Humerus length measurement in Down syndrome screening

I.H. Kalelioğlu

Obstetrics and Gynecology Department, University of Istanbul, School of Medicine, Topkapi/Istanbul (Turkey)

Summary

Purpose of investigation: To compare the predictive values of different humeral shortness assessment methods in Down syndrome screening.

Methods: 674 high-risk singleton pregnancies with a valid last menstrual period (LMP) date were studied. Nomogram and formulas were derived from a subset of the studied group. Sensitivities of fifth percentile and cut-off values of 0.9 for observed-to-expected (obs/exp) humerus length (HL) ratio according to biparietal diameter (BPD) and gestational age (GA) were compared.

Results: Sensitivities were 20%, 46.7% and 60% for the 5th percentile, a cut-off value of 0.9 for obs/exp HL by BPD and a cut-off value of 0.9 for obs/exp HL by GA, respectively.

Conclusion: Using gestational age instead of BPD when calculating expected humeral length may increase the predictive role of humeral shortness in Down syndrome screening of pregnant women with valid and correct LMP.

Key words: Down syndrome; Humerus length.

Introduction

Historically, it is well-known that infants with Down syndrome are shorter than those of the same age group. FitzSimmons *et al.* found humeral shortening more common than femur shortening in autopsy examinations of infants with Down syndrome [1]. Although several series on humeral shortening in the antenatal period have been reported, the results are controversial [2- 6]. The diversity of these results is similar to that found in many studies on femoral length analysis. The assessment method for humeral length (HL) may have an important contribution to the variability in results of studies. Although it is accepted that bone shortening should be expressed as bone ratios to predict Down syndrome and it is a commonly used method in most of the studies, the superiority of this method has not been shown and prospective research, studying which assessment method is superior to others is still needed. Observed to expected (obs/exp) humeral length ratio, -2 SD and biparietal diameter (BPD) to humerus length ratio are the more commonly used methods in assessment. Several methods have been used in different studies but it is too difficult to compare these studies because of the variability in the methods. The aim of the current study in a high-risk population was to determine the most predictive humeral assessment method in Down's syndrome screening in the same population.

Materials and Methods

The study was performed between January 2004 and April 2005, and included Caucasian pregnant women referred for genetic amniocentesis. Women were included within the study if they had a singleton pregnancy, a valid last menstrual period (LMP) date, and a gestation that was between 15 and 22 weeks. Examinations were performed with Aloka Prosound SSD-4000 equipment. Measurement findings were recorded on paper at the time of the examination and stored on an MS Access database later.

The BPD was obtained with an axial plane of the cranium at the level of the thalami, the septum cavum pellucidum, and the third ventricle. Calipers were placed at the outer echo-dense aspect of the proximal parietal bone and the inner echo-dense aspect of the distal parietal bone. HL measurement was made by obtaining the long axis of the humerus in a position that is horizontal or approximately ten degrees deviated from the horizontal. The gain was reduced to limit any side lobe artefact from the ends of the bone. The cursor was placed at the upper corner of each end of the diaphysis.

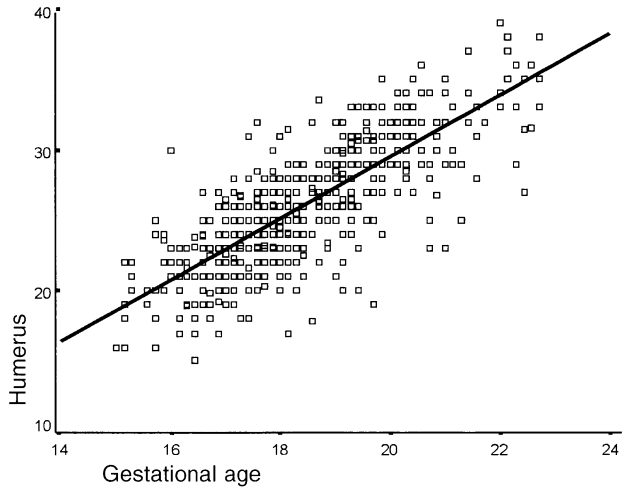
The normal humeral length-related values and ratios according to BPD and gestational age (GA) were derived from a subset of the fetuses which were chromosomally and anatomically normal. HL values were stratified according to the gestational age into one-week intervals (15.0-15.9, 16.0-16.9, etc.) to obtain medians and 5th percentile values according to gestational ages. A linear regression analysis, weighted for the number of observations at each week, provided the formula for expected humeral length based on gestational age. Linear regression analysis was used to predict expected humeral length based on BPD. Prediction values of the 5th percentile and a cut-of value of 0.9 for ratios of observed HL/expected HL in accordance with BPD and observed HL/expected HL in accordance with GA were compared.

