ORIGINAL ARTICLE

The significance of anterolateral neck cysts in early diagnosis of fetal malformations

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ABSTRACT

Objective The objective of this study is to examine the association of lateral fetal neck cysts with increased nuchal translucency, chromosomal abnormalities and fetal malformations.

Method In a consecutive collective of 4216 prenatal ultrasound examinations between 11 and 17 weeks of gestation 32 fetuses with lateral neck cysts were found. The size of the cysts was examined. The association of the findings with increased nuchal translucency, chromosomal aberrations and fetal malformations was examined.

Results All but two out of 32 cases had bilateral cysts. Seventeen fetuses had aneuploidy and an increased nuchal translucency, 15 of those with major structural malformations. Of the 15 fetuses with normal karyotype nine (60%) had an increased nuchal translucency, seven had a fetal malformation or hydrops. A favorable outcome was found in 6/15 fetuses with normal karyotype and normal nuchal translucency. Lateral neck cyst diameter was associated to nuchal translucency, chromosomal abnormality and/or fetal malformations. Cysts smaller than 3 mm had a favorable outcome even in the presence of an increased nuchal translucency.

Conclusion Fetuses with lateral neck cysts often not only present with increased nuchal translucency and chromosomal aberrations but also with fetal malformations. Fetuses with lateral neck cysts and increased nuchal translucency were aneuploid or had a fetal malformation in 85%. Cysts smaller than 3 mm had a favorable outcome.

Funding sources: None
Conflicts of interest: None declared

INTRODUCTION

With continuous advances of ultrasound technology increasingly smaller structures can be visualized early in pregnancy. This highlights the importance of anomaly scan in the first and early second trimester. One of the anomalies detected are anterolateral fetal neck cysts. They may be unilaterally or bilaterally, isolated or accompanied by an increased nuchal translucency. They are believed to arise from delayed communication between the primitive lateral lymphatic neck sacs and the jugular lymphatic veins.[1,2] These anterolateral neck cysts correspond to the jugular lymphatic sacs and must be differentiated from cystic hygroma colli, which are situated in the dorsal position of the fetal neck.[3–5] While a great sum of studies examined dorsal structures like nuchal translucency and cystic hygroma colli, only a small number of articles reviewed anterolateral fetal neck cysts.[1,6–15]

The existing data concerning the relevance of such a finding, especially in isolated forms, are conflicting. It is still not known whether the size of the cysts is correlated with the rate of chromosomal aberrations or the presence of fetal malformations.

The aims of this study were to assess the association of anterolateral neck cysts with increased nuchal translucency, chromosomal abnormalities and fetal malformations. We also examined the association between the size of the cysts and genetic aberrations or fetal malformations.

METHODS

From October 2009 to March 2015 a consecutive collective of 4216 patients between 11 and 17 weeks of pregnancy had an early fetal anomaly scan in our institution. The vast majority of the 4216 patients were low risk (91%). The gestational age was calculated according to the last menstrual period, confirmed by the crown rump length of the first trimester scan. In case of a discrepancy of more than one week the due date was corrected. We performed a data search using GE View Point medical data base system (Version 5.6.23.59). All cases of fetal lateral neck cysts were selected and evaluated retrospectively.

The ultrasound examinations were performed transabdominally, transvaginally or by combining the two methods. A complete anatomical survey was performed on each fetus.

Lateral neck cysts were defined as ≥2.0-mm-sized hypoechoic areas in the anterolateral portion of the fetal neck (Figure 1). Measurements of the size of the cysts were made in three orthogonal planes (length, width, and height). The average diameter was used for statistical evaluation. In case of bilateral cysts ($n=30$) the right and the left sides were evaluated separately.

The anterolateral neck cysts were differentiated from cystic hygroma colli, which is defined as septated, fluid-filled cavities located in the posterior part of the neck. Nuchal translucency was measured in accordance to the guidelines of the Fetal Medicine Foundation.[16] An increased nuchal translucency was defined as being above the 95th percentile for the corresponding week of gestation.

All patients had 1 to 3 ultrasound serial examinations to follow-up the presence and size of the cysts. The final outcome of the fetuses without chromosomal abnormality was evaluated at birth. All fetuses with chromosomal abnormality ended in spontaneous miscarriage or termination of pregnancy.

