

Age-adjusted ultrasound risk assessment for fetal Down's syndrome during the second trimester: description of the method and analysis of 142 cases

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ABSTRACT

Objective To describe and test a method of individual risk assessment for fetal Down's syndrome based on maternal age and second-trimester ultrasound findings.

Design A case-control study of 142 fetuses with Down's syndrome was compared with 930 control fetuses with normal karyotype. All patients underwent second-trimester ultrasound at a single institution with a standardized ultrasound protocol without knowledge of fetal karyotype. Age-adjusted ultrasound risk assessment (AAURA) for Down's syndrome was performed by multiplying the a priori risk, based on maternal age, with likelihood ratios resulting from the presence or absence of specific ultrasound findings for each patient. Individual ultrasound findings were assigned likelihood ratios (LR) as follows: structural abnormality (LR 25), nuchal thickening (LR 18.6), echogenic bowel (LR 5.5), shortened humerus (LR 2.5), shortened femur (LR 2.2), echogenic intracardiac focus (LR 2), and renal pyelectasis (LR 1.6). A normal ultrasound was assigned a LR of 0.4.

Results One or more ultrasound markers were identified in 68.3% (97) of fetuses with Down's syndrome compared to 12.5% of fetuses with normal karyotype. Among fetuses with positive ultrasound, 31% of those with Down's syndrome and 80% of those with normal karyotype showed a single non-structural finding. Using AAURA and a threshold of 1 : 200, 74% (105 of 142) of fetuses with Down's syndrome were identified, including 61.5% (24 of 39) from women aged less than 35 years, 67.2% (45 of 67) from women aged 35–39 years inclusively, and 100% (36 of 36) from women aged 40 years or older. AAURA of 930 fetuses with normal karyotype showed an overall false-positive rate of 14.7%, including 4% (21 of 519) from women aged less than 35 years, 12.5% (42 of 337) from

women aged 35–39 years inclusively, and 100% from women aged 40 years or older.

Conclusions AAURA permits improved individual counselling regarding the risk of fetal Down's syndrome following a second-trimester sonogram. For low-risk women under age 35 years, ultrasound assessment can identify over half of the affected fetuses with Down's syndrome with an acceptable false-positive rate (4%). For women aged 35–39 years, a normal ultrasound can substantially reduce the risk of unnecessary amniocentesis (12.5% from 100%) but will also miss approximately one-third of affected fetuses. Biochemical screening of maternal serum is also suggested for this group. Based on their high a priori risk, women aged 40 years or more should consider genetic amniocentesis regardless of a normal ultrasound.

INTRODUCTION

A variety of ultrasound findings may be seen in fetuses with Down's syndrome, including both structural abnormalities and non-structural abnormalities or 'markers'^{1–7}. In a previous series from this institution of 94 fetuses with Down's syndrome, one or more distinctive ultrasound findings were observed in 25% of fetuses examined during the second trimester⁷. Non-structural findings of nuchal thickening and echogenic bowel were found to be the most common ultrasound findings in the second trimester. However, that review did not consider other abnormalities which have now been associated with Down's syndrome, such as shortened femur or humerus length^{7–10}, renal pyelectasis¹¹ or echogenic intracardiac focus (echogenic chordae tendineae)^{12–14}.

Counselling of patients following a second-trimester ultrasound examination may be difficult, especially when non-structural markers are identified in patients otherwise considered at low risk for fetal chromosome abnormalities. Ultrasound risk assessment should ideally incorporate the a priori risk, based on maternal age, as this risk rises exponentially with age¹⁵. Sufficient data are now available to estimate the combined risk of fetal Down's syndrome based on ultrasound findings and maternal age. In a recent monograph, Snijders and Nicolaides¹⁵ assigned likelihood ratios (LR) for various ultrasound findings based on a literature review and their own extensive experience. Likelihood ratios were approximated as isolated findings, making it possible to multiply each risk estimate when more than one finding was present.

We describe a method for patient-specific risk assessment which we have termed age-adjusted ultrasound risk assessment (AAURA) for Down's syndrome which takes into account the presence or absence of ultrasound findings as well as the a priori risk based on maternal age. This method was applied to 142 fetuses with Down's syndrome examined during the second trimester at a single institution, and compared with a cohort group of 930 fetuses with normal karyotype.

