First-Trimester Fetal Nuchal Translucency Thickness and Risk for Trisomies

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Objective: **To define the relation between fetal nuchal translucency thickness at 10–13 weeks' gestation and the risk for fetal trisomies and pregnancy outcome.**

Methods: **Five hundred sixty fetuses with nuchal translucency thickness of 3–9 mm at 10–13 weeks' gestation were karyotyped. The ratio of the observed number of fetal trisomies to that expected on the basis of maternal age was calculated.**

Results: **The incidence of trisomies 21, 18, or 13 was 18% (102 of 560 cases) and was significantly associated with both maternal age ($r = 0.97$) and fetal nuchal translucency thickness ($r = 0.75$). In 383 fetuses with nuchal translucency of 3 mm, the observed number of fetal trisomies was 23, in contrast to the frequency of 6.0 expected on the basis of maternal age. In 177 fetuses with nuchal translucency of 4 mm or more, 79 cases were observed, compared with 2.7 expected on the basis of maternal age. In fetuses with nuchal translucency of 4 mm or more and normal karyotype, there was a high association with other defects and the prognosis was often poor, whereas the translucency resolved for those with 3 mm and the pregnancy outcome was usually normal.**

Conclusion: **At 10–13 weeks' gestation, fetal nuchal translucency of 3 mm is associated with a fourfold increase, and translucency of greater than 3 mm with a 29-fold increase, in the maternal age-related risk for trisomies 21, 18, and 13. Fetal nuchal translucency of 4 mm or more is associated with poor pregnancy outcome even when the fetal karyotype is normal.** *(Obstet Gynecol 1994;84:420–3)*

During the last 4 years, several prenatal ultrasonographic studies have documented a strong association between an abnormal collection of fluid behind the fetal neck (nuchal translucency) and chromosomal abnormalities in the first trimester of pregnancy. From the combined data of nine series reporting 13–68 cases of abnormal nuchal translucency, 172 (53%) of the 327 fetuses had an abnormal karyotype.[1–9] However, there were large differences between the studies both in the definition of minimum thickness of the abnormal translucency (2–6 mm)[1,9] and in the incidence of chromosomal abnormalities (28–79%).[4,8]

Snijders et al[10] recently established estimates of the maternal age-specific incidence for fetal trisomies in the first trimester of pregnancy. Nicolaides et al[2] previously found that the risk for trisomies in fetuses with nuchal translucency was related both to the thickness of the translucency and maternal age. The aims of the present study were to examine to what extent the incidence of trisomies in pregnancies with fetal nuchal translucency of at least 3 mm is higher than expected on the basis of maternal age alone and to determine pregnancy outcome in the chromosomally normal group.

Materials and Methods

Between January 1990 and February 1994, we performed 98 first-trimester amniocenteses and 462 chorionic villus samplings for fetal karyotyping in 560 pregnancies with fetal nuchal translucency of at least 3 mm at 10–13 weeks plus 6 days' gestation. Data from the first 51 cases were included in a previous publication.[2] One hundred thirty patients were referred from other hospitals, and 430 patients were diagnosed in our center during routine first-trimester scanning for measurement of nuchal translucency thickness. Gestational age was calculated from the maternal menstrual history ($n = 422$) and confirmed by measurement of fetal crown-rump length; for those with irregular periods or uncertain dates, the fetal crown-rump length was used ($n = 138$). The mothers gave written informed consent for fetal karyotyping.

In all cases, a transabdominal ultrasound examination (curvilinear 5-MHz transducer, Aloka 650; Aloka Limited, Tokyo, Japan) was used to image a sagittal section of the fetus for measurement of crown-rump length and the maximum thickness of the subcutaneous

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Table 1. Fetal Nuchal Translucency Thickness and Chromosomal Abnormalities at 10–13 Weeks' Gestation

Nuchal translucency thickness (mm)	*n*	Abnormal karyotype					
		Trisomies					
		21	18	13	21/18/13	45,X	Other
3	383	16	6	1	23 (6%)	1	7 (69,XXX; 69,XXY *n* = 2; 47,XY+fr; 47,XX+22; 47,XXY *n* = 2)
4	67	16	3	2	21 (31%)		2 (69,XXX; 47,XY+20)
5	41	13	5	2	20 (49%)		1 (92,XXYY)
6	21	5	5		10 (48%)	2	
7	17	3	8	1	12 (71%)	3	
8	13	4	1	2	7 (54%)		
9	18	4	4	1	9 (50%)	6	
Total	560	61	32	9	102 (18%)	12	10

translucency between the skin and the soft tissue overlying the cervical spine. Care was taken to distinguish between fetal skin and amnion because both structures appear as thin membranes at this gestation.

The chromosomally normal group was investigated further by detailed ultrasound examination and echocardiography at 20 weeks' gestation and by screening for maternal toxoplasmosis, cytomegalovirus, rubella virus, herpesvirus, parvovirus B19, and coxsackievirus B. Details on pregnancy outcome were obtained from the referring physicians or the patients.

