International Journal of Gynecology & Obstetrics 65 (1999) 137–141

International Journal of GYNECOLOGY & OBSTETRICS

Article

Cut-off criteria for second-trimester nuchal skinfold thickness for prenatal detection of Down syndrome in a Thai population

Y. Tannirandorn*, S. Manotaya, B. Uerpairojkit, S. Tanawattanacharoen, D. Charoenvidhya, S. Phaosavasdi

Department of Obstetrics and Gynecology, Chulalongkorn University, Bangkok, Thailand

Received 25 August 1998; received in revised form 23 December 1998; accepted 5 January 1999

Abstract

Objective: To evaluate the use of progressive cut-offs for nuchal skinfold thickness with advancing gestational age and the commonly applied cut-off method (≥ 6 mm) for prenatal detection of Down syndrome in a Thai population. *Method:* A prospective study was performed by experienced perinatologists on 2150 women undergoing second-trimester amniocentesis for the indications of advanced maternal age and past history of chromosomal abnormality. Reference ranges were established for nuchal skinfold thickness from the 16th to the 24th week, using either gestational-specific centiles or the parametric method. Assaying different cut-off criteria for both centile and the parametric methods were calculated and then compared with the commonly applied cut-off level (≥ 6 mm.). *Results:* There were 2114 chromosomally normal pregnancies, 19 fetuses with Down syndrome (1:113), and 17 other chromosome abnormalities. In fetuses with normal karyotype the nuchal skinfold thickness increased with advancing gestational age [NF (mm) = $-0.502 + 0.212$ GA (week), $r = 0.36$, $P < 0.001$]. The sensitivities of an abnormal nuchal skinfold thickness using different cut-off criteria for detecting Down syndrome were low (5.3–26.3%) with the false positive rates ranging from 2.5 to 16.5%. *Conclusions:* In this study, measurement of second-trimester nuchal skinfold thickness was a poor and unreliable screening test for fetal Down syndrome in a Thai population. © 1999 International Federation of Gynecology and Obstetrics.

Keywords: Down syndrome; Nuchal skinfold; Prenatal diagnosis; Ultrasound

* Corresponding author. Tel: +662 2564824; fax: +662 2564825; e-mail: mfmchula@ksc.th.com

0020-7292/99/$20.00 © 1999 International Federation of Gynecology and Obstetrics.
PII: S0020-7292(99)00014-4

1. Introduction

There has been a gradual evolution in the use of ultrasonography as a screening tool for fetal Down syndrome detection. Initially, interest was limited to the detection of gross anatomic defects. Subsequently, investigators raised the possibility that increased nuchal skinfold thickness increased the Down syndrome risk. Benacerraf et al. [1,2] first described the use of nuchal skinfold measurement for this purpose. In their study this measurement was 43% sensitive for the detection of Down syndrome with a very low false-positive rate of 0.1% [2]. They used the single cut-off for an abnormal nuchal skinfold thickness of ≥ 6 mm in the second-trimester fetuses [1,2]. Since then, there have been several studies using this approach and have reported a wide disparity in Down syndrome detection rates, ranging from 9 to 75% [2–12]. Discrepancies in technique, ultrasound equipment, and population characteristics are likely to explain the variability reported in the nuchal skinfold thickness sensitivity. In addition, nuchal skinfold thickness has been reported to be increased with advancing gestational age in normal fetuses [12,13]. This may also be the cause of disparity in Down syndrome detection rates. Therefore, the cut-off level of nuchal skinfold thickness should be adjusted accordingly. To our knowledge, there has been no report of using this screening method in the Asian population.

The objective of this study was to evaluate the use of progressive cut-offs for nuchal skinfold thickness with advancing gestational age and the commonly applied cut-off method (≥ 6 mm) for prenatal detection of Down syndrome in a Thai population.

2. Methods

A prospective study was performed at the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok, Thailand between October 1993 and December 1997, in which a detailed anatomic survey, long-bone biometry, and nuchal skinfold thickness were obtained on singleton fetuses scheduled for genetic amniocentesis because of age or past history of genetic abnormality. Only cases between 16 and 24 weeks' gestation were included. Patients for whom amniocentesis had been indicated by abnormal sonographic findings, including thickened nuchal skinfold, were excluded. Written informed consents were performed in all cases.

Ultrasound examination was performed transabdominally before amniocentesis, with a 3.5-MHz probe (Aloka SSD 2000, Aloka, Tokyo, Japan) in all of the patients. Nuchal skinfold measurement was obtained at the level of the posterior fossa, from the outer skull table to the surface of the skin as described by Benacerraf and Frigoletto [2]. The intracranial landmarks identified in the measurement plane were the cavum septum pellucidum, cerebral peduncles, and cerebellar hemispheres. Nuchal skinfold measurements were recorded before the results of the karyotype were available.

