International Journal of Gynecology & Obstetrics 73 (2001) 117–123

International Journal of GYNECOLOGY & OBSTETRICS

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Article

Evaluation of fetal femur length to detect Down syndrome in a Thai population

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

Division of Maternal–Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok, Thailand

Received 14 September 2000; received in revised form 4 December 2000; accepted 13 December 2000

Abstract

Objective: To assess the value of femur length shortening for prenatal detection of Down syndrome in a Thai population. *Method*: A prospective study was performed by experienced perinatologists on 3137 women undergoing second-trimester amniocentesis, between 16 and 24 weeks of gestation, for the indications of advanced maternal age and past history of chromosomal abnormality. Biparietal diameter and femur length measurements were obtained before the procedures. Regression equations relating biparietal diameter to femur length were used to calculate observed femur length/expected femur length ratio in the chromosomally normal and Down syndrome fetuses. Sensitivity, specificity, false-positive rate and likelihood ratio of a positive test result at various observed femur length/expected femur length ratios for detection of Down syndrome were calculated. A receiver–operator characteristic curve was used to determine threshold screening ratio. *Results*: There were 3084 chromosomally normal pregnancies, 26 fetuses with Down syndrome (1:118), and 27 other chromosomal abnormalities. The relationship between femur length and biparietal diameter (BPD) was: expected femur length $= -7.631 + 0.814$ BPD, $R^2 = 0.78$, $P < 0.001$). Femur length in Down syndrome fetuses was significantly shorter than in normal fetuses ($P < 0.001$). A ratio of 0.91 for observed femur length/expected femur length yielded a sensitivity of 42.3%, specificity of 86.2%, false positive rate of 13.8% and likelihood ratio of a positive test result of 3.07 (95% CI 1.94–4.84) for detection of Down syndrome. *Conclusions*: In this study, femur length shortening in the second trimester appears to be a useful screening parameter for fetal Down syndrome in a Thai population.

Keywords: Down syndrome; Femur length; Prenatal diagnosis; Ultrasound

* Corresponding author. Tel.: +662-2564824; fax: +662-2564825.
E-mail address: mfmchula@ksc.th.com (Y. Tannirandorn).

0020-7292/01/$20.00
PII: S0020-7292(01)00347-2

1. Introduction

The antenatal detection of Down syndrome before 24 weeks of gestation remains a major epidemiologic challenge [1]. The use of maternal age alone is an ineffective screening tool because only 20% of fetuses affected with Down syndrome are born to women aged 35 years or older at delivery [2,3]. Thus, Down syndrome occurs in an unsuspectingly large population of women aged less than 35 years. Testing this population with invasive procedures using amniocentesis and karyotypic analysis is expensive and beyond the workload of most cytogenetic laboratories especially in the developing country. The improved resolution obtained with current ultrasound equipment has permitted obstetricians to delineate normal fetal biometry and anatomy in increasingly fine detail. There are now several sonographic signs that can be used in the second trimester to identify fetuses with an increased risk of having Down syndrome [4]. One of these signs is a short femur. Several studies initially reported that a short femur can identify 40–70% of Down syndrome fetuses in the second trimester [5–11]. However, subsequent studies have displayed great intercenter variations in the screening efficacy of femur length shortening in the prediction of Down syndrome [12–14]. Possible explanations for these incongruent results may be intercenter variations in patient populations and study designs. According to our knowledge, there is no study of femur length shortening in the screening for Down syndrome in the Asian population.

The purpose of this study was to assess the value of femur length shortening 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 1999, in which a detailed anatomic survey, fetal biometry including biparietal diameter and femur length were obtained on singleton fetuses scheduled for genetic amniocentesis because of advanced 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 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. The biparietal diameter was measured in the usual manner, from the outer edge of the skull to the inner edge of the other side of the skull using the thalami, cavum sepum pellucidum, and the atrial level of the lateral ventricles as internal reference landmarks. The femur lengths were measured by freezing the longest possible length on the screen and measuring it end to end with electronic calipers. Particular attention was paid to ascertaining that the longest possible femur length was obtained. The amniocentesis was performed under continuous ultrasound guidance, using standard procedures with a 21-gauge spinal needle. Cytogenetic studies were performed at the Laboratory of Medical Genetics according to standard techniques. Biparietal diameter and femur length measurements were recorded before the results of the karyotype were available.

All women had reliable menstrual dates, as defined by the following: (1) regular 28–31-day cycles before conception; and (2) no contraceptive use within the previous 3 months. Gestational age was determined by a consistent last normal menstrual period and biparietal diameter.

