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Journal

Prenatal Diagnosis, 39(3)

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Publication Date

2019-02-01

DOI

10.1002/pd.5397

Peer reviewed

HHS Public Access

Author manuscript

Prenat Diagn. Author manuscript; available in PMC 2022 February 01.

Published in final edited form as:

Prenat Diagn. 2019 February ; 39(3): 200–208. doi:10.1002/pd.5397.

A new biometric: *in-utero* growth curves for metacarpal and phalangeal lengths reveals an embryonic patterning ratio

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Abstract

Objective: Develop gestational age specific growth curves for fetal third metacarpal and phalangeal lengths and determine if fetal hand proportion is established *in utero*.

Methods: This prospective cross-sectional study used 2D ultrasound across gestational ages 12–39 weeks to evaluate the third fetal metacarpal and phalangeal measurements. Gestational age specific reference growth curves were developed. Associations between continuous variables were assessed using Spearman correlations (r_s) and restricted cubic splines. A nonlinear biologic regression model was used to predict metacarpal and phalangeal length as a function of gestational age. Measurements derived from five cases of thanatophoric dysplasia were used to determine if brachydactyly could be objectified.

Results: Fetal metacarpal and phalangeal lengths are highly correlated across gestational age (r_s=0.96, p<0.001). The mean fetal metacarpal to phalangeal ratio is constant from gestational age 15 to 39 weeks (r_s =−0.07, p=0.49). Third-digit metacarpal and phalangeal lengths in thanatophoric dysplasia showed brachydactyly in all cases (5/5), and none of the cases (0/5) demonstrated a normal metacarpal to phalangeal ratio of 0.49.

Conclusion: We present gestational age specific reference growth curves for fetal third metacarpal and phalangeal lengths, which may be used to detect brachydactyly. We demonstrate a prenatal metacarpal to phalangeal ratio of 1:2.

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Conflict of interest statement: Lawrence D. Platt has been a speaker for Illumina and serves on their medical advisory board and is treasurer of the Perinatal Quality Foundation. He provides research support and is on the speaker bureau for GE Medical Systems. The remaining authors listed have no disclosures.

Keywords

Brachydactyly; metacarpal; phalange; fetal biometrics; skeletal disorder

Introduction:

Congenital malformations affect at least 3 percent of the births in the United States; however, major limb malformations are individually rare with varying etiologies and degrees of expressivity(1). Upper limb defects occur in approximately 4 out of every 10,000 babies born in the United States (2) and many of these involve the fetal hand.

Brachydactyly is defined as shortened digits, resulting from abnormal development of metacarpals, phalanges, or metatarsals (3). Brachydactyly can result from differential growth of particular bones, and can occur as an isolated malformation, or as part of a more complex malformation syndrome (4, 5).

Fetal long bones, particularly the femora and humeri are evaluated as a routine measurement. However, the bones of the hand, such as the metacarpals and phalanges, are infrequently evaluated, despite recommendations to do so in the setting of a suspected skeletal disorder (6, 7).

To date, there is no standard technique described for the prenatal measurement of the fetal metacarpal and phalanges, and no standardized method to diagnose brachydactyly in utero. In the early 1980's, Merlob and Sivan et al. published postnatal palm-length measurements and third digit phalangeal measurements from normal neonates born between 27 and 41 weeks of gestation(8, 9). Feingold and Bossert published postnatal data (birth to 16 years) describing a ratio of approximately 0.425 between of the length of the middle finger and total hand (10). Prenatal measurements, confirming these results or determining the gestational age when they develop, have not been reported.

Tovbin et al. reported prenatal age-specific reference intervals for phalangeal measurements of all five digits in normal fetuses; however, these were limited to fetuses within the second trimester (15–27 weeks) and metacarpals were not measured (11). Prior to this, Goldstein et al. recommended measurement of the fifth phalanx as a tool to aid in the diagnosis of trisomy 21(15– 23 weeks). The utility of this study is limited to disorders, such as Down syndrome and Noonan syndrome, where the fifth digit is often affected (12).

Given the lack of available data to determine prenatal onset brachydactyly, our objective was to determine predictive gestational age specific growth curves for fetal metacarpal and phalangeal lengths from fetuses spanning all three trimesters, and to evaluate if a growth relationship exists between the metacarpal and phalangeal length in normal fetuses. Our hypothesis is that a postnatal linear growth relationship exists between the metacarpal and phalangeal length and is established early in the prenatal period.

Methods:

This is a prospective cross-sectional study conducted at a referral maternal fetal medicine center that includes providers with a specific expertise in genetic disorders. Approval for this study, which was exempt from informed consent, was granted through the Institutional Review Board at the University of California, Los Angeles (#15–000667). Patients referred for a routine first trimester screening ultrasound, second trimester anatomic survey, or fetal growth evaluation between July 1, 2013 and July 1, 2016 were considered for the primary cohort if they met the following criteria: no evidence of congenital anomalies, a singleton pregnancy, no evidence for early intrauterine growth restriction, established gestational age, and if the fetal hand was visualized in an extended position with the metacarpal and phalangeal bones visible in the anterior-posterior view. Medical records were reviewed for our primary study cohort and maternal age at time of pregnancy and maternal race were recorded. A second group of patients, who were prospectively collected by D.K from 2007–2008, were included to evaluate the reproducibility of the primary cohort. These patients had similar inclusion criteria; however, only metacarpal or phalangeal lengths were obtained, and no patient demographic data was collected on this subset. None of the ascertained fetuses were noted to have abnormalities at birth. A third group of prenatally ascertained hand measurements for cases of postnatally confirmed cases of thanatophoric skeletal dysplasia were included to test the utility of these new reference growth curves in the detection of brachydactyly. The inclusion criteria for this cohort consisted of pregnancies wherein a skeletal dysplasia was suspected prenatally. Measurements were obtained, and the final diagnosis was confirmed with either molecular and/or radiologic analyses postnatally.

