Cystic Hygromas, Nuchal Edema, and Nuchal Translucency at 11–14 Weeks of Gestation

Francisca S. Molina, MD, Kyriaki Avgidou, MD, Karl Oliver Kagan, MD, Sara Poggi, MD, and Kypros H. Nicolaides, MD

OBJECTIVE: To estimate the incidence of septations in fetuses with increased nuchal translucency (NT) thickness, and to investigate the relationship between the length and thickness of the translucency and whether the length or septations provide useful information concerning the fetal karyotype in addition to that provided by the NT thickness alone.

METHODS: We examined 386 fetuses with NT thickness equal to or above the 95th percentile for crown-rump length (CRL). A transverse suboccipitobregmatic section of the fetal head was taken to determine whether the sonolucency was septated, and a midsagittal longitudinal section was used to measure NT thickness, CRL, the longitudinal distance between the occiput and the lower end of the sonolucency toward the fetal sacrum (NT length) and the length between the occiput and the sacral tip (spinal length). Logistic regression analysis was used to investigate the effect on abnormal karyotype of CRL, NT thickness, and percentage of NT length to spinal length.

RESULTS: Septations within the translucency were observed in all fetuses. The fetal karyotype was abnormal in 83 (21.5%) pregnancies, and multiple regression showed that the only significant independent predictor of abnormal karyotype was fetal NT thickness.

CONCLUSION: Septations within the translucency can be seen in all fetuses, and therefore this feature cannot be used to distinguish between increased NT and cystic hygromas. The length of the translucency is related to its thickness and does not give useful information concerning the fetal karyotype in addition to that provided by the NT thickness alone.
(Obstet Gynecol 2006;107:678–83)

LEVEL OF EVIDENCE: II-2

From the Harris Birthright Research Centre for Fetal Medicine, King's College Hospital Medical School, London, United Kingdom.

This study was supported by a grant from the Fetal Medicine Foundation (Charity No: 1037116).

Corresponding author: Professor K. H. Nicolaides, Harris Birthright Research Centre for Fetal Medicine, King's College Hospital Medical School, Denmark Hill, London SE5 8RX; e-mail: kypros@fetalmedicine.com.

ISSN: 0029-7844/06

During the second and third trimesters of pregnancy, abnormal accumulation of fluid behind the fetal neck can be classified as nuchal cystic hygroma or nuchal edema.[1–4] In the case of cystic hygromas, prenatal diagnosis by ultrasonography is based on the demonstration of a bilateral, septated, cystic structure, located in the occipitocervical region.[1,2] They are thought to represent overdistention of the jugular lymphatic sacs as a consequence of failure of communication with the internal jugular vein.[5] Secondary dilatation of the lymphatic channels draining the chest and limbs results in peripheral lymphedema and development of nonimmune hydrops, which is found in about 75% of affected fetuses.[2] In about 75% of fetuses with cystic hygromas, there is a chromosomal abnormality, and in about 95% of cases, the abnormality is Turner syndrome.[2] In the chromosomally normal fetuses, there is a high association with cardiac defects and genetic syndromes, such as multiple pterygium syndrome.[2] The overall prognosis in fetuses with cystic hygromas is poor, and the survival rate is less than 5%.[2] Nuchal edema is considered present if, in the midsagittal plane of the neck, there is subcutaneous edema that produces a characteristic tremor on ballotment of the fetal head.[4] This constitutes the severe end of the spectrum of increased nuchal fold thickness, which is defined as soft-tissue thickening of 6 mm or more, seen in the suboccipitobregmatic view of the fetal head.[3] Nuchal edema may be confined to the neck or it may be generalized, as part of hydrops fetalis. Chromosomal abnormalities are found in about one third of the fetuses, and in about 80% of these, the abnormality is trisomy 21, 18, or 13.[4] Edema is also associated with fetal cardiovascular and pulmonary defects, skeletal dysplasias, congenital infection, and metabolic and hematological disorders; consequently, the prognosis for chromosomally normal fetuses with nuchal edema is poor.[4]

In the late 1980s and early 1990s, with the introduction of first trimester screening, several terms were used to describe the abnormal accumulation of

fluid behind the fetal neck, including cystic hygroma and nuchal edema with or without internal septations. However, in the published reports on first-trimester cystic hygroma, the pattern of associated chromosomal defects, both trisomies and Turners syndrome, was suggestive that the term did not have the same pathophysiological significance as second-trimester cystic hygroma (Table 1).[6–15] Furthermore, there was a wide range in the incidence of chromosomal defects from 28% to 100%.

