Screening for fetal chromosomal abnormalities by maternal serum biochemistry and ultrasound examination of fetal morphology

Kurt Hecher, MD, Rosalinde Snijders, MSc, and Kypros Nicolaides, MRCOG

Harris Birthright Research Centre for Fetal Medicine, King's College Hospital Medical School, London, UK

The failure of screening studies based on maternal age to reduce substantially the birth incidence of chromosomally abnormal babies has stimulated the search for new methods of screening. In this paper we review the latest literature on the two new approaches to screening for fetal chromosomal abnormalities: maternal blood analysis and examination of the fetal anatomy by ultrasound. Preliminary results from maternal serum biochemistry screening indicate that detection of trisomy 21 is significantly improved, and application of biochemical testing may be expanded to the first trimester of pregnancy. Findings from studies on the association between fetal malformations and chromosomal abnormalities indicate that a high percentage of fetuses with an abnormal karyotype can be detected by ultrasound. In order to improve the detection rate and counsel parents appropriately, prospective studies are needed to determine the sensitivity and specificity of different markers in unselected populations of all ages. Information from such studies will also help us to avoid unnecessary anxiety and keep the fetal loss rate due to invasive procedures as low as possible.

Current Opinion in Obstetrics and Gynecology 1993, 5:170–178

Chromosomal abnormalities are important causes of perinatal death and childhood handicap. It is therefore not surprising that a high risk of a cytogenetic disorder is the most common indication for invasive prenatal diagnosis. However, screening for fetal chromosomal abnormalities on the basis of maternal age has not resulted in a substantial fall in the proportion of infants born with an abnormal karyotype [1]. The main reasons for this relative failure are that 1) less than 3% of chromosomally abnormal pregnancies have any risk factor that can be identified before conception, such as parental translocation, 2) screening on the basis of maternal age will identify only about 30% of autosomal trisomies [2•], and 3) there is poor uptake (generally less than 50%) of invasive fetal testing among the at-risk group [3]. Recently, two new approaches to screening have been introduced. The first is based on maternal blood analysis and the second on examination of the fetal anatomy by ultrasound.

Maternal serum biochemistry

In the mid-1980s, investigators reported an association between fetal trisomy 21 and low levels of maternal serum alpha-fetoprotein [4], high levels of human chorionic gonadotropin (hCG) [5], and low levels of unconjugated estriol [6]. Subsequently, it was calculated that if the 5% of the population that should be offered amniocentesis were selected not only on the basis of maternal age but also on the levels of alpha-fetoprotein, unconjugated estriol, and hCG, 60% rather than 30% of fetuses with trisomy 21 would be identified [7]. A recent review of biochemical screening discussed the role of pregnancy dating by ultrasound and the effects of maternal weight, multiple pregnancy, and insulin-dependent diabetes mellitus [8•]. The authors also discussed the controversy concerning the contribution of unconjugated estriol.

Abbreviation

CA-125—cancer antigen-125; **hCG**—human chorionic gonadotropin.

Prospective studies

Three prospective studies involving a total of more than 47,000 pregnancies [9••–11••] have confirmed the effectiveness of screening based on maternal age and the three serum markers at 15 to 22 weeks' gestation (Table 1). The detection rates for trisomy 21 were 48% to 58% with false-positive rates of 3.2% to 4.1%. The thresholds for positive results on screening were different in each study. Two studies included women of all ages [9••,10••], whereas one included only women under 35 years of age [11••].

In all patients with a positive result on screening, an ultrasound scan was performed and the pregnancy dating revised. Consequently 28% to 55% of the cases were reclassified as negative on screening; in this group, at least three women had trisomic fetuses. Wald *et al.* [9••] now recommend that correct dating of the pregnancy always be undertaken before biochemical screening.

One important finding in the study by Wald *et al.* [9••] was that the detection rate for trisomy 21 in the women under 37 years of age was 39%, whereas in those 37 years of age or more, it was 71%. Similarly, in a retrospective study of 142 pregnancies in which the fetuses were trisomic, the combination of maternal age and serum alpha-fetoprotein level was a more effective indicator for fetal trisomy in older than in younger women [2•]

New serum markers

Hogdall *et al.* [12] reported increased maternal serum cancer antigen-125 (CA-125) in 15 pregnancies in which the fetus has Down syndrome, as compared with 60 normal control pregnancies and suggested that CA-125 should be included as a potential marker in future trials. In contrast, Spencer [13•] examined 25 pregnancies in which the fetus has Down syndrome and 125 control pregnancies and concluded that maternal serum CA-125 is not a second trimester marker for Down syndrome. Spencer and Macri [14•] examined 23 pregnancies in which the fetus had Down syndrome and reported that a combination of free β-hCG, alpha-fetoprotein, and maternal age could detect 65% of the cases. Cuckle and Lilford [15] measured maternal serum pregnancy-associated plasma protein A concentrations in 18 pregnancies in which the fetus had Down syndrome at 15 to 20 weeks' gestation. The authors found no significant difference from the concentrations in 90 matched normal control pregnancies.

Other chromosomal abnormalities

Greenberg *et al.* [16•] reported on pregnancies with trisomy 18 and without open neural tube or ventral wall defects. The multiples of the median of alpha-fetoprotein, unconjugated estriol, and hCG were 0.65, 0.56, and 0.32, respectively. However, in some of the cases the levels of alpha-fetoprotein or hCG, or both were markedly increased. Therefore, when prospective screening is undertaken, the possibility of a bimodal distribution of alpha-fetoprotein and hCG levels should be considered.