Regression analysis was performed to evaluate the relationships between biparietal diamater and femur length. An expected femur length was then calculated from the regression equation for each biparietal diameter. A ratio of observed femur length/expected femur length was used to determine the sensitivity, specificity, and false positive rate of the Down syndrome fetuses. A receiver–operator characteristic curve with sensitivity plotted against false–positive rate (1-specific-

ity) for Down syndrome detection was then developed. The optimal screening threshold for Down syndrome detection was derived by inspection of the receiver–operator characteristic curve. The likelihood ratio of a positive test result, defined as the sensitivity of the test divided by the false positive rate, and 95% CI were calculated. Statistical analyses were performed with the SPSS for Window 98 statistical package.

3. Results

A total of 3137 pregnant women were enrolled in the study. Of these, 27 had a non-trisomy 21 chromosomal abnormality. There were a total of 26 fetuses with trisomy 21 in the study population for a prevalence of 1 in 118. This rate, which is almost 6.3 times the general population prevalence of Down syndrome (1/740 births), is attributable to the high-risk nature of our referral population. There were 3084 karyotypically normal fetuses used as a normal population. The mean of maternal age at the time of amniocentesis of the normal group was 37 [$\pm$3.0 (S.D.)] years, whereas the mean of gestational age was 18.8 [$\pm$1.7 (S.D.)] weeks.

Table 1 lists individual BPD and femur length measurements in 26 Down syndrome fetuses. The regression equation relating BPD to FL in the normal population was: Expected FL = $-7.631 + 0.814$ BPD, $R^2 = 0.78$, $P < 0.001$. The regression equation for FL on BPD in Down syndrome fetuses was: Expected FL = $-7.061 + 0.772$ BPD, $R^2 = 0.762$, $P < 0.001$. Fig. 1 shows a graphic display of the regression lines of femur length on BPD, obtained from 3084 karyotypically normal fetuses and 26 Down syndrome fetuses. They are statistically different ($P < 0.001$).

Table 2 shows the sensitivity, specificity, and false positive rate and risk ratio for various observed femur length/expected femur length ratios to detect Down syndrome fetuses. Fig. 2 shows the ROC curve derived from the sensitivities and specificities corresponding to the different observed femur length/expected femur length threshold ratios.

An observed femur length/expected femur length ratio of ≤ 0.91 was selected after reviewing ROC analysis and considering acceptable levels of sensitivity and specificity for screening. With this cutoff ratio, 11 of 26 (42.3%) of fetuses with Down syndrome exhibited a short femur compared with 426 of 3084 (13.8%) fetuses with normal karyotypes. Therefore fetuses with Down syndrome were 3.07 times more likely to exhibit a short femur than karyotypically normal fetuses (likelihood ratio of a positive test result of 3.07, 95% CI 1.94–4.84, Table 2). Fig. 3 individual values for femur length in relation to BPD for 26 Down syndrome fetuses plotted on the regression line from the karyotypically normal fetuses with 5th and 95th percentiles.

For ease of use, Table 3 shows the expected and selected threshold measurements of femur length for any value of BPD between 25 and 65 mm. Threshold measurement were selected as

Table 1
Individual biparietal diameter (BPD) and femur length in 26 Down syndrome fetuses

Case No.	BPD (mm)	Femur length (mm)
1	29	17
2	38	26
3	39	22
4	39	24
5	39	25
6	41	28
7	42	23
8	42	24
9	42	26
10	43	27
11	44	28
12	45	24
13	45	26
14	45	29
15	45	29
16	46	28
17	46	33
18	47	25
19	47	26
20	47	27
21	48	26
22	48	30
23	48	32
24	50	30
25	52	39
26	63	43

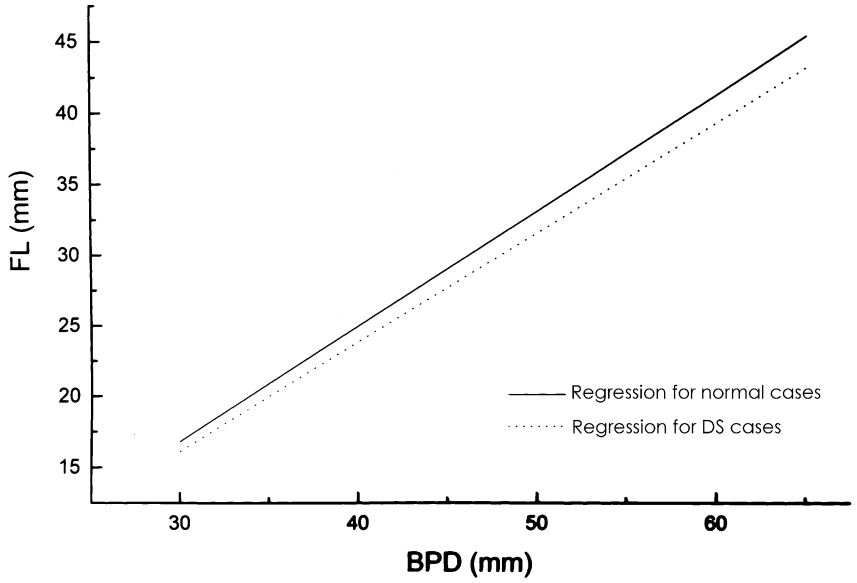

Fig. 1. Regression lines of femur length (FL) on biparietal diameter (BPD) in karyotypically normal fetuses (dashed line) and Down syndrome (DS) fetuses (dotted line).

