Sonographic Markers of Fetal Trisomies

Second Trimester

David A. Nyberg, MD, Vivienne L. Souter, MD, MRCOG

Objective. Second-trimester sonographic findings of fetal trisomy may include structural abnormalities or sonographic markers of fetal aneuploidy. Unlike structural anomalies, sonographic markers of fetal aneuploidy are insignificant by themselves with regard to outcome, are nonspecific—most frequently seen in normal fetuses, and are often transient. Our objective was to review the second-trimester sonographic findings of the major trisomic conditions, trisomies 13, 18, and 21. Methods. We reviewed a number of the most commonly accepted markers, including nuchal thickening, hyperchoic bowel, echogenic intracardiac focus, renal pyelectasis, shortened extremities, mild cerebral ventricular dilatation, and choroid plexus cysts. Markers associated with trisomy 21 were emphasized. Results. The sensitivity of sonography for detection of fetal trisomic conditions varies with the type of chromosome abnormality, gestational age at the time of sonography, reasons for referral, criteria for positive sonographic findings, and the quality of the sonography. As an estimate, 1 or more sonographic findings can be identified in approximately 90% of fetuses with trisomy 13, 80% of fetuses with trisomy 18, and 50% to 70% of fetuses with trisomy 21 (Down syndrome). Conclusions. The presence or absence of sonographic markers can substantially modify the risk of fetal Down syndrome and is the basis of the so-called genetic sonogram. Because maternal biochemical and sonographic markers are largely independent, combined risk estimates will result in even higher detection rates than either alone. Key words: trisomy 21; trisomy 18; trisomy 13; Down syndrome; prenatal sonography; nuchal thickening; hyperechoic bowel; echogenic intracardiac foci; pyelectasis; choroid plexus cyst; ventricular dilatation.

Sonography can show abnormalities in many fetuses with chromosomal aberrations. These may include both major or structural defects and nonstructural findings, also known as sonographic markers. Unlike structural anomalies, sonographic markers of fetal aneuploidy (SMFA) are insignificant by themselves with regard to outcome, are nonspecific—most frequently seen in normal fetuses, and are often transient. The most common SMFA in the second trimester are nuchal thickening, hyperechoic bowel, shortened extremities, renal pyelectasis, echogenic intracardiac foci (EIF), and choroid plexus cysts.

Table 1 summarizes the common structural anomalies and sonographic markers associated with the 3 common trisomic conditions (trisomies 13, 18, and 21). Although each trisomic condition has a typical phenotype, there is wide variation in phenotypic expression. The sensitivity of sonography for detecting these abnormalities varies with a number of factors, including the type of chromosome abnormality, gestational age at the time of sonography.
reasons for referral, criteria for positive sonographic findings, and the quality of the sonography. As an estimate, major or structural abnormalities are seen in 20% of fetuses with trisomy 21 (Down syndrome) during the second trimester, whereas they are seen in most fetuses with trisomies 18 and 13. Combined with SMFA, sonographic findings are identified in approximately 50% to 70% of fetuses with Down syndrome, 80% of fetuses with trisomy 18, and 90% of fetuses with trisomy 13. This emphasizes the potential importance of nonstructural markers in detection of fetal trisomy.

In the following sections, we review the second-trimester sonographic findings of the major trisomic conditions, trisomies 13, 18, and 21. We emphasize fetal Down syndrome because it is the most common trisomic condition, the most likely to result in a surviving neonate, and the most likely to show SMFA without structural anomalies.

### Trisomy 13

In trisomy 13, malformations of the central nervous system are common. These may include holoprosencephaly, agenesis of the corpus callosum, Dandy-Walker malformation, vermian agenesis, and neural tube defects. Other common malformations detected are facial abnormalities, including cyclopia, hypotelorism, and cleft lip and palate (Fig. 1A), renal cystic dysplasia or hydronephrosis, cardiovascular malformations, cystic hygroma, polydactyly, and club or rocker-bottom feet.

### Markers

Nonspecific markers of trisomy 13 may include mild dilatation of the lateral cerebral ventricles, hyperechoic bowel, and EIF. Lehman et al. report- ed EIF in 39% of fetuses with trisomy 13 before 20 weeks. Multiple EIF probably increase the risk of aneuploidy, including trisomy 13 (Fig. 1B). The combination of EIF and a hypoplastic-appearing left side of the heart is a characteristic pattern of trisomy 13 (Fig. 2). We have encountered 1 case of trisomy 13 in which multiple EIF was the only sonographic finding and several other cases in which EIF was the initial finding that led to detection of other subtle anomalies. Because of its association with trisomy 21, EIF is discussed further below (see “Trisomy 21”).

### Trisomy 18

A wide diversity of sonographic and pathologic abnormalities have been associated with trisomy 18 during the second trimester, including cystic
hygroma, nonimmune hydrops, hydrocephalus, spina bifida, diaphragmatic hernia, tracheoesophageal fistula, genitourinary anomalies, cardiovascular malformations, and omphalocele. Subtle abnormalities may include vermian agenesis and small-bowel–containing omphalocele (Fig. 3). Skeletal abnormalities are common and include clenched hands (Fig. 4), club feet, and radial aplasia or limb shortening. In the third trimester, some fetuses with trisomy 18 may primarily have intrauterine growth restriction (IUGR), which is often associated with polyhydramnios.

**Markers**

Subtle or nonstructural findings of trisomy 18 may include choroid plexus cysts, brachycephaly or “strawberry-shaped” head, and single umbilical artery. Of these, choroid plexus cysts (Fig. 5) have been the most controversial and the subject of considerable interest. Like other SMFA, choroid plexus cysts are a relatively common variant during the second trimester, are transient, and have no known effect on fetal development. Unlike some of the other potential markers (e.g., nuchal thickening and hyperchoic bowel), choroid plexus cysts have no known association with other adverse outcomes when the karyotype is normal.