Staples *et al.* [17•], in a study of 12 fetuses with trisomy 18 at 16 to 21 weeks' gestation and 390 normal control fetuses, reported that in the trisomic pregnancies decreased levels of all placental hormones existed, but the most powerful indicators for trisomy 18 were free β-hCG and unconjugated estriol. The authors used algorithms incorporating maternal age and several of the placental hormones to calculate a detection rate of 67%, with a false-positive rate of 3% for a maternal risk of 1:300. It should be noted, however, that on the basis of data provided on the trisomic fetuses, at least as many of them could have been detected by ultrasound because they had major malformations.

Saller *et al.* [18•] published an interesting study on second trimester serum markers in pregnancies in which the fetus has Turner's syndrome. They divided them into two groups: those with and those without hydrops. Although unconjugated estriol was markedly reduced (0.48 multiples of the median) in both hydropic and nonhydropic fetuses, hCG was increased in the hydropic group (3.84 multiples of the median), and decreased in the nonhydropic ones (0.52 multiples of the median). Pregnancies with hydropic fetuses with Turner's syndrome may therefore be detected as being at high risk for trisomy 21, whereas pregnancies with

Table 1. Prospective studies examining the value of maternal serum triple biochemistry testing during the second trimester of pregnancy

Study	Patients, *n*	Maternal age, *y (%)*	Risk cut-off level	Detection rate, *% (n)*	False positive, %	Odds of being affected with a positive result	Cut-off for redating, *d**	Initially screen positive, *n (%)*	Screen positive redated, %	After redating screen positive, *n (%)*	Acceptance rates for invasive testing, %
Wald *et al.* [9••]	12,603	≥37(4.8)	1:250†	48 (12/25)‡	4.1‡	1:43‡	≥17	731(5.8)	28	526(4.2)	75
Haddow *et al.* [10••]	25,207	≥37(2.0) ≥35(4.9)	1:190§	58 (21/36)	3.8	1:45	≥10	1661(6.6)	42	962(3.8)	79
Phillips *et al.* [11••]	9530	≥35(0.0)	1:274§	57(4/7)	3.2	1:76	≥10	686(7.2)	55	307(3.2)	70

*Discrepancy in gestation from ultrasonographic findings and last menstural period.
†At term.
‡Women < 37 years old: detection rate = 39%, false positive rate = 3.3%, odds of being affected = 1:56. Women ≥ 37 years old: detection rate = 71%, false positive rate = 20%, odds of being affected = 1:25.
§Second trimester.

nonhydropic fetuses with Turner's syndrome will appear at high risk for trisomy 18. The authors suggest that the morphologic defect of hydrops, rather than the aneuploidy itself, may be responsible for the elevated hCG levels.

Kaffe and Hsu [19•] compared three different study groups referred for amniocentesis. The indications were low levels of maternal serum alpha-fetoprotein, (n = 1098), high levels of alpha-protein (n = 45), and "maternal anxiety" between 30 and 33 years of age (n = 361). The overall frequency of chromosome anomalies was similar in the group with low alpha-fetoprotein (1.27%) and the maternal anxiety group (1.38%). A relatively higher frequency (2.02%) was found in the group with high alpha-fetoprotein. Comparing patients of the same age (30 to 33 years) showed only small and not significant differences between the group with low levels of alpha-fetoprotein (1.97%) and the anxiety group (1.38%). The highest incidence of trisomy 21 was found in low alpha-fetoprotein group, whereas the highest incidence of other anomalies was found in the high alpha-fetoprotein group. As there is no good correlation between alpha-fetoprotein levels and chromosomal anomalies other than trisomy 21, the authors conclude that accessibility to amniocentesis rather than alpha-fetoprotein screening would lead to the detection of other chromosomal anomalies and therefore recommend lowering the maternal age limit for amniocentesis to 30 years.

First trimester serum markers

Recent interest has focused on possible biochemical markers for detection of chromosomal abnormal fetuses during the first trimester of pregnancy (Table 2). In pregnancies complicated by trisomy 21, levels of maternal serum alpha-fetoprotein and unconjugated estriol appear to be decreased, total hCG level is normal and free β-hCG level is increased. In the presence of trisomies 18 and 13, alpha-fetoprotein and unconjugated estriol levels are normal and both total and free β-hCG levels are decreased [20•,21•,22]. There are contradictory results concerning maternal serum CA-125. One study reports decreased levels [23] and another study reports increased levels in trisomy 21–affected pregnancies [12]. Maternal serum pregnancy-associated plasma protein A is markedly reduced in pregnancies in which the fetus has Down syndrome [24•]; 12 of 19 affected cases had values below the 10th percentile. In contrast, there was no significant difference between maternal serum placental protein 14 levels in affected pregnancies as compared with normal pregnancies. As pregnancy-associated plasma protein A was found to increase strikingly over the period of 6 to 12 weeks' gestation, accurate dating of pregnancy will be necessary if this serum marker is to be used as a first trimester screening test [25].