In 1992, we introduced the term nuchal translucency (NT) thickness to standardize the technique of measuring the fluid, irrespective of whether it is septated and whether it is confined to the neck or envelopes the whole fetus.[16] The rationale was that it is possible to standardize and audit the results of a measurement but not those of a subjective appearance. The NT thickness is usually measured with the fetus in the midsagittal position, in which case the appearance of the fluid is homogeneously translucent. Furthermore, increased NT is associated with trisomy 21, Turner syndrome, and other chromosomal abnormalities, as well as many fetal malformations and genetic syndromes,[17,18] and the incidence of these abnormalities is related to the thickness rather than the appearance of NT.[19–21]

Recently, the term cystic hygroma has been reintroduced, to apparently describe a distinct entity from NT. Cystic hygroma was defined as an enlarged sonolucency with clearly visible septations extending along the fetal body axis, in contrast to NT, which was described as a nonseptated sonolucent area confined to the fetal neck.[22]

The aims of this study are, first, to estimate the incidence of septations in fetuses with increased NT thickness, and second, to investigate the relationship between the length and thickness of the translucency and whether the length and septations provide useful information concerning the fetal karyotype in addition to that provided by the NT thickness alone.

PATIENTS AND METHODS

In the Fetal Medicine Centre, first-trimester screening for chromosomal defects, since 1999, is performed considering a combination of maternal age, fetal NT thickness, and maternal serum–free ß-hCG and pregnancy associated plasma protein A (PAPP-A) at $11^{0/7}$ to $13^{6/7}$ weeks of gestation.[23] Patient-specific risks are calculated by a multivariable approach in which the maternal age–related risk is multiplied with each likelihood ratio derived from the fetal NT and maternal weight–adjusted serum-free β-hCG and PAPP-A. The parents are counseled regarding the estimated risk for trisomy 21, and if they consider this risk to be high, they have an invasive diagnostic test– chorionic villus sampling or amniocentesis.

A screening study involving 96,127 pregnancies, established that the 95th percentile of vertical thickness of NT, measured in the midsagittal section of the fetus, increased linearly with fetal crown-rump length (CRL) from 2.1 mm at a CRL of 45 mm to 2.7 mm for CRL of 84 mm.[19]

In this study, which was performed between January 2003 and June 2005, in the cases undergoing chorionic villous sampling and in which the fetal NT thickness was equal to or above the 95th percentile for CRL, in addition to the measurement of the fetal NT thickness and CRL, we also measured NT length (Fig. 1). This was defined as the longitudinal distance between the occiput and the lower end of the sonolucency toward the fetal sacrum (NT length) and expressed as a percentage of the length between the

Table 1. Reports on First-Trimester Cystic Hygroma Describing the Pattern of Associated Chromosomal Defects

Author	Gestational Age (wk)	N	Chromosomal Defect			
			Total (%)	Trisomy 21, 18, or 13	Turner Syndrome	Other
Pons et al[6] (1989)	11–14	4	4 (100.0)	3	1	–
Cullen et al[7] (1990)	10–13	29	15 (51.7)	8	4	3
MacLeod and Hugo[8] (1991)	10–14	5	4 (80.0)	2	2	–
Shulman et al[9] (1992)	10–13	18	9 (50.0)	7	2	–
Suchet et al[10] (1992)	9–14	13	8 (61.5)	–	7	1
van Zalen-Sprock et al[11] (1992)	10–14	4	2 (50.0)	2	–	–
Ville et al[12] (1992)	9–14	56	16 (28.6)	11	4	1
Johnson et al[13] (1993)	10–14	68	41 (60.3)	27	9	5
Nadel et al[14] (1993)	10–15	22	19 (86.4)	10	9	–
Trauffer et al[15] (1994)	10–14	43	21 (48.8)	14	4	3
Total		262	139 (53.1)	84	42	13

