Natural Evolution of Nuchal Thickness in Trisomy-21 Fetuses

ANTONI BORRELL, PhD, DOLORS COSTA, PhD, JOSEP M. MARTINEZ, PhD, M. TERESA FARRÉ, MD, JOSEP CARARACH, MD, AND ALBERT FORTUNY, PhD

Objective: To assess the natural evolution of nuchal thickness in trisomy-21 fetuses.

Methods: Serial measurements of nuchal thickness were performed over a 1- to 6-week period in 45 consecutive fetuses with trisomy 21, between the 10th and the 23rd weeks of pregnancy. To avoid a gestational age confounding effect, nuchal thickness also was expressed in standard deviations (SDs) for the corresponding gestational week. In addition, the changes were assessed in terms of the presence of clinical positive thickening, considered as such when the measurement was above 2.5 SD.

Results: A mean increase of 1.8 mm (95% confidence interval [CI] 1.3, 2.3) for nuchal thickness was observed for a mean period of 21 days. When corrected by gestational age, the mean increase of 0.3 SD (95% CI -0.2, 0.9) was found to be not significant. No clinically relevant nuchal thickening changes were recorded (51% versus 69%) at re-examination.

Conclusion: Nuchal thickening at re-examination is observed in a similar proportion of trisomy-21 fetuses as when first observed. (Obstet Gynecol 1998;91:78–81. © 1998 by The American College of Obstetricians and Gynecologists.)

The use of fetal nuchal skinfold thickness measurement as an ultrasound marker for Down syndrome was first suggested by Benacerraf et al1 in 1985. In their first large series reporting on midtrimester fetuses, nuchal thickness was used to predict 43% of the fetuses with Down syndrome, with a false-positive rate of only 0.1%. When nuchal thickness was measured in first-trimester fetuses, it identified 86% of the cases of trisomy 21 with a 4.5% false-positive rate (Szabo J, Gellen J. Nuchal fluid accumulation in trisomy 21 detected by vagino-sonography in first trimester [letter]. Lancet 1990;2:1133).3

More recently, universal ultrasound screening is being proposed to detect aneuploidy at 10–14 weeks' gestation.4 However, information available on the natural evolution of nuchal thickening of fetuses with an abnormal karyotype is limited to the data obtained in 14 fetuses with trisomy 21 in two studies.5,6 To assess the natural evolution of nuchal thickness using serial measurements in trisomy-21 fetuses, 45 consecutive affected cases were studied in our unit.

Materials and Methods

During a 4-year period (October 1991–September 1995), 35 trisomy-21 fetuses were diagnosed using amniotic fluid cells taken between 13 and 18 weeks' gestation. In addition, for a 3-year period (October 1992–September 1995) 15 further trisomy-21 fetuses were diagnosed between 10 and 13 weeks' gestation using chorionic villous sampling. In all cases, nuchal thickness was first measured prospectively in a suboccipitobregmatic view of the fetal head (Hitachi EUB 415; Hitachi Medical Corp., Tokyo, Japan) before the invasive diagnostic procedure. Early scans were done vaginally, and scans in the second trimester were performed transabdominally.7 Indications for cytogenetic studies were as follows: advanced maternal age (68%), positive biochemical screening (16%), previous anomaly (4%), fetal structural anomaly (6%), and nuchal thickening (6%). Mean maternal age was 37.7 years, and 21% of the women were under 35.

In 45 of these 50 affected fetuses, nuchal thickness was reassessed in a subsequent ultrasound examination 1–6 weeks later, when the cytogenetic report was delivered to the patient. In two pregnancies, a fetal demise was detected at re-examination, and three pregnant women refused the follow-up scan. The observed changes in nuchal thickness were recorded for each case. Mean differences in thickness for the elapsed period and mean daily differences were established.

To avoid any gestational age confounding effect, nuchal thickness also was expressed as a standard deviation (SD) score, above or below the mean for the
corresponding gestational week. Reference intervals for the chromosomally normal population have been established and reported elsewhere. Ninety-five percent confidence intervals (CIs) were calculated for relevant means and proportions in the assessment of changes.

Changes in nuchal thickening were also assessed in terms of the clinically relevant positive thickening, considered to be present only when the measurement was above 2.5 SD for the corresponding gestational week. These limits were as follows: 3.06 mm (10 weeks), 2.92 mm (11 weeks), 3.34 mm (12 weeks), 3.63 mm (13 weeks), 4.66 mm (14 weeks), 4.57 mm (15 weeks), 4.78 mm (16 weeks), 5.21 mm (17 weeks), and 5.29 mm (18 weeks). The calculation of the appropriate sample size estimated that 36 cases were required for paired observations, using an $\alpha$ error of 5% and a power of 80% for expected prevalences of nuchal thickening of 75% and 40% in the first and second trimester, respectively, as reported in the literature.8,9

Results

Forty-five trisomy-21 fetuses had nuchal thickness measured twice, at mean gestational age of 14.3 weeks (range 10–22 weeks) and 17.2 weeks (range 11–23 weeks). Mean nuchal thickness was 4.8 mm (range 1.2–14 mm) for the first measurement and 6.6 mm (range 2–17 mm) for the second measurement. Thus, nuchal thickness showed a mean increase of 1.8 mm (95% CI 1.3, 2.3; range 1–7 mm) for a mean period of 21 days (range 6–42 days) between ultrasound examinations, with a mean daily increase of 0.1 mm (range 0.05–1 mm). Serial measurements showed that nuchal thickness increased in 36 of the 45 fetuses (80%), remained the same in seven (15%), and decreased in two (4%) (Figure 1).

