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Fetal development of the hand, digits and digit ratio (2D:4D)

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Abstract

Objective: The purpose of this study was to investigate growth patterns in human hands, digits and digit ratio (2D:4D) during the fetal period.
Methods: The study is carried out on 161 human fetuses (83 males, 78 females) free from external pathology or malformation with ages ranging between 9 and 40 weeks of gestation. Following general external measurements, length and width of the hand, digit lengths separate for each hand was measured, hand index and the ratio of the lengths of the 2nd finger to the 4th finger (2D:4D index) was computed.
Results: Means and standard deviations of the parameters with respect to gestational weeks, months and trimesters were calculated. There was a significant correlation between all parameters and gestational age ($p<0.001$). No significant differences were observed between sexes or sides for any of the parameters ($p>0.05$). 2D:4D ratio was significantly higher in females compared to males ($p<0.05$) and mean 2D:4D did not change with gestational age.
Conclusion: Detailed information of hand and digit parameters related to the fetal period will reveal the extent of biological variations of hand and digit parameters to be used in future studies. We hope that data acquired in this study will facilitate other studies on hand and digit anomalies, pathologies and variations as well as diagnoses and treatments of such conditions conducted in obstetrics, perinatology, forensic medicine and fetal pathology departments.

1. Introduction

The development of the skeletal system takes place in an order just like other systems. The upper extremities start to develop on the 26—27th days of the gestation. On the other hand, hands and the nails, develop between 21 and 24 weeks

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of gestation [1,2]. There are numerous ultrasound studies on the development of the fetal extremities many of which aimed to detect intrauterine growth retardation in early stages of pregnancy, establish fetal weight or gestational age [2]. In some of these studies the relation between bone development and hormones is established and this relation is implicated as the sign of some diseases [3—6]. Robinson and Manning [3] reported that 2D:4D ratio positively correlated with estrogen and negatively correlated with testosterone. Manning et al. [4—6] confirmed this finding in a number of studies [4—6]. Kjaer et al. [7] assessed the relation between Down's syndrome and hand development and found that the middle phalanx of the 5th finger was the last to develop in autism. Manning et al. [5] found the 2D:4D ratio smaller in children with Down's syndrome and argued that this might be a sign of the condition. Brown et al. [8] compared the 2D:4D ratio in patients with congenital adrenal hyperplasia (CAH) and found that 2D:4D ratio on the right hand of the female patients and the left hand of the male patients was significantly lower than the controls without CAH. Buck et al. [9] conducted a similar study and compared male CAH patients with female patients only to find the ratio to be smaller in males. It is noteworthy that previous studies on hand morphology and 2D:4D ratio used adult subjects and hand radiographs [7,10—12]. Studies pertaining to the fetal period are ultrasound studies conducted during pregnancy [13,14]. However these studies present findings of post-20th week period. In particular there are no studies which report 2D:4D in fetuses. Here we present cross-sectional measurements of 2D:4D from fetuses of gestational age 9 to 40 weeks.

2. Material and method

This study is carried out on 161 aborted human fetuses (83 males, 78 females) aged between 10 and 40 weeks of gestation. Cases that did not have any external pathology or anomaly were obtained from Isparta Maternity and Children's Hospital between 1997 and 2002. Written consent from the families and an approval from the Ethics Board of Süleyman Demirel University Faculty of Medicine were obtained prior to the commencement of the study.

Gestational ages of the fetuses were determined based on the Crown Rump Length (CRL) until 12th week and bi-parietal diameter, head circumference, femur length and foot length between 13—40 weeks of gestation [1]. Cases were stratified based on the gestational age: Group 1 (1st

Table 1 Means of general parameters during fetal period with respect to gestational weeks