For the primary cohort, three operators (D.K. Y.A. and R.R) recorded the measurements through sonographic evaluation as described below. The third digit was located by visualizing all five digits, numbering the fetal thumb as digit one, then counting in the radial to ulnar direction, identifying the third digit. Measurements were taken if the fetal hand was visualized in the anterior-posterior view, in complete extension. The extended digit was magnified to approximately 2/3 of the screen. Of note, we used established principles of sonographic evaluation of bone with respect to the technique of maintaining the insonation angle close to 45 degrees or 135 degrees. The fetal phalange was measured by placing the first caliper on the proximal portion of the proximal phalange and the second caliper on the distal portion of the distal phalange [Figure 1A]. The fetal metacarpal was measured by placing the first caliper on the proximal portion of the metacarpal bone and the second caliper on the distal portion of the metacarpal bone [Figure 1B]. The third digit was chosen for measurement as it is one of the longest digits, and easiest to visualize, as well as postnatal studies also use the third phalange for determination of brachydactyly (10). 2D images were obtained with GE Voluson 730, E8 or E10 with both 2–4 and 6–8MHz transducers. All measurements were reviewed for consistency and accuracy of measurement. Measurements were recorded in the same manner for the second and third cohort of patients.

For our primary cohort, gestational age at time of ultrasound, femur length with concurrent femur length percentile, and abdominal circumference with concurrent abdominal circumference percentile were recorded. Femur length and percentile were recorded in order to compare the association between metacarpal and phalangeal length with

established skeletal growth measurements. Abdominal circumference and percentile were recorded in order to compare metacarpal and phalangeal length with established soft tissue measurements. Femur length and abdominal circumference percentiles were derived using the gestational age specific reference intervals published by Doubilet et al (13).

Statistical methods: Complete descriptive statistics are provided for maternal age, maternal race, gestational age, metacarpal length, phalangeal length, femur length, and femur length percentile, abdominal circumference, and abdominal circumference percentile for the primary cohort. Normal quantile plots were examined to determine if these distributions conformed to the normal distribution.

Metacarpal and phalangeal lengths were plotted across gestational ages and an initial curve was fit using restricted cubic splines to assess their association. The measurements and spline curves were consistent with a biological non-linear regression model of the form: [$Y = A+BX/(C + X)$] where Y was the mean metacarpal or phalangeal length in centimeters, and X was gestational age in weeks. The residual standard deviation (SDe) was modeled as an increasing linear function of age of the form $SDe = a + b X$.

In addition to the mean values, the 2.5^{th}, 5^{th}, and 95% prediction bounds at a given gestational age were computed based on this non constant SDe. This model reaches a ceiling or maximum value of A+B, where B is the change from minimum to maximum metacarpal and phalangeal length. The rate of change was determined by the ratio of B to C where B/C is the initial rate of change. The R squared (R^2) statistic is reported to quantify model-fit. Applying this equation and comparisons of the primary cohort to the validation cohort, and the combined primary and validation cohort, established internal reproducibility.

The relationship between metacarpal to phalangeal length ratio versus gestational age lengths was assessed by the Spearman correlation for patients in our primary cohort. Further, we examined scatter plots and computed the Pearson correlation coefficients to assess the linear associations between metacarpal and phalangeal lengths and known fetal biometry measurements. Linearity was assessed among these measurements by comparison to fitted splines.

Analyses of spline curve fit, Spearman and Pearson correlations, and the non-linear regression models were carried out using SAS 9.4 (SAS INC, Cary, NC) and R 3.3 (R Foundation for statistical computing, http://www.r-project.org). Parametric data were expressed as the mean +/− standard deviation and Student *t*-test was used for comparison. Measurements from our third cohort were plotted on our reference growth curves for metacarpal length, phalangeal length, and for metacarpal to phalangeal length ratio using Excel (version 14.1.0).

Results:

One hundred and five fetuses met inclusion criteria into the primary study cohort. Maternal characteristics for the primary and third cohort (thanatophoric dysplasia) are described in Table 1. There were no significant differences between these two groups. The validation

group consisted of 172 third phalangeal and 167 third metacarpal lengths measured across gestational age.

Gestational age specific reference growth curves for metacarpal and phalangeal length:

Metacarpal and phalangeal measurements were plotted across gestational ages (12–39 weeks). The restricted cubic splines fit suggested that the mean metacarpal and phalangeal measurements were consistent with the nonlinear model ($Y = A + B\ x\ /(C + x)$). This model was applied to metacarpal and phalangeal lengths from the original cohort (n=105), the validation cohort (phalangeal length, n= 167 and metacarpal length, n= 172), as well as the combined primary and validation cohort (phalangeal length, n= 272 and metacarpal length, n= 277). All results were highly similar with R square values: R^2: 0.916, 0.873, 0.898 respectively for metacarpal lengths and R^2: 0.914, 0.863, 0.890 respectively for phalangeal lengths. Since results from all three experimental data sets were almost identical, we reported results based on combined data as our final model [Figures 2a, 2b].

