

The Genetic Sonogram

A Method of Risk Assessment for Down Syndrome in the Second Trimester

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Objective. To determine the risk of Down syndrome in fetuses with sonographic markers using the Bayes theorem and likelihood ratios. **Methods.** We prospectively evaluated the midtrimester sonographic features of fetuses with Down syndrome and compared them with euploid fetuses. Patients were referred for an increased risk of aneuploidy and evaluated for the presence of structural defects, a nuchal fold, short long bones, pyelectasis, an echogenic intracardiac focus, and hyperechoic bowel. All fetuses underwent amniocentesis at the time of sonographic assessment. The sensitivity, specificity, and likelihood ratios for markers were calculated both as nonisolated and isolated findings. **Results.** There were 164 fetuses with Down syndrome and 656 euploid fetuses. The presence of any marker resulted in sensitivity for the detection of Down syndrome of 80.5% with a false-positive rate of 12.4%. The absence of any markers conferred a likelihood ratio of 0.2, decreasing the risk of Down syndrome by 80%. As an isolated marker, the nuchal fold had an "infinite" likelihood ratio for Down syndrome; a short humerus had a likelihood ratio of 5.8, whereas structural anomalies had a likelihood ratio of 3.3. Other isolated markers had low likelihood ratios because of the higher prevalence in the unaffected population. The likelihood ratios for the presence of 1, 2, and 3 of any of the markers were 1.9, 6.2, and 80, respectively. **Conclusions.** Although an isolated marker with a low likelihood ratio may not increase a patient's risk of Down syndrome, the presence of such a marker precludes reducing the risk of aneuploidy. Clusters of markers appear to confer a higher risk. **Key words:** aneuploidy risk assessment; fetal Down syndrome markers; genetic sonogram; prenatal sonography; trisomy 21.

Abbreviations

BPD, biparietal diameter; DS, Down syndrome; EIF, echogenic intracardiac focus; LR, likelihood ratio

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Neonates with Down syndrome (DS) have a variety of physical features that are potentially detectable by prenatal sonography, including redundant skin on the neck, cardiac abnormalities, short stature, and gastrointestinal anomalies. Many of these features can be identified in the fetus between 15 and 20 weeks' gestation, making sonography an effective tool in the prenatal identification of fetuses with DS.¹⁻¹⁷ The clinical utility of sonography in this endeavor has been hotly debated since its inception.¹⁸⁻²⁰ It is undeniable that certain physical features of fetuses with DS can be identified sonographically. A few of these features represent actual structural abnormalities that have clinical consequences regardless of karyotype. Most, however, are considered traits or markers that often have no serious clinical importance with the exception of

their relationship with aneuploidy. To make matters more complicated, these features may be transient, resolving by the third trimester of gestation.^{21,22} Although each of the markers has fair sensitivity for DS, several of them, most notably a short femur, pyelectasis, and an echogenic intracardiac focus (EIF), occur quite frequently as isolated findings in the unaffected population. This further flames the controversy of obstetric sonography in the detection of DS, especially in the low-risk patient.²³ Although there is an ongoing debate regarding the clinical use of these markers in low-risk patients, the ability to lower the risk of aneuploidy in high-risk patients who have normal sonographic findings has been gaining momentum.^{2-5,7,12-16}

In this article, we report our prospective experience on the genetic sonogram and its clinical use, based on a large group of consecutive second-trimester fetuses with DS and control fetuses with normal karyotypes. We evaluated the significance of the sonographic markers as both isolated and nonisolated findings and calculated the likelihood ratios (LRs) with which the a priori risk may be adjusted by using the Bayes theorem to determine a patient's specific risk of carrying a fetus with DS.^{24,25} This allows parents to consider their individual risk estimate of carrying a fetus with DS and to decide whether to pursue amniocentesis, a procedure that carries a small but definite risk of pregnancy loss.

Materials and Methods

This study was done over an 11-year period between 1990 and 2000. The study group comprised consecutive fetuses with DS by karyotype who were initially referred to our facility for sonography and amniocentesis because of an increased risk of aneuploidy based on maternal serum screening results, maternal age, or family history. The control group comprised euploid fetuses by karyotype referred for the same evaluation on the basis of the same indications.