Age (weeks)	*N*	Fetal weight (g)	Crown—rump length (CRL)	Head circumference	Bi-parietal diameter (BPD)	Femur length	Foot length
9	4	18	60	63	16	14	9
10	3	20	75	66	18	19	11
11	5	35	80	76	23	21	14
12	9	45	95	78	22	13	16
13	11	55	106	90	22	16	16
14	18	98	120	99	26	17	22
15	6	110	132	112	30	20	22
16	1	125	140	124	34	23	24
17	7	143	147	138	37	26	28
18	6	197	162	150	40	30	30
19	5	213	170	162	43	33	35
20	6	240	175	172	48	35	40
21	6	350	185	187	50	38	42
22	7	400	211	199	53	41	43
23	5	501	218	208	57	43	44
24	7	707	231	219	60	48	52
25	2	750	245	233	63	50	52
26	3	800	248	244	65	52	54
27	4	851	261	254	67	54	56
28	3	1044	272	264	71	58	60
29	4	1319	280	273	73	60	66
30	4	1490	283	282	76	62	70
31	7	1500	288	288	78	65	71
32	4	1700	300	296	80	67	74
33	3	2000	310	303	82	69	75
34	2	2100	315	310	84	70	77
35	3	2150	325	317	87	72	78
36	3	2200	330	324	89	75	79
37	2	2300	353	334	91	76	80
38	1	2400	360	341	92	78	80
39	2	2450	380	347	95	80	81
40	8	2581	406	352	97	82	82

Table 2a Means of hand and digit measurements during the fetal period with respect to gestational weeks (mm)

Age (weeks)	Wrist width	Hand length	Hand width	Palmar length	1st metacarpal length	1st digit length	2nd digit length	3rd digit length	4th digit length	5th digit length
9	4	9	4	6	2	3	4	5	4	3
10	5	12	5	7	2	4	5	6	5	3
11	6	14	6	9	3	4	6	7	5	4
12	6	16	7	12	3	4	7	9	8	6
13	6	17	8	12	4	5	8	10	8	7
14	6	20	10	13	4	7	10	12	10	8
15	7	24	11	15	4	8	11	13	11	9
16	7	26	11	16	5	9	12	14	12	10
17	7	28	12	18	5	9	13	14	13	10
18	8	31	13	20	5	10	14	17	14	11
19	9	33	15	21	5	11	15	18	16	11
20	10	35	16	22	6	12	16	20	17	13
21	11	36	18	22	6	12	17	20	18	15
22	12	37	20	23	7	13	18	21	19	15
23	13	39	21	24	7	14	19	22	20	16
24	14	41	24	26	8	15	20	25	22	17
25	15	44	25	27	8	15	21	25	23	18
26	15	46	26	28	8	16	22	27	23	19
27	16	48	28	30	9	16	22	29	23	19
28	16	50	30	31	10	18	23	30	28	20
29	17	52	31	32	10	19	24	31	29	21
30	18	54	32	33	11	20	26	31	30	22
31	19	56	32	34	11	20	28	32	30	23
32	20	58	33	35	11	21	30	32	32	24
33	21	58	34	36	11	21	30	33	32	25
34	21	59	34	37	12	21	31	33	22	25
35	22	60	35	37	12	22	31	34	33	26
36	22	61	35	39	12	22	31	34	33	26
37	23	61	36	39	13	22	32	35	33	27
38	23	62	37	30	13	22	33	35	34	28
39	24	63	38	41	14	22	33	36	34	28
40	24	64	39	42	14	22	33	36	34	28

trimester), Group 2 (2nd trimester), Group 3 (3rd trimester) and Group 4 (term) comprised fetuses with gestational ages less than 12 weeks, between 13 to 25 weeks, between 26 to 37 weeks, and between 38 to 40 weeks, respectively. Cases were also classified into groups according to their gestational months; 3 months: 9—12 weeks, 4 months: 13—16 weeks, 5 months: 17—20 weeks, 6 months: 21—24 weeks, 7 months: 25—28 weeks, 8 months: 29—32 weeks, 9 months: 33—36 weeks, and 10 months: 37—40 weeks. Cases with an anomaly or pathology of the extremities, hand or finger were not included in the study.