All metacarpal and phalangeal length measurements were plotted along growth curves as a function of gestational age and are shown in Figures 3a and 3b. The distribution of values allowed for calculation of the 95^{th}, 5^{th}, and 2.5^{th} percentiles. Using the final model based on all data, for a given gestational age, the following model equations for mean metacarpal and phalangeal length can be employed: Mean metacarpal length: $Y = -0.925 + 5.17x/(47.4 + x)$ ($n = 277$, $R^2 = 0.898$), Mean phalangeal length: $Y = -1.47 + 11.4/(63.9 + x)$ ($n = 273$, $R^2 = 0.89$), Y = length in centimeters, x = gestational age. Using the final model based on all data, for a given gestational age, the following equation allowed calculation of the standard deviation (SD) for metacarpal and phalangeal length. Metacarpal length: $SD = -0.016 + 0.0047x$. Phalange length: $SD: -0.085 + 0.0115x$.

Metacarpal and phalangeal length relationship:

The data demonstrated that prior to 15 weeks, the mean metacarpal to phalangeal ratio (MC/PH) increased from 0.40 to 0.49 (r_s=0.1723, p value = 0.0774) [Figure 4a]. This indicated that at gestational ages less than15 weeks, the phalangeal length or ossification was greater than that of the metacarpal. After 15 weeks of gestation, the mean MC/PH ratio approached 0.49 and remained constant until 39 weeks ($r_s = -0.07$, p=0.49) [Figure 4b]. After 15 weeks of gestation the MC/PH ratio followed a normal distribution (mean = 0.49, SD=0.06, and 80% prediction interval: 0.41 to 0.57). Using minimum and maximum metacarpal and phalangeal ratios from our normative data, a value below 0.41 or above 0.57 after 15 weeks would be considered abnormal.

Correlation between metacarpal length, phalangeal length, femoral length and abdominal circumference measurements:

Metacarpal and phalange measurements were compared with femoral length and abdomen circumference parameters that were taken at the same visit. These measurements were compared using Pearson correlations in order to assess the reliability of the *de novo* measurements with known fetal biometric measurements. Figure 5 demonstrated a correlation between metacarpal length and phalangeal length, and among known biometric measurements (femur length and abdominal circumference), reaching nearly a perfect

correlation value of 1 ($r = 1.0$, $p < .001$) across all measurements. Linearity was confirmed among the biometric measurements, after evaluating the comparison between each of the fitted splines versus linear and noting a departure of linearity of less than 2 percent (R^2 change = 0.0 – 1.67%) for all 6 comparisons.

Metacarpal and phalangeal values in thanatophoric dysplasia

Prenatal measurements of the fetal third metacarpal, phalange and MC/PH ratios of five fetuses with confirmed thanatophoric dysplasia were plotted on the generated reference curves based on gestational age at time of evaluation (Figure 6a, 6b, 6c). We used these cases as a test because thanatophoric dysplasia is one of the most common skeletal disorders, postnatal brachydactyly has been established in this disorder, and the final diagnosis could be assured. Metacarpal lengths for three out of five fetuses with thanatophoric dysplasia fell below the 5th percentile (8.4%, 7.5%, 3.4%, 0.8%, and 0.3%. Four out of five phalangeal measurements plotted below the 5th percentile (9.5%, 1.5%, 1.4%, 0.5%, and 0.1%). Of note, in every case of prenatally suspected thanatophoric dysplasia (5 out of 5), either the individual metacarpal or phalange measurement fell below the 5th percentile, capturing 100% of cases of brachydactyly. In thanatophoric dysplasia, brachydactyly results from shortening of both the metacarpal and phalangeal lengths, but notably with a greater effect on the phalangeal lengths. Four out of the four (100%) abnormal measurements of the phalangeal length fall below the 2.5th percentile, compared to two out of the three (75%) abnormal measurements of the metacarpal length. This is reflected in the MC/PH ratio, which is abnormal in three out of the five cases (60%), demonstrating that the majority of these fetuses had abnormal proportion to their hands as well. It is worth noting that the two values of MC/PH ratio that fall within the normative bounds are well above the 50 percentile (78.7%, 84.5%), which corresponds to the disproportionately smaller phalanges, compared to the metacarpal bones. None of the hands in thanatophoric dysplasia showed the normal MC/PH ratio of 0.5 (Figure 6c), supporting the hand proportions can be ascertained prenatally.

Discussion:

In this study, we defined gestational age specific reference growth curves for the fetal third metacarpal and phalange and demonstrate that their pattern of growth correlates linearly with established biometric measurements. Our findings show that after 15 weeks there is a relationship, specifically a 1:2 ratio, between the length of the third metacarpal and phalange similar to the postnatal ratio described by Feingold et al (10) and supports the hypothesis that this pattern of normal proportion is established *in utero* or during the prenatal period. This 1:2 relationship of the metacarpal to phalange remains constant throughout gestational ages 15 – 39 weeks. Prior to 15 weeks, the ratio is steadily increasing from 0.4 to 0.5, which suggests that at gestational ages less than 15 weeks, the metacarpal growth or endochondral ossification is delayed relative to that of the phalanges. Established patterns of limb development describe ossification of the distal phalanges around 8 weeks, then the metacarpals, followed by the proximal and medial phalanges at approximately 9 −11 weeks of gestation (14, 15). While, the exact growth patterns of the bones in the fetal hand have not

been previously described, we believe that our ultrasound-derived results describe normative growth patterns.