All examinations were performed using high-resolution ultrasound devices (Voluson E8 Expert, 6 to 12 MHz or Voluson 730 Expert, 5 to 9 MHZ vaginal, 4 to 8 MHz abdominal, GE Medical Systems Kretz Ultrasound, Zipf, Austria; IU22, Philipps, 3 to 10 MHz vaginal, 1 to 5 MHz abdominal, Solingen).

Included were all fetuses with and excluded all fetuses without anterolateral neck cysts.

We then examined the association of lateral neck cysts with increased nuchal translucency, chromosomal aberrations and fetal malformations. Moreover, we evaluated whether there was an association between the size of the anterolateral neck cysts and a genetic abnormality or fetal malformation.

Conventional fetal karyotyping was performed using chorionic villous sampling in early gestation, or amniocentesis starting from 15th week of gestation. All genetic procedures were performed following genetic counselling.

Ethical approval was not required for the study because of the retrospective analysis of the normal clinical data.

Statistical analysis

The differences between two groups were tested using the Kruskal–Wallis test (SOFA Statistics AGPL3 license 2009–2015 Paton-Simpson & Associates Ltd.), which is a non-parametric method for testing whether samples originate from the same distribution.

RESULTS

Characteristics of the collective

Out of 4216 patients examined in the study period 32 fetuses (0.76%) with anterolateral neck cysts were diagnosed. The majority had bilateral cysts ($n=30$; 93.7%). One of the two fetuses with unilateral cyst had a normal outcome, the other a trisomy 21.

The median maternal age was 33 years (22–45 years) with a median gestational age at diagnosis of 13 + 3 weeks (range 11 + 6–17 + 4 weeks).

All patients received a first trimester scan in our institution except for two patients. One of these patients first presented at 16 + 5 weeks of pregnancy, the other at 17 + 4 weeks. Both had an increased nuchal translucency diagnosed by their referring obstetrician. The first case had nuchal edema at the time of presentation and ended in spontaneous miscarriage at 21 + 6 weeks of pregnancy. The other case had trisomy 21 associated with atrioventricular septal defect and multiple soft markers.

Chromosomal aberrations were present in 53.1% (17/32). In nine fetuses trisomy 21 (28.1%) was found, in seven fetuses trisomy 18 (21.9%) and in one trisomy 13. Out of these 15 fetuses (46.9%) with normal karyotype 5 had structural malformations.

Collective with abnormal karyotype

The description of the collective with abnormal karyotype is shown in Figure 2a. All of these fetuses had an increased nuchal translucency. In the group with trisomy 21 associated major structural malformations were found in 88.9%, in 66.7% accompanying soft markers for chromosomal abnormalities. All of the pregnancies were terminated.

In the group with trisomy 18 associated major structural malformations were found in 85.7%. All of these fetuses ($n=6$) had termination of pregnancy, one ended in a spontaneous miscarriage. The pregnancy with trisomy 13 had associated major malformations and ended in a spontaneous miscarriage at 15 weeks of gestation.

Collective with normal karyotype

Out of the 15 fetuses with lateral neck cysts and normal karyotype nine had an increased nuchal translucency (Figure 2b). Of these fetuses seven had prenatal abnormalities (Table 1). Major malformations were seen in four fetuses (spontaneous miscarriage

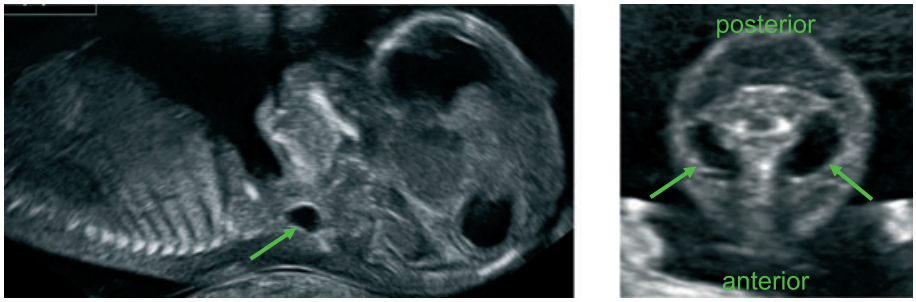

Figure 1 Lateral neck cysts are shown, represented by small hypoechoic structures situated anterolateral in the fetal neck