Firstly the measurements of the external features, i.e., fetal weight, CRL, bi-parietal diameter, head circumference, femur length and foot length were carried out. A

Table 2b Means and standard deviations (mm) of hand and digit measurements during the fetal period with respect to trimester groups

Group	*N*	Wrist width	Hand length	Hand width	Palmar length	1st metacarpal length	1st digit length	2nd digit length	3rd digit length	4th digit length	5th digit length
1st trimester (9—12 weeks)	21	8 ± 6	14 ± 3	6 ± 2	9 ± 3	3 ± 2	6 ± 7	6 ± 1	7 ± 2	11 ± 13	6 ± 7
2nd trimester	87	11 ± 9	29 ± 9	15 ± 6	18 ± 6	5 ± 3	10 ± 4	14 ± 5	16 ± 5	15 ± 5	12 ± 4
3rd trimester (26—37 weeks)	42	19 ± 4	55 ± 9	32 ± 6	35 ± 7	11 ± 2	21 ± 4	29 ± 5	32 ± 6	29 ± 5	24 ± 5
Term (38—40 weeks)	11	24 ± 3	63 ± 5	38 ± 3	41 ± 6	13 ± 3	22 ± 2	32 ± 3	36 ± 3	34 ± 3	27 ± 2
Total (9—40 weeks)	161	14 ± 10	36 ± 18	20 ± 11	23 ± 11	7 ± 4	13 ± 7	18 ± 10	20 ± 10	19 ± 10	15 ± 8

$p < 0.05$: Differences in wrist width and 1st digit length among groups except between groups 3 and 4.

Table 2c Means and standard deviations (mm) of hand and digit measurements during the fetal period with respect to month groups

Group	*N*	Wrist width*	Hand length**	Hand width**	Palmar length**	1st metacarpal length**	1st digit length***	2nd digit length***	3rd digit length***	4th digit length***	5th digit length***
3rd month (9—12 weeks)	21	6±3	14±3	6±2	9±3	3±2	4±1	6±1	7±2	6±2	6±7
4th month (13—16 weeks)	36	8±4	21±5	10±3	14±3	4±4	7±2	10±3	12±3	10±3	8±2
5th month (17—20 weeks)	24	9±2	30±6	15±4	19±4	5±1	10±2	15±3	17±3	15±3	12±3
6th month (21—24 weeks)	27	13±3	38±6	21±4	24±4	7±2	13±3	19±3	22±3	20±3	16±3
7th month (25—28 weeks)	14	15±2	47±7	28±4	30±5	9±1	18±3	25±4	28±3	25±3	21±3
8th month (29—32 weeks)	20	20±4	57±9	34±5	36±7	11±1	22±4	30±6	33±6	31±6	26±5
9th month (33—36 weeks)	9	22±3	60±8	36±5	39±7	12±7	22±3	32±2	35±3	32±3	27±2
10th month (37—40 weeks)	10	24±3	64±4	38±3	42±6	13±3	23±2	33±3	36±3	34±3	28±2

* $p<0.05$: Difference between month groups except consecutive months.
** $p<0.05$: Difference between month groups except between 8 and 9, and 9 and 10 months groups.
*** $p<0.05$: Differences between month groups except between 8, 9, and 10 months groups.

caliper, measuring tape, plastic ruler or compasses were used for the measurements. This was followed by bilateral measurements of the hands and digits.

Wrist width: transverse distance between the outermost points of the radius and ulna (styloid processes) on the distal end of the forearm.
Hand length: distance between the transverse axis corresponding to the wrist width and the tip of the middle (3rd) finger.
Hand width: transverse distance between the outermost points of the 2nd and 5th metacarpophalangeal joints.
1st metacarpal length: distance between the midpoints of the first carpometacarpal and first metacarpophalangeal joints.
1st digit length: distance between the midpoint of the first metacarpophalangeal joint and the tip of the 1st digit.
2nd digit length: distance between the midpoint of the second metacarpophalangeal joint and the tip of the 2nd digit.
3rd digit length: distance between the midpoint of the third metacarpophalangeal joint and the tip of the 3rd digit.
4th digit length: distance between the midpoint of the fourth metacarpophalangeal joint and the tip of the 4th digit.
5th digit length: distance between the midpoint of the fifth metacarpophalangeal joint and the tip of the 5th digit.

Indices derived from hand and digit measurements.

Hand index = [(hand width / hand length) × 100]
2D : 4D *index* = [(length of the 2nd digit / length of the 4th digit) × 100].