Ultrasound examination of fetal morphology

Most fetuses with major cytogenetic abnormalities have either external or internal defects [26] that can be recognized by detailed ultrasonographic examination. Although many of the ultrasound markers for chromosomal abnormalities are major defects, which are easily

Table 2. The value of maternal serum biochemistry testing during the first trimester of pregnancy

Study	Chromosomal abnormality	Patients, *n*	Gestational age, *wk*	Serum marker	Multiples of the median	Difference from controls
van Lith *et al.* [23]	Trisomy 21	9	9–10	CA-125	0.39	Significantly lower
Hogdall *et al.* [12]	Trisomy 21	14	8–12	CA-125	?	Significantly higher
Crandall *et al.* [20•]	Trisomy 21	10	9–12	AFP	0.75	Significantly lower
				uE_3	0.73	Significantly lower
	Trisomy 18	7		AFP	1.10	Not significant
				uE_3	1.10	Not significant
Johnson *et al.* [21•]	Trisomy 21	11	8–12	AFP	0.67	Significantly lower
				hCG	0.91	Not significant
	Trisomy 18	7		AFP	1.30	Not significant
				hCG	0.32	Significantly lower
	Trisomy 13	5		AFP	0.50	Not significant
				hCG	0.65	Significantly lower
Spencer *et al.* [22]	Trisomy 21	13	7–13	Free βhCG	1.85	Significantly higher
	Trisomy 18	5		Free βhCG	0.17	Significantly lower
Wald *et al.* [24•]	Trisomy 21	19	9–12	PAPP-A	0.23	Significantly lower
				PP 14	0.93	Not significant

AFP—alpha-fetoprotein; βhCG—β-human chorionic gonadotropin; CA-125—cancer antigen-125; hCG—human chorionic gonadotropin; PAPP-A—pregnancy-associated plasma protein A; PP14—placental protein-14; uE_3—unconjugated estriol.

detected at routine examination, others are more subtle and need to be specifically sought out. Therefore, before undertaking any study on the possible effectiveness of ultrasonography in screening for fetal chromosomal abnormalities, it is essential to establish the types of chromosomal abnormalities associated with a given malformation and the ultrasonographically detectable phenotypic expression of the different types of chromosomal abnormalities.

In a study of 2086 fetuses where prenatal karyotyping was undertaken after ultrasonographic examination had revealed fetal malformations, growth retardation, or both, chromosomal abnormalities were detected in 301 (14%) cases [27••]. Table 3 provides data on the incidence of different types of chromosomal abnormalities for the commonest defects. The commonest chromosomal abnormality was trisomy 18, followed by trisomy 21, triploidy, Turner's syndrome, unbalanced chromosomal rearrangements, and trisomy 13. Trisomy 18 was associated with strawberry-shaped head, choroid plexus cysts, facial cleft, micrognathia, heart defects, exomphalos, malformations of the hands and feet, and growth retardation. In fetuses with trisomy 13, defects included holoprosencephaly, facial cleft, cardiac defects, hydronephrosis, polydactyly, overlapping fingers, and talipes. In cases of trisomy 21, the associated defects were often more subtle and included nuchal edema, macroglossia, atrioventricular septal defects, mild hydronephrosis, sandal gap, and clinodactyly. Turner's syndrome was frequently associated with nuchal cystic hygromata, generalized edema, brachycephaly, and cardiac defects. Triploidy was characterized by early-onset, severe asymmetrical growth retardation, ventriculomegaly, and syndactyly; molar placenta was found in only six of the 42 cases.

Chromosomal abnormalities were more common among fetuses with multisystem malformations (29%) than those with isolated defects (2%); the risk increased with the number of defects, and was 95% when more than eight defects were present. The frequency of chromosomal abnormalities increased with maternal age, but if fetal karyotyping had been restricted to mothers more than 35 years of age, large proportions of chromosomally abnormal fetuses would not have been diagnosed prenatally (64% to 7%).

Table 3. Gestation at referral and frequency of chromosomal abnormalities for ultrasonographically detectable fetal malformations and growth retardation*

Defect	Median (range) gestation at referral, *wk*	Patients with chromosome abnormality/total with defect, *n(%)*		Chromosomal abnormalities					
				Trisomy					
		Isolated†	Multiple	21	18	13	Triploidy	Turner's syndrome	Other‡
Brachycephaly	23 (17–38)	—	43/114 (38)	7	19	5	3	8	1
Strawberry-shaped head	24 (16–39)	—	44/54 (82)	—	43	—	1	—	—
Microcephaly	22 (18–37)	0/1	8/51 (16)	1	1	3	—	—	3
Ventriculomegaly	23 (16–38)	2/42	40/144 (28)	7	12	3	12	3	5
Holoprosencephaly	22 (17–36)	0/7	15/51 (29)	—	3	11	—	—	1
Choroid plexus cyst	21 (16–38)	1/49	33/72 (46)	2	30	1	—	—	1
Posterior fossa cyst	22 (16–38)	0/1	21/44 (48)	—	8	6	3	—	4
Facial cleft	22 (17–37)	0/8	31/56 (55)	1	10	15	1	—	4
Micrognathia	23 (17–37)	—	37/56 (66)	—	21	3	9	—	4
Macroglossia	24 (20–37)	—	10/13 (77)	9	—	—	—	—	1
Nuchal edema	21 (16–38)	0/12	53/132 (40)	31	5	7	2	3	5
Cystic hygromata	19 (16–35)	0/4	35/48 (73)	1	1	—	—	33	—
Hydrops	26 (16–39)	7/104	18/106 (17)	14	1	2	2	2	4
Diaphragmatic hernia	21 (17–38)	0/38	17/41 (41)	—	10	2	1	—	4
Heart defect	23 (17–39)	0/4	101/152 (66)	21	37	14	4	16	9
Exomphalos	21 (16–39)	1/30	41/86 (48)	—	32	7	1	—	2
Duodenal atresia	32 (20–36)	1/6	9/17 (53)	10	—	—	—	—	—
Esophageal atresia	27 (20–37)	0/1	18/23 (78)	1	17	—	—	—	—
Renal defects	22 (16–40)	9/482	87/360 (24)	23	25	20	5	8	15
Abnormal extremities	23 (16–40)	0/18	195/457 (43)	35	71	21	38	22	8
Growth retardation	28 (17–39)	4/251	133/424 (31)	13	48	15	40	9	12