Evaluation of the fetal hand can provide insight into disorders that have a profound effect on the development of the skeletal system. There are hundreds of prenatal-onset genetic conditions including syndromes, aneuploidies, and specifically skeletal dysplasias and dysostoses with abnormal hand findings, particularly affecting size (16). In some disorders, the phalanges are primarily affected, in some the metacarpals or palm length, and in some, both sets of bones are affected. With advancing ultrasound technology, our ability to visualize fetal structures has greatly enhanced. Prior studies have reported reference growth curves for the fetal hand (8, 11, 12), but have restricted clinical utility given the measurements have been limited to the second trimester and only to the fetal phalanges. More recently, a large study by Zhou et al, report on the utility of using the planar view of the fetal metacarpals to increase the diagnosis rate of fetal forearm and hand abnormalities but did not report on objective measurements (17). While this study underscores the importance of evaluating the fetal hand, we propose that the use of standardized curves and the additional measurement of the phalanx as we describe in this study adds an objective measure and can result in increased rates of refined prenatal diagnoses.

Strengths and weaknesses of the study are as follows. Strengths include the unbiased and prospective nature of data collection, the use of a secondary cohort to assess reproducibility of the primary cohort, and documentation of both the metacarpal and phalangeal bones from 12 to 39 weeks of gestation. In addition, although we used 90% normative values, in order to increase the sensitivity of the reference curves, we included a minimum curve at 2.5%. Values below this limit should alert the physician to a concern for brachydactyly either as an isolated pattern or associated with syndromic disorders. We believe values below the 5^{th} percentile warrant serious consideration of brachydactyly either as an isolated finding or as a part of a larger pattern of abnormalities; however, inclusion of the 2.5^{th} percentile on our reference growth curve was an attempt to avoid false positive results and to increase the negative predictive value of this tool.

A main weakness is that this study, by necessity, must be a cross-sectional, not longitudinal assessment since this would expose individual fetuses to weekly ultrasound. A further weakness is that only the third digit was evaluated. The third digit was chosen given that it is one of the longest digits and thought to be most technically feasible digit to measure; however, if fetal position limits visualization of this digit, we recognize that the clinician would be unable to use these reference curves in a clinically meaningful way. Furthermore, the phenotype of brachydactylies can also present with shortened metacarpals and phalanges of digits 1–5 in variable manners. For example, brachydactyly D/E primarily affects the thumb and fourth digit, and evaluation of only the 3^{rd} phalanx may not address all forms of syndromic brachydactyly (5).

Despite these limitations, we believe that our data can serve as a reference for evaluation of the metacarpal and phalangeal length in clinical situations. If metacarpal and phalangeal lengths are measured below our gestational age specific reference intervals, one may need to consider brachydactyly as a finding, perhaps associated with other concomitant

findings. An additional abnormality in the MC/PH ratio may help to further categorize the type of brachydactyly. This information may allow for differentiation between types of dysostoses and skeletal disorders, specifically, those with disproportion of the metacarpals and phalanges versus those with symmetric brachydactyly.

For example, skeletal disorders that have a profound effect on the epiphyses of long bones such as the type II collagen disorders, including spondyloepiphyseal dysplasia congenital (SEDC), will be predicted to have normal metacarpal and phalangeal lengths, as well as normal MC/PH ratios based on known postnatal phenotype (18, 19). This is in contrast to disorders due to heterozygosity for mutations in the gene encoding *Fibroblast Growth Factor Receptor 3 (FGFR3)* (4). This lethal disorder is associated with brachydactyly and trident configuration typically recognized as a postnatal finding (20, 21). Our data demonstrate that in thanatophoric dysplasia, brachydactyly (metacarpal and phalangeal length, as well as in altered MC/PH ratios, as shown in Figure 6) is prenatal in onset and could be used to refine the differential diagnoses. This refinement is essential in directing molecular diagnosis and management of the gestation.

Conclusion:

These new reference curves have value, as both a new fetal biometric measurement, and as an additional tool to potentially diagnose and differentiate between skeletal disorders that may or may not be associated with brachydactylies, but all have shortening of the appendicular skeleton. Providing the practitioner with these prenatal reference growth curves allows for immediate phenotypic information to objectively determine the presence of fetal brachydactyly. We believe that with the availability of newer and more advanced technology, our approach outlines a feasible method of measuring the fetal hand. Once familiar with our method, practitioners can use our new gestational age specific reference curves to utilize a new fetal biometric when evaluating a fetus suspected to have either a limb malformation, heritable forms of brachdactylies, or a genetic syndrome associated with disproportion in the hand.

Acknowledgments

Funding statement:

The authors acknowledge support from the National Institutes of Health R25 HD078229 (Rare Disease Clinical Research Training Program) awarded to R.R. and D.K. and this study was also supported in part by National Institutes of Health R01AR066124 to D.K.

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What's already known on this topic?

- Standardized methods to prenatally diagnose skeletal abnormalities are limited
- The definition of prenatal brachydactyly has not been established

What does this study add?