Each fetus underwent a sonographic examination between 15 and 20 weeks' gestation followed by amniocentesis for fetal karyotype. The findings of the sonography were prospectively recorded in the medical record before the knowledge of karyotype. The presence or absence of sonographic markers was determined prospectively and documented in the medical record at the time of the original scan.

Fetuses referred to our laboratory for sonograms specifically for the presence of suspected abnormalities or markers detected by outside scans or with known karyotypes were excluded from the study. Fetuses who did not undergo amniocentesis in our laboratory in the 15- to 20-week gestational age window were also excluded. Patients who had a genetic sonogram and subsequently returned for their amniocentesis after counseling were also removed from the study group.

The study was conducted over 4 consecutive stages: stage 1, January 1, 1990, through August 31, 1991; stage 2, September 1, 1991, through December 31, 1993; stage 3, January 1, 1994, through December 31, 1996; and stage 4, January 1, 1997, through December 31, 2000. The sonographic markers evaluated in stage 1 did not include the EIF or hyperechoic bowel. In stage 2, hyperechoic bowel was included. In stages 3 and 4, all the described markers were evaluated (see below). All scans were done with a 128XP or Sequoia system (Acuson, a Siemens Company, Mountain View, CA) or an ATL HDI 5000 system (Philips Ultrasound, Bothell, WA) with a variable-focus transducer (3.5–5 MHz).

All fetuses with trisomy 21 by karyotype based on amniocentesis done at the time of the initial sonogram made up the study group. The control fetuses were chosen with a 4:1 ratio to the study group and represented a consecutive sample of fetuses scanned over each of the 4 stages of the study. These fetuses all had normal karyotypes determined by amniocentesis at the time of the initial scan done in our laboratory. All fetuses in this study were prospectively evaluated in the same manner. Outcomes were obtained by review of the medical records.

Each sonographic examination included a structural fetal survey, which was as detailed as possible given the limitations of gestational age. Biometric measurements obtained included biparietal diameter (BPD) and femoral and humeral lengths, measured by electronic calipers. The femur length was considered short if the ratio of the measured to expected femoral lengths was 0.91 or less (expected femoral length = $-9.3105 + 0.9028 \times \text{BPD}$).²⁶ The humeral length was considered short if the ratio of the measured to expected lengths was less than 0.90 (expected humeral length = $-7.9404 + 0.8492 \times \text{BPD}$).²⁷ These formulas are based on previous studies published from this laboratory; however, the

femur length formula was derived by using data from fetuses with DS scanned before this study began. The humeral length formula was developed by using data from fetuses with DS scanned predominantly before the current study group; however, it did include 2 fetuses from the current study group who were evaluated in early 1990. Data from the fetuses in the first 3 stages of the study have been used in 3 previously published studies in which the genetic scoring index was evaluated.^{1,2,4} In this study, we focused on the development of LRs for the sonographic findings as isolated and nonisolated entities as well as the clinical ramifications that the sonographic findings have.

Each fetus was prospectively evaluated for the presence of a nuchal fold of 6 mm or greater.²⁸⁻³¹ A nuchal fold measuring between 5 and 5.9 mm was considered "borderline." For the purposes of this study, the data were examined with the use of both thresholds. The nuchal fold was measured in a standard fashion by a modified axial view of the fetal head, which included the cerebral peduncles and cerebellum, and placement of calipers from the outside of the occipital bone to the skin edge.

An EIF was considered present when there was a discrete dot in either cardiac ventricle as bright as bone.^{32,33} Hyperechoic bowel was present when the fetal bowel was as bright as bone.³⁴ Pyelectasis was present when the anteroposterior diameter of the renal pelvis was 4 mm or greater.³⁵ Major structural abnormalities included ventriculomegaly, heart defects, and other anatomic malformations. Cystic hygromas were considered equivalent to a thickened nuchal fold.

The sensitivity was calculated as the proportion of cases with positive test results. The false-positive rate was calculated as the proportion of control fetuses with positive test results; this is equivalent to 1 - specificity. The LR was calculated as the sensitivity/false-positive rate.