From Nicolaides [27••]; with permission.
†1 trisomy 8, 9 trisomy 21, 2 trisomy 22; 1 duplication marker; 1 each deletion of 2q, 3p, and 5p, 4 deletions of 4p; unbalanced translocations (1;1) and (11;12): 2 Turner's syndrome; 2 47XXY, 1 47XYY.
‡1 trisomy 8, 2 each trisomies 9 and 22; 2 isochromosome 12p; 1 each duplications 4q, 11p, marker; 1 each deletion of 3p, 5p, 5q, 6p, 7q, 8q, 8p, 9p, 13q, 14q, 21q, 3 deletions of 2q and 5 of 4p; unbalanced translocations (1;1), (11;12), (4;15), and (17;19); 3 47XXY; 2 47XYY.

The value of isolated markers

There is continuing controversy surrounding the possible significance of apparently isolated defects such as choroid plexus cysts and pyelectasis [28•,29••]. One possible explanation for this controversy is that the populations examined by various authors may differ in the incidence of chromosomal abnormalities caused by factors like maternal age. It is therefore necessary to establish by large prospective studies the exact maternal age–independent risk for chromosomal abnormalities of the various isolated defects.

Corteville *et al.* [29••], examined 5944 fetuses and noted pyelectasis in 17.4% (4 of 23) of those with Down syndrome and in 2% (120 of 5876) of the normal fetuses. The predictive value of 1:90 compared favorably with other accepted indications for karyotyping, but after exclusion of fetuses with concomitant sonographic abnormalities the predictive value of isolated pelvic dilatation fell to 1.340. Therefore, the authors recommend that karyotyping should be done only in those cases in which other risk factors, such as advanced maternal age, low maternal serum alpha-fetoprotein, or additional sonographic abnormalities are present.

New ultrasound markers

In a study of 33 fetuses with cisterna magna measuring 10 mm or more at 16 to 38 weeks' gestation, 18 (55%) had chromosomal abnormalities, mainly trisomies 18 or 13 [30•]. The risk for chromosomal abnormalities was much higher in fetuses with multisystem malformations and in those for whom the enlarged cisterna magna was not associated with lateral cerebral ventriculomegaly.

Frontothalamic distance is measured from the inner table of the frontal bone to the posterior thalamus. In a study of 19 fetuses with Down syndrome and 125 normal control fetuses at 16 to 21 weeks' gestation, the frontothalamic distance to biparietal diameter ratio was significantly lower in the fetuses with Down syndrome [31•]. When the observed-to-expected ratio was 0.84 or less, the positive predictive value was 1.2% for a population with a 0.37% risk for Down syndrome; the sensitivity and specificity were 21% and 95%, respectively.

In some fetuses with trisomy 18 there is a characteristic flattening of the occiput and narrowing of the frontal part of the head known as strawberry-shaped head that is best seen in the suboccipital-bregmatic view of the head. The narrow bifrontal region may be due to hypoplasia of the face and frontal cerebral lobes; flattening of the occiput may be due to hypoplasia of the hindbrain. In a series of 54 fetuses with strawberry-shaped head, all had additional malformations and 43 (80%) had trisomy 18 [32•].

Nyberg *et al.* [33] described an association between chromosomal abnormalities and echogenic bowel, which was present in 7% of second trimester fetuses with Down syndrome. Scioscia *et al.* [34•] karyotyped 19 fetuses with echogenic bowel at 15 to 26 weeks' gestation finding trisomy 21 in five and trisomy 18 in one (32%). However, in four of the chromosomally abnormal fetuses there were additional malformations, and in five of the cases there was advanced maternal age or low maternal serum alpha-fetoprotein. Dicke and Crane [35•] found a chromosomal abnormality (trisomy 18) in only one of the 30 cases they studies (3.3%). In this case additional malformations were present.

In a postmortem study of fetuses with Down syndrome, FitzSimmons *et al.* [36] reported that shortening of the long bones in the upper extremity was more pronounced than that of long bones in the lower extremity. Two studies [37•,38•] that evaluated the utility of ultrasonographic measurements of the humerus at 15 to 22 weeks' gestation for detection of Down syndrome reached different conclusions. Rodis *et al.* [37•] found retrospectively that in five of 11 cases of trisomy 21 the humerus length versus biparietal diameter was below the 5th percentile of their reference range. In contrast, Rotmensch *et al.* [38•] found shortening of the humerus in only one of 43 fetuses with Down syndrome. Humerus length versus gestational age below the 5th percentile yielded a 64% sensitivity and a positive predictive value of 6.8% in the first study, whereas a ratio of 0.90 for observed-to-expected humeral length yielded a sensitivity of 28% and a positive predictive value of 1.23% in the second study. The variability of different measurement techniques, ultrasound equipment, operator experience, and the use of different discriminators as well as considerable overlap of actual long bone lengths between fetuses with Down syndrome and unaffected fetuses may be responsible for such different results and restrict their utility.