Results

Six hundred and seventy-four of 720 women who underwent invasive procedures during this time period were appropriate for inclusion criteria and enrolled in the study. Mean maternal ages were 37.4 ± 4.54 (range 27-44) in women who were carrying DS-affected fetuses and 33.9 ± 95.81 (range 16-48) in women who were carrying non-DS-affected fetuses. Mean gestational age at sonographic examination was 18.3 ± 1.5 (range 15-22.7) weeks in Down's syndrome and 18.3 ± 1.5 (range 15-22.7) weeks in normal fetuses.

The features of 620 fetuses were used to calculate percentiles and ratios. A linear increase in humeral length was observed between 15 and 22 weeks of gestation. Formulas derived from weighted regression analysis to calculate expected humeral length according to gestational ages was [(2.128*gestational week) - 12.385]. Distribu-

Revised manuscript accepted for publication June 27, 2006



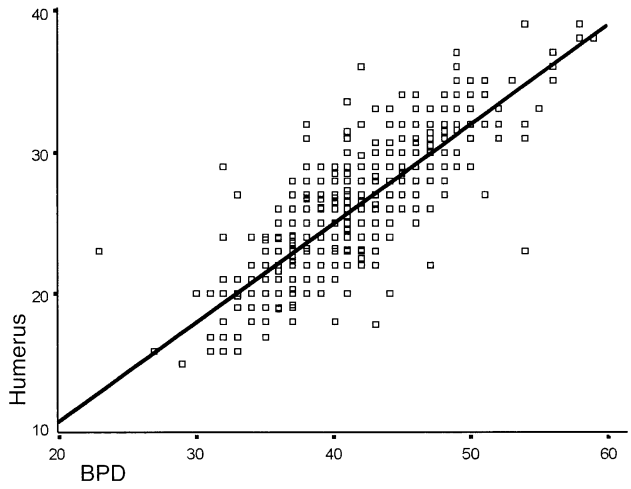


Figure 1. — Distribution and linear regression line of humerus length according to gestational age.
Figure 2. — Distribution and linear regression line of humerus length in accordance with biparietal parameter.

tion and linear regression line of humerus length according to gestational age is shown in Figure 1. Fifth percentiles of humerus length between 15 and 22 weeks were 16, 17.1, 20, 21.7, 22, 25.9, 23 and 27 mm, respectively. Percentiles values of humerus length according to gestational age are given in Table 1. A linear increase was also observed in humerus length with increasing BPD values and formula derived from linear regression analysis was [(0.699*BPD) – 3.0880.]. Distribution and linear regression line of humerus length in accordance with BPD is represented in Figure 2.

Table 1. — *Percentile values of humerus length (HL) between 15 and 22 weeks of gestation.*

		n	Percentiles								
			1	2.5	5	10	25	50	75	90	95
Gestational ages (weeks)	15	23	16	16	16	16	18	20	22	24	24
	16	81	15.1	17	17.1	18.2	19.5	21	23	24.8	26.9
	17	177	18	19	20	21	22	24	25	27	28
	18	153	17.4	20	21.7	23	24	26	27	28	29
	19	99	19	20	22	25	26	29	30	32	33
	20	49	23	23.5	25.9	27	29	31	33	34	34.5
	21	19	23	23	23	25	29	32	33	35	37
	22	19	27	27	27	29	33	35	37	39	39

In the study, 15 fetuses with Down syndrome and 12 fetuses with other chromosomal abnormalities were identified. Other chromosomal abnormalities were trisomy 18 in five fetuses, 47 XXX in one fetus, balanced rearrangement in three fetuses and unbalanced rearrangement in three fetuses. Gestational ages, measurements and ratios of cases with Down's syndrome are shown in Table 2. In 647 fetuses, chromosomal analyses showed no abnormalities. Twenty-seven fetuses were sonographically found to have congenital anomalies. These anomalous cases were excluded in calculation of percentiles and ratios but not excluded from the study because of the fact that shortness of humerus was not considered as an isolated marker in this study.