- This study presents gestational age-specific reference growth curves for fetal metacarpal and phalange length
- We establish an in-utero relationship between fetal metacarpal and phalange length of 1:2
- Prenatally measured metacarpal and phalange lengths were plotted on the new reference growth curves to accurately detect brachydactyly in postnatally confirmed cases of thanatophoric dysplasia

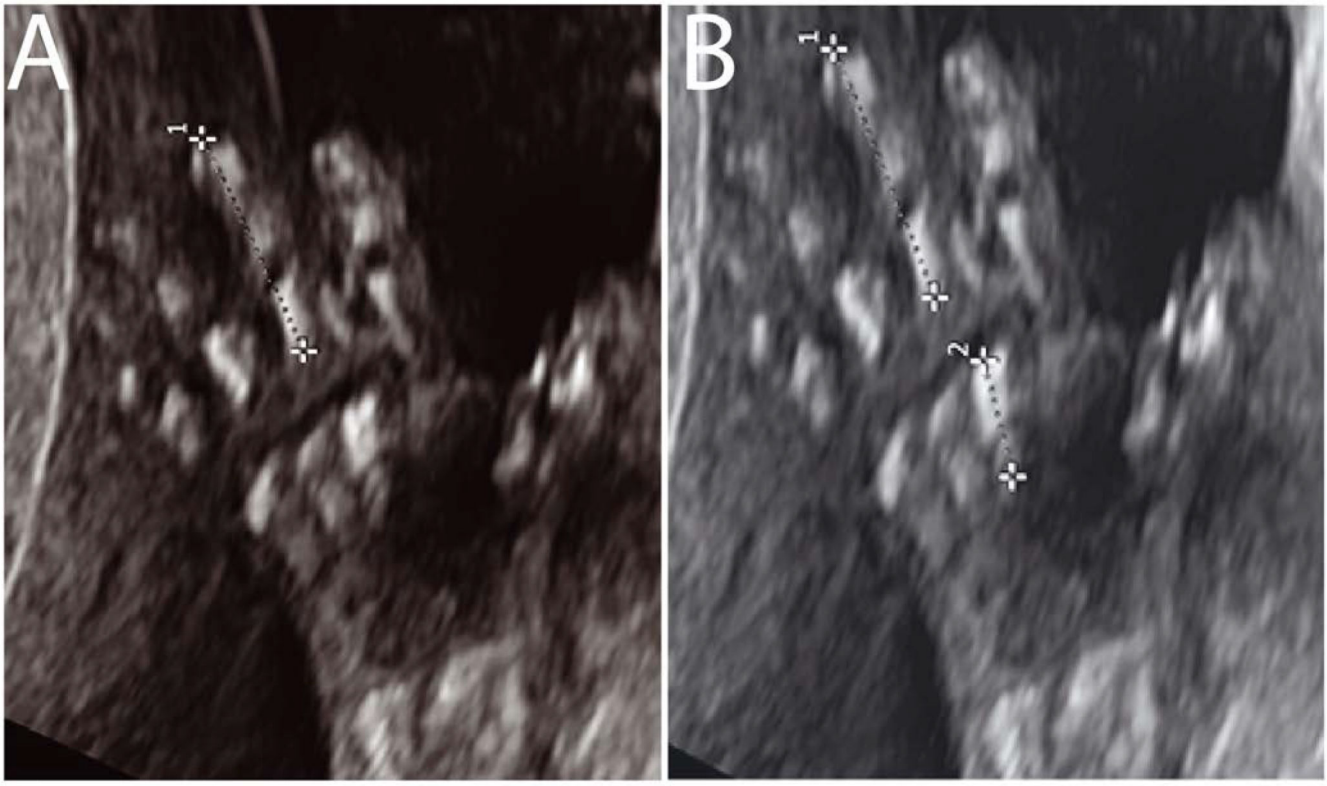

Figure 1.
Measurements of the fetal 3rd phalange [1A] and metacarpal [1B] demonstrating how each value was obtained.