First trimester ultrasound markers

Recent publications have suggested a possible association between abnormal nuchal fluid and chromosomal abnormalities in the first trimester of pregnancy (Table 4). One prospective study involved 827 women with singleton pregnancies undergoing first trimester fetal karyotyping because of advanced maternal age, parental anxiety, or family history of a chromosomal abnormality in the absence of balanced parental translocation [51••]. Transabdominal ultrasound examination was performed to obtain a sagittal section of the fetus for measurement of the maximum thickness of the subcutaneous translucency between the skin and the soft tissue overlying the cervical spine. The incidence of chromosomal defects was 3% (28 of 827 cases). In the 51 (6%) fetuses with nuchal translucency of 3 to 8 mm in thickness, the incidence of chromosomal defects was 35% (18 cases). In contrast, only 10 of the remaining 776 (1%) fetuses were chromosomally abnormal. This screening study therefore established that:

1) The presence of fetal nuchal translucency of 3 mm or more is associated with a more than tenfold

increase and absence of translucency, with a threefold decrease in risk for chromosomal abnormality;

2) The risk of chromosomal abnormalities increases with increasing thickness of the nuchal translucency;

3) The pattern of associated chromosomal defects, trisomies rather than Turner's syndrome, is similar to that observed in second trimester fetuses with nuchal edema rather than with cystic hygromata; and

4) The sensitivity of the test for trisomy 21 is more than 75%, and the incidence of nuchal translucency of 3 mm or more in chromosomally normal fetuses is approximately 4%.

In a study of 25 chromosomally abnormal fetuses the crown-rump length at 9 to 12 weeks was not significantly different from that of 500 normal control fetuses [53•].

Conclusions

The failure of screening studies based on maternal age to reduce substantially the birth incidence of chromosomally abnormal neonates has stimulated the search for new methods of screening. It appears that the combination of maternal age and serum biochemistry has better sensitivity in the detection of trisomy 21. Although the importance of this finding must not be underestimated, very little attention has yet been given to the potential consequences of widespread introduction of maternal serum biochemistry screening, including the need for new approaches to counseling both young and older women, the implications of replacing screening for all chromosomal abnormalities with that for just trisomy 21, and the late diagnosis with this method at a time when use of first trimester amniocentesis or chorionic villus sampling is increasing. Some of these issues may be resolved by the discovery that altered maternal biochemistry is found in other chromosomal abnormalities and during the first trimester of pregnancy.

The incidence of chromosomal abnormalities for ultrasonographically detectable fetal malformations or growth retardation or both is much higher than the incidence reported in screening studies based on advanced maternal age or maternal serum biochemistry. However, there are no prospective studies on the sensitivity of second trimester ultrasound screening for chromosomal defects in unselected populations. Al-

Table 4. Summary of reported series on first trimester fetal nuchal edema or cystic hygromata providing data on the presence of associated chromosomal defects

			Abnormal karyotype					
	Gestation,	Total,	Total,	Turner's	Trimsomy			
Study	*wk*	*n*	*n (%)*	syndrome	13	18	21	Others
Gustavii and Edvall [39]	12	1						
Dallapiccola *et al.* [40]	12	1						
Reuss *et al.* [41]	12	1	1 (100)	1				
Reuss *et al.* [42]	10	1						
Pons *et al.* [43]	11–14	4	4 (100)	1		3		
Bronshtein *et al.* [44]	11–12	2	1 (50)				1	
Cullen *et al.* [45]	11–13	29	15 (52)	4		2	6	3*
Szabo and Gellen [46]	11–12	8	7 (88)				7	
Hill *et al.* [47]	13–14	2	2 (100)			2		
Shulman *et al.* [48•]	10–13	32	15 (47)	4	3	4	4	
van Zalen-Sprock *et al.* [49•]	10–14	18	5 (28)			1	3	1†
Schulte-Vallentin and Schindler [50]	10–14	8	7 (88)				7	
Nicolaides *et al.* [51••]	10–13	51	18 (35)		2	4	10	2‡
Ville *et al.* [52•]	9–14	85	24 (28)	4	1	9	9	1§
Total	10–14	243	99 (41)	14	6	25	47	7

*47XY + 15/46XX, 49XXXXY, 47XX-21 + der (21)t(18q;21p).
†45X-15 + der (15) + t(Y;15).
‡47XY + fragment, trisomy 22.
§47XXX.

though there is a rapidly increasing list of subtle deviations from normality in anatomy and measurements in fetuses with Down syndrome the incidence of these markers is quite high (1% to 5%) and the positive predictive value is around 1%. The implications in terms of parental anxiety, risk of fetal death or damage, and economic cost of invasive testing remain to be discussed.

The implementation of maternal serum biochemistry screening requires accurate dating of pregnancies by ultrasonography. When such a scan is undertaken at 10 to 14 weeks' gestation, the presence of nuchal translucency may well prove to be the most efficient method of screening for all major trisomies. Ultrasonography allows examination of the fetus and diagnosis of fetal disease, whereas measurement of maternal parameters provides only an indirect diagnosis of fetal abnormality.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
- • Of special interest
- •• Of outstanding interest

1. CUCKLE HS, NANCHAHAL K, WALD NJ: Birth Prevalence of Down's Syndrome in England and Wales. *Prenat Diagn* 1991, 11:29–34.