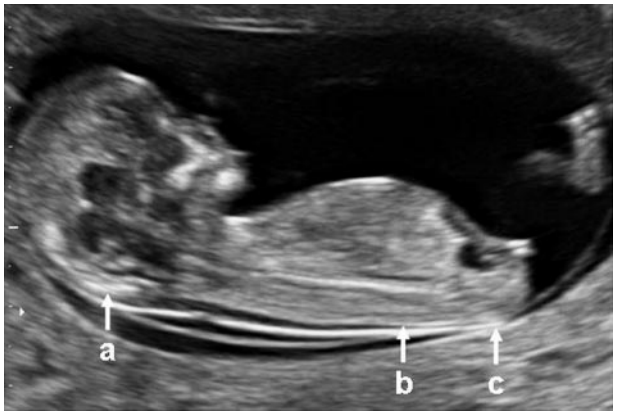

Fig. 1. Longitudinal section of a 12-week-old fetus demonstrating the measurement of the fetal nuchal translucency length, between the occiput *(a)* and the lower end of the sonolucency *(b)* and the spinal length, between the occiput *(a)* and the sacral tip *(c)*.

Molina. Nuchal Translucency and Cystic Hygromas. Obstet Gynecol 2006.

occiput and the sacral tip (spinal length). A transverse suboccipitobregmatic section of the fetal head was also obtained to determine whether or not the sonolucency was septated.

Approval for the study was obtained from King's College Hospital Research Ethics Committee.

Regression analysis was used to examine the significance of the association between NT thickness and percentage of NT length to spinal length. The prevalence and distribution of chromosomal defects were estimated for each NT category: between the 95th percentile for CRL and 3.4 mm, 3.5–4.4 mm, 4.5–5.4 mm, 5.5–6.4 mm, and 6.5 mm or more. The patients were subdivided into those with abnormal and normal karyotype, and logistic regression analysis was used to investigate the effect on abnormal karyotype of gestational age in days, fetal CRL in millimeters, fetal NT in millimeters, NT length to spinal length as a percentage, and presence or absence of septations. Multiple logistic regression analysis was subsequently performed to determine the significant independent contribution of those variables yielding a $P < .05$ in the univariable analysis.

RESULTS

Fetal karyotyping was carried in 386 singleton pregnancies with increased NT thickness. The median maternal age was 36 (range 22–46) years and the median fetal CRL was 65 (range 45–84) mm. A transverse suboccipitobregmatic plane of the fetal head was successfully imaged in 378 (97.9%) fetuses, and septations within the translucency were observed in all cases (Fig. 2).

The NT length and spinal length were measured in all 386 fetuses. There was a significant association between NT thickness and percentage of NT length to spinal length ($r = 0.791$, $P < .001$; Fig. 3). In all fetuses with NT thickness of 6 mm or more, the