We detected three, seven and nine Down syndrome fetuses out of 15 total cases by the 5th percentile, a cut-off value of 0.9 for obs/exp HL by BPD and a cut-off value of 0.9 for obs /exp HL by GA, respectively. Contingency tables are shown in Table 3. Sensitivities were 20%, 46.7% and 60% for the 5th percentile, a cut-off value of 0.9 for obs/exp HL by BPD and a cut-off value of 0.9 for obs/exp HL by GA, respectively. All the prediction values of the methods are given in Table 4.

Table 2. — *Gestational ages, measurements and ratios of cases with Down's syndrome.*

Case	GA	BPD	HL	5p	exp/obs HL By GA	exp/obs HL By BPD
1	19	44	29	0	1,0339	1,0481
2	15	35	16	0	0,8190	0,7484
3	20	37	26	0	0,8616	1,1416
4	17	43	23	0	0,9667	0,8528
5	20	39	24	1	0,7953	0,9928
6	20	47	31	0	1,0273	1,0414
7	17	38	21	0	0,8826	0,8946
8	18	43	22	0	0,8487	0,8157
9	17	35	21	0	0,8826	0,9823
10	16	35	19	0	0,8770	0,8888
11	17	34	18	1	0,7565	0,8704
12	16	37	22	0	1,0155	0,9659
13	18	40	24	0	0,9259	0,9649
14	21	29	13	1	0,4024	0,7565
15	22	54	34	0	0,9874	0,9810

GA: gestational age; BPD: biparietal diameter; HL: humerus length; exp/obs: expected/observed.

Table 3. — *Gestational ages, measurements and ratios of cases with Down's syndrome (DS).*

		DS (n)	Non-DS (n)	Total (n)
5th percentile	positive	3	33	36
	negative	12	626	638
Obs/Exp HL based on BPD < 0.90	positive	7	96	103
	negative	8	563	571
Obs/Exp HL based on GA < 0.90	positive	9	120	129
	negative	6	539	545
Total		15	659	674

Exp: expected; HL: humerus length; BPD/Obs: biparietal parameter observed; GA/Obs: gestational age/observed.

Table 4. — *Predictive values of different methods.*

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
5th percentile	20	95	8.3	98.1
Obs/Exp HL based on BPD (< 0.90)	46.7	85.4	6.8	98.6
Obs/Exp HL based on GA HL (< 0.90)	60	81.2	7	98.9

Exp: expected; Obs: observed; HL: humerus length; BPD: biparietal diameter; GA: gestational age.

Discussion

Since the early 1990s screening of Down syndrome has progressively improved. In the early 1990s serum screening tests were the only available tests to screen Down syndrome. The progressive development in sonography technology has facilitated the use of sonography in Down syndrome screening, even in the first trimester. Today many authors use complicated, expensive high-technologies and standardization required methods to increase the success of Down syndrome screening. Unfortunately, although these attempts have increased the detection rates they are complicated and are not easy to use. Most require high technology and continuous quality assessment that make such methods inappropriate for screening. On the other hand, for a long time it has been well known that babies with Down syndrome have shorter humerus lengths than normal counterparts. Furthermore measurement of humerus length is easy to perform using standard equipment with a little effort. In 1991, Benaceraff *et al.* were the first to report the probable use of humeral length measurement for Down syndrome [2]. A ratio of measured-to-expected humeral length of less than 0.90 identified 12 of 24 fetuses (50%) with Down syndrome in this study. The same year after Benaceraff's first report, Rodis *et al.* reported a 64% sensitivity and a 6.8% PPV using the 5th percentile [7]. Rodis also studied the BPD/FL ratio and using the 95th percentile as a cut-off he also detected 64% fetuses with Down syndrome without any contribution to screening with the 5th percentile only. Two years later, in 1993, Nyberg *et al.* reported a 24.4% sensitivity using a 0.9 cut-off obs/exp HL ratios. In 1994 Biagiotti et al. reported 37% sensitivity and 12% false-positive rate, using also a 0.9 cut-off level of obs/exp HL ratios [8]. In 1997 Borell *et al.* detected a 43% sensitivity and a 8% false-positive rate using a cut-off level of 1.5 SD [4]. In the current study we detected sensitivities of 20%, 46.7% and 60% for the 5th percentile, a cut-off value of 0.9 for obs/exp HL by BPD and a cut-off value of 0.9 for obs/exp HL by GA, respectively. The most sensitive method in the current study was usage of a cut-off value of 0.9 for obs/exp HL by GA. This method has not been studied before and our preliminary results must be confirmed by further studies. Only a few studies in high-risk populations have attempted to find out the most predictive humerus assessment method in Down's syndrome screening.