METHODS

We reviewed prenatal sonographic findings in 142 consecutive fetuses with trisomy 21 examined during the second trimester at a single high-risk center, studied from January 1990 to September 1996. In all instances, sonography was performed without knowledge of the karyotype and before genetic evaluation. Genetic, birth and pathology records were matched with ultrasound records to ensure inclusion of all fetuses with trisomy 21 who underwent prenatal ultrasound examination during the time period.

The mean maternal age was 36.2 years (SD 5.2 years, range 17–45 years). The mean menstrual age at examination was 16.8 weeks (SD 1.8 weeks, range 14–21 weeks). Patients were referred for a variety of clinical indications, most commonly advanced maternal age ($n = 108$). Other reasons for referral for ultrasound examination included abnormal 'triple screen' profile of α -fetoprotein (AFP), estriol and human chorionic gonadotropin (hCG) levels ($n = 18$); decreased AFP ($n = 7$); elevated AFP ($n = 2$); a family history of Down's syndrome or chromosomal abnormalities ($n = 2$); size/dates discrepancy ($n = 2$); and fetal screen ($n = 3$). Ten additional affected fetuses, referred because of abnormalities seen on an ultrasound examination at a different institution, were excluded from this study.

A comparison group of 930 consecutive fetuses was selected during a 5-month period in 1996 (May–October). The ultrasound protocol for these patients was identical to that of the study group and all sonograms were performed without knowledge of the fetal karyotype. The average maternal age of the comparison group was 32.7 years (SD 5.4 years, range 17–46 years). The mean menstrual age at

examination was 17.6 weeks (SD 1.9 weeks, range 14–21 weeks). Patients referred because of an abnormal ultrasound scan and/or abnormal fetal karyotype were excluded. Indications for ultrasound examination in these patients included confirmation of dates/fetal survey ($n = 386$), advanced maternal age ($n = 317$), abnormal 'triple screen' profile of AFP, estriol and hCG levels ($n = 96$); decreased AFP ($n = 7$); elevated AFP ($n = 23$); a family or personal history of congenital anomalies ($n = 36$); post-cerclage placement ($n = 9$), teratogen exposure ($n = 26$), size/dates discrepancy ($n = 20$); diabetes ($n = 6$); and vaginal bleeding ($n = 4$).

Ultrasound examination was performed by a systematic protocol. All patients were initially scanned by trained technologists, each certified by the Registry of Diagnostic Medical Sonographers (RDMS). Standard fetal biometry included measurements of head circumference, biparietal diameter, abdominal circumference, femur length and humerus length. Thorough anatomical survey included views of the brain (transthalamic, transventricular and transcerebellar views), spine, stomach, kidneys, urinary bladder, abdominal wall, face, heart and distal extremities. Measurements were obtained of the nuchal thickness (transcerebellar view) and renal pelvis in the anteroposterior dimension. All data were then entered into a computer. Images and the preliminary report were reviewed by one of four experienced sonologists, each with postgraduate training in high-risk obstetric ultrasound. Additional brief scanning of the patient by the sonologist was performed for confirmation of normal or abnormal findings. Genetic amniocentesis, when performed, was carried out later the same day in the perinatal department. Trisomy 21 was determined by genetic amniocentesis in all cases of Down's syndrome. In the control group, normal karyotype was determined by genetic amniocentesis in 455 cases and by clinical assessment after birth in 475.

Data analysis included only prospective ultrasound findings, recorded in the final ultrasound report, with the exception of echogenic intracardiac focus ('echogenic chordae tendineae'). Because this marker has only recently been associated with Down's syndrome^{13,14}, the original films were also retrospectively reviewed by two observers for its presence or absence, without knowledge of fetal karyotype. Abnormalities that were prospectively evaluated included nuchal thickening, echogenic bowel, shortened femur, shortened humerus, renal pyelectasis and 'structural' abnormalities. Structural abnormalities included cardiac defects, hydrops, cystic hygroma with internal septation, duodenal atresia and cerebral ventricular dilatation.