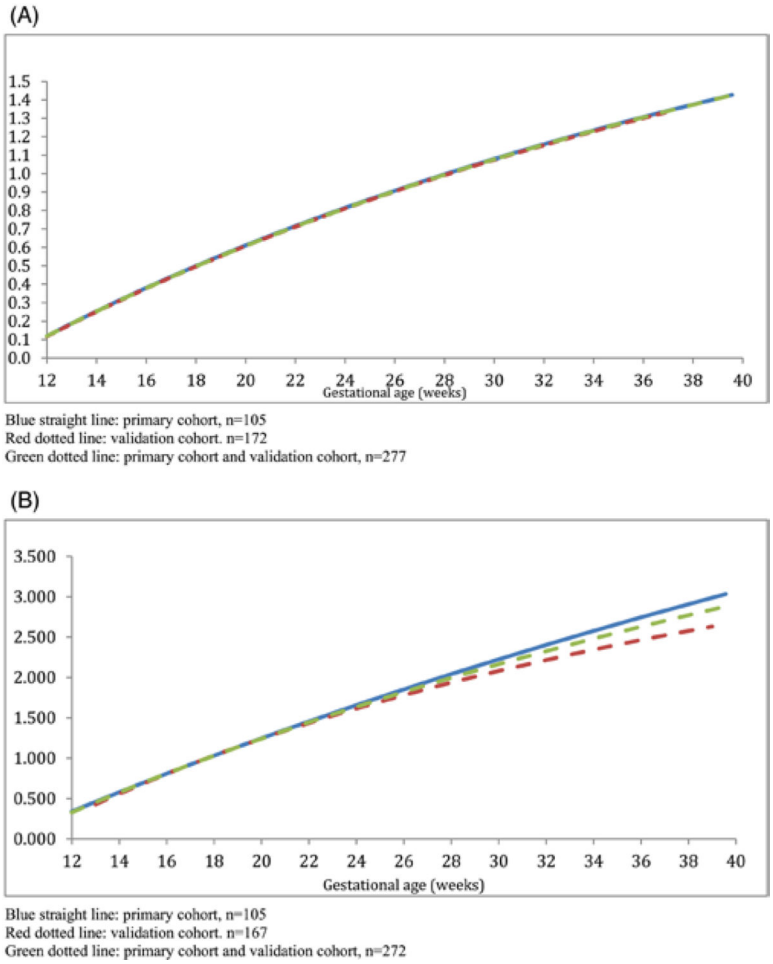

Figure 2.

a. Model comparison: Metacarpal length (centimeters) versus gestational age (weeks)

b: Model comparison: Phalangeal length (centimeters) versus gestational age (weeks)

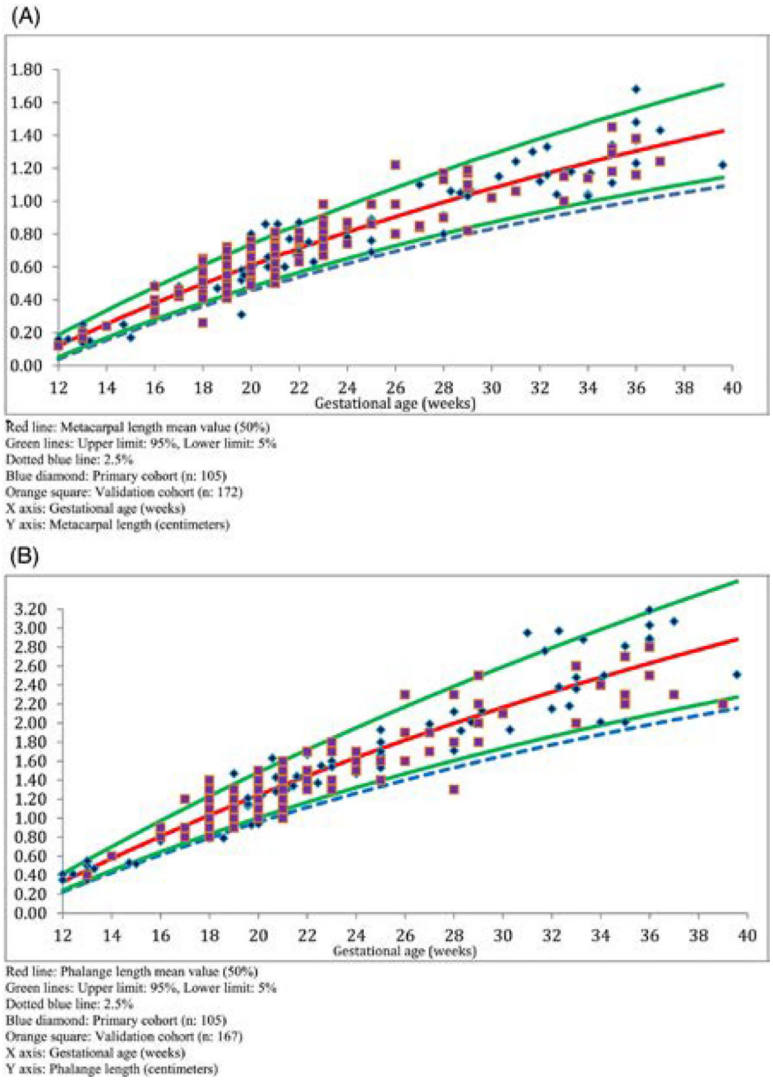

Figure 3.

a: Gestational age specific reference growth curve for 3rd metacarpal length (centimeters)

b: Gestational age specific reference growth curve for 3rd phalangeal length (centimeters)