2. • ZEITUNE M, AITKEN DA, CROSSLEY JA, YATES JRW, COOKE A, FERGUSON-SMITH MA: Estimating the Risk of a Fetal Autosomal Trisomy at Mid-Trimester Using Maternal Serum Alpha-Fetoprotein and Age: A Retrospective study of 142 Pregnancies. *Prenat Diagn* 1991: 11:847–857.

The detection rate for trisomies 21, 18, and 13 was 37% for the combination of maternal serum alpha-fetoprotein and age, and 30% for age (>35 years) alone.

3. YOUINGS S, GREGSON N, JONES P: The Efficacy of Maternal Age for Screening for Down's Syndrome in Wessex. *Prenat Diagn* 1991, 11:419–425.

4. MERKATZ IR, NITOWSKY HM, MACRI JN, JOHNSON WE: An Association Between Low Maternal Serum α-Fetoprotein and Fetal Chromosomal Abnormalities. *Am J Obstet Gynecol* 1984, 148:886–894.

5. BOGART MH, PANDIAN MR, JONES OW: Abnormal Maternal Serum Chronic Gonadotropin Levels in Pregnancies with Chromosome Abnormalities. *Prenat Diagn* 1987, 7:623–630.

6. CANICK JA, KNIGHT GJ, PALOMAKI GE, HADDOW JE, CUCKLE HS, WALD NJ: Low Second Trimester Maternal Serum Unconjugated Oestriol in Pregnancies with Down's Syndrome. *Br J Obstet Gynaecol* 1988, 95:330–333.

7. WALD NJ, CUCKLE HS, DENSEM JW, NANCHAHAL K, ROYSTON P, CHARD GS, HADDOW JE, KNIGHT GS, PALOMAKI GE, CANICK JA: Maternal Serum Screening for Down's Syndrome in Early Pregnancy. *BMJ* 1988, 297:883–887.

8. • WALD NJ, KENNARD A: Prenatal Biochemical Screening for Down's Syndrome and Neural Tube Defects. *Curr Opin Obstet Gynecol* 1992, 4:302–307.

Review article.

9. •• WALD NJ, KENNARD A, DENSEM JW, CUCKLE HS, CHARD T, BUTLER L: Antenatal Maternal Serum Screening for Down's Syndrome: Results of a Demonstration Project. *BMJ* 1992, 305:391–394.

Prospective maternal serum triple biochemistry screening study for Down syndrome in 11,993 women less than 37 years of age and 630 women 37 years of age or more.

10. •• HADDOW JE, PALOMAKI GE, KNIGHT GJ, WILLIAMS J, PULKKINEN A, CANICK JA, SALLER DN, BOWERS GB: Prenatal Screening for Down's Syndrome with Use of Maternal Serum Markers. *N Engl J Med* 1992, 327:588–593.

Prospective maternal serum triple biochemistry screening study for Down syndrome in 24,706 women less than 37 years of age and 501 women 37 years of age or more.

11. •• PHILLIPS OP, ELIAS S, SHULMAN LP, ANDERSEN RN, MORGAN CD, SIMPSON JL: Maternal Serum Screening for Fetal Down Syndrome in Women Less than 35 Years of Age Using α-Fetoprotein, hCG and Unconjugated Estriol: A Prospective 2-Year Study. *Obstet Gynecol* 1992, 80:353–358.

Prospective maternal serum triple biochemistry screening study for Down syndrome in 9530 women less than 35 years of age.

12. HOGDALL CK, HOGDALL EVS, ARENDS J, NORGAARD-PEDERSEN B, SMIDT-JENSEN S, LARSEN SO: CA-125 as a Maternal Serum Marker for Down's Syndrome in the First and Second Trimesters. *Prenat Diagn* 1992, 12:223–227.

13. • SPENCER K: Maternal Serum CA125 is Not a Second Trimester Marker for Down's Syndrome. *Ann Clin Biochem* 1991, 28:299–300.

Observational study.

14. • SPENCER K, MACRI JN: Early Detection of Down's Syndrome Using Free Beta Human Choriogonadotropin. *Ann Clin Biochem* 1992, 29:349–350.

Observational study.

15. CUCKLE H, LILFORD RJ: Pregnancy Associated Plasma Protein A in Down's Syndrome [Letter]. *BMJ* 1992, 305:425.

16. • GREENBERG F, SCHMIDT D, DARNULE AT, WEYLAND BR, ROSE E, ALPERT E: Maternal Serum α-Fetoprotein, β-Human Chorionic Gonadotropin, and Unconjugated Estriol Levels in Midtrimester Trisomy 18 Pregnancies. *Am J Obstet Gynecol* 1992, 166:1388–1392.

Observational study.

17. • STAPLES AJ, ROBERTSON EF, RANIERI E, RYALL RG, HAAN EA: A Maternal Serum Screen for Trisomy 18: An Extension of Maternal Serum Screening for Down Syndrome. *Am J Hum Genet* 1991, 49:1025–1033.

Observational study.

18. • SALLER DN, CANICK JA, SCHWARTZ S, BLITZER MG: Multiple-Marker Screening in Pregnancies with Hydropic and Nonhydropic Turner Syndrome. *Am J Obstet Gynecol* 1992, 167:1021–1024.