Variables that may influence detection of choroid plexus cysts include gestational age, the thoroughness of the sonography, the threshold for calling a finding a choroid plexus cyst, underlying risk factors, and reasons for referral. It should be noted that studies that restrict patients to those with known karyotypes may be biased, because sonographic findings influence patients’ decisions about invasive testing. High-risk patients with SMFA are more likely to undergo invasive testing than low-risk patients with the same findings. For this reason, a higher risk will be found among patients who choose invasive testing compared with patients who do not. Snijders et al reported that among 107 fetuses with isolated choroid plexus cysts who had karyotyping, 2 had chromosome defects (1 each of trisomy 18 and 21), whereas no chromosome abnormality was found among the 174 fetuses

**Figure 1.** Trisomy 13. **A**, Bilateral cleft lip and plate. Coronal view of the face shows features of bilateral cleft lip and palate, seen as premaxillary protrusion (arrows). O indicates orbits. **B**, Bilateral EIF. Transverse view of the heart with the apex away from the transducer shows prominent bilateral EIF (arrows). No other abnormalities were identified in this fetus. LV indicates left ventricle; RV, right ventricle; and Sp, spine.
with choroid plexus cysts who did not have amniocentesis. Similar results can be found with other SMFA.

The prevalence of choroid plexus cysts in the general population has been reported as 0.5% to 3.6%, with most studies reporting in the range of 1% to 2%.\textsuperscript{23,24} At our own center, which has high-risk patients, we observe choroid plexus cysts in approximately 3.5% of fetuses at 14 to 20 weeks. In comparison, choroid plexus cysts are observed in 30% to 40% of fetuses with trisomy 18 before 20 weeks. This might suggest a high risk for trisomy 18 when choroid plexus cysts are identified prenatally. However, because most fetuses with trisomy 18 have other abnormalities, the risk from isolated choroid plexus cysts is relatively low.

Snijders et al\textsuperscript{22} observed choroid plexus cysts in 50% of fetuses with trisomy 18 and 1% of karyotypically normal fetuses. They found that isolated choroid plexus cysts carried only a marginally increased risk (likelihood ratio <2) for trisomy 18, but the presence of another abnormality increased the risk approximately 20 times (Table 2). The authors suggested that maternal age should be the main factor in deciding whether to offer fetal karyotyping when isolated choroid plexus cysts are detected. Similar opinions have been reached by a number of other authorities, including Chitty et al,\textsuperscript{25} who evaluated 658 fetuses with choroid plexus cysts.

Two meta-analyses found higher likelihood ratios for isolated choroid plexus cysts and trisomy 18 compared with that of Snijders et al.\textsuperscript{22} Ghidini and colleagues\textsuperscript{26} observed that isolated choroid plexus cysts were detected in 6.7% (13 of 194) of fetuses with trisomy 18 and 0.9% (752 of 79,583) of control fetuses, yielding a likelihood ratio of 7.1. In another report, Yoder et al\textsuperscript{27} evaluated 13 prospective studies comprising 246,545 second-trimester scans and found a likelihood ratio of 13.8 for trisomy 18. Despite this relatively high likelihood ratio, the authors concluded that fetal karyotyping should be offered only when maternal age at delivery is 36 years or older or when the risk for trisomy 18 detected by serum multiple-marker screening is more than 1 per 3000.

Among other variables, there is good evidence to suggest that larger choroid plexus cysts further increase the risk of trisomy 18 compared with smaller cysts (Fig. 6).\textsuperscript{28–32} Such large cysts undoubtedly take longer to resolve, supporting

---

**Figure 2.** Trisomy 13 and EIF. Four-chamber view of the heart shows EIF (arrow) in the left ventricle and the disproportionately smaller size of the left ventricle and left atrium compared with the right-sided chambers. A ventricular septal defect is also present. Other anomalies included single umbilical artery and probable cleft lip and palate. LA indicates left atrium; LV, left ventricle; RA, right atrium; and RV, right ventricle.

**Figure 3.** Trisomy 18 and omphalocele. Transverse view of the abdomen at 17 weeks shows small-bowel–containing omphalocele (arrows). A strawberry-shaped head was also present. Sp indicates spine.
observations that delayed resolution of choroid plexus cysts carries an increased risk for trisomy 18. Whether the cysts are unilateral or bilateral does not appear to be significant, although it is probably true that large cysts also tend to be bilateral.

All of these findings indicate that detection of a choroid plexus cyst, as with any SMFA, should initiate a renewed search for other abnormalities. A choroid plexus cyst can be presumed to be isolated only after a detailed fetal survey fails to show structural abnormalities or other SMFA. As an isolated finding after high-quality sonography, and assuming the patient is otherwise considered at low risk for fetal aneuploidy, we think that detection of choroid plexus cysts should not alter obstetric management. Additional reassurance can be obtained by correlating sonographic findings with serum biochemical markers.33,34 Because choroid plexus cysts always resolve, follow-up sonography is of no value in decision making unless it is done to detect other abnormalities that were previously missed (e.g., cardiac defects).