Estimates of the maternal age-related risks for fetal trisomies 21, 18, or 13 at 9–14 weeks' gestation were used to calculate the expected incidences.[10] The ratio of observed to expected number of cases was calculated. Regression analysis was applied to examine the association between the incidence of fetal trisomies and nuchal translucency thickness and maternal age, respectively.

Results

The median maternal age was 35 years (range 19–47), and the median gestational age was 12 weeks (range 10–13). The fetal karyotype was normal in 436 cases and abnormal in 124, including 102 with trisomies 21, 18, or 13 (Table 1). In one case with fetal nuchal translucency of 3 mm, analysis of chorionic villi showed mosaicism of 46,XX/47,XX+20; fetal blood analysis at 20 weeks showed a normal 46,XX karyotype.

The incidence of trisomies was significantly associated with fetal nuchal translucency thickness ($r = 0.75$, $P < .05$) (Table 1) and maternal age ($r = 0.97$, $P < .01$) (Table 2). The observed numbers of trisomies in the 383 cases with fetal nuchal translucency of 3 mm and the 177 with nuchal translucency greater than 3 mm were approximately four times and 29 times higher, respectively, than the numbers expected on the basis of maternal age (Table 3).

One hundred twenty-one of the 124 pregnancies with fetal chromosomal abnormalities were terminated at the parents' request. In three cases, one with fetal Turner syndrome (nuchal translucency thickness 3 mm) and two with trisomy 21 (nuchal translucency thickness of 3 and 9 mm, respectively), the pregnancies are continuing.

Table 4 shows the pregnancy outcomes in the chromosomally normal group. The maternal immunoglobulin (Ig) M was positive for parvovirus B19 in one case, toxoplasmosis in one case, and coxsackievirus B in two cases. In these four cases, the fetal nuchal translucency (thickness 4–5 mm) resolved by 20 weeks and the pregnancies are continuing. In all other cases, the infection screen was negative.

Among 352 chromosomally normal fetuses with nuchal translucency of 3 mm, there were three fetal deaths and three terminations of pregnancy after the diagnosis of a major diaphragmatic hernia at 16 weeks, hydrops at 18 weeks, and tricuspid atresia with transposition of the great vessels at 20 weeks, respectively (Table 4). In all other cases, ultrasound examination at 16–20 weeks demonstrated resolution of the translucency and normal fetal anatomy; 153 pregnancies resulted in the delivery of healthy infants and 193 pregnancies are continuing.

Among 84 chromosomally normal fetuses with nuchal translucency of at least 4 mm, there were 28 live

Table 2. Maternal Age and Fetal Chromosomal Abnormalities in 560 Fetuses With Nuchal Translucency Thickness of 3 mm or More at 10–13 Weeks' Gestation

Age (y)	*n*	Abnormal karyotype					
		Trisomies					
		21	18	13	21/18/13	45,X	Other
20–24	29	3			3 (4%)	2	
25–29	82	3	3	1	7 (9%)	5	2 (69,XXX; 69,XXY)
30–34	133	10	2		12 (9%)	3	4 (69,XXX; 47,XXY *n* = 2; 92,XXYY)
35–39	213	25	16	5	46 (22%)	2	1 (69,XXY)
40–44	97	19	10	3	32 (29%)		3 (47,XX+22; 47,XY+fr; 47,XY+20)
45–49	6	1	1		2 (33%)		
Total	560	61	32	9	102 (18%)	12	10

Table 3. Observed Number of Trisomies 21, 18, and 13 in Relation to Fetal Nuchal Translucency Thickness and Expected Number of Trisomies on the Basis of Maternal Age

Nuchal translucency thickness (mm)	*n*	Observed			Expected by age			Observed/expected		
		21	18/13	21/18/13	21	18/13	21/18/13	21	18/13	21/18/13
3	383	16	7	23	4.20	1.81	6.01	3.8	3.9	3.8
4	67	16	5	21	0.71	0.31	1.02	22.5	16.0	20.6
5	41	13	7	20	0.53	0.23	0.76	24.5	30.0	26.3
≥6	69	16	22	38	0.65	0.28	0.93	24.6	78.6	40.9
Total	560	61	41	102	6.09	2.63	8.72	10.0	15.6	11.7

births, five fetal or neonatal deaths, and 18 induced abortions; 33 pregnancies are continuing (Table 4). One of the survivors has Stickler syndrome, but the others are healthy. The terminations were performed because of either progressive hydrops (six) or the diagnosis of fetal abnormalities (five cases of major exomphalos, including one with anencephaly, three with cardiac defects, and one each with holoprosencephaly, amnion disruption sequence, arthrogryposis, and gonadal dysgenesis). The case of gonadal dysgenesis had a normal male karyotype, but female genitalia were detected at the 20-week scan and confirmed at fetoscopy.