Observational study.

19. • KAFFE S, HSU LYF: Maternal Serum α-Fetoprotein Screening and Fetal Chromosome Anomalies: Is Lowering Maternal Age for Amniocentesis Preferable? *Am J Med Genet* 1992, 42:801–806.

Observational study. The authors propose that efforts should be directed at making amniocentesis more accessible to patients who request it.

20. • CRANDALL BF, GOLBUS MS, GOLDBERG JD, MATSUMOTO M: First-Trimester Maternal Serum Unconjugated Oestriol and Alpha-Fetoprotein in Fetal Down's Syndrome. *Prenat Diagn* 1991, 11:377–380.

Observational study.

21. • JOHNSON A, COWCHOCK FS, DARBY M, WAPNER R, JACKSON LG: First Trimester Maternal Serum Alpha-Fetoprotein and Chorionic Gonadotropin in Aneuploid Pregnancies. *Prenat Diagn* 1991, 11:443–450.

Observational study.

22. SPENCER K, MACRI JN, AITKEN DA, CONNOR JM: Free β-hCG as First-Trimester Marker for Fetal Trisomy [Letter]. *Lancet* 1992, 339:1480.

23. VAN LITH JMM, MANTINGH JR, BEEKHUIS JR, DE BRUIJN HWA: First Trimester CA 125 and Down's Syndrome. *Br J Obstet Gynaecol* 1991, 98:493–494.

24. • WALD N, STONE R, CUCKLE HS, GRUDZINKAS JG, BARKAI G, BRAMBATI B, TEISNER B, FUHRMANN W: First Trimester Concentrations of Pregnancy Associated Plasma Protein A and Placental Protein 14 in Down's Syndrome. *BMJ* 1992, 305:28.
Observational study.

25. MACINTOSH MCM: Pregnancy Associated Plasma Protein [Letter]. *BMJ* 1992, 305:425.

26. JONES KL: *Smith's Recognizable Patterns of Human Malformation.* 4th edn. London: WB Saunders; 1988.

27. •• NICOLAIDES KH, SNIJDERS RJM, GOSDEN RJM, BERRY C, CAMPBELL S: Ultrasonographically Detectable Markers of Fetal Chromosomal Abnormalities. *Lancet* 1992, 340:704–707.
Description of the association between phenotype and different types of chromosomal abnormalities in 2086 fetuses with malformations, growth retardation, or both.

28. • PERPIGNANO MC, COHEN HL, KLEIN VR, MANDEL FS, STRELTZOFF J, CHERVENAK FA, GOLDMAN MA: Fetal Choroid Plexus Cysts: Beware the Smaller Cyst. *Radiology* 1992, 182:715–717.
Retrospective study of 3679 patients with choriod plexus cysts. Authors report a remarkably high probability of chromosomal abnormality in fetuses with isolated choroid plexus cysts (1.1% for trisomy 21, 3.4% for trisomy 18).

29. •• CORTEVILLE JE, DICKE JM, CRANE JP: Fetal Pyelectasis and Down Syndrome: Is Genetic Amniocentesis Warranted? *Obstet Gynecol* 1992, 79:770–772.
Study of 5944 consecutive fetuses for the presence of pyelectasis. The authors address important issues of an isolated marker and recommend that amniocentesis should be reserved for cases that present with other risk factors.

30. • NYBERG DA, MAHONY BS, HEGGE FN, HICKOK D, LUTHY DA, KAPUR R: Enlarged Cisterna Magna and the Dandy-Walker Malformation: Factors Associated with Chromosome Abnormalities. *Obstet Gynecol* 1991, 77:436–442.
Observational study.

31. • BAHADO-SINGH RO, WYSE L, DORR MA, COPEL JA, O'CONNOR T, HOBBINS JC: Fetuses with Down Syndrome Have Disproportionately Shortened Frontal Lobe Dimensions on Ultrasonographic Examination. *Am J Obstet Gynecol* 1992, 167:1009–1014.
Observational study.

32. • NICOLAIDES KH, SALVESEN D, SNIJDERS RJM, GOSDEN CM: Strawberry-Shaped Skull in Fetal Trisomy 18. *Fetal Diagn Ther* 1992, 7:132–137.
Observational study.

33. NYBERG DA, RESTA RG, LUTHY DA, HICKOK DE, MAHONY BS, HIRSCH JH: Prenatal Sonographic Findings of Down Syndrome: Review of 94 Cases. *Obstet Gynecol* 1990, 76:370–377.

34. • SCIOSCIA AL, PRETORIUS DH, BUDORICK NE, CAHILL TC, AXELROD FT, LEOPOLD GR: Second-Trimester Echogenic Bowel and Chromosomal Abnormalities. *Am J Obstet Gynecol* 1992, 167:889-894.
Observational study reporting a high incidence of chromosomal abnormalities (32%) and no cases of cystic fibrosis.

35. • DICKE JM, CRANE JP: Sonographically Detected Hyperechoic Fetal Bowel: Significance and Implications for Pregnancy Management. *Obstet Gynecol* 1992, 80:778–782.
Observational study reporting a high incidence of cystic fibrosis (13%) and a relatively low incidence of chromosomal abnormalities (3%).