Criteria for abnormalities are shown in Table 1. Nuchal thickening was considered to be present when the nuchal fold measured more than 5 mm in the anteroposterior plane on standard off-axial views which include the cisterna magna and cerebellum¹⁶. Shortened femur and shortened humerus were determined by actual and expected measurements compared to the biparietal diameter, as previously reported¹⁰. The femur was considered to be shortened when the measured/expected ratio was

0.91 or less, and the humerus was considered to be shortened when the measured/expected ratio was 0.89 or less, based on formulas previously published¹⁰. Renal pyelectasis was considered when the renal pelvis of either kidney measured more than 3 mm in the anteroposterior plane. Echogenic bowel was subjectively interpreted as

moderate–markedly echogenic, corresponding to grades 2–3 in a previously described grading system⁵. Echogenic intracardiac focus was observed as a discrete bright focus within the heart, usually seen in the left ventricle.

The age-related (a priori) probability of Down's syndrome during the second trimester was derived from Snijders and Nicolaides¹⁵ and is expressed as odds (1 : _) in Table 2. For ages less than 20 years, the risk for a 20-year-old woman was utilized. The post-ultrasound (post priori) probability of Down's syndrome was determined by Bayes theorem, and can be expressed as $P(DS) = S \cdot AR / ((S \cdot AR) + FP \cdot (1 - AR))$ where AR = age-related probability, S = sensitivity of ultrasound scan and FP = false-positive rate. The probability was then expressed as an odds, calculated as $1/P(DS)$. As a more direct calculation, the post-ultrasound odds of Down's syndrome can also be shown to be $O(DS) = O(MA)/LR + 1 - 1/LR$ where O(MA) is the odds of Down's syndrome based on maternal age and LR is the likelihood ratio. Unless the risk is unusually high, this can be approximated as $O(DS) = O(MA)/LR$.

The likelihood ratio for each ultrasound marker is defined as sensitivity/false-positive rate as an isolated finding. Likelihood ratios have been reported by Snijders and Nicolaides¹⁵ as follows: nuchal thickening (LR 18.6), echogenic bowel (LR 5.5), shortened femur (LR 2.2) and renal pyelectasis (LR 1.6). Additional likelihood ratios were estimated for shortened humerus (LR 2.5), echogenic intracardiac focus (LR 2) and structural abnormality (LR 25). Since likelihood ratios were determined as independent factors for isolated findings, the overall likelihood ratio was determined by multiplication of likelihood ratios when

Table 1 Ultrasound criteria and likelihood ratios assigned for detection of trisomy 21. Asterisk indicates likelihood ratios assigned from data of Snijders and Nicolaides¹⁵ as an isolated finding. Likelihood ratios for other sonographic findings were assigned on the basis of prior experience from this institution

<i>Sonographic finding</i>	<i>Criteria</i>	<i>Likelihood ratio assigned</i>
Structural defect	cardiac defect, cystic hygroma with or without hydrops, cerebral ventricular dilatation	25
Nuchal thickening	> 5 mm in the anteroposterior plane	18.6*
Echogenic bowel	subjectively increased, grades 2 or 3	5.5*
Short humerus	observed/predicted ratio ≤ 0.89	2.5
Short femur	observed/predicted ratio ≤ 0.91	2.2*
Echogenic intracardiac focus	present or absent	2
Renal pyelectasis	> 3 mm in the anteroposterior plane	1.6*
Normal ultrasound scan	none of the above	0.4

Table 2 Maternal age-specific odds (1 : _) of fetal Down's syndrome during the second trimester based on non-structural findings