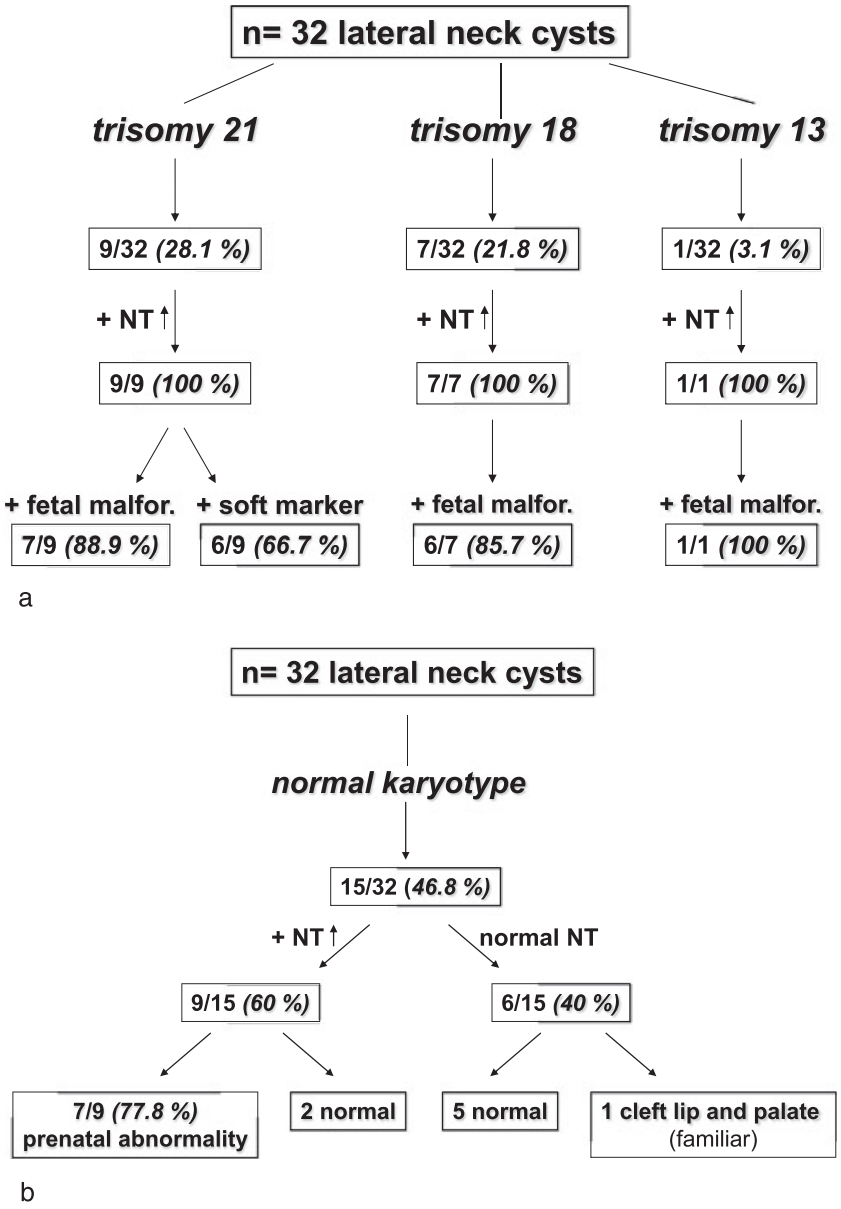

Figure 2 (a) The flow chart represents the association between lateral neck cysts and chromosomal abnormalities. The number of cases with increased nuchal translucency and fetal malformations is shown as well. (b) The flow chart represents the association between lateral neck cysts and normal karyotype. The number of cases with increased nuchal translucency and fetal malformations is shown as well

or termination of pregnancy); minor malformations were seen in one and hydrops in two fetuses (both had lateral neck cysts smaller than 3 mm).

Out of the fetuses with normal karyotype and normal nuchal translucency ($n = 6$), three had soft markers for chromosomal abnormalities (shortened nasal bone, echogenic cardiac focus, and suspicious biochemistry). All but one of the six fetuses had a normal outcome (Figure 2b).

Fetuses with increased nuchal translucency

In total there were 26 fetuses with increased nuchal translucency. Seventeen had trisomy 13, 18, or 21, seven had fetal malformations and two had a normal outcome (Figure 2b). Twenty-one fetuses ended or in spontaneous miscarriages ($n = 3$; all fetuses hydropic, one of them with trisomy 13, one with holoprosencephaly and short limbs) or in termination of pregnancy ($n = 18$).