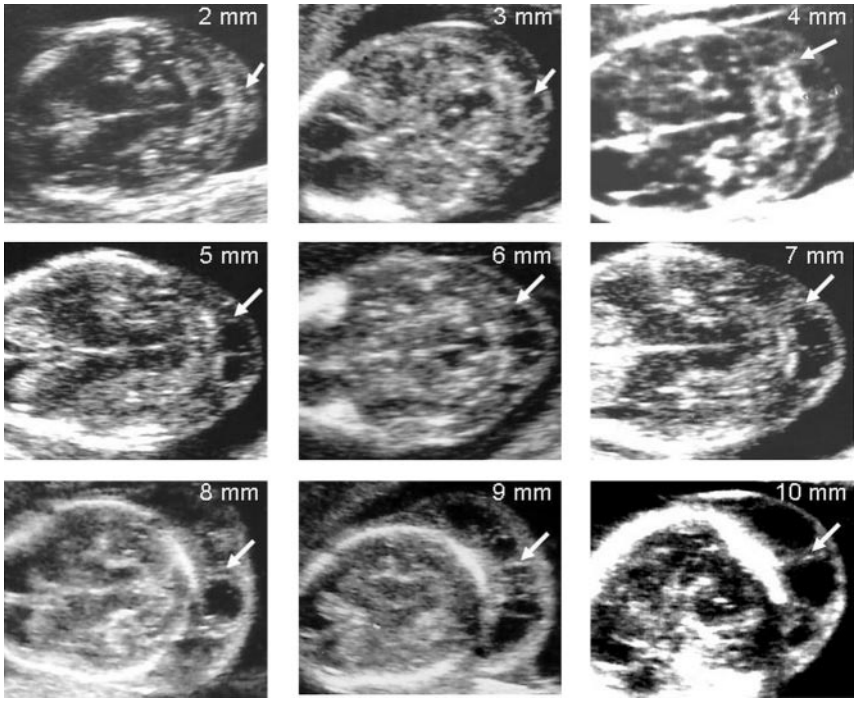

Fig. 2. Transverse suboccipitobregmatic sections of the fetal head demonstrating the presence of septated sonolucency in fetuses with nuchal translucency thickness between 2 mm and 10 mm in thickness at 11–$13^{6/7}$ weeks of gestation. The *arrows* point to the septations.

Molina. Nuchal Translucency and Cystic Hygromas. Obstet Gynecol 2006.

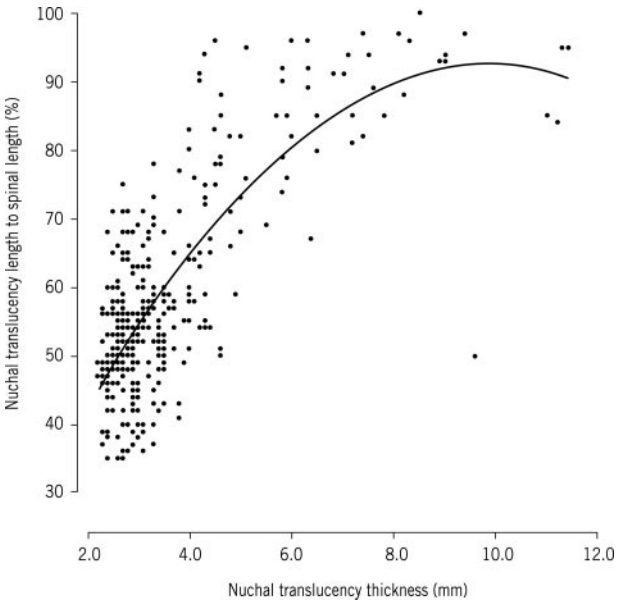

Fig. 3. Relation between percentage of nuchal translucency length to spinal length and nuchal translucency thickness.
Molina. Nuchal Translucency and Cystic Hygromas. Obstet Gynecol 2006.

percentage of NT length to spinal length was 80% or more, except in two of the fetuses with Turner syndrome, in which the increased NT thickness was confined to the neck and thorax (Fig. 4).

The fetal karyotype was abnormal in 83 (21.5%, 95% confidence interval 17.4–25.6%) pregnancies, including 52 cases of trisomy 21 (Table 2). Univariable regression analysis demonstrated that significant predictors of abnormal karyotype were gestational age, fetal CRL, fetal NT, and NT length to spinal length, but multiple regression showed that the only significant independent predictor was fetal NT (Table 3).