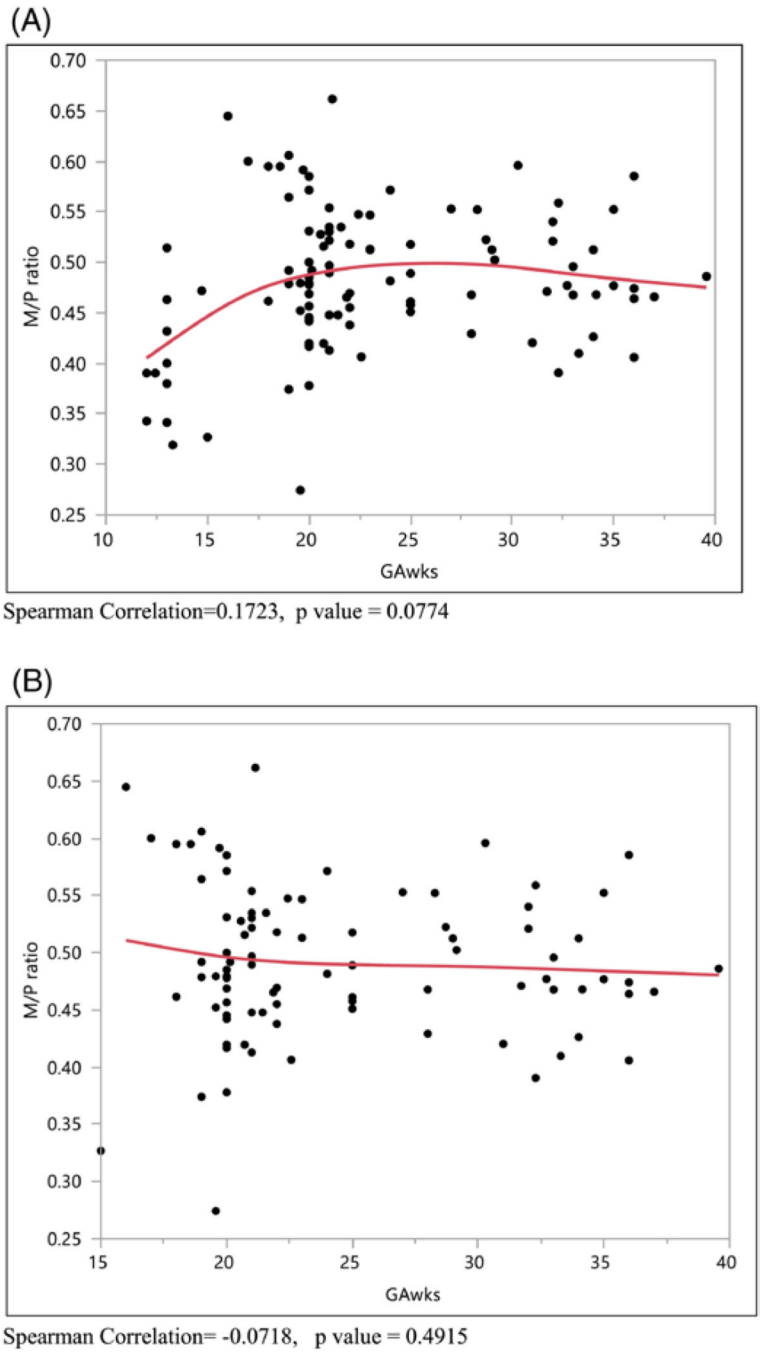

Figure 4.