<i>Maternal age (years)</i>	<i>Pre-US odds (1 : _)</i>	<i>Normal US scan (1 : _)</i>	<i>Nuchal thickness (1 : _)</i>	<i>Echogenic bowel (1 : _)</i>	<i>Short humerus (1 : _)</i>	<i>Short femur (1 : _)</i>	<i>EIF (1 : _)</i>	<i>Renal pyelectasis (1 : _)</i>
20	1176	1960	63	214	511	470	588	735
21	1160	1933	62	211	504	464	580	725
22	1136	1893	61	207	494	454	568	710
23	1114	1857	60	203	484	446	557	696
24	1087	1812	58	198	473	435	544	679
25	1040	1733	56	189	452	416	520	650
26	990	1650	53	180	430	396	495	619
27	928	1547	50	169	403	371	464	580
28	855	1425	46	155	372	342	428	534
29	760	1267	41	138	330	304	380	475
30	690	1150	37	125	300	276	345	431
31	597	995	32	109	260	239	299	373
32	508	847	27	92	221	203	254	318
33	421	702	23	77	183	168	211	263
34	342	570	18	62	149	137	171	214
35	274	457	15	50	119	110	137	171
36	216	360	12	39	94	86	108	135
37	168	280	9	31	73	67	84	105
38	129	215	7	23	56	52	65	81
39	98	163	5	18	43	39	49	61
40	74	123	4	13	32	30	37	46
41	56	93	3	10	24	22	28	35
42	42	70	2	8	18	17	21	26
43	31	52	2	6	13	12	16	19
44	23	38	1	4	10	9	12	14

US, ultrasound; EIF, echogenic intracardiac focus

more than one marker was present. When the ultrasound examination is normal, the likelihood ratio is determined by the false-negative rate/specificity. Although Snijders and Nicolaides¹⁵ assumed a LR of 0.6 for a normal ultrasound scan, the current model of AAURA assumes a LR of 0.4 (higher sensitivity) based on previous sampling at this institution.

RESULTS

Among 142 fetuses with trisomy 21, one or more distinctive ultrasound findings were identified in 97 (68.3%). One or more 'structural' abnormalities were found in 31 (21.8%) fetuses: 15 with cardiac defect, 12 with cystic hygroma (five with cardiac defects), four with hydrops or hydrothorax and five with cerebral ventricular dilatation (one with additional cardiac defect) and one with suspected duodenal atresia. Twenty-four (77%) with structural abnormalities also had one or more non-structural markers.

A total of 160 non-structural ultrasound findings were obtained in 86 (60.6%) fetuses with Down's syndrome. Non-structural findings included 33 (23.2%) nuchal thickening, 28 (19.7%) echogenic bowel, 30 (21.1%) shortened femur, 27 (19%) shortened humerus, 24 (18%) echogenic intracardiac focus and 18 (12.7%) renal pyelectasis (Table 3). Among the 97 fetuses with distinctive ultrasound findings, 30 (31%) showed a single non-structural finding of nuchal thickening ($n = 6$), short femur ($n = 7$), short humerus ($n = 4$), echogenic intracardiac focus ($n = 8$), pyelectasis ($n = 3$) or echogenic bowel ($n = 2$).

Among the comparison group, one or more distinctive ultrasound findings were detected in 12.5% (116 of 930) of all patients (Table 3). Of these, 93 (80%) showed an

isolated non-structural finding of nuchal thickening ($n = 3$), echogenic bowel ($n = 5$), pyelectasis ($n = 24$), short femur ($n = 33$), short humerus ($n = 2$) or echogenic intracardiac focus ($n = 26$).

Ultrasound findings were independent of maternal age; one or more findings were present in 12.9% (67 of 519) of those less than 35 years, 11.9% (35 of 294) in those aged 35–38 inclusively, and 12% (14 of 117) in those aged 39 or more. Individual ultrasound findings included four (0.4%) nuchal thickening, eight (0.9%) echogenic bowel, 51 (5.5%) shortened femur, 43 (4.6%) shortened humerus, 11 (1.2%) echogenic intracardiac focus, 27 (2.9%) renal pyelectasis and three (0.3%) structural abnormalities.

