

# Investigation of Bone Ratios for Prenatal Fetal Assessment in Taiwanese Population

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## ABSTRACT

The purpose of this study is to calculate the ratios of fetal limb bone to nasal bone length (NBL) obtained by transabdominal ultrasound between 19 and 28 weeks of gestation. Cross-sectional data were obtained from 1408 women with singleton pregnancies who underwent an advanced prenatal ultrasound examination from August 2006 to September 2008. The single measurement plane of fetal limb bones was on the longest section of each structure with appropriate image magnification. To assess repeatability of the intraobserver, two repeated measurements were obtained in 44 fetuses. The ratio of fetuses with biparietal diameter (BPD)/NBL was compared with those of fetal limb bones/NBL. The mean ratio was found between fetal NBL measurements and BPD (7.240), humerus length (HL) (4.807), radius length (RL) (4.157), ulna length (UL) (4.502), femur length (FL) (5.131), tibia length (TL) (4.528), and fibula length (FiL) (4.507). The reference ranges of fetal long bone length/NBL ratios for the second trimester was established by transabdominal sonography. There were no significant increases in these ratios with gestational age, especially the HL/NBL ratio.

**Keywords:** Nasal Bone Length; Limb Bone; Ratio; Second Trimester; Ultrasound

## 1. Introduction

In aneuploid chromosomes, Down syndrome has a high incidence rate in newborns [1]. The methods of screening for chromosome anomalies, excluding amniocentesis, rely on maternal age and maternal serum biochemical markers. Recently, fetal genetic ultrasound screening has been proposed as an additional screening tool for aneuploidy [2]. Down syndrome fetuses usually have facial abnormalities, with especially an absent fetal nasal bone (NB) or NB hypoplasia due to delayed NB ossification, which have been observed as a fetal sonographic soft marker of Down syndrome [3].

Recent reports suggested that evaluation of the fetal NB might help to identify fetuses at risk of Down syndrome. It has been reported that about 65% of Down syndrome fetuses have absent or short NB in fetal NB screening at the first and second trimesters [4]. Only 1~2% of normal karyotype fetuses have been observed [5-7]. Down syndrome and absent or hypoplastic fetal NB show similar evidence of high sensitivity, high specificity, and low false-positive rate for Down syndrome screening by fetal NB examination [8-11].

Published data have shown that when comparing Down Syndrome fetuses with euploid fetuses, Down Syndrome fetuses were more frequently associated with NB hypoplasia [12-15]. Reviewing several past studies, in addition to discussing the relationship between nasal bone length (NBL) and gestational age or biparietal diameter (BPD), the BPD/NBL ratio  $\geq 10$  and  $\geq 11$  were proposed for the definitions of nasal bone hypoplasia in the second trimester [13,15-19].

The fetal NB assessment is a very important part of prenatal fetal examination. It is a useful diagnostic and screening tool for Down syndrome. The purpose of this study was to investi-

gate the distributions of fetal limb bones length with respect to NBL and to compare the differences of ratios between fetal BPD/NBL and fetal limb bone/NBL.

## 2. Methodology

### 2.1. Subjects

The cross-sectional fetal long bone measurements were carried out with 1408 pregnancies as a part of advanced prenatal ultrasound examination from August 2006 to September 2008. The gestational age of the fetuses was calculated from the accurate estimated date of confinement obtained from patients. If the estimated date of confinement was uncertain, the difference between the ultrasonically estimated gestational age and determined gestational age was assumed to be less than 10 days [20]. The exclusion criteria included previous history of chromosome abnormalities, fetal structural anomalies, and maternal complications.

### 2.2. Ultrasound

The fetal NBL was measured in the strict sagittal view of the fetal head under appropriate image magnification (**Figure 1**) [5,21]. independent document. Please do not revise any of the current designations.

In order to avoid false finding that the NB was either absent or shortened, the angle of the fetal nose was maintained between  $45^\circ$  and  $135^\circ$  [12,22]. The BPD was measured on the transverse axial section of the fetal head – which included the midline falx and the thalami symmetrically positioned on either side of the falx – from the outer edge of the nearer parietal bone to the inner edge of the more distant parietal bone whilst visual-

lizing the septum pellucidum at one-third along the frontal-occipital distance. The single measurement plane of six limb bones (humerus, ulna, radius, femur, tibia, and fibula) was on the longest section of each structure with appropriate image magnification (occupy three quarters of the screen). In addition, the transducer needed to be aligned to the long axis of the limb bone to obtain a proper plane of the section. The ossified portion of diaphysis and metaphysics were measured, while the cartilaginous ends of the limb bones were excluded [23,24]. To assess repeatability of the intraobserver, two repeated measurements were obtained from 44 fetuses randomly chosen during the process of ultrasound screening. The mean differences between the two measurements and the Cronbach's Alpha value were calculated.