The effect of race and ethnicity on regression formulas was not studied. In 2003, Zelop *et al.* reported that genetic sonographic norms do not require race- or ethnic-specific formulas for humeral length [9]. In 2004 Mastrobattista *et al.* confirmed Zelop *et al's* results [10]. As can be seen, different methods were used in different studies and it is too difficult to compare these studies because of the variability in the methods. Lack of standardization to evaluate humeral shortness causes conflicts between results. Differences in the regression lines of normal fetuses and diversity in cut-off values used were notable among studies. Furthermore self-regression equations were not used in some studies. Thus a wide range of sensitivity and false-positive rates available in the literature make humeral shortness less valuable in Down syndrome screening. Another issue is that all the studies on humeral shortness were performed in high-risk populations and confirmation of results of studies with low-risk populations is needed.

Conclusion

The predictive ability of humerus length is currently unknown, even in high-risk populations. The best method to evaluate humeral shortness must be determined and the results must be confirmed in studies with low-risk populations. In the current study, usage of a cut-off value of 0.9 for obs/exp HL by GA was detected as the most sensitive method. This finding must be confirmed by further studies. Too much effort is still required to get the real predictive value of humerus shortness.

References

[1] FitzSimmons J., Droste S., Shepard T.H., Pascoe-Mason J., Chinn A., Mack L.A.: "Long-bone growth in fetuses with Down syndrome". *Am. J. Obstet. Gynecol.*, 1989, *161,* 1174.

[2] Benacerraf B.R., Neuberg D., Frigoletto F.D. Jr.: "Humeral shortening in second-trimester fetuses with Down syndrome". *Obstet. Gynecol.*, 1991, *77,* 223.

[3] Rotmensch S., Luo J.S., Liberati M., Belanger K., Mahoney M.J., Hobbins J.C.: "Fetal humeral length to detect Down syndrome". *Am. J. Obstet. Gynecol.*, 1992, *166,* 1330.

[4] Borrell A., Costa D., Ojuel J., Martinez J.M., Seres A., Margarit E., Fortuny A.: "Limited effectiveness of femur and humerus shortening as markers of Down syndrome in early midtrimester fetuses". *Fetal. Diagn. Ther.,* 1997, *12,* 156.

[5] Tannirandorn Y., Manotaya S., Uerpairojkit B., Tanawattanacharoen S., Wacharaprechanont T., Charoenvidhya D.: "Value of humerus length shortening for prenatal detection of Down syndrome in a Thai population". *J. Obstet. Gynaecol. Res.,* 2002, *28,* 89.

[6] Vergani P., Locatelli A., Ghidini A., Mariani E., Strobelt N., Biffi A., Pezzullo J.C.: "Caveats for the use of humerus length in the prediction of fetal Down syndrome". *Fetal. Diagn. Ther.,* 2003, *18,* 190.

[7] Rodis J.F., Vintzileos A.M., Fleming A.D., Ciarleglio L., Nardi D.A., Feeney L. *et al.*: "Comparison of humerus length with femur length in fetuses with Down syndrome". *Am. J. Obstet. Gynecol.*, 1991, *165,* 1051.

[8] Biagiotti R., Periti E., Cariati E.: "Humerus and femur length in fetuses with Down syndrome". *Prenat. Diagn.*, 1994, *14,* 429.

[9] Zelop C.M., Borgida A.F., Egan J.F.: "Variation of fetal humeral length in second-trimester fetuses according to race and ethnicity". *J. Ultrasound Med.*, 2003, *22,* 691.

[10] Mastrobattista J.M., Pschirrer E.R., Hamrick M.A., Glaser A.M., Schumacher V., Shirkey B.A.: "Humerus length evaluation in different ethnic groups". *J. Ultrasound Med.*, 2004, *23,* 227.

Address reprint requests to:
I.H. KALELIOĞLU, M.D.
Necati Alburs S. Cihan A. 5/12
34349 Gayrettep/Istanbul (Turkey)