Statistical analyses were performed by SAS software (SAS Institute Inc, Cary, NC). Comparisons between groups were made with χ^2 tests.

Results

Between 1990 and 2000, 164 consecutive fetuses with DS scanned between 15 and 20 weeks' gestation were identified. The karyotypes were based on amniocentesis performed at the time

of the sonographic evaluation. These were compared with 656 fetuses with normal karyotypes determined by amniocentesis and scanned over the same gestational age window in the same manner. The case-control ratio was 1:4. In stage 1, there were 26 cases and 104 controls; stage 2 had 27 cases and 108 controls; stage 3 had 62 cases and 248 controls; and stage 4 had 49 cases and 196 controls.

The mean gestational age for the fetuses was 16.4 weeks for both the fetuses with DS and the control fetuses ($P = .7$). The mean maternal age for women carrying fetuses with DS was 36.7 years, and the mean age for women carrying control fetuses was 36 years ($P = .06$).

The indications for amniocentesis and sonographic evaluation included the following:

1. Advanced maternal age: DS cases, 128 (78.1%) of 164, compared with controls, 544 (82.9%) of 656;
2. Abnormal serum screen results increasing the risk of aneuploidy: DS cases, 44 (26.8%) of 164, compared with controls, 101 (15.4%) of 656;
3. Family history of DS: DS cases, 1 (0.6%) of 164, compared with controls, 12 (1.8%) of 656; and
4. Elevated α -fetoprotein level: DS cases, 1 (0.6%) of 164, compared with controls, 17 (2.6%) of 656.

Several patients had more than 1 indication listed on the referral and are listed accordingly.

Table 1 shows the sensitivity, 1 - specificity (false-positive rate), and LRs for the detection of DS based on the presence of various markers. The presence of any marker resulted in sensitivity for the detection of DS of 80.5% with a false-positive rate of 12.4%. The presence of any markers resulted in an LR of 6.5 for DS. Conversely, these data also showed that the absence of any markers (normal genetic sonogram) resulted in an LR of 0.2 for DS, which decreased the a priori risk of DS by 80%.

The most sensitive sonographic markers for DS included the nuchal fold, short humerus and femur, and an EIF. However, the false-positive rate was also the highest for a short femur and an EIF, resulting in lower LRs.

Of all the sonographic markers, any finding of a nuchal fold carried the highest LR for DS. A

Table 1. Likelihood Ratios for Sonographic Markers

Marker	All Cases			Isolated Markers		
	DS, n (%)	Control, n (%)	LR (CI)	DS, n (%)	Control, n (%)	LR (CI)
Nuchal fold ≥ 6 mm	71/164 (42.3)	3/656 (0.5)	94.7 (30.2–296.7)	6/164 (3.7%)	0/656 (0%)	NC
Nuchal fold ≥ 5 mm	77/164 (47.0)	5/656 (0.8)	61.6 (25.3–149.7)	ND	ND	ND
Short humerus	73/150 (48.7)	12/579 (2.1)	23.5 (13.1–42.1)	3/150 (2.0)	2/579 (0.4)	5.8 (0.98–34.3)
Short femur	88/164 (53.7)	35/656 (5.3)	10.1 (7.1–14.3)	7/164 (4.3)	24/656 (3.7)	1.2 (0.51–2.7)
Hyperechoic bowel	18/138 (13.0)	5/552 (0.9)	14.4 (5.4–38.1)	0/138 (0)	4/552 (0.7)	NC
EIF	38/111 (34.2)	19/444 (4.3)	8.0 (4.8–13.3)	6/111 (5.4)	17/444 (3.8)	1.4 (0.6–4.3)
Pyelectasis	35/164 (21.3)	16/656 (2.4)	8.8 (5.0–15.4)	5/164 (3.1)	13/656 (2.0)	1.5 (0.6–4.3)
Anomaly	44/164 (26.8)	8/656 (1.2)	22 (10.6–45.8)	5/164 (3.1)	6/656 (0.9)	3.3 (1.0–10.8)
Any marker	132/164 (80.5)	81/656 (12.4)	6.5 (5.3–8.1)	ND	ND	ND
No abnormality	32/164 (19.5)	575/656 (87.7)	0.22 (0.16–0.30)	ND	ND	ND

Isolated humerus denominator includes missing humeri. Isolated hyperechoic bowel included periods 2, 3, and 4. Isolated EIF includes periods 3 and 4. CI indicates 95% confidence interval; NC, not calculable; and ND, not determined.

nuchal fold of 6 mm was associated with an LR of 94.7. When a threshold of 5 mm or greater was used, the LR for DS was 61.6.