The age-adjusted risk for Down's syndrome when a single non-structural ultrasound marker was identified is summarized in Table 2. When more than one ultrasound marker is present, AAURA requires multiplication of likelihood ratios and cannot be easily tabulated, since any combination of ultrasound markers is possible. The sensitivities of AAURA applied to the 142 fetuses with Down's syndrome are summarized in Table 4, and the false-positive rates for the 930 fetuses with normal karyotype are summarized in Table 5. Assuming a threshold value of 1 : 200 for recommending amniocentesis, AAURA detected 74% (105 of 142) of fetuses with trisomy 21 (Table 4) including 78.6% (81 of 103) from women 35 or older, and 61.5% (24 of 39) from women younger than 35. In the comparison group with normal karyotype, AAURA showed an overall false-positive rate of 14.7% (137 of 930) including 4% (21 of 519) for women aged less than 35, and 28.2% (116 of 411) for women aged 35 and older. The latter group yielded a false-positive rate of 12.5% (42 of 337) for women aged 35 to 39 years, inclusively, and 100% (74 of 74) for women aged 40 and older.

Table 3 Sonographic findings in 142 second-trimester fetuses with trisomy 21 compared to 930 fetuses with normal karyotype

Sonographic finding	Down's syndrome ($n = 142$)	Controls ($n = 930$)	Calculated likelihood ratio*	<i>p</i> Value
Structural defect	31 (21.8%)	3 (0.3%)	71	< 0.01
Nuchal thickening	33 (23.2%)	4 (0.4%)	58	< 0.01
Echogenic bowel	28 (19.7%)	8 (0.9%)	21.9	< 0.01
Short humerus	27 (19%)	11 (1.2%)	15.8	< 0.01
Short femur	30 (21.1%)	43 (4.6%)	4.6	< 0.01
Echogenic intracardiac focus	24 (17%)	33 (3.5%)	5.1	< 0.01
Renal pyelectasis	18 (12.7%)	27 (2.9%)	4.8	< 0.01
Any finding	97 (68.3%)	116 (12.5%)	5.4	< 0.01

*Sensitivity/false-positive rate

Table 4 Sensitivity of age-adjusted ultrasound risk assessment (AAURA) for Down's syndrome by maternal age and various thresholds for recommending amniocentesis

Maternal age (years)	<i>n</i>	Number of patients with positive screen (threshold)				
		1 : 100	1 : 150	1 : 200	1 : 250	1 : 300
< 35	39	21 (53.8%)	22 (56.4%)	24 (61.5%)	25 (64.1%)	27 (69.2%)
35–39	67	43 (64.2%)	45 (67.2%)	45 (67.2%)	48 (71.6%)	48 (71.6%)
40+	36	32 (88.9%)	36 (100%)	36 (100%)	36 (100%)	36 (100%)
All	142	96 (67.6%)	103 (72.5%)	105 (74%)	109 (76.8%)	109 (76.8%)

Table 5 False-positive rates of age-adjusted ultrasound risk assessment (AAURA) for Down's syndrome, categorized by maternal age and various thresholds of amniocentesis

Maternal age (years)	n	Number of patients with positive screen (threshold)				
		1 : 100	1 : 150	1 : 200	1 : 250	1 : 300
< 35	519	5 (1%)	7 (1.4%)	21 (4.0%)	26 (5.0%)	32 (6.2%)
35–39	337	29 (8.6%)	40 (11.9%)	42 (12.5%)	78 (23.1%)	78 (23.1%)
40+	74	45 (60.8%)	74 (100%)	74 (100%)	74 (100%)	74 (100%)
All	930	79 (8.5%)	121 (13%)	137 (14.7%)	178 (19.1%)	184 (19.8%)

Table 6 Risk of fetal Down's syndrome, expressed as odds (1 : _) categorized by maternal age and presumed sensitivity of ultrasound

	Age (years)											
	34	35	36	37	38	39	40	41	42	43	44	45
Age risk	342	274	216	168	129	98	74	56	42	31	23	18
Post-ultrasound risk												
sensitivity 10%, LR 1.02	334	268	211	164	126	114	72	55	41	30	23	18
sensitivity 20%, LR 0.91	376	301	237	185	142	114	81	62	46	34	25	20
sensitivity 30%, LR 0.80	430	344	271	211	162	123	93	70	53	39	29	22
sensitivity 40%, LR 0.68	501	401	316	246	189	114	108	82	61	45	33	26
sensitivity 50%, LR 0.57	601	481	379	295	226	172	129	98	73	54	40	31
sensitivity 60%, LR 0.45	751	602	474	368	283	214	162	122	91	67	49	38
sensitivity 70%, LR 0.34	1001	802	632	491	376	286	215	162	121	89	66	51
sensitivity 80%, LR 0.23	1501	1202	947	736	564	428	322	243	181	133	98	76
sensitivity 90%, LR 0.11	3002	2403	1893	1471	1127	855	643	485	362	265	195	151