a: Metacarpal to phalangeal ratio across gestational ages 12–39 weeks

b: Metacarpal to phalangeal ratio across gestational ages 15–39 weeks

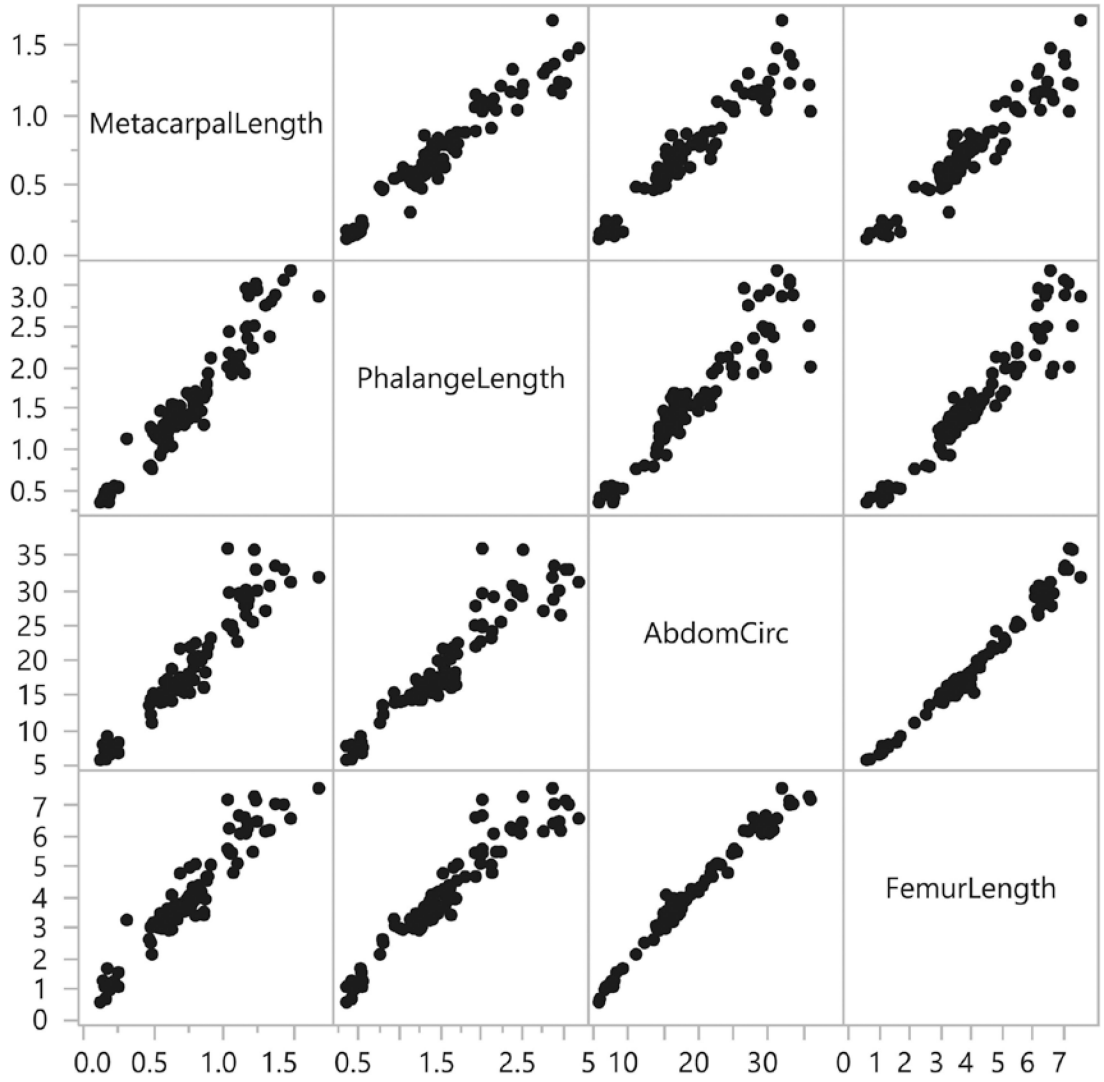

Figure 5:
Correlations among fetal biometric measurements: metacarpal, phalange, abdominal circumference, and femur length

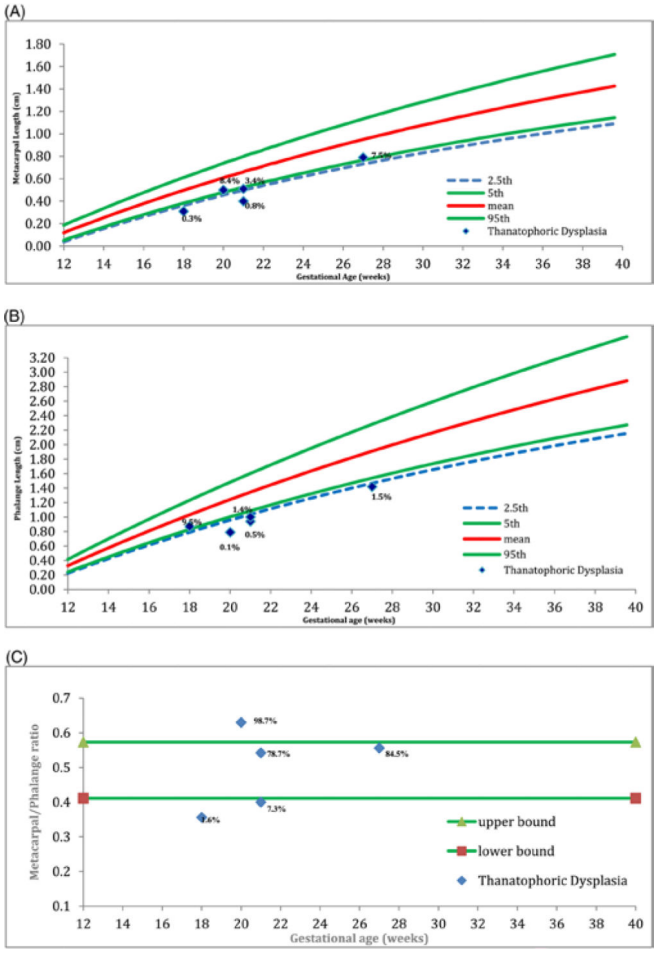

Figure 6.

a: Ultrasound metacarpal measurements (centimeters) for thanatophoric dysplasia

b: Ultrasound phalangeal measurements (centimeters) for thanatophoric dysplasia

c: Ultrasound derived metacarpal to phalangeal ratio in 5 cases of thanatophoric dysplasia

Table 1.

Descriptive characteristics

	Normal N (%)	Mean	SD	TD N (%)	Mean	SD	*P* value
Maternal age (years)	105	34.40	4.51	5	33.00	6.27	0.55
Maternal race	100			4			0.37
Caucasian	70 (70)			1 (25)			
Asian	18 (18)			2 (50)			
Hispanic	5 (5)			1 (25)			
Black	5 (5)			0			
Native American	2 (2)			0			
Gestational age (weeks)	105	23.06	6.68	5	21.40	3.36	0.58
Metacarpal length (cm)	105	0.74	0.33	5	0.50	0.18	0.11
Phalange length (cm)	105	1.54	0.68	5	1.00	0.25	0.08
Femur length (cm)	104	4.01	1.67	4	5.57	6.75	0.12
Abdominal circumference (cm)	92	18.90	7.39	4	18.20	4.51	0.85
Metacarpal/phalange ratio	105	0.48	0.07	5	0.50	0.12	0.54

Metacarpal and phalanges Z-score calculators

ENTER VALUES IN GREEN CELLS		ENTER VALUES IN GREEN CELLS	
Metacarpal length (cm) vs gestational age		Phalange length (cm) vs gestational age	
GESTATIONAL AGE IN WEEKS	20	GESTATIONAL AGE IN WEEKS	25
(must be > 11 weeks)		(must be > 11 weeks)	
Mean	0.608	Mean	1.730
SD	0.079	SD	0.203
ENTER DESIRED PERCENTILE CONFIDENCE INTERVAL	99%	ENTER DESIRED PERCENTILE CONFIDENCE INTERVAL	95%
Value	0.791	Value	2.063
ENTER MEASURED METACARPAL LENGTH (cm)	0.750	ENTER MEASURED PHALANGES LENGTH (cm)	1.73
Z score	1.802	Z score	0.000
Percentile	96.4%	Percentile	50.0%