A short humerus carried the second highest LR for DS. A short humerus was identified in 48.7% of fetuses with DS compared with 2.1% of control fetuses, yielding an LR of 23.5.

Major structural anomalies were found in 44 (26.8%) of 164 fetuses with DS compared with 8 (1.2%) of 656 control fetuses, yielding an LR of 22. Forty-four fetuses with DS had at least 1 structural malformation, including 29 heart defects and 16 fetuses with ventriculomegaly. Four fetuses with DS were hydropic, and 1 each had a non-hydronephrotic renal abnormality, a small stomach, and a clubfoot.

The presence of at least 1 of these 3 markers, a nuchal fold, short humeral length, and an anomaly, resulted in sensitivity of 65.2% for the detection of fetal DS (107 of 164) with specificity of 96.8% (635 of 656). As shown in Table 2, the LRs for the presence of 1, 2, and 3 of any of the markers were 1.9, 6.2, and 80, respectively.

Table 1 also shows the sensitivity, false-positive rate, and LRs for the detection of DS for the same sonographic markers when they were seen as isolated findings. As an isolated finding, the nuchal fold retained the highest LR for aneuploidy; because there were no control fetuses with this finding, the LR based on our data was not calculable (infinite). It is important to note, however, that this finding usually occurs with other markers of aneuploidy and was isolated only 8% of the time when it was present. An isolated short humerus had the next highest LR for aneuploidy (5.8) and was isolated just 6% of the time when it was seen. An anomaly was an iso-

lated finding in 21% of fetuses in which an anomaly was detected and carried an LR of 3.3 for aneuploidy.

Although a short femur is one of the most sensitive markers for detecting DS, it is also the least specific. An isolated short femur occurred in 25% of fetuses in which a short femur was detected. An isolated short femur was equally prevalent in the population with DS and the euploid population, yielding an LR of 1.2 when found as an isolated marker. Hyperechoic bowel was not present as an isolated finding in any fetus with DS. An EIF had a high false-positive rate and was isolated 40% of the time when it was seen, resulting in an LR of only 1.4. The same is true for pyelectasis, in which 35% of patients had pyelectasis as the only finding, resulting in an LR of 1.5.

As isolated findings, the femoral length, pyelectasis, and EIF have low LRs because of the similar prevalence of the isolated markers in the euploid population compared with the population with DS. If, however, the femoral length, EIF, hyperechoic bowel, and pyelectasis were evaluated in such a manner that at least 2 of these were considered as positive findings, then an additional 7 fetuses with DS would be identified (114 of 164) which would result in overall detection of 69.5% of fetuses with DS, with specificity of 96.5% (633 of 656).

From a different perspective, if the nuchal fold, a structural anomaly, and a short humerus were excluded, because each is considered sufficient to exceed the commonly accepted threshold for offering amniocentesis, then the LR for the presence of at least 2 of the 4 remaining markers (pyelectasis, EIF, hyperechoic bowel, and short femur) would be 14 for the detection of fetal DS.

We have not been able to evaluate the combination of 2 or more specific markers in more detail because of the small number of patients with any given combination of markers. It is evident, however, that the most highly correlated markers were short humerus and femur, with a correlation coefficient of 0.71. As noted previously, the LR of an isolated short femur was 1.2, and that for an isolated short humerus was 5.8. When the combination of a short femur and humerus without additional markers was evaluated, the LR was reduced to 4 for fetal DS. The nuchal fold and humerus had a correlation coefficient of 0.52. Other combinations had correlation coefficients of less than 0.5.