DISCUSSION

The findings of this study confirm that, first, there is a high association between increased NT and trisomy 21 as well as other chromosomal defects, and second, the incidence of chromosomal defects increases with NT thickness.[16,19–21] In a previous, more extended study of 11,315 pregnancies with increased NT, the fetal karyotype was abnormal in 2,168 (19.2%), and the incidence of chromosomal defects increased with NT thickness from about 7% for those with NT between the 95th percentile for CRL and 3.4 mm to 20% for NT of 3.5–4.4 mm, 50% for NT of 4.5–6.4 mm, and 75% for NT of 6.5 mm or more.[21] Furthermore, the distribution of NT was different for each type of chromosomal defect; in the majority of fetuses with trisomy 21 the NT thickness was below 4.5 mm, whereas in the majority of fetuses with trisomies 13 or 18 it was 4.5–8.4 mm, and in those with Turner syndrome it was 8.5 mm or more.

The data demonstrate that septations within the translucency can be seen in all fetuses with increased NT, provided the fetal neck is examined in the transverse suboccipitobregmatic plane. The ability to observe such septations is simply dependent on, first, obtaining the correct transverse plane of the fetal head and neck with the septations being parallel to the transducer, and second, on the use of the appropriate gain on the settings of the machine.

The data also demonstrate that the length of extension of NT from the cervical toward the sacral region is related to the thickness of NT. This is not surprising and it is comparable to ankle edema in postnatal life, which like increased NT, has a multifactorial etiology; the more the edema, the higher up the legs it can be demonstrated. The study has also shown that, whatever association there is between the length of NT and abnormal fetal karyotype, this association is a mere consequence of the fact that a higher NT thickness corresponds to a greater length.

In the early 1990s, the term "increased NT thickness" was introduced to describe the abnormal accumulation of fluid under the skin behind the fetal neck. The methodology for measuring NT thickness is

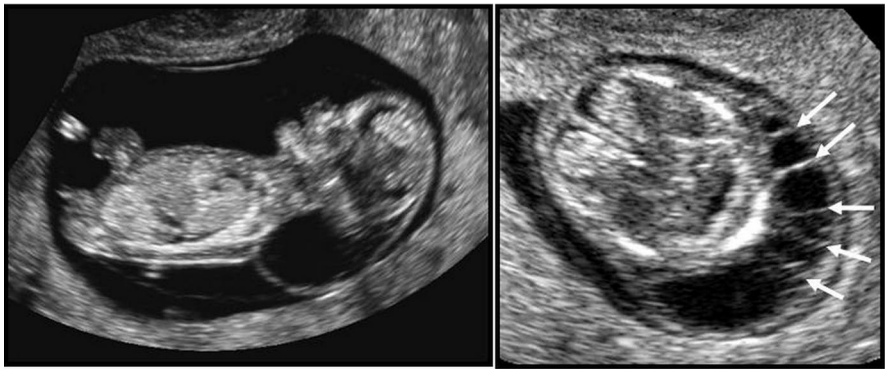

Fig. 4. Transverse and longitudinal sections of a 12-week-old fetus with Turner syndrome demonstrating septated sonolucency, 9 mm in thickness, which was confined to the neck and upper thorax. The *arrows* on the right point to the septations.
Molina. Nuchal Translucency and Cystic Hygromas. Obstet Gynecol 2006.

Table 2. Incidence of Chromosomal Defects in fetuses With Increased Nuchal Translucency Thickness

		Abnormal Karyotype				
Nuchal Translucency (mm)	N	Total*	Trisomy 21†	Trisomy 18 or 13†	Turner Syndrome†	Other†
95th percentile–3.4	268	23 (8.6, 5.2–12.0)	15 (28.9)	4 (20.0)	–	4 (57.1)
3.5–4.4	60	20 (33.3, 21.1–45.6)	15 (28.9)	4 (20.0)	–	1 (14.3)
4.5–5.4	18	11 (61.1, 36.2–86.1)	7 (13.4)	3 (15.0)	1 (25.0)	–
5.5–6.4	14	9 (64.3, 35.6–93.7)	5 (9.6)	3 (15.0)	–	1 (14.3)
≥ 6.5	26	20 (76.9, 59.6–94.3)	10 (19.2)	6 (30.0)	3 (75.0)	1 (14.3)
Total	386	83 (21.5, 17.4–25.6)	52 (100)	20 (100)	4 (100)	7 (100)

* Percentages in parentheses with 95% confidence interval are based on row totals.
† Percentages in parentheses are based on column totals.