Gestational age was determined by a consistent last normal menstrual period and biparietal diameter.

The mean values for nuchal skinfold thickness and 95% confidence intervals (CI) were established for each gestational week. Reference intervals were calculated, using either a centile or a parametric method.

Three different methods of selecting cut-off levels were tested: (1) standard deviations (SD) from the gestational-specific mean; (2) gestational-specific centiles; and (3) ≥ 6 mm.

The sensitivity, specificity, accuracy, false-positive rates, positive and negative predictive values were calculated from the selecting cut-off levels in the prediction for Down syndrome.

Statistical analyses were performed with the SPSS for the Windows 95 statistical package.

3. Results

A total of 2150 pregnant women were enrolled in the study. Of these, 17 had a non-Trisomy 21 chromosomal abnormality. There were a total of 19 fetuses with trisomy 21 in the study population for a prevalence of one in 113. This rate, which is almost 6.5 times the general population preva-

lence of Down syndrome (1/740 births), is attributable to the high-risk nature of our referral population. There were 2114 chromosomally normal fetuses used to construct the reference ranges. The mean of maternal age at the time of amniocentesis of the normal group was 36.9 [±2.9 (S.D.)] years, whereas the mean of gestational age was 18.5 [±1.7 (S.D.)] weeks.

For the measurements made on chromosomally normal fetuses, the nuchal skinfold thickness (NT) correlated linearly with gestational age (GA) [NT (mm) = −0.502 + 0.212 GA (week), $r = 0.36$, $P < 0.001$]. There was no difference in nuchal skinfold thickness between male and female fetuses. Reference intervals using either a centile or a parametric method are shown in Table 1.

The scatter plotting of nuchal skinfold measurements for Down syndrome fetuses by gestational age is shown in Fig. 1.

In the screening for Down syndrome, the sensitivity, specificity, accuracy, false-positive rates, positive and negative predictive values, using three described cut-off methods, are shown in Table 2.

4. Discussion

Recognition of excess nuchal skinfold thickness during the second trimester was the first sonographic screening test reported for Down syndrome [1,2]. Other sonographic screening tests for the detection of Down syndrome include short femur lengths, short humerus lengths, and an increased biparietal diameter-to-femur length ratio [14,15]. Other ultrasound findings are also known to place a pregnancy at increased risk of Down syndrome. These include renal pyelectasis, a hypoplastic fifth midphalanx, cardiac abnormalities, hyperechogenic bowel, a short frontal lobe, small ear length, and duodenal atresia [16,17]. Analysis of the detection and false-positive rates for these various individual sonographic characteristics reveals none to be consistently superior to excess nuchal skinfold thickness [18].

The efficacy of nuchal skinfold thickness as a screening test for Down syndrome has been evaluated during the past decade. Various investigators have published data using this approach in the Caucasian population and have reported a wide disparity in Down syndrome detection rates, ranging from 9 to 75% with false-positive rates ranged from 0 to 9% [2–12]. Standardized methods of measurement and normal values for nuchal skinfold thickness in the Caucasian population also have been published [2,6,10–13]. The commonly used cut-off level in the second trimester is ≥6 mm. However, it has been reported that nuchal skinfold thickness in the normal fetuses increased with advancing gestation [12,13]. Therefore a method based on a progressive rise of the cut-off appears to be a more rational approach.

The mean nuchal skinfold thickness in our study was found to be increased with advancing gesta-

Table 1
Nomogram of nuchal skinfold thickness for each gestational week in the chromosomally normal population ($N = 2114$)

GA (week)	*N*	Mean (mm)	95% CI of mean	S.D. (mm)	10th centile (mm)	50th centile (mm)	90th centile (mm)	95th centile (mm)
16	123	2.8	2.7–2.9	0.8	2.0	3.0	4.0	4.0
17	488	3.0	2.9–3.1	0.9	2.0	3.0	4.0	5.0
18	705	3.3	3.2–3.4	0.9	2.0	3.0	4.1	5.0
19	335	3.6	3.5–3.7	0.9	2.0	3.2	5.0	5.0
20	155	3.7	3.5–3.9	1.0	2.0	4.0	5.0	5.0
21	157	3.9	3.8–4.1	1.1	3.0	4.0	5.0	6.0
22	84	4.1	3.9–4.3	1.1	3.0	4.0	5.0	6.0
23	40	4.4	4.1–4.8	1.0	3.0	4.0	6.0	6.0
24	23	4.3	3.9–4.7	1.0	3.0	4.0	6.0	6.0

Abbreviations. GA, gestational age; CI, confidence interval; and S.D., standard deviation.