LR, likelihood ratio of normal ultrasound scan for identification of trisomy 21, calculated as false-negative rate/specificity. False-negative rate = (1 – sensitivity), and specificity assumed to be 0.88 with the use of multiple ultrasound markers

Because the a priori risk is sufficiently high for women aged 40 years and older, a normal ultrasound scan cannot reduce the post priori risk below a threshold of 1 : 200 based on the current model of AAURA. This 'critical' maternal age for a normal ultrasound scan can be increased with the presumed sensitivity of ultrasound for detection of Down's syndrome (Table 6).

DISCUSSION

A growing number of ultrasound markers have been recognized that increase the risk for fetal Down's syndrome^{1–17}. Use of multiple markers increases the sensitivity of ultrasound for detection of Down's syndrome, but at the cost of a higher false-positive rate. An earlier study from this institution, using relatively few ultrasound markers, identified one or more distinctive findings in 25% of second-trimester fetuses with Down's syndrome and approximately 1% of normal fetuses⁷. In comparison, use of multiple ultrasound markers in an ultrasound 'panel' identified one or more distinctive findings in 68% of fetuses with Down's syndrome in the present study, but in 12.5% of normal fetuses. Not surprisingly, ultrasound findings were more likely to be isolated and non-structural in normal fetuses (80%) compared to those with Down's syndrome (31%).

Optimal risk assessment would take into account both the ultrasound findings and the a priori risk based on maternal age to determine a more precise risk. Until recently, however, insufficient data have been available to determine the precise risk for individual ultrasound

findings or the combination of ultrasound findings. The present study presents a model for estimating patient-specific risk for fetal Down's syndrome based on the presence or absence of multiple ultrasound findings, combined with maternal age. We have termed this method age-adjusted ultrasound risk assessment (AAURA). This individual risk estimate can be derived from the various tables provided here and elsewhere¹⁰, or can be easily calculated by a hand-held calculator.

An advantage of AAURA is that it permits the use of multiple ultrasound markers for fetal Down's syndrome, even for minor ultrasound findings that are not considered significant as an isolated finding. Individual ultrasound findings are not considered equally, but rather weighted by the strength of individual findings, expressed as a likelihood ratio. In a different approach, Benacerraf and colleagues have devised a scoring system that weights individual ultrasound findings by assigning a score of either 2 or 1^{18,19}. The likelihood ratios used in the current model of AAURA were largely taken from the work of Snijders and Nicolaides¹⁵, who estimated them from extensive analysis of multiple studies. As these authors did not report likelihood ratios for structural abnormalities, shortened humerus or echogenic intracardiac focus, these criteria were assigned relative values according to previous experience at this institution.

A major benefit of AAURA is the assignment of a patient-specific risk of fetal Down's syndrome when one or more ultrasound markers are identified. This benefit is most useful in women who otherwise would be considered at low risk on the basis of maternal age alone. For women

younger than 35 years, AAURA identified 61.5% (24 of 39) fetuses with Down's syndrome. Importantly, AAURA helped to minimize the overall false-positive screen in this group by assigning relatively low likelihood ratios to minor findings and incorporating a priori risk based on maternal age. As a result, AAURA was falsely positive in only 4% of women under age 35 years in this study.

Increasingly, a normal ultrasound scan has also been used to help reduce the risk of Down's syndrome for women who are 35 years or older and who wish to avoid genetic amniocentesis^{17,19-21}. Reduction of risk is most useful for women in an intermediate age group. For women aged 35-39 years, a normal ultrasound scan could reduce the rate of amniocentesis from 100% to 12.5%, but would also miss approximately one-third of affected fetuses, according to the current study. Because of their high a priori risk, women aged 40 or more remain at risk despite a normal ultrasound scan. This 'critical' maternal age at which amniocentesis should be recommended despite a normal ultrasound scan will necessarily vary with the presumed sensitivity and likelihood ratio of ultrasound (Table 6).