### 2.3. Statistics

In this study, statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS, Ver. 13.0 for Windows; Chicago, IL, USA). A probability value of  $p < 0.05$  was considered statistically significant. The mean, standard deviation (SD), 95% confidence interval of mean for BPD/NBL and fetal long bones/NBL were calculated. Furthermore, the correlation of gestational age and fetal long bones/NBL ratios were analyzed by Pearson correlation.

## 3. Results

**Table 1** represents the mean, standard deviation (SD), 95% confidence interval of mean for the ratios of the BPD/NBL, humerus length (HL)/NBL, ulna length (UL)/NBL, radius length (RL)/NBL, femur length (FL)/NBL, tibia length (TL)/NBL, and fibula length (FiL)/NBL

The linear regression examining the HL/NBL ratio versus gestational age for our study population indicates that the ratio did not change with gestational age. Although the regression reveals that the BPD/NBL ratio decreases slightly with gestational age for fetuses, the change was not statistically significant, which is similar to the previous literature.

**Table 2** and **Table 3** show the mean, SD, 95% confidence interval of mean for the ratios of the BPD and HL to NBL with advancing gestational age.



**Figure 1.** Mid-sagittal view showing detection and measurement of the nasal bone.

In addition, the correlation coefficients between gestational age and ratios of the fetal long bones to NBL were calculated by Pearson correlation. **Table 4** shows the correlation coefficients between gestational age and the ratios of the BPD and HL to NBL.

**Table 1.** Distribution of the ratios of biparietal diameter (BPD) to nasal bone length (NBL) and fetal long bone lengths to NBL.

	Mean	SD	95% Confidence Interval of Mean	
			Lower Bound	Upper Bound
BPD/NBL	7.240	0.8487	7.194	7.285
HL/NBL	4.807	0.5782	4.768	4.846
RL/NBL	4.157	0.5023	4.123	4.191
UL/NBL	4.502	0.5494	4.465	4.539
FL/NBL	5.131	0.6336	5.088	5.174
TL/NBL	4.528	0.5609	4.490	4.565
FiL/NBL	4.507	0.5541	4.469	4.544

SD: standard deviation, SE: standard error, humerus length (HL), radius length (RL), ulna length (UL), femur length (FL), tibia length (TL), fibula length (FiL).

**Table 2.** Distribution of the ratio of biparietal diameter (BPD) to nasal bone length (NBL) against weeks of gestation.

	Mean	SD	95% Confidence Interval of Mean	
			Lower Bound	Upper Bound
19 <sup>+0</sup> -19 <sup>+6</sup>	7.500	0.9933	7.122	7.878
20 <sup>+0</sup> -20 <sup>+6</sup>	7.292	0.8878	7.153	7.430
21 <sup>+0</sup> -21 <sup>+6</sup>	7.212	0.8071	7.110	7.313
22 <sup>+0</sup> -22 <sup>+6</sup>	7.212	0.8492	7.118	7.306
23 <sup>+0</sup> -23 <sup>+6</sup>	7.333	0.8617	7.221	7.444
24 <sup>+0</sup> -24 <sup>+6</sup>	7.082	0.7409	6.952	7.212
25 <sup>+0</sup> -25 <sup>+6</sup>	7.236	0.9428	7.019	7.453
26 <sup>+0</sup> -26 <sup>+6</sup>	7.263	0.9209	7.020	7.505
27 <sup>+0</sup> -27 <sup>+6</sup>	7.228	0.7812	7.021	7.436
28 <sup>+0</sup> -28 <sup>+6</sup>	7.184	0.8161	6.894	7.473

SD: standard deviation, nasal bone length (NBL), biparietal diameter (BPD).

