. At the same time, a normal second-trimester ultrasound can reduce the risk of fetal Down syndrome approximately threefold, and this can normalize patients who have borderline positive results form first-trimester screening (risk 1 in 100 to 1 in 300).

Results of the FASTER trial show that use of a second-trimester genetic sonogram can both improve the detection rate and lower the false positive rate in patients who have undergone first-trimester screening [84].

**Other advantages of first-trimester screening**

**Other chromosome abnormalities**

Nuchal translucency is also increased with other chromosome abnormalities, including trisomies 13 and 18, Turner’s syndrome, triploidy, and unbalanced translocations [Fig. 6] [85]; however, first-trimester biochemical markers may differ from those typically associated with trisomy 21. In trisomies 18 and 13, maternal serum free \( \beta \)-hCG and PAPP-A are decreased [86,87]. In cases of sex chromosomal anomalies, maternal serum free \( \beta \)-hCG is normal and PAPP-A is low [88]. Triploidy of paternal origin, which is associated with a partial molar placenta, has greatly increased levels of free \( \beta \)-hCG, whereas PAPP-A is mildly decreased [89]. In con-

![Fig. 6. Increased nuchal translucency and trisomy 18. Large nuchal translucency measurement was noted and cytogenetic testing revealed trisomy 18.](image-url)
Table 3: Abnormalities and genetic syndromes reported in association with increased nuchal translucency and normal karyotype

<table>
<thead>
<tr>
<th>Central nervous system defect</th>
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<td>Dandy-Walker malformation</td>
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<td>Diastematomyelia</td>
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Table 3: (continued)

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<td>Zellweger syndrome</td>
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<td>Body stalk anomaly</td>
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<td>(limb body wall complex)</td>
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<td>Brachmann-de Lange syndrome</td>
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<td>CHARGE association</td>
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<td>EEC syndrome</td>
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<td>Stickler syndrome</td>
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<td>Unspecified syndrome</td>
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<td>Severe developmental delay</td>
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Abbreviation: EEC syndrome, ectrodactyly-ectodermal dysplasia-cleft palate syndrome.


Trast, digynic triploidy, characterized by severe asymmetrical fetal growth restriction, is associated with markedly decreased maternal serum free β-hCG and PAPP-A. Screening by a combination of fetal NT, free β-hCG, and PAPP-A can identify
about 90% of these anomalies for a screen positive rate of 1%.

**Birth defects in euploid fetuses who have increased nuchal translucency**

Extensive studies have now established that, in chromosomally normal fetuses, increased NT is associated with a wide range of fetal defects and genetic syndromes [Table 3].

The prevalence of birth defects and adverse outcome also increases with increasing NT measurements [Table 4]. Souka and colleagues [90] reported that the overall risk of adverse outcome, including miscarriage and intrauterine death, was 32% for those who had NT of 3.5 to 4.4 mm, 49% for NT of 4.5 to 5.4 mm, 67% for NT 5.5 to 6.4 mm, and 89% for those who had NT of 6.5 mm or more. Among 1080 surviving fetuses who had NT of 3.5 mm or more, 5.6% had abnormalities requiring medical or surgical treatment or leading to mental handicap. The chance of no defect among live births was 86% for those who had NT of 3.5 to 4.4 mm, 77% for those who had NT of 4.5 to 5.4 mm, 67% for those who had NT of 5.5 to 6.4, and 31% for those who had NT of 6.5 mm or more.

An association between increased NT and cardiac defects was first noted by Hyett and coworkers [20] in both chromosomally abnormal and normal fetuses. This has subsequently been confirmed by a number of studies [91–100]. A retrospective study of 29,154 chromosomally normal singleton pregnancies identified major defects of the heart and great arteries in 50 cases, and 56% of these had NT measurement translucency above the 95th percentile [101]. In chromosomally normal fetuses, the prevalence of major cardiac defects increases exponentially from 1.6 per 1000 for NT less than 95th percentile, 1% for NT between 2.5 and 34 mm, 3% for NT 3.5% to 4.4%, 7% for NT 4.5% to 5.4%, 20% for NT 5.5 to 6.4 mm, 30% for NT 6.5 mm or more.