Table 3 Correlation coefficients (*r*) between hand and digit parameters during the fetal period

	Age (weeks)	Wrist width	Hand length	Hand width	Palmar length	1st metacarpal length	1st digit length	2nd digit length	3rd digit length	4th digit length
Wrist width	0.79									
Hand length	0.94	0.94								
Hand width	0.94	0.97	0.98							
Palmar length	0.92	0.93	0.98	0.99						
1st metacarpal length	0.61	0.97	0.60	0.60	0.57					
1st digit length	0.87	0.96	0.91	0.90	0.87	0.64				
2nd digit length	0.94	0.97	0.98	0.97	0.94	0.62	0.92			
3rd digit length	0.94	0.97	0.98	0.97	0.94	0.62	0.91	0.99		
4th digit length	0.82	0.97	0.86	0.86	0.84	0.60	0.80	0.87	0.87	
5th digit length	0.89	0.97	0.93	0.93	0.90	0.65	0.86	0.94	0.94	0.92

For all parameters, $p<0.001$.

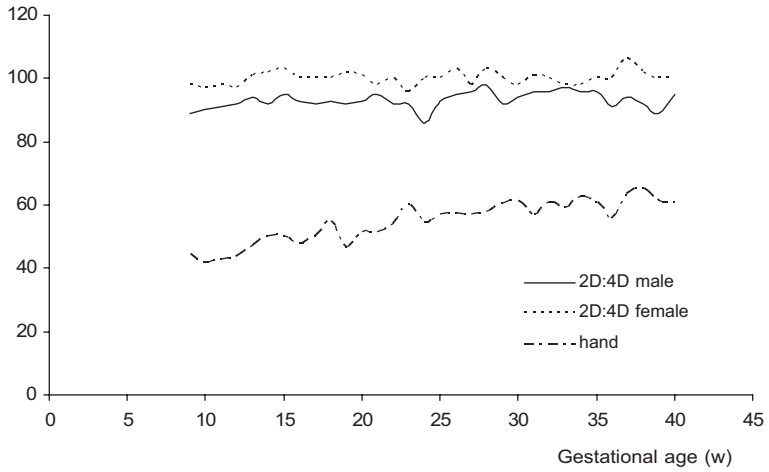

Figure 1 Prenatal changes in hand index and 2D:4D ratio. While the difference in hand index between sexes was not significant, difference in 2D:4D index was. Hand index = [(hand width / hand length)] × 100], 2D:4D index = [(length of the 2nd digit / length of the 4th digit) × 100].

SPSS statistical software (SPSS Inc, Chicago, IL) was used to calculate the means of all parameters with respect to gestational age and groups (trimesters and months). A p value of less than 0.05 was taken as significant. Measurements related to the weeks were expressed as mean; related to months and groups were expressed as mean ± standard deviation. Non-parametric tests were used to compare months and groups due to small sample size. Analysis of variance was tested using Kruskall Wallis test and two-by-two comparisons among significant groups were performed with Mann—Whitney *U* test. Degrees of significance were evaluated with Bonferroni correction. Relationship between variables was tested using Pearson's correlation test.

3. Findings

The first stage of the study comprised the measuring the general external features of 161 fetuses (83 males and 78 females) aged between 9 and 40 weeks of gestation. There were no differences in general external features between sexes ($p > 0.05$). Number of cases and means of the measurements with respect to gestational weeks are presented in Table 1. The means of finger lengths were determined from the right and left hand fingers. Hand and digit parameters separate for both hands did not show sex or laterality differences ($p > 0.05$). Means of the parameters with respect to gestational weeks and means and standard deviation of the parameters with respect to the trimesters and months are given in Tables 2a, 2b—c. There was a significant relation between all parameters and gestational age ($p < 0{,}001$, Table 3). Trimester and month groups between which there were significant differences are presented in Tables 2a and 2b.

In the next stage, the changes in hand and 2D:4D indices throughout the fetal period were determined (Fig. 1). There were no significant changes in 2D:4D over gestational ages. There was no correlation between 2D:4D and gestational ages ($p > 0.05$). While the difference in hand index between sexes was not significant, difference in 2D:4D index was ($p < 0.05$, Fig. 1, Table 4a). The increase in hand width exceeded hand length during the fetal period and with the exception of between 3rd trimester and term group there was a significant difference in hand index between trimester groups. This was true for month groups as well except between 7, 8, 9, and 10 month groups ($p < 0.05$, Tables 4a and 4b). Digit index (2D:4D) did not change significantly throughout the fetal period and no significant differences were observed in this index in either sex between trimester or month groups ($p > 0.05$). Although females had longer 2nd finger than 4th finger compared to males, statistically the difference between the lengths of the 2nd and 4th fingers was not significant in either sex ($p > 0.05$).