Trisomy 21

Structural or major abnormalities in trisomy 21 include cardiac defects, hydrops, and cystic hygroma. Rarely, duodenal atresia can also be seen before 20 weeks, especially when combined with esophageal atresia.35–37

Table 2. Approximate Risk of Trisomy 18 in Fetuses With Choroid Plexus Cysts

<table>
<thead>
<tr>
<th>Gestational Age, wk</th>
<th>Baseline Risk</th>
<th>Isolated Cyst</th>
<th>Other Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–24</td>
<td>1:4500</td>
<td>1:2950</td>
<td>1:225</td>
</tr>
<tr>
<td>25–29</td>
<td>1:3600</td>
<td>1:2300</td>
<td>1:175</td>
</tr>
<tr>
<td>30–34</td>
<td>1:2000</td>
<td>1:1300</td>
<td>1:100</td>
</tr>
<tr>
<td>35–39</td>
<td>1:750</td>
<td>1:470</td>
<td>1:35</td>
</tr>
<tr>
<td>40–44</td>
<td>1:400</td>
<td>1:100</td>
<td>1:10</td>
</tr>
</tbody>
</table>

Data from Snijders et al.22

Figure 4. Trisomy 18 and clenched hand. A typical clenched hand (H) is shown.

Figure 5. Trisomy 18 and choroid plexus cyst. Image of the head at 18 weeks shows a typical choroid plexus cyst (arrow) measuring 5 mm. Other abnormalities in this case included a diaphragmatic hernia, a cardiac defect, and probably micrognathia.

Figure 6. Trisomy 18 and large choroid plexus cyst. A large choroid plexus cyst (C) measuring 16 mm in length is shown in the dependent ventricle. No other sonographic abnormalities were identified in this case.
Compared with fetuses with trisomies 18 and 13, fetuses with trisomy 21 are unlikely to have structural abnormalities before 20 weeks. Sohl et al.\(^3\) found major abnormalities in 16.4% of fetuses with trisomy 21, and we found major abnormalities in 16.7% before 20 weeks, after exclusion of patients referred for sonographically detected abnormalities.\(^3\) A slightly higher frequency (21.8%) of structural abnormalities was found in a previous study at our center, but that study included referred patients and also categorized mild ventricular dilatation as a major abnormality for consistency with previous studies.\(^4,5\) Studies that include patients referred for sonographically detected abnormalities will have a higher rate of major abnormalities.

The low detection rate of structural abnormalities reflects the low sensitivity of sonography for detection of cardiac defects among fetuses with trisomy 21 before 20 weeks. We consistently detect cardiac defects in less than 10% of fetuses with trisomy 21, although the mean gestational age at the time of scanning is 16.9 weeks for these pregnancies. Improved detection of cardiac defects would be expected even a few weeks later. Using nonspecific cardiac findings, such as right-left disproportion, pericardial effusion, and tricuspid regurgitation, DeVore et al.\(^6\) reported cardiac findings in 76% of fetuses with trisomy 21, but just 9% had an endocardial cushion defect. The mean gestational age for sonography in that study was also 18 weeks.

A study by Paladini and colleagues\(^7\) suggested what is possible under ideal conditions. Scanning at an optimal gestational age (24 weeks), under optimal conditions (in a dedicated fetal echocardiographic center), with inclusion of subtle ventricular septal defects, and with previous knowledge of fetal karyotype, they were able to detect heart defects in just more than half of fetuses with Down syndrome.

### Markers

A large number of potential SMFA have been described in association with trisomy 21 during the second trimester (Table 1).\(^,4,5,4-7\) Among these, we routinely evaluate nuchal thickening, hyperechoic bowel, EIF, shortened limbs, and pyelectasis, because they can be easily sought during the course of routine second-trimester sonography. Other potential markers include a widened pelvic angle,\(^8,9\) shortened frontal lobes,\(^10,11\) small ears,\(^12\) clinodactyly,\(^13\) and right-left disproportion of the heart, among others. Another potential marker for trisomy 21, although not related to fetal anatomy, is unfused amnion and chorion after 14 weeks.\(^14\)

The sensitivities of most sonographic markers are low, particularly compared with that of nuchal translucency in the first trimester (Table 3). However, the incremental value of each marker improves the overall sensitivity of second-trimester sonography so that 1 or more markers are observed in more than 50% of fetuses with trisomy 21 at our center. When SMFA are combined with major abnormalities, our overall sensitivity of second-trimester sonography is 69%.

The use of sonographic markers, usually a panel of markers, to modify the risk of fetal Down syndrome is widely referred to as a “genetic sonogram.” The actual sensitivity of a genetic sonogram will depend on various factors, including the markers sought, gestational age, reasons for referral,\(^5,6\) and, of course, the quality of the sonography. Considering these variables and differences in the types of sonographic markers used (Table 4), the results for genetic sonograms from different centers are surprisingly similar (Table 5). Reported detection rates have ranged from 59% to 82%. Detection rates exceeding 90% have even been reported, including a high detection rate for cardiac abnormalities.\(^6\)

The risk of fetal trisomy 21 increases dramatically with the number of markers present (Table 6). Two or more markers are detected in nearly one third of fetuses with trisomy 21 at our center, compared with less than 2% in normal fetuses. In comparison, a single marker is observed in more than 11% of normal fetuses compared with 22.6% of fetuses with trisomy 21. Similarly, Sohl et al.\(^3\) observed a single marker in 14.6% of normal fetuses. On the basis of these data, a single

### Table 3. Frequency of Sonographic Markers (Without Structural or Major Abnormalities) in Fetuses With Trisomy 21

<table>
<thead>
<tr>
<th>Sonographic Marker</th>
<th>Trisomy 21 (n = 186), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuchal thickening</td>
<td>32.3</td>
</tr>
<tr>
<td>Hyperechoic bowel</td>
<td>17.2</td>
</tr>
<tr>
<td>Short humerus</td>
<td>18.3</td>
</tr>
<tr>
<td>Short femur</td>
<td>26.3</td>
</tr>
<tr>
<td>EIF</td>
<td>23.1</td>
</tr>
<tr>
<td>Pyelectasis</td>
<td>11.3</td>
</tr>
</tbody>
</table>

Data from Swedish Medical Center (Seattle, WA).
marker increases the risk 2-fold; 2 markers increase the risk nearly 10-fold; and 3 or more markers increase the risk more than 100-fold. The actual risk will depend on the type as well as the number of markers present.