When nuchal thickness was expressed as an SD score, a slight increase was observed in the mean value of 0.3 SD (95% CI –0.2, 0.9; range –3.1–3.9 SD), with a mean daily increase of 0.03 SD (range –0.2–0.6 SD). In 28 (62%) of the fetuses, there was a relative increase, and a decrease was observed in the remaining 17 (38%) (Figure 2). In addition, the qualitative analysis showed a nonsignificant rise of cases with nuchal thickening (from 51% [95% CI 37, 66] to 69% [95% CI 55, 82]). No changes were recorded in 19 of the fetuses (42%) in whom positive nuchal thickening persisted, nor in ten (22%) in whom nuchal thickening remained negative. Furthermore, appearance of thickening was observed in 12 fetuses (27%) and vanishment in four (9%).

Discussion

There is increasing evidence that nuchal thickness may be a valid ultrasound marker for the more common fetal aneuploidies including trisomies 21 and 18, and monosomy X. Although nuchal skinfold thickness measurement was initially proposed for second-trimester fetuses, more recently emphasis has been placed on first-trimester nuchal translucency measurement for earlier detection.

The results reported in the prospective first-trimester and second-trimester series have been controversial. Second-trimester studies reported sensitivities for Down syndrome ranging from 16% to 78%, with false-positive rates between 0.3% and 8.5%.10–16 Regarding
first-trimester series, a multicenter study, with more than 42,000 pregnancies screened, showed that nuchal translucency combined with maternal age allows the detection of 75% of the trisomy-21 fetuses, with a 4% false-positive rate. These excellent results have not been confirmed consistently by other studies, which have demonstrated sensitivities ranging from 30% to 57% and false-positive rates of 1% to 10%. Unfortunately, no comparative studies have been reported regarding the screening performance for trisomy 21 in different gestational periods. In our unit, according to preliminary results comparing the detection performance, the interval between 10 and 18 weeks appeared to be uniformly optimal, with the exception of weeks 10–11.

Generally speaking, first-trimester screening is preferred in European centers because it provides earlier results, and there is a common belief that nuchal thickening may disappear in the second trimester. Classic cystic hygroma has been reported to vanish in the second trimester in fetuses with trisomy 21, similarly to more recently described vanishing nuchal edema in chromosomally normal fetuses. Thus, it has been assumed widely that this “transient appearance” effect also may be applied to nuchal edema in trisomy-21 fetuses, without evidence from serial studies. In contrast, our study shows that nuchal thickness increased in 80% of the trisomy-21 fetuses, especially those first seen at 10–13 weeks (88%) (Figure 1). After correction for gestational age, and although a relative increase was still observed in 62% of the cases (Figure 2), the mean increase did not reach statistical significance.

On the other hand, in a clinically relevant assessment of nuchal thickening (presence or absence), vanishment of nuchal thickening was seen in only 9% of the studied fetuses in contrast with 27% of the cases in which it appeared. However, the observed rise at re-examination in positive thickening (from 51% to 69%) did not reach statistical significance, possibly due to the limitations imposed by the sample size. Obviously, it is difficult to re-examine a large sample of fetuses with trisomy 21, as the mothers usually undergo pregnancy termination and therefore do not return for follow-up scans.

Serial measurements in fetuses with trisomy 21 have been reported in two studies. In the first series, four of the eight cases reviewed retrospectively showed nuchal thickening in the first trimester, and that number increased to six by the second trimester. In the third trimester, nuchal thickening remained present in only one fetus because spontaneous resolution occurred in five fetuses between 20 and 27 weeks’ gestation. In the second study, in which only affected fetuses with first-trimester (11–13 weeks) nuchal thickening were enrolled, nuchal thickening persisted only in two of six at 18–21 weeks. The first report supports a rationale for second-trimester measurement, whereas the natural evolution between 14 and 18 weeks remains unclear in the second.

The assessment of the natural evolution of nuchal thickness is crucial before recommending universal first-trimester ultrasound screening for aneuploidy. Our data show that in trisomy-21 fetuses nuchal thickening persists longer than suggested. In this regard, two
major issues need to be clarified in further studies to establish the optimal gestational period in which to screen. First, the period with the minimal overlapping in nuchal thickening curves between affected and non-affected fetuses must be defined, and second, the bias of preferential identification of those trisomy-21 fetuses destined to die in utero must be quantitated.20,27

References


Address reprint requests to:
Antoni Borrell, MD, PhD
Prenatal Diagnosis Unit, Hospital Clinic
Department of Obstetrics and Gynecology
University of Barcelona Medical School
Villarreal, 170
Barcelona, 08036
Catalonia
Spain

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