4. Discussion and conclusion

Parts and the shape of the hand and the digits reflect developmental characteristics of the individual during the

Table 4a Means and standard deviations of hand and digit indices during the fetal period with respect to trimester groups

Age (weeks)	*N*		Hand index*	2D:4D index**	
	Male	Female	Male + female	Male	Female
1st trimester (9—12 weeks)	14	7	43.5 ± 5.6	94.5 ± 9.4	97.6 ± 3.6
2nd trimester (13—25 weeks)	39	48	51.4 ± 6.1	93.6 ± 5.1	101.6 ± 6.7
3rd trimester (26—37 weeks)	24	18	59.3 ± 4.6	96.2 ± 3.6	100.0 ± 3.5
Term (38—40 weeks)	6	5	60.2 ± 4.9	93.2 ± 5.0	100.8 ± 4.7
Total (9—40 weeks)	83	78	53.1 ± 7.6	94.5 ± 5.7	100.6 ± 6.3

* $p < 0.05$: Difference between trimester groups except 3rd trimester and term fetuses.
** $p > 0.05$: No difference between groups in either sex.

Table 4b Means and standard deviations of hand and digit indices during the fetal period with respect to month groups

Group	*N*		Hand index*	2D:4D index**	
	Male	Female	Male+female	Male	Female
3rd month (9–12 weeks)	14	7	43.5±5.6	94.5±9.4	97.6±3.6
4th month (13–16 weeks)	20	16	49.0±5.5	94.2±6.7	105.6±8.2
5th month (17–20 weeks)	7	17	51.3±5.8	93.0±1.2	100.9±4.5
6th month (21–24 weeks)	12	15	54.7±5.7	92.8±2.9	98.1±4.6
7th months (25–28 weeks)	7	7	58.3±3.1	95.8±2.8	100.9±5.2
8th month (29–32 weeks)	11	9	59.8±5.1	96.2±3.8	99.4±2.1
9th month (33–36 weeks)	6	4	60.4±5.5	96.6±4.4	102.3±3.9
10th month (37–40 weeks)	6	4	59.7±4.9	93.2±5.0	99.2±3.7

* $p<0.05$: Differences between month groups except between 7, 8, 9, and 10 months groups.
** $p>0.05$: No difference between groups in either sex.

fetal and postnatal period. For this reason researchers conducted many ultrasound studies during intrauterine period on the development of the fetal extremities [13,14]. Length parameters of both hands are shown to correlate with CRL and it has been emphasized that hand parameters are good indicators of general fetal development and congenital deformities [7,15–17]. Brons et al. [13], based on their ultrasound study during intrauterine period, claimed that fetal extremity length measurements are helpful to verify the presence of skeletal dysplasia. Budarick et al. [14] assessed fetal hand and digits using 3-dimensional ultrasound and proposed that 3D ultrasound had potential to provide detailed information of the fetal hand and fingers.

Previous ultrasound studies, including those with 3D ultrasound, have reported difficulties encountered while imaging the hand and fingers, especially during 1st and 2nd trimesters. We measured the lengths of the hand and fingers between 9–40 weeks of gestation and found a significant relationship between hand and digit lengths and gestational age all throughout this period ($p<0.001$, Table 3). Data acquired in this study includes detailed information on the intrauterine development of the fetal extremities, in particular hand and digits.

Previous studies did not find a significant gender difference with respect to hand and digit measurements during the fetal life. However, a sex difference between 2nd and 4th digit lengths has been established in adults [18,19]. In the majority of males the ring finger (4th digit) is longer than the index finger (2nd digit). The present study failed to find any laterality differences in hand and digit parameters between sexes or sided either ($p>0.05$). When we compared the hand and digit parameters among trimester groups, we found significant differences in wrist width and 1st digit length among all groups with the exception of between Groups 3 and 4 ($p<0.05$, Table 2a). Comparison of hand and digit parameters among month groups revealed significant differences in all but between 8th, 9th and 10th months ($p<0.05$, Table 2b), indicating that digits reaches its term length in the last trimester.