With a normal ultrasound scan, the current model of AAURA reduces the risk of Down's syndrome by approximately 60%, using a likelihood ratio (LR) of 0.4. This likelihood ratio is supported by the current study, which found that a normal ultrasound scan carried a sensitivity of 68% for any ultrasound marker (32% false-negative rate) and 12% false-positive rate (88% specificity), resulting in a likelihood ratio of 0.36 (32/88). Other centers may choose either higher or lower likelihood ratios for a normal ultrasound scan, based on their own experience. Two other studies^{19,20} using multiple sonographic markers reported a similar false-positive rate of 13%, but higher sensitivities of 86% and 87%. Using the sonographic scoring index method, Bromley and colleagues²² reported that a score of 1 or more showed a sensitivity of 83% but a higher false-positive rate of 17.5%. At the other extreme, Stoll and co-workers²³ reported that the sensitivity of the ultrasound scan for detection of Down's syndrome in a low-risk population was just 18.5% (10/54), although this series was completed prior to 1987 and looked only at structural malformations.

It is of interest to compare the assigned likelihood ratios in the current model of AAURA (Table 1) with the calculated ratios of sensitivity/false-positive rate in the current study (Table 3). Because the assigned likelihood ratios are based on isolated ultrasound findings, they are less than the calculated ratios (Table 3). However, the relative strength of each ultrasound finding is similar. For example, the calculated ratio for nuchal thickening (58) was the highest of any of the non-structural markers and was also assigned the highest likelihood ratio (18.6). Only the humerus length criterion showed a higher calculated ratio than might be expected from the likelihood ratio assigned to it.

A basic assumption of AAURA is that the ultrasound findings are independent of maternal age. Results of the present study support this assumption, as the false-positive

rate among the control group was found to be independent of maternal age. This observation is consistent with other studies that have shown that ultrasound findings and maternal age are independent¹⁵. It is not yet known whether ultrasound findings are also independent of maternal serum biochemical markers. A previous study from this institution among women with positive serum screens found the sensitivity of ultrasound for fetal Down's syndrome (50%)²⁴ to be similar to that of other studies of women with a normal screen. This limited information suggests that ultrasound and biochemical screening may be largely independent.

A valid concern of ultrasound screening for Down's syndrome is variation between centers and operator dependence. Because any positive ultrasound finding increases the risk, a thorough search for the ultrasound findings is necessary before concluding that the ultrasound scan is normal. A further problem of ultrasound screening is that many of the criteria used to assess the risk of fetal Down's syndrome depend on measurements that reach a certain threshold (Table 2). When measurements are borderline, as they often are, small differences in measurements can result in large differences in risk assessment. Also, the threshold approach does not account for increasing risk with the severity of the abnormality.

The current model of AAURA includes a number of assumptions that can be easily modified. For example, the assigned likelihood ratio for each ultrasound marker can be modified as needed. Also, additional ultrasound markers can be incorporated in the ultrasound 'panel'. Modifications of AAURA could account for any co-dependency of ultrasound findings if they are found in future studies. Future modifications of AAURA could also account for gradations in risk based on a range of measurements rather than a single threshold, as has been applied to nuchal translucency during the first trimester²⁵. When systematic differences are found between centers, multiples of the median (MoM) could be utilized.

We conclude that AAURA provides a framework for assessing the risk of fetal Down's syndrome following a second-trimester sonogram at 15-20 weeks. For low-risk women under age 35 years, AAURA can identify over half of the fetuses affected with Down's syndrome with an acceptable false-positive rate (4%). Ultrasound can also reduce the probability of fetal Down's syndrome for women in an intermediate age range (35-39 years), whereas women in the highest risk group (40 years or more in this study) should consider genetic amniocentesis regardless of a normal ultrasound scan. It is hoped that future screening will include both biochemical markers and ultrasound findings to report a single combined risk estimate.

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