The clinical implication of these observations is that patients found to have increased NT should undergo formal fetal echocardiography. Certainly,

<table>
<thead>
<tr>
<th>Nuchal translucency measurement</th>
<th>Aneuploidy</th>
<th>Death</th>
<th>Major anomaly</th>
<th>Alive and well</th>
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<tbody>
<tr>
<td>&lt;95th percentile</td>
<td>.2%</td>
<td>1.3%</td>
<td>1.6%</td>
<td>97%</td>
</tr>
<tr>
<td>95th–99th</td>
<td>3.7%</td>
<td>3.3%</td>
<td>2.5%</td>
<td>93%</td>
</tr>
<tr>
<td>3.5–4.4 mm</td>
<td>21.1%</td>
<td>2.7%</td>
<td>10%</td>
<td>70%</td>
</tr>
<tr>
<td>4.5–5.4 mm</td>
<td>33.3%</td>
<td>3.4%</td>
<td>18.5%</td>
<td>50%</td>
</tr>
<tr>
<td>5.5–6.4%</td>
<td>50.5%</td>
<td>10.1%</td>
<td>24.2%</td>
<td>30%</td>
</tr>
<tr>
<td>6.5 mm</td>
<td>64.5%</td>
<td>19%</td>
<td>46.2%</td>
<td>15%</td>
</tr>
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</table>

Data from Refs. [19,42,90,103].

Fig. 7. Discrepant nuchal translucency measurements in monochorionic twins. (A) This fetus shows nuchal translucency measurement (NT) of 2 mm at 12 weeks. The co-twin showed nuchal translucency measurement of 1.1 mm. (B) Velamenous cord insertion is also apparent. This monochorionic twin pregnancy showed signs of severe twin-twin transfusion syndrome by 18 weeks.
the overall prevalence of major cardiac defects in such a group of fetuses (about 2%) is similar to that found in pregnancies affected by maternal diabetes mellitus or who have a history of a previously affected offspring, which are well-accepted indications for fetal echocardiography. Improvements in the resolution of ultrasound machines have now made it possible to undertake detailed cardiac scanning as early as 14 weeks [87,102].

It should be emphasized to the parents that increased NT per se does not constitute a fetal abnormality, and that, once chromosomal defects have been excluded, nearly 90% of liveborns who have fetal translucency below 4.5 mm have healthy live births. If the fetus survives until midgestation, and if a targeted ultrasound at 20 to 22 weeks fails to reveal any abnormality, the risk of adverse outcome is not statistically increased [103]. The rate of

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**Fig. 8.** Normal face at 13 weeks. (A) Sagittal view shows normal facial profile including nasal bone. (B) 3D multi-planar ultrasound with surface rendering shows normal facial features.

**Fig. 9.** Normal brain at 12 weeks. (A) Transabdominal scans show that the normal choroid plexus dominates the cerebral hemispheres. (B) Transvaginal scan on the same patient better shows normal anatomy.
development delay is also not statistically increased among fetuses who have increased NT [104].

**Twins and multiple gestations**

First-trimester screening can be effectively used for twin pregnancies [105]. Detection rates for Down syndrome are in the range of 75% to 85%, with a 5% false-positive rate [106]. Therefore, effective screening and diagnosis of major chromosomal abnormalities can be achieved in the first-trimester, allowing the possibility of earlier and therefore safer selective feticide for those parents that choose this option.

Discrepant NT measurements also appear to be a nonspecific early marker of twin-twin transfusion syndrome among monochorionic twins [Fig. 7]. In a study of 132 monochorionic twin pregnancies, including 16 that developed severe twin-to-twin transfusion syndrome at 15–22 weeks of gestation, increased NT (above the 95th percentile of the normal range) at the 11 to 14 week scan was associated with a fourfold increase in risk for the subsequent development of severe twin-to-twin transfusion syndrome [107]. It is possible that increased NT thickness in the recipient fetus may be a manifestation of heart failure caused by hypervolemic congestion. With advancing gestation and the development of diuresis that would tend to correct the hypervolemia and reduce heart strain, both the congestive heart failure and NT resolve.

Severe complications unique to monochorionic pregnancies, such as reversed arterial perfusion syndrome or acardiac twin, and conjoined twins, can be diagnosed during the first trimester. Twin reversed arterial perfusion (TRAP) has been reported at 10 to 12 weeks using both TVS and color Doppler [108,109]. Conjoined twins have also been frequently diagnosed during the first trimester.

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*Fig. 10. Normal anatomy. (A) Transvaginal scan at 13 weeks shows normal four-chamber view of the heart. (B) Transabdominal scan at 13 weeks shows normal fluid-filled stomach. (C) Transabdominal scan of the pelvis at 12 weeks shows a normal urinary bladder between the two umbilical arteries, seen with color flow Doppler. A normal urinary bladder is less frequently seen than the stomach.*
and have been detected as early as 8 to 9 weeks [110–118].