Discussion

This study confirms the strong association between chromosomal abnormalities and fetal nuchal translucency of at least 3 mm at 10–13 weeks' gestation. The data suggest that nuchal translucency of 3 mm is associated with a fourfold increase and translucency of greater than 3 mm a 29-fold increase in the maternal age-related risk for trisomies 21, 18, and 13. Furthermore, in chromosomally normal fetuses with translucency of 4 mm or more, there was a high incidence of other defects and the prognosis was often poor,

Table 4. Nuchal Translucency Thickness and Outcome of Chromosomally Normal Fetuses

Nuchal translucency thickness (mm)	Total	Continuing	Alive	Perinatal death		Termination of pregnancy	
				n	Abnormalities	*n*	Abnormalities
3	352	193	153	3	None (IUD at 15 wk) None (IUD at 13 wk) IUGR (IUD at 30 wk)	3	Diaphragmatic hernia at 16 wk Tricuspid atresia at 20 wk Hydrops at 18 wk
4	44	19	20	2	None (IUD at 16 wk) PPROM (IUD at 20 wk)	3	Hypoplastic left heart at 19 wk Exomphalos at 12 wk Exomphalos at 13 wk
5	20	10	3	2	None (IUD at 16 wk) None (IUD at 15 wk)	5	Hypoplastic left heart at 16 wk Tricuspid atresia at 24 wk Holoprosencephaly at 20 wk Exomphalos at 13 wk Gonadal dysgenesis at 23 wk
6	9	4	1			4	Exomphalos at 13 wk Anencephaly, exomphalos at 12 wk Amnion disruption sequence at 16 wk Arthrogryposis at 16 wk
7	2			1	Charge syndrome (NND at 35 wk)	1	Hydrops at 12 wk
8	6		4			2	Hydrops at 15 wk Hydrops at 17 wk
9	3					3	Hydrops at 15 wk Hydrops at 13 wk Hydrops at 12 wk
Total	436	226	181	8		21	

IUD = intrauterine death; IUGR = intrauterine growth retardation; PPROM = preterm premature rupture of membranes; NND = neonatal death.

whereas translucencies of 3 mm resolved and the pregnancy outcome was usually normal.

In the second trimester, pathologic accumulation of fluid in the nuchal region is classified as nuchal edema or nuchal cystic hygroma.[11,12] Nuchal edema is due to subcutaneous accumulation of fluid, producing a characteristic tremor on ballottement of the fetal head. It has a diverse etiology, including trisomies, cardiovascular and pulmonary defects, skeletal dysplasias, congenital infections, and hematologic and metabolic disorders.[11] Cystic hygromas are bilateral, septated, cystic structures, thought to represent overdistention of the jugular lymphatic sacs, and are strongly associated with Turner syndrome.[12] In our study[2] of first-trimester fetuses, we used the term translucency, rather than edema or cystic hygroma, because this was the ultrasonographic feature that was observed.

Previous ultrasonographic studies did not take into account maternal age when reporting the incidence of chromosomal abnormalities.[1,3–9] This often led to conflicting results, presumably because of differences in the maternal age distribution of the populations examined. Snijders et al[10] provided data on the maternal age-specific incidence of fetal trisomies at 9–14 weeks' gestation. These data have made it possible to calculate the expected incidence of the three trisomies in our study group; from the ratios of expected to observed incidences, it is possible to derive risks taking into account maternal age and fetal nuchal translucency thickness.

This was not a screening study and so it does not provide data on the incidence of nuchal translucency at or above 3 mm in the general population. However, in a previous screening study,[2] we reported that 80% of fetuses with trisomy 21, 18, or 13 had translucency of at least 3 mm, whereas the incidence of the same translucency in chromosomally normal fetuses was approximately 4.5%. Therefore, for the same false-positive rate, the sensitivity of screening for fetal trisomies by fetal nuchal translucency thickness compares favorably with the values of 20–30% and 50–60%, respectively, for screening by maternal age or maternal age and serum biochemistry.[13–15]

This study provides the basis for counseling parents when first-trimester scanning demonstrates fetal nuchal translucency of 3 mm or more. When the translucency is 3 mm, the parents can be given a statistical risk of fetal trisomy and offered the options of other noninvasive methods of predicting risks (such as maternal biochemistry at 16 weeks and detailed ultrasonography at 20 weeks) or invasive testing by first-trimester chorionic villus sampling or second-trimester amniocentesis. If the karyotype is normal, the parents can be encouraged to continue with the pregnancy, because the translucency is likely to resolve and pregnancy outcome is usually normal. When the translucency is 4 mm or more, the parents can be counseled in favor of early testing because the risk of fetal trisomies is dramatically greater. Furthermore, they should be made aware that even if the fetal karyotype is normal, the risk of other fetal defects or perinatal death is increased.

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