Association between size of the lateral neck cysts, fetal outcome, and nuchal translucency at first presentation

In total 10 fetuses had a normal karyotype without fetal malformations. Conversely, 22 fetuses had either an abnormal karyotype or fetal malformations or both. In fetuses with a normal outcome median cyst size at the first presentation (median 13 + 2 weeks of pregnancy) on the left side of the neck was 3.16 mm, whereas in the others the median cyst size was 4.63 mm ($p = 0.002$). The same goes for the cyst size on the right, median 2.98 mm versus 4.68 mm ($p = 0.003$).

The size of the cysts was significantly associated with the nuchal translucency ($p = 0.008$ for the left; $p = 0.023$ for the

Table 1 The table shows the specification of the seven fetuses with normal karyotype, bilateral neck cysts, and increased nuchal translucency (NIHF = non immunologic hydrops fetalis, CCA = agenesis of corpus callosum)

Fetal malformations prenatal ($n = 7$)	Outcome
NIHF with skin edema, bilateral hydrothorax, ascites, and shortening of femora	*Spontaneous miscarriage*
Eventeration, left sided amelia, and skin edema	*Termination* (malformations confirmed by pathology)
Soft marker (reverse Flow Ductus venosus, TI) at 13 + 0; CCA, arachnoidal cyst, arthrogryposis multiplex congenita at 21 + 4 weeks	*Termination* (malformations confirmed by pathology)
NIHF with skin edema, ascites, doubled left kidney with hydronephrosis, left sided club foot	*Doubled left kidney with hydronephrosis, left sided club foot*
Skin edema, micrognathia, and short nasal bone	*Termination* (malformations confirmed by pathology)
NIHF with skin edema, left sided hydrothorax, hydronephrosis at 12 + 2 weeks; normal at 19 + 5 weeks	*Normal outcome*
Bilateral pleural effusion, pericardial effusion, ascites at 12 + 5; normal at 21 + 5 weeks	*Normal outcome*

right). The mean cyst size in fetuses with NT > 95th percentile was significantly higher compared with the fetuses with normal NT (4.43 mm vs 2.41 mm for the left side and 4.56 mm vs 3.14 for the right side).

Fetuses with cysts smaller than 3 mm ($n = 5$) had a normal outcome even in cases with increased nuchal translucency ($n = 2$). The median size of the cysts in fetuses with trisomies 21, 18, and 13 were 3.8 mm, 4.3 mm, and 3.7 mm, respectively. Fetuses with normal chromosomes but malformations had a median size of the cysts of 3.9 mm. Fetuses with normal chromosomes but without malformations had a median size of the cysts of 2.6 mm. This difference was statistically significant ($p < 0.005$).

Follow up of the lateral neck cysts

All patients without abortion or termination of pregnancy had 1 to 3 follow-up ultrasound examinations. A second ultrasound was performed in 18 fetuses (median 17 + 3 weeks of pregnancy) and a third ultrasound in 6 fetuses (median 18 + 0 weeks of pregnancy; Figure 3).

In fetuses with an unfavorable outcome the mean diameter of the cysts was increased at the second ultrasound compared with the first ultrasound (7.21 mm on the left side, $p = 0.005$; and 6.65 mm, $p = 0.004$ on the right side). At the third ultrasound the median size of the cysts decreased to 4.5 mm on the left side and 4.7 mm on the right side.

Out of the 10 fetuses with normal outcome (included 1 fetus with cleft lip and palate) in 8 fetuses the lateral neck cysts vanished at least at 21 + 6 weeks of gestation. The remaining 2 fetuses were lost on follow-up after 14 + 0 weeks of gestation.