The use of multiple sonographic markers will improve the sensitivity of sonography for detection of fetal Down syndrome but at the cost of a higher false-positive rate if the presence of any single marker is considered a positive finding. This high false-positive rate can understandably lead to considerable anxiety and inconsistent management among low-risk patients. Sonologists should attempt to minimize these false-positive results among low-risk patients but should maximize the sensitivity in high-risk patients.

To optimize clinical management of sonographic markers, Benacerraf and colleagues devised a scoring index in which 2 points are given for structural abnormalities or nuchal thickening and 1 point is given for the other markers. Amniocentesis is offered to those with a score of 2 or greater. This approach avoids the false-positive rates from a single marker, except for nuchal thickening, which is appropriately considered a high-risk marker. The scoring index system can be modified to incorporate maternal age by giving 1 point for women 35 years of age or older and 2 points for women 40 years of age or older (Table 7).

Another method of optimizing sonographic findings is to integrate the risk of sonographic markers with the a priori risk based on maternal age. This has been termed “age-adjusted ultrasound risk assessment” (AAURA) for Down syndrome. The sonographic markers are weighted by the strength of individual findings, expressed as likelihood ratios (Table 7). The post priori risk is estimated by the likelihood ratios, and the a priori risk is based on maternal age (Table 8).

When AAURA is used, both the sensitivity of fetal Down syndrome and the false-positive rate increase with maternal age. This is appropriate

Table 4. Components of the Second-Trimester Genetic Sonogram Reported in Various Studies for Detection of Fetal Down Syndrome

<table>
<thead>
<tr>
<th>Report</th>
<th>Nuchal</th>
<th>Humerus</th>
<th>Femur</th>
<th>Renal</th>
<th>HB</th>
<th>EIF</th>
<th>CC</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benacerraf et al.</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>DeVore</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nyberg et al.</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Bahado-Singh et al.</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Vergani et al.</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Sohl et al.</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vintzileos</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

CC indicates choroid plexus cysts; HB, hyperechoic bowel; and ++++, multiple other findings.

Table 5. Sensitivities and False-Positive Rates Reported for Genetic Sonograms From Different Centers

<table>
<thead>
<tr>
<th>Report</th>
<th>n</th>
<th>Sensitivity, %</th>
<th>FP rate, %</th>
<th>LR</th>
<th>LR Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benacerraf et al.</td>
<td>45</td>
<td>73</td>
<td>4.4</td>
<td>16.5</td>
<td>0.28</td>
</tr>
<tr>
<td>DeVore</td>
<td>15</td>
<td>73</td>
<td>7.4</td>
<td>9.9</td>
<td>0.29</td>
</tr>
<tr>
<td>Bromley et al.</td>
<td>53</td>
<td>75</td>
<td>5.7</td>
<td>13.1</td>
<td>0.27</td>
</tr>
<tr>
<td>Nyberg et al.</td>
<td>142</td>
<td>74</td>
<td>14.7</td>
<td>5</td>
<td>0.30</td>
</tr>
<tr>
<td>Bahado-Singh et al.</td>
<td>24</td>
<td>60</td>
<td>4.5</td>
<td>13.3</td>
<td>0.41</td>
</tr>
<tr>
<td>Bahado-Singh et al.</td>
<td>31</td>
<td>73.5</td>
<td>15</td>
<td>4.9</td>
<td>0.31</td>
</tr>
<tr>
<td>Vergani et al.</td>
<td>22</td>
<td>59</td>
<td>5.3</td>
<td>11.1</td>
<td>0.43</td>
</tr>
<tr>
<td>Sohl et al.</td>
<td>55</td>
<td>67</td>
<td>19.4</td>
<td>3.5</td>
<td>0.41</td>
</tr>
<tr>
<td>Vintzileos</td>
<td>34</td>
<td>82</td>
<td>9</td>
<td>9.1</td>
<td>0.20</td>
</tr>
<tr>
<td>Nyberg et al.</td>
<td>186</td>
<td>69.9</td>
<td>13.3</td>
<td>5.3</td>
<td>0.36</td>
</tr>
</tbody>
</table>

FP indicates false-positive; and LR, likelihood ratio. LR = sensitivity/FP rate; and LR negative = false negative rate/specificity = (1 – sensitivity)/(1 – FP rate).
because older women desire high sensitivity, and
the clinical alternative is amniocentesis for all
women 35 years of age or older (100% false-pos-
itive rate). At the same time, AAURA minimizes
the false-positive rate for younger women (4%
false-positive rate) but still has satisfactory sen-
sitivity (61.5%). Very similar results can be
obtained with the modified scoring index
method, which incorporates maternal age,
although AAURA has the advantage of providing
a patient-specific risk estimate.60 Because sono-
graphic findings appear to be largely indepen-
dent of both maternal age and biochemical
analytes,61–63 we think that the risk from bio-
chemical screening (serum markers plus mater-
nal age risk) can be substituted for maternal age
risk alone when known.
AAURA, or any method of risk assessment,
requires knowledge of the risks associated with
individual sonographic markers. In the follow-
ing sections, individual markers are discussed
in greater detail.