Table 3. Regression Analysis in the Prediction of Abnormal Karyotype in Fetuses with Increased Nuchal Translucency Thickness

		Chromosomal Abnormality			
		Univariable Analysis		Multivariable Analysis	
Variable	Median (range)	OR (95% CI)	*P*	OR (95% CI)	*P*
Gestational age (day)	88 (77–97)	0.92 (0.87–0.97)	< .002	0.97 (0.88–1.07)	.562
Crown-rump length (mm)	65 (45–84)	0.95 (0.92–0.97)	< .001	0.98 (0.93–1.04)	.532
Nuchal translucency thickness (mm)	3.0 (2.2–11.4)	2.07 (1.69–2.52)	< .001	1.69 (1.25–2.28)	< .001
Nuchal translucency length to spinal length (%)	55 (35–100)	1.07 (1.05–1.09)	< .001	1.02 (0.99–1.05)	.179

OR, odds ratio; 95% CI, 95% confidence interval.

reproducible, and the measurement can be subjected to external quality assurance.[20] However, those performing the NT scan should receive training and acquire expertise in doing so.[20] Extensive research in the last 15 years has established that increased NT is associated with chromosomal defects, many fetal malformations, and genetic syndromes, and the incidence of these abnormalities is related to the thickness, rather than the appearance, of NT.[17–21] The likelihood ratios for trisomies 21, 18, and 13, for deviations in the measured NT from the normal median for CRL, have been validated by prospective screening studies involving many hundreds of thousands of patients.[20] The measurement of fetal NT can be combined with maternal serum–free ß-hCG and PAPP-A at 11–13$^{6/7}$ weeks to give accurate patient-specific risks and provide the most effective method of screening for trisomy 21, with a detection rate of 90% for a false positive rate of 5%.[20,23] Further improvement in first-trimester screening can be achieved by the inclusion of assessment of the nasal bone and flow in the tricuspid valve and ductus venosus, with a detection rate of more than 90% for a false-positive rate of less than 3%.[24] During the second trimester, increased NT usually resolves, but in a few cases, it evolves into nuchal edema or true cystic hygromas.[1,2]

It was recently suggested that first-trimester cystic hygroma constitutes such a unique and easily identifiable marker that, in contrast to NT, it can be implemented in population screening without the need for sonographers to receive special training and ongoing surveillance to confirm accuracy of diagnosis.[22] Furthermore, it was recommended that, after the diagnosis of cystic hygromas, it is unnecessary for maternal serum–free ß-hCG and PAPP-A to be measured and for software to be used for calculation of patient-specific risk of chromosomal defects. Instead, the parents should be counseled that 50% of fetuses will have a chromosomal abnormality.[22] However, the findings of the present study have demonstrated that, first, when visualized appropriately all increased NTs contain septae, second, the length of NT correlates with its thickness, and third, the risk of a chromosome abnormality is not dependent on the length of the translucent area once its thickness is accounted for. Consequently, cystic hygroma does not constitute a distinct entity in the first trimester that confers a special risk status independent of the NT thickness.

REFERENCES

1. Chervenak FA, Isaacson G, Blakemore KJ, Breg RW, Hobbins JC, Berkowitz RL, et al. Fetal cystic hygroma: cause and natural history. N Engl J Med 1983;309:822–5.