The sensitivity and specificity of these markers for detecting fetuses affected by DS did not vary significantly based on gestational age. In fetuses between 15 and 17 weeks of age (110 fetuses with DS and 463 control fetuses), the sensitivity for the presence of any marker for the detection of DS was 80% with specificity of 88.1%, whereas for fetuses between 17 and 20 weeks' gestation, the sensitivity for detecting DS was 81.5% with specificity of 86.5%. The difference in sensitivity was not statistically significant ($P = .8$). Although the specificity was somewhat higher in the earlier gestational age window, this difference did not reach statistical significance ($P = .6$).

The prevalence values of the markers in the final (fourth) stage of the study have not been included in any prior report; therefore, they are also reported separately. The prevalence values of the nuchal fold, short humerus, anomalies, and hyperechoic bowel were not statistically different in fetuses with DS and control fetuses between this fourth period and the earlier study stages. In stage 4, the prevalence of the EIF increased to 16% from 5.8% ($P < .05$); the prevalence of pyelectasis increased to 9.4% from 4.9% ($P < .05$); and the prevalence of a short femur increased to 18% from 13.7% ($P = .02$). In the fourth period, the sensitivity and specificity for detecting DS were as follows for the following markers: nuchal fold, 37% and 99.5%; humerus, 50% and 97%; femur, 53% and 91%; hyperechoic bowel, 4% and 98%; EIF, 44% and 91%; pyelectasis, 31% and 96%; and anomalies, 24% and 97%. The total detection rate for DS on the basis of any marker in the fourth quarter was 86% with specificity of 76%. From a different viewpoint, if positive findings included an abnormal nuchal fold, a major anomaly, or at least 2 of the other

Table 2. Likelihood Ratios of Any 1, 2, or 3 Markers

No. of Markers	DS (n = 164)	Control (n = 656)	LR	CI
0	32	575	0.2	0.16–0.30
1	32	66	1.9	1.3–2.9
2	20	13	6.2	3.1–12.1
3	40	2	80	19.5–327.6
4	28	0	ND	ND
5	9	0	ND	ND
6	3	0	ND	ND

Nuchal fold was 6 mm or greater. CI indicates 95% confidence interval; and ND, not determined.

(minor) markers, the sensitivity and specificity for the fourth period would be 61% and 93%, respectively.

Discussion

It has been traditional to consider an individual with a risk of fetal DS of 1/270 or greater as “high risk” and those with risk below this threshold as “low risk.” In accordance with those principles, amniocentesis is generally offered to those individuals whose risk of aneuploidy is 1/270 or greater based on advanced maternal age, serum triple screening, or both.³⁶ The sonographic markers have provided a method of further evaluating the fetus for morphologic signs of DS to further refine each patient's individual risk of having an affected fetus. With the use of the Bayes theorem, the a priori risk of carrying a fetus with DS (risk based on serum screening or maternal age) can be multiplied by the LR of the presence of a sonographic finding, resulting in a new risk (posterior risk) estimate for carrying a fetus with DS.^{24,25} This approach of refining risk by using sonography has gained momentum and popularity among patients at a high baseline risk of carrying a fetus with DS.

Our data show that detailed sonography in the second trimester that yields normal findings (i.e., no markers) can reasonably reduce the risk of fetal DS in high-risk patients. In this study, 80.5% of fetuses with DS had at least 1 sonographic finding compared with 12.4% of control fetuses. Conversely, 19.5% of fetuses with DS had normal findings on the genetic sonogram (no markers), compared with 87.7% of control fetuses. A scan with normal results yielded an LR of

0.2, which translates clinically into an 80% reduction of the a priori risk of carrying a fetus with DS. This revised risk estimate allows the parents to decide, on the basis of their individual risk assessment, whether to pursue invasive testing to obtain a definitive karyotype. Nyberg and colleagues⁸ reported a negative LR of 0.36 for DS. Devore¹⁷ reported a negative LR of 0.11 to 0.42 depending on the sonographic markers used to identify fetuses with DS. This is in a range similar to others, in which the LR of negative or normal results ranged from 0.11 to 0.43.^{2-5,7,12-16} Smith-Bindman et al¹⁸ disagreed and reported that the negative LR was not low enough to decrease the risk of a fetus's having DS. This may be because in their analysis, the negative LRs were based on the absence of an isolated marker, not the absence of all markers. Indeed, if one were to calculate the negative LR from their data looking at all markers, the negative LR would be 0.33.^{18,37} One can reasonably conclude that in experienced hands, genetic sonography in which none of the markers for aneuploidy is identified can reduce the risk of carrying a fetus with DS by 60% to 80%. This may be the singularly most clinically useful ramification of the genetic sonogram, because many women are opting to decline traditional recommendations for amniocentesis based on age alone.^{10,38}