Nuchal Thickening
Redundant skin at the back of the neck is a
characteristic clinical feature of infants with
trisomy 21 and was first reported by Down in
1866.64 Benacerraf and coworkers65–67 first
reported the sonographic correlate of this clin-
ic feature in terms of nuchal thickening dur-
ing the second trimester (Fig. 7), and thus
began the search for other sonographic mark-
ers. Nuchal thickening remains one of the
most sensitive and important markers of tri-
somy 21 during the second trimester. Indeed,
although other criteria vary among centers,
nuchal thickening is universally used as a
marker for trisomy 21. Although the sensitivity
and false-positive rates will vary with gesta-
tional age and the exact criteria for a positive
finding, sensitivities in the range of 20% to 40%
are most common.
On the basis of early experience, Benacerraf et
al.65 suggested that a threshold of 6 mm or
greater after 15 weeks indicated a high risk of
trisomy 21. However, in a subsequent study
they observed that none of 303 normal fetuses
showed nuchal thickening of greater than 5
mm up to 20 weeks.66 Several prospective stud-
ies have since suggested that 5 mm is a better
threshold, which results in improved sensitivity
and only a slight increase in the false-positive
rate. We have used a 5-mm cutoff for the last 10
years.68–70
A number of studies have shown that normal
nuchal thickness varies with gestational age,
which should not be surprising. This suggests
that, as a further refinement, gestational age-
specific criteria should be used for increased
nuchal thickness rather than a single cutoff.71–73
Gestational age-specific criteria may include
observed-to-expected or observed-minus-
expected nuchal thickness or a comparison of
nuchal thickness with other biometric mea-
urements, such as biparietal diameter and
femur and humerus length. The use of multi-
ple-of-the-median data, comparing the actual
nuchal measurement with the expected mea-
surement, would permit calculation of likeli-
hood ratios and would also permit integration
with maternal serum biochemical markers for
a combined risk. Bahado-Singh and coworkers
have reported multiples of the median and esti-
mated likelihood ratios.71–73

Table 6. Comparison of Number of Markers in Fetuses With Down Syndrome and Controls

<table>
<thead>
<tr>
<th>No. of Markers or Major Abnormality</th>
<th>Down Syndrome (n = 186), % (n)</th>
<th>Control (N = 8712), % (n)</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>31 (58)</td>
<td>86.7 (7541)</td>
<td>0.36</td>
</tr>
<tr>
<td>1</td>
<td>22.6 (42)</td>
<td>11.3 (987)</td>
<td>2.0</td>
</tr>
<tr>
<td>2</td>
<td>15.1 (28)</td>
<td>1.5 (136)</td>
<td>9.6</td>
</tr>
<tr>
<td>3+</td>
<td>14.5 (27)</td>
<td>0.1 (11)</td>
<td>115</td>
</tr>
<tr>
<td>Major abnormality</td>
<td>16.7 (31)</td>
<td>0.4 (37)</td>
<td>39.2</td>
</tr>
</tbody>
</table>

LR indicates likelihood ratio; LR = percent Down syndrome cases/control cases.

Table 7. Comparison of 2 Methods for Assessing the Risk of Fetal Down Syndrome Based on Sonographic Findings: AAURA and the Index Scoring System

<table>
<thead>
<tr>
<th>Sonographic Finding</th>
<th>LR (AAURA)</th>
<th>Index Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural defect</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Nuchal thickening</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Hyperechoic bowel</td>
<td>6.7</td>
<td>1</td>
</tr>
<tr>
<td>Short humerus</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>EIF</td>
<td>1.8</td>
<td>1</td>
</tr>
<tr>
<td>Short femur</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>Pyelectasis</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>Age 35–39 y</td>
<td>Risk based on age (Table 8)</td>
<td>1</td>
</tr>
<tr>
<td>Age 40+ y</td>
<td>Risk based on age (Table 8)</td>
<td>2</td>
</tr>
<tr>
<td>If normal</td>
<td>0.4</td>
<td>0</td>
</tr>
</tbody>
</table>

Likelihood ratios (LR) reported are those calculated as isolated markers, from Nyberg et al.39 Slightly different likelihood ratios were assumed previously in the description of AAURA.45
Hyperechoic Bowel

Like other nonstructural markers, hyperechoic bowel is nonspecific and is most commonly observed in normal fetuses. However, it is observed with increased frequency in fetuses with aneuploidy, including trisomy 21 (Fig. 8).\textsuperscript{74–78} Hyperechoic bowel has also been reported in association with bowel atresia, congenital infection, and, rarely, meconium ileus secondary to cystic fibrosis.\textsuperscript{79,80} An increased risk of IUGR, fetal death, and placenta-related complications is also recognized as being associated with hyperechoic bowel.\textsuperscript{81}

Despite its subjectivity, the prevalence of hyperechoic bowel among normal fetuses (0.5%) has been remarkably consistent at our center in the last decade and is also similar to that in other reports, suggesting that different centers can agree on the presence of hyperechoic bowel. We use a grading system for hyperechoic bowel, with grade 1 being mildly echogenic and typically diffuse, grade 2 being moderately echogenic and typically focal, and grade 3 being very echogenic, similar to that of bone structures.\textsuperscript{82} The echogenicity of normal bowel also increases with transducer frequency,\textsuperscript{83} although this effect is uniform, whereas true hyperechoic bowel tends to be focal. To minimize subjectivity, some authors consider only bowel that is markedly hyperechoic, whereas we and others\textsuperscript{84,85} recognize both moderate and markedly hyperechoic bowel (grades 2 and 3) as a risk factor for fetal aneuploidy (Fig. 8). If only grade 3 hyperechoic bowel were recognized, the sensitivity would be decreased, but the risk (likelihood ratio) would be increased.