DISCUSSION

There are few articles in the literature dealing with fetal anterolateral neck cysts and their clinical significance.[1,8,17] Some authors referred to them as "nuchal blebs," "non-septated cystic hygoma," or "jugular lymphatic sacs."[2,6,7,9,18–20] They are transient findings predominantly present during the first anomaly scan between 14 and 16 weeks of pregnancy.[1,6–8,18–20] In our study they could be seen from 11 + 6 until 21 + 6 weeks of gestation. After 21 + 6 weeks all cysts had vanished. There was a bias concerning the time of vanishing of the cysts during pregnancy because of the high incidence of early spontaneous miscarriage or termination of pregnancy in the cases with chromosomal aberrations or fetal

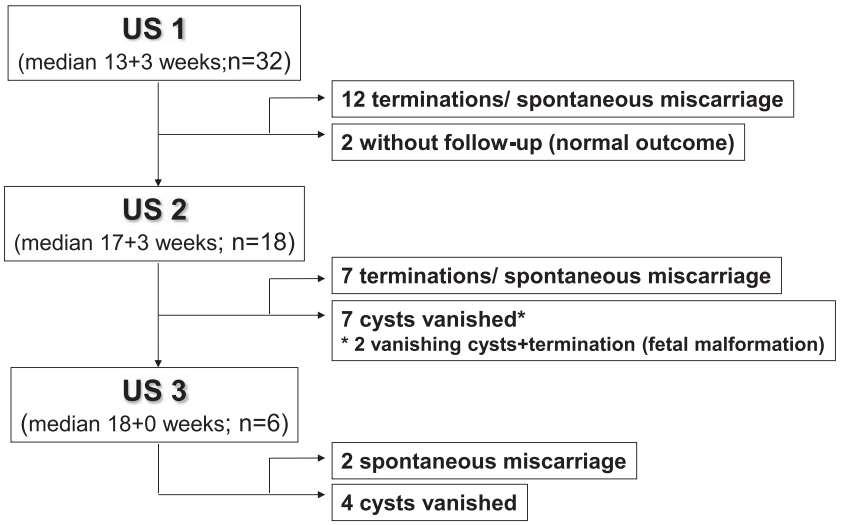

Figure 3 The flow chart shows the follow-up of the fetuses with lateral neck cysts

malformations ($n = 21$), allowing follow-up only in the remaining cases.

In the literature no significant difference was reported if the cysts were uni- or bilateral.[8] In our collective we had only two fetuses with unilateral neck cyst, one of them with trisomy 21, the other with normal outcome. Because of the low number of unilateral cases we cannot compare their outcome to the bilateral cases.

We could show that all isolated cases with normal nuchal translucency had a favorable outcome with normal genetics, even in the presence of soft markers.

On the other hand 65.4% of the cases combined with increased nuchal translucency had an aneuploidy. This is in accordance with the literature.[1,8,10] Nicolaides et al.[10] report a duplication of aneuploidies in the combined cases. Achiron et al.[1] also found no genetic abnormality in the isolated forms, but 25% abnormal karyotypes in the combined forms.

Of importance is not only the presence of the anterolateral cysts but also their size. We included fetuses with neck cysts of ≥2 mm in the study. In the literature only a few authors examined the size of the cysts. Sharony et al.[8] included fetuses with cysts >2.5 mm.

We found a significant association between the size of the cysts and the nuchal translucency. Nevertheless, we encountered a normal outcome in fetuses with cysts smaller than 3 mm, even in the presence of an increased nuchal translucency.

There was a significant association between the size of the cysts and the fetal outcome. Larger cysts were associated with an unfavorable outcome. The cysts with the greatest diameter were found in fetuses with trisomy 18 (median 4.3 mm), followed by those with trisomy 21 (median 3.8 mm) and those with normal karyotype but malformations (median 3.9 mm). The smallest diameter of the cysts was found in euploid fetuses without malformations (median 2.6 mm). This difference was statistically significant ($p < 0.05$). Bekker et al.[20] also found in a collective of 74 fetuses with increased nuchal translucency highly significant larger cyst volumes in aneuploid compared with euploid fetuses.

CONCLUSION

We could show in our study that fetal lateral neck cysts are transient. If smaller than 3 mm or isolated they are associated with a favorable outcome. On the other hand, in case of the presence of an increased nuchal translucency there was a highly significant association to an adverse outcome, that is chromosomal abnormality, spontaneous miscarriage, termination of pregnancy, or fetal malformation. The presented results help counseling the parents and avoid unnecessary invasive procedures. On the contrary, in the presence of other factors like increased nuchal translucency further investigations are mandatory.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- There is an association between lateral neck cysts, increased nuchal translucency, and fetal aneuploidy.

WHAT DOES THIS STUDY ADD?

- Fetuses with lateral neck cysts in combination with increased nuchal translucency showed a significant risk for aneuploidy and structural malformations compared with euploid fetuses. Further, cysts smaller than 3 mm have a favorable outcome regardless of the nuchal translucency.