Table 2
Sensitivity, specificity, false positive rate (FPR), and likelihood ratio of a positive test result (LR +) for various thresholds of femur length

Threshold	Sensitivity	Specificity	FPR	LR + (95% CI)
0.85	15.4	96.8	3.2	4.81 (1.91–12.05)
0.86	15.4	95.8	4.2	3.67 (1.47–9.20)
0.87	19.2	94.6	5.4	3.56 (1.60–7.96)
0.88	23.1	93.2	6.8	3.40 (1.66–6.92)
0.89	26.9	91.0	9.0	2.99 (1.58–5.70)
0.90	30.8	89.3	10.7	2.88 (1.60–5.16)
0.91	42.3	86.2	13.8	3.07 (1.94–4.84)
0.92	42.3	84.3	15.7	2.69 (1.71–4.25)
0.93	42.3	81.3	18.7	2.26 (1.43–3.56)
0.94	46.2	77.2	22.8	2.03 (1.33–3.08)
0.95	46.2	72.4	27.6	1.67 (1.10–2.54)

observed femur length/expected femur length ratio of ≤ 0.91.

4. Discussion

The role of ultrasonographic screening for Down syndrome is still evolving. Recognition of

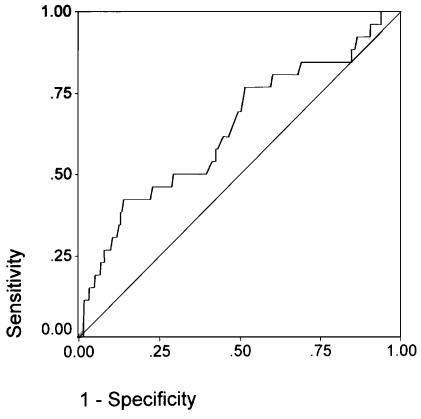

Fig. 2. Receiver–operator characteristic curve derived from the sensitivities and specificities corresponding to the different observed femur length/expected femur length threshold ratios.

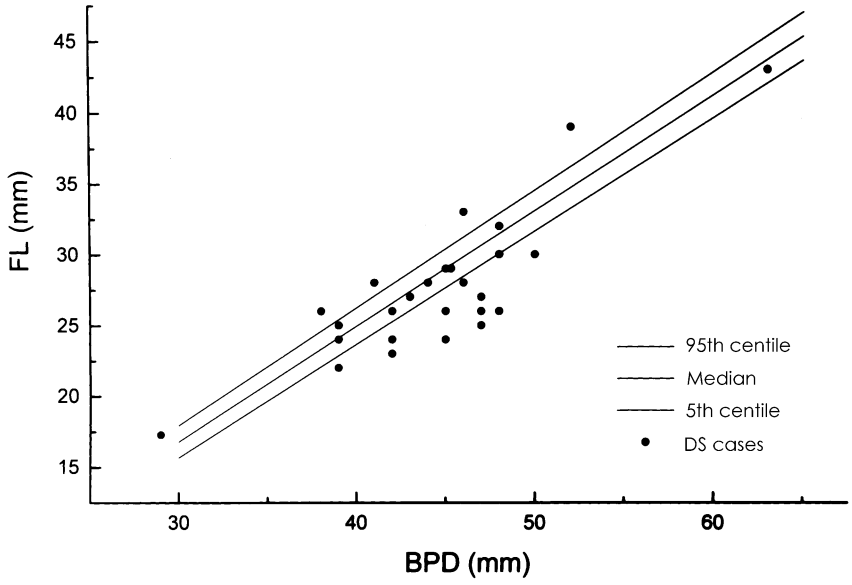

Fig. 3. Regression of femur length (FL) on biparietal diameter (BPD) with 5th and 95th percentiles. Individual values for Down syndrome (DS) fetuses are plotted.

excess nuchal skinfold thickness during the second trimester was the first sonographic screening test reported for Down syndrome in the Caucasian population [5]. However, in a Thai population we have previously reported that the measurement of second-trimester nuchal skinfold thickness was a poor and unreliable screening test for fetal Down syndrome [15]. In addition, ear length, fronto-thalamic distance, hypoplasia of the middle phalanx of the fifth digit, short humeral length, cardiac defects have also been proposed as ultrasonographic markers for Down syndrome fetuses [16]. However, some of these ultrasonographic findings may not be readily apparent or easy to obtain for the average sonographer on a routine examination. The use of standard ultrasound biometry to differentiate Down syndrome from normal fetuses has great appeal.