Table 8. A Priori Risk of Down Syndrome, Expressed as Odds Ratio, Based on Maternal Age During the Second Trimester

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1:1176</td>
</tr>
<tr>
<td>21</td>
<td>1:1160</td>
</tr>
<tr>
<td>22</td>
<td>1:1136</td>
</tr>
<tr>
<td>23</td>
<td>1:1114</td>
</tr>
<tr>
<td>24</td>
<td>1:1087</td>
</tr>
<tr>
<td>25</td>
<td>1:1040</td>
</tr>
<tr>
<td>26</td>
<td>1:990</td>
</tr>
<tr>
<td>27</td>
<td>1:928</td>
</tr>
<tr>
<td>28</td>
<td>1:855</td>
</tr>
<tr>
<td>29</td>
<td>1:760</td>
</tr>
<tr>
<td>30</td>
<td>1:690</td>
</tr>
<tr>
<td>31</td>
<td>1:597</td>
</tr>
<tr>
<td>32</td>
<td>1:508</td>
</tr>
<tr>
<td>33</td>
<td>1:421</td>
</tr>
<tr>
<td>34</td>
<td>1:342</td>
</tr>
<tr>
<td>35</td>
<td>1:274</td>
</tr>
<tr>
<td>36</td>
<td>1:216</td>
</tr>
<tr>
<td>37</td>
<td>1:168</td>
</tr>
<tr>
<td>38</td>
<td>1:129</td>
</tr>
<tr>
<td>39</td>
<td>1:98</td>
</tr>
<tr>
<td>40</td>
<td>1:74</td>
</tr>
<tr>
<td>41</td>
<td>1:56</td>
</tr>
<tr>
<td>42</td>
<td>1:42</td>
</tr>
<tr>
<td>43</td>
<td>1:31</td>
</tr>
<tr>
<td>44</td>
<td>1:23</td>
</tr>
</tbody>
</table>

Figure 7. Trisomy 21 and nuchal thickening. Mild nuchal thickening is shown (6 mm), delineated by calipers.

Figure 8. Trisomy 21 and hyperechoic bowel (HB). Moderately echogenic bowel is shown; it is not quite as echogenic as the adjacent bone. H indicates heart; and IW, iliac wing.
Skeletal Abnormalities

Short stature is a characteristic feature of children with trisomy 21, associated with disproportionately short proximal long bones (femur and humerus). Limb shortening can also be detected in some fetuses with trisomy 21 during the second trimester. However, there is considerable overlap in bone measurements between affected and unaffected fetuses. A shortened humerus appears to be a slightly more specific indicator than a shortened femur. Results probably vary with gestational age, ethnic group, possibly fetal gender, and criteria used, as well as systematic differences in long-bone measurements. Despite these variables, this marker is commonly used at screening centers. The most common method for determination of shortened humerus and femur is comparing the actual measurement with the expected measurement, typically based on biparietal diameter or another dating parameter rather than gestational age. Until now, we have used a single cutoff of 0.91 multiples of the median for a short femur and 0.89 for a short humerus. However, like nuchal measurements, optimal results would be expected by multiple-of-the-median data and corresponding likelihood ratios rather than a single cutoff. These methods are best performed by computer calculations. Other skeletal abnormalities associated with trisomy 21 are clinodactyly (shortened middle phalanx of the fifth finger) and a widened pelvic angle. Although both are well-known clinical features of trisomy 21, these can be difficult to assess on second-trimester sonography and therefore are not typically included in most screening programs.

Renal Pyelectasis

Mild pyelectasis (hydronephrosis) has been associated with an increased risk of aneuploidy, primarily for trisomy 21. However, it is most commonly seen as a normal variant and appears more commonly in male fetuses. The prevalence of pyelectasis undoubtedly varies with gestational age even during the time of second-trimester scans (14–22 weeks). A mild degree of renal pyelectasis may fluctuate during the course of a single examination.

Studies are conflicting regarding the possible influence of pyelectasis from maternal hydration as well as the degree of fetal bladder distention. Robinson and colleagues found that the anteroposterior renal pelvic diameter increased with maternal hydration in both normal fetuses and those with pyelectasis and was independent of the state of the fetal bladder, whereas Petrikovsky et al found that the degree of fetal bladder distention was important.

Renal pyelectasis is measured as the fluid-filled renal pelvis in an anteroposterior dimension. We prefer measurement when the kidneys and spine are oriented toward or away from the transducer rather than to the side. The threshold for a positive finding varies among centers, but the most common criteria are greater than 3 to 4 mm. Ideally, gestational age-dependent criteria might be used in the future.

Using a cutoff of greater than 3 mm, we observe pyelectasis in about 3% of normal fetuses at our center. Snijders and Nicolaides estimate that mild pyelectasis increases the risk of trisomy 21 by 1.6-fold over the baseline risk. Our own analysis is consistent with this risk, although this risk may not be increased when pyelectasis is isolated. The lack of association as an isolated finding has also been suggested by other studies, although one center has shown an association as an isolated finding.

Echogenic Intracardiac Foci (or Papillary Muscle Calcification)

Echogenic intracardiac foci as SMFA are the most recent, and probably the most controversial, of the sonographic markers that have been described. It is a common finding during the second trimester, observed in 3% to 4% of normal fetuses. The prevalence appears to be significantly higher among Asian populations; Shipp et al found EIF 3 times more often among Asian patients compared with white patients. That finding is important, because an estimation of risk derived from white populations may not apply to Asian women.