**Table 3.** Distribution of the ratio of humerus length (HL) to nasal bone length (NBL) against weeks of gestation.

	Mean	SD	95% Confidence Interval for Mean	
			Lower Bound	Upper Bound
19 <sup>+0</sup> -19 <sup>+6</sup>	4.803	0.5607	4.590	5.017
20 <sup>+0</sup> -20 <sup>+6</sup>	4.711	0.5729	4.622	4.801
21 <sup>+0</sup> -21 <sup>+6</sup>	4.688	0.5637	4.617	4.759
22 <sup>+0</sup> -22 <sup>+6</sup>	4.712	0.5864	4.647	4.777
23 <sup>+0</sup> -23 <sup>+6</sup>	4.835	0.6163	4.756	4.915
24 <sup>+0</sup> -24 <sup>+6</sup>	4.662	0.5418	4.567	4.757
25 <sup>+0</sup> -25 <sup>+6</sup>	4.718	0.6419	4.570	4.866
26 <sup>+0</sup> -26 <sup>+6</sup>	4.683	0.5260	4.544	4.821
27 <sup>+0</sup> -27 <sup>+6</sup>	4.827	0.6241	4.661	4.993
28 <sup>+0</sup> -28 <sup>+6</sup>	4.631	0.6116	4.415	4.848

SD: standard deviation, nasal bone length (NBL), humerus length (HL).

**Table 4. Pearson correlation coefficients of gestational age with ratios of the BPD/NBL and HL/ NBL.**

	GA	BPD/NBL	HL/NBL
GA	1	-.031	.001

gestational age (GA), nasal bone length (NBL), biparietal diameter (BPD), humerus length (HL)

The study of intraobserver variability showed mean differences between the two measurements ranging from  $-0.0591$  to  $0.1682$  and Cronbach's Alpha value ranging from  $0.997$  to  $0.999$ .

#### 4. Discussion

The present study provides the ratios of fetal limb bones to NBL with reference range from 19 to 28 weeks of gestation in normal Taiwanese fetuses. Each woman contributed one set of measurements taken during advanced prenatal ultrasound examination and assessment. No significant change in the BPD/NBL ratio, HL/NBL ratio, UL/NBL ratio, and RL/NBL ratio with gestational age were demonstrated in our population (Pearson correlation coefficient  $< 0.05$ ).

According to previous published studies, the BPD/NBL ratio was first described in 2005. A total of 136 fetuses were evaluated for the association between the BPD/NBL ratio and trisomy 21 in the second-trimester [19]. In many subsequent studies, assessments of the NBL/BPD ratio were done in the second trimester. In recent studies, the optimal threshold values for the BPD/NBL ratio were investigated for detection of trisomy 21.

The ultrasound measurements were done in 239 women with a singleton pregnancy at 15-20 weeks of gestation at Massachusetts General Hospital, USA. The receiver operating characteristic curve for the BPD/NBL ratio showed that using a cutoff value of 9 or greater resulted in 100% of fetuses with Down syndrome and 22% of euploid fetuses. If the cutoff value were raised to 10 or greater, then 81% of fetuses with Down syndrome and 11% of euploid fetuses would be identified. If the cutoff value was 11 or greater, 69% of fetuses with Down syndrome would be identified, compared with 5% of euploid fetuses [17]. This was consistent with the others in the literature.

In this study, we calculated not only the fetal BPD/NBL ratio but also ratios of the fetal limb bones to NBL between 19 and 28 weeks. Besides, the fetal biometry and limb bones length in our study were compared with previously reported measurements from other populations [25,26]. The biometry, limb bones length, and fetal weight were all in the normal range. Moreover, the HL/NBL ratio did not change with gestational age. The Pearson product-moment correlation coefficient of the HL/NBL with gestational age was lower than those of ratios with gestational age.

The NB hypoplasia or absence is an important marker for Down syndrome. The combination of other makers with the NB assessment was associated with an improvement in detecting the risk of Down syndrome [27]. Thus, there is a need to establish the specific evaluated formulas by NBL with different methods.

In this pilot study, our data have established the reference ra-

tio of the fetal limb bones to NBL in normal singleton Taiwanese fetuses. To our knowledge, this is the first prospective study to evaluate the ratios of the fetal limb bones to NBL in the second trimester. Our data also show that the HL/NBL ratio does not change with advancing gestational age. Comparing with the lower limb, it is usually easier to visualize the upper limb. The humerus is the easiest of the upper limb bones to define with ultrasound, as it has less freedom of movement than the forearm. We determined that the HL/NBL ratio was superior to that of BPD or other limb bones ratios. Additional verification for detecting the risk of chromosomal aneuploidy is required before this approach can be applied in a clinical setting. This study points out a better clinical approach for evaluating fetuses with skeletal anomalies or risk of aneuploid chromosomes in the general population.

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