Short stature is a well-recognized feature of Down syndrome infant. Whether shortening of the femur length in the second trimester fetuses is sufficient to aid in the prenatal detection of Down syndrome is controversial, especially in the Asian population. Femur length can be compared with either menstrual age or other ultrasonographic measurements (e.g. the BPD). Because of the uncertainty in the menstrual history, we used an internal comparison of the femur length with the BPD. It has been reported from the Caucasean populations that the femur length is significantly shortened in the second trimester Down syndrome fetus [5–11]. Benacerraf et al. [5] reported a 68% sensitivity for detection of Down syndrome with a ratio of 0.90 observed femur length/expected femur length. However, other authors obtained remarkably lower sensitivities [12–14]. Our data on 26 Down syndrome fetuses confirm that femur length is significantly shorter in Down syndrome fetuses than in normal fetuses. An observed femur length/expected femur length ratio of 0.91 identified Down syndrome fetuses with a sensitivity of 42.3% and a specificity of 86.2%, while exposing 13.8% (false positive rate) of these pregnancies to the risks of genetic amniocentesis, which is superior to the use of maternal age alone. Comparing to the study of Benacerraf et al. [5], our study in a Thai population have lower sensitivity and higher false positive rate. This means that the accuracy of this measurement and the applicability of the published ratios may vary between different units. This discrepancy could be partially explained by differ-

Table 3
Expected and threshold levels of femur length compared with any given biparietal diameter (BPD)[a]

BPD (mm)	Expected femur length (mm)	Threshold femur length (mm)
25	12.7	11.5
26	13.5	12.3
27	14.4	13.0
28	15.2	13.8
29	15.9	14.5
30	16.8	15.2
31	17.6	16.0
32	18.4	16.7
33	19.2	17.5
34	20.0	18.2
35	20.8	18.9
36	21.7	19.7
37	22.5	20.4
38	23.3	21.2
39	24.1	21.9
40	24.9	22.6
41	25.7	23.4
42	26.5	24.1
43	27.3	24.9
44	28.2	25.6
45	29.0	26.4
46	29.8	27.1
47	30.6	27.8
48	31.4	28.6
49	32.2	29.3
50	33.0	30.1
51	33.9	30.8
52	34.7	31.5
53	35.5	32.3
54	36.3	33.0
55	37.1	33.8
56	37.9	34.5
57	38.7	35.2
58	39.6	36.0
59	40.4	36.7
60	41.2	37.5
61	42.0	38.2
62	42.8	39.0
63	43.6	39.7
64	44.4	40.4
65	45.3	41.2

[a] Femur length threshold is observed femur length/expected femur length ratio of ≤ 0.91.

ences between the ultrasonography laboratories, measurement technique and population. In addition, the accuracy in detecting Down syndrome also depends on the normal control used to define the threshold ratios, and the results will also vary between institutions. This implies that each center should determine its own sensitivity, specificity and false-positive rate for Down syndrome within that institution before using femur length as a screening tool in the second trimester. Although this and previous studies of femur length shortening have been directed to high-risk (over age 35 years) populations, available data suggest that ultrasonographic detection of shortened femur lengths may also be useful in detection of Down syndrome among low-risk individuals [4]. Assuming a prevalence of Down syndrome of 1:700 for women under 35 years old, a short femur (observed femur length/expected femur length ratio of ≤ 0.91) carries 1:228 risk of Down syndrome. This value exceed the currently accepted risk of a 35-year-old woman (1:270) [3,4]. Risk estimates of Down syndrome based on femur length measurement might also be combined with double or triple markers (maternal alpha-fetoprotein, human chorionic gonadotropin, and estriol) to further refine the risk of Down syndrome [11]. More study is needed about the accuracy of combination of femur length measurement and double or triple serum screening. However, we do not recommend that women 35 years old or older be advised against undergoing amniocentesis because of a lack of short femur. We would recommend that fetuses with short femurs on ultrasound examination be evaluated for Down syndrome by amniocentesis and karyotypic analysis. Despite our encouraging results, extrapolation of our data to other Asian countries is not recommended without independent verification.

In conclusion, our data support the previous reports studied in the Caucasian population that second trimester Down syndrome fetuses have shorter femur length, as compared with their normal counterparts. Femur length measurement in the second trimester may be used for screening of Down syndrome fetus in the Thai population.

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