Because EIF is a subjective finding, its detection depends on a variety of factors, including resolution of the sonographic equipment, technique, thoroughness of the examination, and the sonographer’s experience. Fetal position is also important, because intracardiac foci are best visualized when the cardiac apex is oriented toward the transducer. Despite these variable factors, similar detection rates of EIF from different studies suggest that experienced sonographers can largely agree on its presence or absence. Like many sonographic markers, it typ-
ically resolves by the third trimester despite the outcome.\textsuperscript{109}

Roberts and Genest\textsuperscript{110} were the first to suggest an association between aneuploidy and mineralization of the papillary muscle in a pathologic study. Mineralization of the papillary muscle was observed in 2\% of normal fetuses compared with 16\% (20 of 126) of those with trisomy 21 and 39\% (9 of 23) of those with trisomy 13. Similar but slightly higher rates of EIF have been observed in sonographic studies during the second trimester, possibly because small foci may have escaped pathologic detection. Comparison of these data, as well as direct correlation by Brown et al,\textsuperscript{111} suggests that EIF correlates with papillary muscle mineralization that can be seen histologically.

In 2 sonographic studies of EIF and aneuploidy, Bromley et al\textsuperscript{112} detected EIF in 4.7\% (62 of 1312) of control fetuses compared with 18\% (4 of 22) of those with trisomy 21, and Lehman et al\textsuperscript{6} reported EIF in 39\% of fetuses with trisomy 13 before 20 weeks. A number of studies have confirmed an association between EIF and trisomy 21 (Fig. 9)\textsuperscript{113–118} with few exceptions.\textsuperscript{119–121} The likelihood ratio of EIF in trisomy 21 has been estimated in the range of 1.8 to 4.2.

The risk of aneuploidy from isolated EIF, as well as other SMFA, may be underestimated among low-risk patients because of incomplete ascertainment. Few patients with an isolated marker undergo chromosome analysis unless they are already considered at high risk. In one of the few studies to address this issue, Simpson and colleagues\textsuperscript{114} evaluated 205 fetuses with isolated EIF from low-risk patients. Clinical follow-up was obtained by way of a standard questionnaire completed by the parents when the infants were 6 weeks old. Two infants (1\%) proved to have aneuploidy (1 trisomy 21 and 1 unbalanced translocation).

On the other hand, the risk of EIF and other markers is probably overestimated in studies in which the fetal karyotype is known for all patients, because sonographic findings influence patient decision making. Many high-risk patients now wait for the results from the second-trimester sonogram before deciding to undergo genetic amniocentesis, and high-risk patients are appropriately more likely to undergo genetic amniocentesis than low-risk patients on the basis of the same sonographic findings. We observed EIF in 5.4\% of fetuses with known normal karyotypes compared with 3.9\% of all consecutive patients who had normal or presumed normal fetal karyotypes. Previous studies confined to known karyotypes have also shown a higher prevalence of EIF. This emphasizes the potential for bias in studies of sonographic markers that restrict patients to those with known fetal karyotypes.

Multiple or large EIF may be important variables when considering genetic amniocentesis.\textsuperscript{122–125} Bettelheim et al\textsuperscript{122} found EIF located in the left ventricle in 96\% of cases, in combined left and right ventricles in 4.3\%, and isolated to the right ventricle in just 0.7\% (1 of 150). Bromley et al\textsuperscript{116} concluded that right-sided and bilateral EIF combined together had an approximately 2-fold greater risk of aneuploidy compared with left-sided foci, and others have also found that echogenic foci involving both ventricles are more associated with aneuploidy. Wax and Philput\textsuperscript{123} reported that aneuploidy was more common when echogenic foci involved both ventricles compared with either ventricle alone. Vibhakar et al\textsuperscript{117} found that of 15 fetuses with multiple EIF 10 (67\%) had abnormal karyotypes, and only 2 of those had other sonographically detected abnormalities besides EIF. More recently, Wax and colleagues\textsuperscript{125} correlated an increased risk of aneuploidy with the conspicuity of EIF. Our own observations agree that multiple or unusually prominent EIF appear to carry a greater risk.
Mild Ventricular Dilatation

The size of the lateral ventricles remains relatively constant throughout gestation, with a mean diameter of 6.1 ± 1.3 mm and slightly larger ventricles in male than in female fetuses (6.4 versus 5.8 mm). Ventriculomegaly is suspected when the atrial diameter reaches 10 mm, although separation of the dependent choroid from the medial ventricular wall may be visible evidence of early ventricular dilatation.

Mild ventricular dilatation deserves comment because it has been associated with trisomy 21 as well as other aneuploidies. Although some authors have categorized it as a major abnormality, we think it shares similar characteristics (nonspecific, common in normal fetuses, and often transient) with other minor markers. It is more likely to be seen as a normal variant later in the second trimester (after 20 weeks) and in male fetuses.

In a series by Bromley et al, 12% (5 of 43) of fetuses with mild ventriculomegaly (ventricular diameter, 10–12 mm) had abnormal karyotypes (3 trisomy 21 and 2 trisomy 18), although all of these had other findings. Similarly, in our most recent series of trisomy 21, mild cerebral ventricular dilatation was observed in 4.3% (8 of 186) of affected fetuses, but all had other findings, including structural defects (n = 3), 3 or more minor markers (n = 3), or nuchal thickening alone (n = 2).