**Structural defects detected during the first trimester**

Use of a systematic survey can demonstrate normal anatomic development in the first trimester, similar to the fetal survey performed during the second trimester. Normal structures that can be visualized include the brain, choroid plexi, posterior fossa, face, heart, thorax, abdomen, stomach, urinary bladder, and all four extremities, including both feet and hands [Figs. 8–10]. In addition, the individual digits of each hand can usually be counted by 12 weeks. Fetal gender can be reliably determined by 13 weeks, and by 12 weeks in most cases [Fig. 11] [119]. When deviation from normal anatomy is recognized, a number of birth defects can be detected during the first trimester. Detection varies significantly between centers, with increasing detection by a thorough systematic survey and greater use of transvaginal ultrasound and three-dimensional (3D) multiplanar ultrasound.

![Fig. 11. Normal genitalia. (A) Male genitalia at 13 weeks. (B) Female genitalia at 12 weeks.](image)

![Fig. 12. Anencephaly/acrania at 12 weeks. The normal calvarium is not visualized and the shape of the brain is slightly abnormal. Anencephaly/acrania can be easily missed at this gestational age.](image)
Ossification of the fetal cranium begins and accelerates after 9 weeks [120,121], so that anencephaly can be diagnosed as early as 9 to 10 weeks [122]. Anencephaly can also be easily overlooked during the first trimester, however, because it initially is seen as acrania with absent calvarium but relatively normal amount of brain. Careful scrutiny will show an abnormal shape and appearance of the brain caused by the lack of the supporting calvarium [Fig. 12]. The sagging appearance of the brain may show “Mickey Mouse” ears.

Posterior cephaloceles have been diagnosed as early as 12 weeks [123], and alobar holoprosencephaly has been diagnosed as early as 10 weeks [124,125], but other brain abnormalities cannot reliably detected until later.

Spina bifida can occasionally be detected before the 12th postmenstrual week by noting irregularities of the bony spine or a bulging within the posterior contour of the fetal back [126]. There are also well-established additional sonographic findings that can enhance the detection of spina bifida, namely “the lemon sign” or “the banana sign” [127,128], and these may be evident as early as 12 weeks, although they can be initially subtle [129–131]. With high quality imaging, which may include tansvaginal scans, a normal posterior cerebellum and cisterna magna should be apparent, and this finding excludes all but the mildest forms of spina bifida.

Cleft lip and palate have been diagnosed in utero as early as the 13 to 14 weeks [132]. Bilateral cleft lip and palate may appear initially only as a an echogenic median mass, which actually is the premaxillary protrusion, made up of soft tissue, and at times of osseous and dental structures [Fig. 13] [133]. Because bilateral cleft lip and palate is associated with a high rate of aneuploidy and other birth defects, close follow-up, genetic counseling, and amniocentesis should be offered.

Ocular abnormalities such as hyper- and hypotelorism, anophthalmia and microphthalmia, have been diagnosed from 12 to 16 weeks [134–136]. Congenital cataracts has been diagnosed as early as 12 to 14 weeks [137,138].

By 12 to 14 weeks, a four-chamber view of the heart can be consistently imaged [139–142]. The great arteries can also be imaged by 11 to 12 weeks in many cases. As with normal anatomy later in the second trimester, the right and left ventricles should be of approximately the same size, the heart should not occupy more than one third of the thoracic cavity, and the heart apex should be oriented obliquely to the left anterior thorax.

**Fig. 13.** Bilateral cleft lip associated with trisomy 13 at 13 weeks. (A) Sagittal view shows abnormal soft tissue protruding just below the nose (arrow). (B) Transverse view confirms this finding. Bilateral cleft lip and palate was diagnosed (arrow). (C) Umbilical cord cyst (arrow, C) was also noted. (D) Follow-up 3D rendered image at 17 weeks confirms bilateral cleft lip and palate with premaxially protrusion. Other findings identified on the follow-up ultrasound, but not seen on the first-trimester scan, included echogenic intracardiac focus in the left ventricle, mildly hypoplastic left ventricle and atrium, micro-opthalmia, echogenic kidneys, and polydactyly.
Achiron and colleagues [143] reported eight cases of heart defects among approximately 1000 fetuses scanned by transvaginal ultrasound between 10 and 12 weeks. Only one fetus had an abnormal karyotype (45XO), but all fetuses showed other anomalies. Based on this experience, detection of isolated heart abnormalities is likely to remain difficult before 14 weeks.

Abdominal and truncal defects may be diagnosed during the first trimester, and these include omphalocele, gastroschisis [144,145], ectopia cordis [146,147], and body-stalk anomaly [148,149]. Omphaloceles may be categorized as those containing both bowel and liver (extracorporeal liver) and those containing only bowel (intracorporeal liver). Intracorporeal omphalocele can only be reliably diagnosed after 12 postmenstrual weeks, because of the difficulty in distinguishing it from physiologic midgut herniation [150,151]. Such omphaloceles have a high rate of fetal aneuploidy [152,153]. Extracorporeal omphalocele can be diagnosed as early as 9 to 10 weeks [154–156], and these may

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**Fig. 15.** Normal hands. (A) 2D ultrasound at 12 weeks, 3 days shows normal hand with four fingers and one thumb. (B) Another fetus at 13 weeks shows normal hand and extremities with 3D surface rendering.