The difficulty is in counseling families when markers are found. This is especially true when the marker is isolated or in a patient at previously low risk of DS. Our LRs for isolated findings are comparable with those reported by Nyberg et al.⁸ They are also not dissimilar to those reported in a meta-analysis on the use of the second-trimester sonogram for the detection of DS by Smith-Bindman et al,¹⁸ although our conclusions differ markedly as to the clinical relevance of the findings (Table 3).

The markers with the highest LRs for DS more often are clustered with other markers and are present in isolation in only a few instances. The challenge that arises when an isolated marker with high sensitivity but a low LR is encountered is how to translate the finding in a clinically useful manner. Although an individual isolated marker may not carry a markedly increased risk of DS, this does not negate the clinical relevance of the finding. Many parents at increased risk of carrying a fetus with DS on the basis of maternal age or abnormal serum test results use the findings on the genetic sonogram to adjust their

a priori risk of having an affected fetus. Although an isolated short femur or other marker with a low LR will not substantially increase the risk of carrying a fetus with DS, neither can the estimated risk be reduced. The patient at higher risk of aneuploidy who has a fetus with a single marker such as pyelectasis, a short femur, or an EIF will have a revised risk estimate that is essentially unchanged from her a priori risk. In that circumstance, amniocentesis would be recommended should prenatal diagnosis be desired. Findings such as a thickened nuchal fold, a short humerus, a major anatomic abnormality, and any cluster of markers will carry higher LRs and will further raise the patient's risk of carrying a fetus with DS. This may prompt the parents to consider the option of invasive testing.

The importance and optimal course of action in a low-risk patient with a marker on prenatal sonography are controversial and not well established. The results of this study aid in interpreting the clinical importance of a marker in this group of patients. The Bayes theorem can also be used to assess risk in patients at low risk of aneuploidy. If an isolated marker with an LR close to 1 is found (a short femur, EIF, or pyelectasis), the patient's risk of having an affected fetus changes only minimally from her a priori risk and is probably not clinically relevant. The patient's revised risk of carrying a fetus with DS would remain below the commonly accepted threshold for recommending amniocentesis; therefore, offering invasive testing would not be warranted. In our opinion, within the current paradigm of practice, an extensive discussion of risk revision need not be undertaken unless the revised risk estimate exceeds the threshold for offering invasive testing. This principle is similar to that based on counseling for advanced maternal age or serum screening results. In the event that a patient has declined serum screening and is still eligible on the basis of gestational age, a discussion of the components of risk assessment may be warranted. If a patient at low risk is found to have a thickened nuchal fold, a major anomaly, a short humerus, or an aggregate of markers, the pattern of findings may result in a high enough LR that the revised risk estimate exceeds the commonly accepted threshold for offering amniocentesis. In this case, correlation with maternal serum screening to establish an optimal a priori risk estimate would be recommended, and the patient should be made aware of the findings.^{39,40}

Table 3. Comparison of Studies

Isolated Marker	LR			
	Nyberg et al ⁷	Nyberg et al ⁸	Smith-Bindman et al ¹⁸	This Study
Major anomaly	25	ND	ND	3.3
Nuchal fold	18.6	11	17	NC
Short humerus	2.5	5.1	7.5	5.8
Short femur	2.2	1.5	2.7	1.2
Hyperechoic bowel	5.5	6.7	6.1	Not seen isolated
Pyelectasis	1.6	1.5	1.9	1.5
EIF	2	1.8	2.8	1.4

NC indicates not calculable; and ND, not determined.

If the revised risk remains elevated above the commonly accepted threshold for offering amniocentesis, the procedure should be offered to the patient when prenatal diagnosis is desired.