On the other hand, Pilu et al evaluated 31 fetuses with isolated borderline ventricular dilatation (10–15 mm) and found 3 with aneuploidy (2 with trisomy 21 and 1 with trisomy 13). In a review of the literature including their own cases (n = 234), chromosomal aberrations, mostly trisomy 21, were observed in 3.8%. Vergani et al evaluated 82 cases of mild ventriculomegaly (10–15 mm) and found aneuploidy in 2 cases, both of which were associated with advanced maternal age. Seven additional cases of aneuploidy were associated with other anomalies. Current experience suggests that mild cerebral ventricular dilatation increases the risk for fetal aneuploidy, although this risk remains difficult to determine. Further studies are needed, including studies comparing ventricular measurements of fetuses with trisomy 21 and normal fetuses.

Choroid Plexus Cysts

Although an association between choroid plexus cysts and trisomy 18 has been clearly established, a possible link with trisomy 21 has been controversial. Among 1346 fetuses with isolated choroid plexus cysts reviewed by Yoder et al, 5 had trisomy 21. The calculated likelihood ratio for trisomy 21 was 1.87, but this did not reach statistical significance (P = .16). Our own analysis suggests that choroid plexus cysts are statistically more likely in fetuses with trisomy 21 but not as isolated findings. We think that as an isolated finding after high-quality sonography, and assuming the patient is otherwise considered at low risk for fetal aneuploidy, detection of choroid plexus cysts should not alter obstetric management.

Reduction of Risk in Women Otherwise Considered at High Risk

Increasingly, normal sonographic findings are used to help reduce the risk of Down syndrome for women who otherwise would be considered at risk for fetal trisomy 21. Reduction of risk is most useful for women in an intermediate age group, 34 to 40 years, and for women with intermediate risk based on biochemical screening (risk 1:100). To what degree the risk is reduced depends on a variety of factors, including the number and type of criteria used, individual thresholds, and, undoubtedly, the gestational age at the time of scanning. Despite differences among centers, most recent studies (Table 5) suggest that a likelihood ratio in the range of 0.3 to 0.4 can be assigned to a normal sonographic finding. These likelihood ratios correspond to a 60% to 70% reduction of risk. With the use of a larger number of criteria or a higher threshold, sensitivity of sonography approaching 90% has been reported. Vintzileos and colleagues used a large number of SMFA but applied them only to reduce the risk among low-risk patients.

Comparison of Sonography and Biochemical Analysis

How does second-trimester sonography compare with second-trimester biochemical screening? Surprisingly little data are currently available regarding this. It appears that the reported
sensitivity for sonography in detecting Down syndrome at centers that have high-risk patients is similar to that of second-trimester biochemical screening. Considering the maternal age distribution at the centers with high-risk patients that have reported results, the false-positive results of sonography are also similar to those of biochemical screening. One difference is that negative serum biochemical test results can reduce the risk much more than can normal sonographic findings. Also, biochemical testing is more widely available than high-quality sonography.

It now seems clear that a combined risk estimate using both sonography and biochemical testing will be more effective than either alone. A combined risk would also be less confusing than competing results from each. To date, however, few studies have evaluated the effectiveness of combining sonography and biochemical screening in the second trimester, even though a large number of reports have addressed this combined risk for the first trimester. Roberts and colleagues found that sonography improved detection over that of second-trimester biochemical screening alone from 65% to 80%. Bahado-Singh et al. have also shown that incorporation of humerus length and nuchal thickness significantly improves the receiver operator curves of biochemical risk assessment alone. Addition of inhibin to the standard triple-marker test would further increase second-trimester detection of trisomy 21 to 75% on the basis of biochemical screening alone. Optimal sonographic risk assessment will require computer calculations using risk estimates from multiple-of-the-median data from specific measurements (e.g., nuchal thickening and limb length).

In another development, urinary biochemical markers may also prove to be effective in the detection of trisomy 21. Bahado-Singh and colleagues have reported that urinary hyperglycosylated human chorionic gonadotropin (hCG) is superior to the 3 analytes of the triple-marker screen. In a study, urine hyperglycosylated hCG was combined with urine β-core fragment serum α-fetoprotein and maternal age to yield a detection rate of 96% with a 5% false-positive rate or 94% sensitivity with a 3% false-positive rate. Incorporation of sonographic biometric measurements with urinary analytes further improves screening performance. Using sonographic measurements of humeral length and nuchal thickness combined with hyperglycosylated hCG, Bahado-Singh et al. found a 91.3% detection rate with a 3.2% false-positive rate. The area under the receiver operator curve was 0.986 (P < .001), and that combination was superior to hyperglycosylated hCG plus age alone or any other second-trimester screening protocol.

The Future

First-trimester nuchal translucency screening and biochemical markers have proved to be effective for detection of fetal aneuploidy. At this time, it remains uncertain whether first-trimester screening is more effective than second-trimester screening and what the ultimate role of second-trimester screening will be. Wald et al. have proposed that the combination of first-trimester nuchal translucency screening with both first- and second-trimester biochemical screening might be able to achieve 85% sensitivity for trisomy 21 with only a 1% false-positive rate. If validated clinically, this approach would significantly lower the predictive value of second-trimester sonographic markers. On the other hand, Bahado-Singh and coworkers have shown that sonographic markers can also be correlated with second-trimester biochemical markers to provide similar high detection rates. Only time will tell whether sonographic markers associated with aneuploidy during the second trimester will ultimately have the same interest they do today.

References


74. Nyberg DA, Dubinsky T, Resta RG, Mahony BS, Hickok DE, Luthy DA. Echogenic fetal bowel during...


98. Petrikovsky BM, Cuomo MI, Schneider EP, Wyse LJ, Cohen HL, Lesser M. Isolated fetal hydronephrosis:


106. Levy DW, Mintz MC. The left ventricular echogenic focus: a normal finding. AJR Am J Roentgenol 1988; 150:85–86.