**Fig. 16.** Normal limbs. (A) 3D surface rendering image shows poor visualization of extremities. (B) Transvaginal scans better shows normal extremities.
also be associated with fetal aneuploidy and other birth defects, including cardiac defects [Fig. 14].

The kidneys assume their final position within the renal fossa by 11 weeks [157]. Using transvaginal ultrasound, the kidneys can be consistently imaged by 12 to 13 weeks [158–160]. Cystic kidneys can sometimes be diagnosed during the first trimester. Multicystic dysplastic kidney disease has been diagnosed as early as 12 to 15 weeks [160]. Infantile polycystic kidney disease has also been diagnosed by 13 to 16 weeks by demonstration of enlarged, echogenic kidney. [161,162], although oligohydramnios may not develop until after 16 weeks.

The urinary bladder becomes apparent at 10 to 12 weeks, but like the kidney, it does not become consistently imaged until the 13th week [162], at which time cyclical filling and emptying of the fetal bladder should be apparent. Obstructive uropathy at the level of the urethra results in an enlarged urinary bladder (megacystis), which has been diagnosed as early as the 11th week [163,164]. It has been suggested that the diagnosis of megacystis can be reliably diagnosed when the urinary bladder measures more than 15 mm during the first trimester [165]. Affected fetuses seen during the first trimester have a high rate of associated anomalies and aneuploidy [166].

Fig. 17. Normal extremity movements at 13 weeks. Three images obtained within a few seconds of one another (A,B,C) show normal extremities with active normal movement.
The limbs begin to develop toward the end of the sixth week with development of the upper limbs before the lower limbs [167], and they can be imaged by the eighth week [168]. By 12 weeks the hands, fingers, feet, and toes can be consistently imaged [Fig. 15]. Use of transvaginal sonography and 3D ultrasound with surface rendering can aid in visualization of the extremities [Fig. 16]. By the 12th week, the long bones, phalanges, ilium, and scapula begin to ossify; the metacarpals and metatarsals ossify by 12 to 16 weeks [169]. Active fetal movements can be observed after 10 weeks [170]. Normal fetal activity is particularly apparent using real-time 3D (“4D”) ultrasound with surface rendering [Fig. 17].

A variety of skeletal abnormalities can be detected during the first trimester, including amputation defects and certain lethal skeletal dysplasias [Fig. 18]; however, their detection clearly varies with gestational age. In one of the largest reported series of prenatally diagnosed skeletal abnormalities in the first and early second trimesters, Bronshtein and coworkers [171] were able to detect 96% of the anomalies between 14 to 16 weeks, 3% between 12 to 14 weeks, and 1% at 10 to 12 weeks. Osteogenesis imperfecta (OI) is one of the lethal skele-

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**Fig. 18.** Clubfeet at 12 weeks. (A) Transabdominal scan at 12 weeks, 4 days shows clubbed foot (arrow, F). (B) 3D surface rendered image confirms severe bilateral clubfeet (arrow). This was also confirmed on follow-up scans at 18 weeks.
tal dysplasias that has been diagnosed as early as 13 to 15 weeks [172–175]. Sirenomelia has been diagnosed as early as 11 to 14 weeks using transvaginal ultrasound [176–179]. It is expected that akiensia can be detected during the first trimester. Polydactyly can also be detected during the first trimester, and this can be aided by use of 3D multiplanar ultrasound.

Summary

Screening for fetal chromosome abnormalities, particularly for trisomy 21, has made dramatic advances in the last 15 years. These advances have both complicated screening and provided couples with more effective screening options. More effective screening has demonstrated that patients who traditionally were considered “high risk”—particularly patients aged 35 or older—can be at lower risk for aneuploidy and other birth defects than a 20-year-old woman who does not undergo screening. This has resulted in a clear trend in the reduction of amniocentesis for these patients, and at the same time has made screening available for younger patients who share the 2% to 3% risk of birth defects that all pregnancies carry. More effective screening translates into lower procedural-related losses of normal fetuses, and better use of resources.

The trend toward earlier detection of structural defects during the first trimester will undoubtedly continue as ultrasound resolution and 3D multiplanar ultrasound continue to improve. Conversely, a normal systematic survey at this time can be reassuring and can help to exclude a variety of major defects. Based on the presence or absence of findings, patients can then be triaged into early follow-up and possible amniocentesis at 14 to 16 weeks, or a later detailed anatomic survey at 18 to 20 weeks.

References


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[170] Timor-Tritsch IE, Monteagudo A, Peisner DB.