Although specific combinations of the markers with lower LRs (hyperechoic bowel, short femur, EIF, and pyelectasis) could not be evaluated because of the small numbers of patients, the presence of 2 or more of these markers resulted in an LR of 14. This suggests that the presence of several markers that might not be of concern in isolation carries much more importance when they occur in aggregates. This is in agreement with the work of Sohl et al,¹⁴ who noted that clusters of markers greatly increased the likelihood of a karyotypic abnormality compared with the presence of a single marker. In contrast, the presence of short long bones that involve both the humerus and the femur appears to be less important than the finding of an isolated short humerus. This may possibly reflect the relative contribution of constitutionally small individuals.

In prior publications, we devised an arbitrary scoring index in which markers considered "major" were given a score of 2 (nuchal fold and major anomaly) and the other markers were considered "minor" and were each given a score of 1 (short femur, short humerus, EIF, pyelectasis, and bright bowel). We then suggested that amniocentesis was indicated when the sonographic score was 2 or higher. Using the scoring index as described, we were able to identify 75% of fetuses with DS, with a false-positive rate of 5.7%.⁴ The overall results using the scoring index or LRs for risk assessment are remarkably similar. This is in accord with the work of Winter et al,⁴¹ who compared the use of the scoring index (our data) with the use of LRs (their data) and found remarkably similar results as well. With

either method, a minor marker in isolation should not be enough to warrant invasive testing in a low-risk patient. On the other hand, a minor marker may be the basis by which parents at higher a priori risk decide to reconsider invasive testing.

A limitation of this study is that we included only patients at increased risk of aneuploidy who had sonography immediately followed by amniocentesis for karyotype. This reflects only a portion of women who have sonography at our facility and does not include any information on patients who declined amniocentesis and subsequently may have had an infant with DS. Conversely, we excluded patients who chose to have amniocentesis on the basis of the presence of sonographic markers. We have applied our LRs to all patients who had sonographic markers identified during their scans. We do recognize that these data were generated on high-risk patients and are being used to readjust risk estimates on all patients. This is based on an assumption that the prevalence of markers in fetuses with DS does not vary depending on the age and serum screening status of their mothers. We did show that a thickened nuchal fold is a powerful marker for DS in low-risk patients in a previous study, which showed that fetuses with a nuchal fold of 6 mm or greater in women younger than 35 years with a normal maternal serum α -fetoprotein level were affected 24% of the time.⁴² Further study in this area is necessary to confirm this.

Another limitation is the difference between the results from the fourth study group compared with those of the earlier periods in our study. There was a higher prevalence of pyelectasis and EIF in the fourth period, which resulted in both a higher detection rate of DS (sensitivity, 86%) and lower specificity (76%). It is possible

that this difference is due to the fact that the data in this study span 10 years, and the quality of sonographic machines and our awareness of these findings have increased over the years. Although the resultant higher false-positive rate may be disturbing, the use of LR (particularly for isolated minor markers) will not alter many patients' baseline risk appreciably and therefore will not change their risk of fetal DS. In most low-risk patients, only the nuchal fold, a major anomaly, or at least 2 of the other (minor) markers would likely change a patient's risk enough to warrant invasive testing.

Sonography cannot be used to diagnose or exclude aneuploidy. It provides a noninvasive means by which to adjust the a priori risk on the basis of a variety of sonographic features. The LRs derived in this data set can be used to adjust the a priori risk of the patient's carrying a fetus with DS. This allows the parents to balance the risk that their fetus may have DS with the risk of losing the pregnancy as a result of an invasive procedure to determine karyotype. Although traditionally, a threshold of 1/270 has been used to offer invasive testing, the ultimate decision concerning prenatal diagnosis must be individual. The potential of losing a pregnancy from a complication of amniocentesis is not equivalent to giving birth to a child with DS, and each outcome carries a different degree of devastation depending on the couple involved.

We believe that there are enough cumulative data to suggest that amniocentesis for advanced maternal age alone is no longer appropriate in the new millennium. We envision a practice paradigm in which risk assessment for DS is based on first- and second-trimester screening with biochemical markers and sonography to provide each patient with an individual risk assessment before deciding on whether to pursue invasive testing.

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