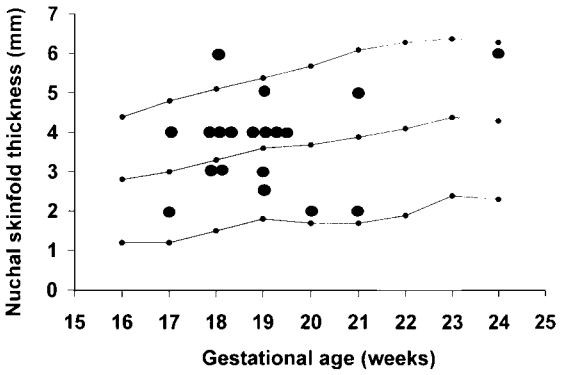

Fig. 1. Measurements of 19 Down syndrome fetuses and reference intervals (mean ± 2.0 S.D.) for nuchal skinfold thickness plotted against gestational age.

tion. The mean ± S.D. increased steadily from 2.8 ± 0.8 mm at 16 weeks to 4.3 ± 1.0 mm at 24 weeks of gestation in chromosomally normal fetuses. Our results are similar to the study of Grandjean et al. [12], who demonstrated an increase of nuchal skinfold thickness from 3.1 ± 0.8 mm at 16 weeks to 4.5 ± 1.1 at 23–24 weeks of gestation. Our patients were selected on the basis of age and history of genetic abnormalities and not because of observed fetal abnormalities. We assumed that the normal fetuses in our population were representative of normal fetuses in the general population. As suggested by Grandjean et al. [12] and Borrell et al. [13], we thought it was unlikely that the risk criteria used had any influence on the soft-tissue nuchal skinfold thickness of the fetuses in the absence of chromosomal abnormalities. Therefore the nomogram of nuchal skinfold thickness for each gestational week in our normal fetuses was assumed to be representative of that in the general population.

In this study, in spite of selecting cut-off levels from different methods, excess nuchal skinfold thickness had low detection rates (5.3–26.3%) for fetal Down syndrome in the second trimester of pregnancies compared with 20–25% using maternal age ≥ 35. Our population was extremely homogeneous, as it was confined to patients with advanced maternal age and past history of genetic abnormality. We excluded fetuses with sonographic abnormalities to avoid applying a screening test in an inappropriate setting. This restriction allowed us to gather data that would be most useful in a clinical setting, i.e. to determine the risk of Down syndrome based on nuchal skinfold thickness in otherwise sonographically normal pregnancies. This approach may lead to inflated Down syndrome detection rates. A clear limitation of the present series is related to the fact that our findings are in a high-risk population ascertained because of the indication of a prenatal diagnostic procedure. The screening test performance is likely to be poorer in a low-risk or unselected population. However, sensitivities and false-positive rates used in the comparison of different cut-off criteria are not affected by the prevalence of the studied condition and they should remain more or less the same.

Each center must analyze its own data regarding nuchal skinfold thickness and counsel patients according to the results. It is inappropriate to rely on published data from other investigators. In

Table 2
Sensitivity, specificity, accuracy, false positive rate, and positive and negative predictive values at different cut-off levels in the prediction of fetal Down syndrome

Cut-off level	Sensitivity (%)	Specificity (%)	Accuracy (%)	False positive rate (%)	Predictive value	
					PPV (%)	NPV (%)
≥ Mean + S.D.	21.0	85.2	84.7	14.7	1.3	99.2
≥ Mean + 1.5 S.D.	15.8	91.2	90.5	8.8	1.6	99.2
≥ Mean + 2.0 S.D.	5.3	97.4	96.6	2.5	1.8	99.1
≥ 90th Centile	26.3	83.5	82.9	16.5	1.4	99.2
≥ 95th Centile	15.8	90.0	89.4	9.9	1.4	99.2
≥ 6 mm	10.5	97.6	96.8	2.7	3.8	99.2

Abbreviations. PPV, positive predictive value; and NPV, negative predictive value.

addition, it remains unclear why some centers report that the sonographic finding of excess nuchal skinfold thickness is useful as a screening test for Down syndrome and others do not. We encourage further investigation to evaluate the usefulness of this sonographic sign in high risk and low risk pregnancies for screening of fetal Down syndrome, especially in Asian population.

In summary, measurement of second-trimester nuchal skinfold thickness is a poor and unreliable screening test for the detection of fetal Down syndrome in our population. In women with risk factors for fetal chromosomal abnormalities such as advanced maternal age or abnormal serum markers, definitive diagnostic testing with amniocentesis, chorionic villus sampling or fetal blood sampling remains the standard of care.

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