36. FITZSIMMONS J, DROSTE S, SHEPARD TH, PASCOE-MASON J, CHINN A, MACK LA: Long Bone Growth in Fetuses with Down Syndrome. *Am J Obstet Gynecol* 1989, 161:1174–1177.

37. • RODIS JF, VINTZILEOS AM, FLEMING AD, GIARLEGLIO L, NARDI DA, FEENEY L, SCORZA WE, CAMPBELL WA, INGARDIA C: Comparison of Humerus Length with Femur Length in Fetuses with Down Syndrome. *Am J Obstet Gynecol* 1991, 165:1051–1056.
Observational study.

38. • ROTMENSCH S, LUO JS, LIBERATI M, BELANGER K, MAHONEY MJ, HOBBINS JC: Fetal Humeral Length to Detect Down Syndrome. *Am J Obstet Gynecol* 1992, 166:1330–1334.
Observational study.

39. GUSTAVII B, EDVALL H: First-Trimester Diagnosis of Cystic Nuchal Hygroma. *Acta Obstet Gynecol Scand* 1984, 63:377–378.

40. DALLAPICCOLA B, ZELANTE L, PERLA G, VILLANI G: Prenatal Diagnosis of Recurrence of Cystic Hygroma with Normal Chromosomes. *Prenat Diagn* 1984, 4:383–386.

41. REUSS A, PIJPERS L, SCHAMPERS PTFM, WLADIMIROFF JW, SACHS ES: The Importance of Chorionic Villus Sampling After First Trimester Diagnosis of Cystic Hygroma. *Prenat Diagn* 1987, 7:299–301.

42. REUSS A, PIJPERS L, VAN SWAAIJ E, JAHODA MGJ, WLADIMIROFF JW: First-Trimester Diagnosis of Recurrence of Cystic Hygroma Using a Transvaginal Ultrasound Transducer: Case Report. *Eur J Obstet Gynecol Reprod Biol* 1987, 26:271–273.

43. PONS JC, DIALLO AA, EYDOUX P, RAIS S, DOUMERC S, FRYDMAN R, PAPIERNIK E: Chorionic Villus Sampling After First Trimester Diagnosis of Fetal Cystic Hygroma Colli. *Eur J Obstet Gynecol Reprod Biol* 1989, 33:141–146.

44. BRONSHTEIN M, ROTTEM S, YOFFE N, BLUMENFELD Z: First Trimester and Early Second Trimester Diagnosis of Nuchal Cystic Hygroma by Transvaginal Sonography: Diverse Prognosis of the Septated from the Non Septated Lesion. *Am J Obstet Gynecol* 1989, 161:78–82.

45. CULLEN MT, GABRIELLI S, GREEN JJ, RIZZO N, MAHONEY MJ, SALAFIA C, BOVICELLI L, HOBBINS JC: Diagnosis and Significance of Cystic Hygroma in the First Trimester. *Prenat Diagn* 1990, 10:643–651.

46. SZABO J, GELLEN J: Nuchal Fluid Accumulation in Trisomy-21 Detected by Vaginosonography in First Trimester [Letter]. *Lancet* 1990, 336:1133.

47. HILL LM, MACPHERSON T, RIVELLO D, PETERSON C: The Spontaneous Resolution of Cystic Hygromas and Early Fetal Growth Delay in Fetuses with Trisomy 18: Case Report. *Prenat Diagn* 1991, 11:673–677.

48. • SHULMAN LP, EMERSON D, FELKER R, PHILLIPS O, SIMPSON J, ELIAS S: High Frequency of Cytogenetic Abnormalities with Cystic Hygroma Diagnosed in the First Trimester. *Obstet Gynecol* 1992, 80:80–82.
Observational study.

49. • VAN ZALEN-SPROCK RM, VAN VUGT JMG, VAN GEIJN HP: First-Trimester Diagnosis of Cystic Hygroma: Course and Outcome. *Am J Obstet Gynecol* 1992, 167:94–98.
Observational study.

50. SCHULTE-VALLENTIN M, SCHINDLER H: Non-Echogenic Nuchal Oedema as a Marker in Trisomy 21 Screening [Letter]. *Lancet* 1992, 339:1053.

51. •• NICOLAIDES KH, AZAR G, BYRNE D, MANSUR C, MARKS K: Fetal Nuchal Translucency: Ultrasound Screening for Chromosomal Defects in First Trimester of Pregnancy. *BMJ* 1992, 304:867–869.
Screening study on the incidence of nuchal translucency and its association with chromosomal abnormalities in 827 fetuses undergoing first trimester karyotyping.

52. • VILLE Y, LALONDRELLE C, DOUMERC S, DAFFOS F, FRYDMAN R, OURY JF, DUMEZ Y: **First-Trimester Diagnosis of Nuchal Anomalies: Significance and Fetal Outcome.** *Ultrasound Obstet Gynecol* 1992, 2:314–316.

Observational study.

53. • LEELAPATANA P, GARRETT WJ, WARREN PS: **Early Growth Retardation in the First Trimester: Is it Characteristic of the Chromosomally Abnormal Fetus?** *Aust N Z J Obstet Gynaecol* 1992, 32:95–97.

Observational study that answers its own question negatively.

Kurt Hecher, MD, Rosalinde Snijders, MSc, and Kypros Nicolaides, MRCOG, Harris Birthright Research Centre for Fetal Medicine, King's College Hospital Medical School, Denmark Hill, London SE5 8RX, UK.