REFERENCES

1. Achiron R, Yagel S, Weissmann A, *et al.* Fetal neck cysts: early second-trimester transvaginal diagnosis, natural history and clinical significance. Ultrasound Obstet Gynecol 1995;6:396–9.
2. Haak MC, Bartelings MM, Jackson DG, *et al.* Increased nuchal translucency is associated with jugular lymphatic distension. Hum Reprod 2002;17:1086–92.
3. Ville Y, Lalondrelle C, Doumerc S, *et al.* First-trimester diagnosis of nuchal anomalies: significance and fetal outcome. Ultrasound Obstet Gynecol 1992;2:314–6.
4. Taipale P, Hillesmaa V, Salonen R, *et al.* Increased nuchal translucency as a marker for fetal chromosomal defects. N Engl J Med 1997;337:1654–8.
5. Bekker MN, van den Akker NMS, de Mooij YM, *et al.* Jugular lymphatic maldevelopment in Turner syndrome and trisomy 21: different anomalies leading to nuchal edema. Reprod Sci 2008;15:295–304.
6. Bronshtein M, Rottem S, Yoffe N, *et al.* First-trimester and early second trimester diagnosis of nuchal cystic hygroma by transvaginal sonography: diverse prognosis of the septated from the nonseptated lesion. Am J Obstet Gynecol 1989;161:78–82.
7. Bronshtein M, Bar-Hava I, Blumenfeld I, *et al.* The difference between septated and nonseptated nuchal cystic hygroma in the early second trimester. Obstet Gynecol 1993;81:683–7.
8. Sharony R, Tepper R, Fejgin M. Fetal lateral neck cysts: the significance of associated findings. Prenat Diagn 2005;25:507–10.
9. Rotmensch S, Celentano C, Sadan O. et al.:Familial occurrence of isolated nonseptated nuchal cystic hygromata in midtrimester of pregnancy. Prenat Diagn 2004;24:260–4.
10. Nicolaides KH, Brizot ML, Snijders RJ. Fetal nuchal translucency: ultrasound screening for fetal trisomy in the first trimester of pregnancy. Br J Obstet Gynaecol 1994;101:782–6.
11. Benacerraf BR, Barss VA, Laboda LA. A sonographic sign for the detection in the second trimester of the fetus with Down's syndrome. Am J Obstet Gynecol 1985;151(8):1078–9.
12. Snijders RJ, Johnson S, Sebire NJ, *et al.* First-trimester ultrasound screening for chromosomal defects. Ultrasound Obstet Gynecol 1996;7: 216–26.
13. Bernard P, Chabaud J, Le Guern H, *et al.* Cystic hygroma of the neck. Antenatal diagnosis, prog nostic factors, management. 42 cases. J Gynecol Obstet Biol Reprod 1991;20:487–95.
14. Gedikbasi A, Oztarhan K, Aslan G, *et al.* Multidisciplinary approach in cystic hygroma: prenatal diagnosis, outcome, and postnatal follow up. Pediatr Int 2009;51:670–7.
15. Moscoso G. Fetal nuchal translucency: a need to understand the physiological basis. Ultrasound Obstet Gynecol 1995;5:6–8.
16. Pandya PP, Snijders RJ, Johnson SP, *et al.* Screening for fetal trisomies by maternal age and fetal nuchal translucency thickness at 10 to 14 weeks of gestation. Br J Obstet Gynaecol 1995;102: 957–62.

17. Abi-Nader K, Filippi E, Pandya P, *et al.* Bilateral neck cysts as an isolated sonographic finding in the antenatal detection of fetal aneuploidy: a case report. Cases J 2009;2:8322.
18. Zimmer EZ, Drugan A, Ofir C, *et al.* Ultraound imaging of fetal neck anomalies: Implications for the risk of aneuploidy and structural anomalies. Prenat Diagn 1997;17:1055–8.
19. Bekker MN, Haak MC, Rekoert-Hollander M, *et al.* Increased nuchal translucency and distended jugular lymphatic sacs on first-trimester ultrasound. Ultrasound Obstet Gynecol 2005;25:239–45.
20. Bekker MN, Twisk JW, Bartelings MM, *et al.* Temporal relationship between increased nuchal translucency and enlarged jugular lymphatic sacs. Obstet Gynecol 2006;108:846–53.