Sex hormones were argued to influence digit development, 2D:4D ratio in both hands is the major sex difference [18,20]. Furthermore, evidence suggests that 2D:4D ratio shows ethnic differences [20]. The effects of alcohol exposure during fetal life on digit ratio have been studied on rats [21]. Sex differences in 2D:4D ratio becomes evident during the fetal life [22,23]. Lutchmaya et al. [22] investigated the effects of fetal testosterone and estrogen on 2D:4D ratio. To the best of our knowledge, there are no published studies on the 2D:4D ratio of the human fetus. Previous studies in newborns and during childhood suggested that this ratio might be a good parameter to assess fetal development and reported significant relationships between hand and 2D:4D ratios and congenital adrenal hyperplasia, Asperger's syndrome and Down's syndrome [5,7,9,17,23]. Manning et al. [5] conducted a study on patients with Asperger's syndrome and autism and found the 2D:4D ratio was lower than mean values of the population. A lower 2D:4D ratio in newborns with 21-hydoxylase deficiency is believed to be due to prenatal levels of testosterone and estrogen [12]. Manning et al. [4] emphasized that high 2D:4D ratio in male children might be related to germ cell failure. They also claimed that 2D:4D ratio related negatively to sperm count and testosterone concentration and positively to estrogen, luteinizing hormone and prolactin. Also it has been argued that 2D:4D ratio in adults is a good predictor of congenital adrenal hyperplasia [8,9]. No changes were observed in hand and 2D:4D indices throughout the fetal life (Fig. 1). There was a sex difference in 2D:4D but not hand index ($p<0.05$, Fig. 1, Table 4a). Comparison of groups for hand index showed that the increase in hand width exceeded that of hand length, there were significant differences between trimester groups except between 3rd trimester and term and months groups except between 7, 8, 9, and 10 months ($p<0.05$, Tables 4a and 4b). On the other hand, 2D:4D index, did not differ between sexes throughout the prenatal period and there were no differences between trimester or month groups ($p>0.05$). Even though the 2nd digit is longer than 4th digit in females there were no significant differences between sexes with respect to these parameters ($p>0.05$).

Compared to other fetal biometric parameters, data on the development of the hand and 2nd and 4th digits in newborns is not sufficient to detect or identify malformation syndromes but provide important clues to define pathologic processes in premature and newborn babies [17]. In newborns finding abnormal hand, 2nd and 4th digit lengths may be an important evidence of fetal dysgenesis. Many researchers propose that the relation between hormones and digit length in newborns and children may be used to identify numerous illnesses [4–6,24,25]. For instance Kjaer et al. [7] showed that prenatal ossification of the 5th digit in Down's syndrome was delayed. With that respect, having presented prenatal hand and digit parameters, this study

may be helpful for studies trying to disclose the relationship between hormonal balance and hand and digits.

When we investigated sex differences in 2nd and 4th digit lengths we found that in female fetuses the 2nd digit was longer then the 4th though the difference was not statistically significant. Therefore we believe that 2D:4D ratio was not established in utero but, as suggested by Okten et al. [12] and Manning et al. [5,6,24,25] later in childhood. Evidence suggests that the rate of growth of the 2nd digit compared to the 4th digit in females becomes higher in utero since the length of the 2nd digit did not exceed the 4th in newborns and 2D:4D ratio changed in favor of the 2nd digit later in the childhood. The finding of this study that digit ratio increased more during prenatal and immediate postnatal (newborn) periods may assist figuring out the ratios later in childhood. Data obtained in this study would also facilitate the assessment of the newborns and early diagnosis of endocrine disorders.

This study includes detailed information on fetal hand and 2D:4D ratios that have not been described elsewhere. Therefore we believe parameters presented in this pioneering study will be useful to assess fetal development and early detection of pathologies and anomalies.

The finding of sex differences in 2D:4D that appear to change little across gestation is further support for an effect of sex hormones on the prenatal formation of 2D:4D. We hope that data acquired in this study will facilitate other studies on hand and digit anomalies, pathologies and variations as well as diagnoses and treatments of such conditions conducted in obstetrics, perinatology, forensic medicine and fetal pathology departments.

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