2. Azar G, Snijders RJM, Gosden CM, Nicolaides KH. Fetal nuchal cystic hygromata: associated malformations and chromosomal defects. Fetal Diagn Ther 1991;6:46–57.
3. Benacerraf BR, Gelman R, Frigoletto FD. Sonographic identification of second-trimester fetuses with Down's syndrome. N Engl J Med 1987;317:1371–6.
4. Nicolaides KH, Azar G, Snijders RJM, Gosden CM. Fetal nuchal edema: associated malformations and chromosomal defects. Fetal Diagn Ther 1992;7:123–31.
5. Van der Putte SCJ. Lymphatic malformation in human fetuses: a study of fetuses with Turner's syndrome or status Bonnevie-Ullrich. Virchows Arch A Pathol Anat Histol 1977;376: 233–46.
6. 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;33:141–6.
7. Cullen MT, Gabrielli S, Green JJ, Rizzo N, Mahoney MJ, Salafia C, et al. Diagnosis and significance of cystic hygroma in the first trimester. Prenat Diagn 1990;10:643–51.
8. MacLeod AM, McHugo JM. Prenatal diagnosis of nuchal cystic hygroma. Br J Radiol 1991;64:802–7.
9. 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;80:80–2.
10. Suchet IB, van der Westhuizen NG, Labatte MF. Fetal cystic hygromas: further insights into their natural history. Can Assoc Radiol J 1992;43:420–4.
11. Van Zalen-Sprock MM, van Vugt JMG, van Geijn HP. First-trimester diagnosis of cystic hygroma: course and outcome. Am J Obstet Gynecol 1992;167:94–8.
12. Ville Y, Borghi E, Pons JC, Lelorc'h M. Fetal karyotype from cystic hygroma fluid. Prenat Diagn 1992;12:139–43.
13. Johnson MP, Johnson A, Holzgreve W, Isada NB, Wapner RJ, Treadwell MC, et al. First-trimester simple hygroma: cause and outcome. Am J Obstet Gynecol 1993;168:156–61.
14. Nadel A, Bromley B, Benacerraf BR. Nuchal thickening or cystic hygromas in first- and early second-trimester fetuses: prognosis and outcome. Obstet Gynecol 1993;82:43–8.
15. Trauffer ML, Anderson CE, Johnson A, Heeger S, Morgan P, Wapner RJ. The natural history of euploid pregnancies with first-trimester cystic hygromas. Am J Obstet Gynecol 1994; 170:1279–84.
16. Nicolaides KH, Azar G, Byrne D, Mansur C, Marks K. Fetal nuchal translucency: ultrasound screening for chromosomal defects in first trimester of pregnancy. Br Med J 1992;304: 867–89.
17. Souka AP, Snidjers RJM, Novakov A, Soares W, Nicolaides KH. Defects and syndromes in chromosomally normal fetuses with increased nuchal translucency thickness at 10–14 weeks of gestation. Ultrasound Obstet Gynecol 1998;11:391–400.
18. Souka AP, Von Kaisenberg CS, Hyett JA, Sonek JD, Nicolaides KH. Increased nuchal translucency with normal karyotype. Am J Obstet Gynecol 2005;192:1005–21.
19. Snijders RJM, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal translucency thickness at 10–14 weeks of gestation: Fetal Medicine Foundation First Trimester Screening Group. Lancet 1998;351:343–6.
20. Nicolaides KH. Nuchal translucency and other first-trimester sonographic markers of chromosomal abnormalities. Am J Obstet Gynecol 2004;191:45–67.
21. Kagan KO, Avgidou K, Molina FS, Gajewska K, Nicolaides KH. Relation between increased fetal nuchal translucency thickness and chromosomal defects. Obstet Gynecol 2006; 107:6–10.
22. Malone FD, Ball RH, Nyberg DA, Comstock CH, Saade GR, Berkowitz RL, et al. First-trimester septated cystic hygroma: prevalence, natural history, and pediatric outcome. Obstet Gynecol 2005;106:288–94.
23. Avgidou K, Papageorghiou A, Bindra R, Spencer K, Nicolaides KH. Prospective first-trimester screening for trisomy 21 in 30,564 pregnancies. Am J Obstet Gynecol 2005;192:1761–7.
24. Nicolaides KH, Spencer K, Avgidou K, Faiola S, Falcon O. Multicenter study of first-trimester screening for trisomy 21 in 75,821 pregnancies: results and estimation of the potential impact of individual risk-orientated two-stage first-trimester screening. Ultrasound Obstet Gynecol 2005;25:221–6.