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Correlation between 2nd to 4th digit ratios and ultrasonographic measurements of urethrovaginal space

2.-4. parmak uzunlukları oranı ile ultrasonografik üretrovajinal alan ölçümlerinin korelasyonu

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ÖZ

Amaç: İkinci- dördüncü parmak uzunlukları oranı (2D:4D), fetal yaşamda androjen maruziyetinin bir göstergesi olarak kullanılır. Ürogenital sistem ve parmak uzunluğunun farklılaşmasının Homeobox genleri (HoxA ve HoxD) tarafından kontrol edildiği bilinmektedir. Bu nedenle parmakların antropometrik özellikleri ile bağlantılı faktörlerin genetik ve hormonal temele bağlı olarak ürogenital anatomi ile ilişkili olması beklenir. Bu çalışmanın amacı 2D:4D oranı ile üretrovajinal aralık ölçümleri arasındaki korelasyonun değerlendirilmesidir.

Gereç ve yöntemler: Bu prospektif kohort çalışmada üreme dönemindeki otuz bir kadının sonuçları değerlendirilmiştir. Ellerin dijital antropometrik ölçümler ve üretrovajinal aralığın ultrasonografik ölçümleri yapılmış, bu parametreler arasındaki korelasyon değerlendirildi.

Bulgular: Sağ ve sol el 2D:4D oranı ile üretrovajinal boşluk uzunluğu arasında anlamlı negatif korelasyon saptandı (sırasıyla p=0,007 ve p=0,003). Proksimal, orta ve distal segmentteki üretrovajinal boşluğun kalınlığı da her iki el için 2D:4D oranı ile negatif korelasyon gösterdi.

Sonuç: Mevcut çalışmanın bulguları 2D:4D oranı ile üretrovajinal boşluk ölçümleri arasında negatif bir korelasyon olduğunu göstermiştir. Bu verilerden elde edilen sonuçlar, intrauterin fetal androjen maruziyeti ve kadın genital anatomisi arasındaki ilişki hakkında gelecekteki araştırmalar için bir temel teşkil edecektir. Bu çalışma ayrıca UVS' nin anatomik özelliklerine ilişkin ek kanıtlar sağlamıştır.

Anahtar kelimeler: parmak oranı, kadın, genital anatomi, üretrovajinal boşluk

ABSTRACT

Objective: Second to fourth digit (2D:4D) ratio is used as an indicator of androgen exposure in fetal life. It is known that the differentiation of urogenital tract and finger length are both controlled by Homeobox genes (HoxA and HoxD). Therefore, factors that are connected with anthropometric characteristics of fingers are expected to be in relation with urogenital anatomy, depending on genetic and hormonal basis. Aim of the study is to evaluate the correlation between 2D:4D ratio and urethrovaginal space measurements.

Materials and methods: In this prospective cohort study, digital anthropometric measurements of hands and ultrasonographic measurements of urethrovaginal space were evaluated and the correlation between these parameters were assessed in a sample of women in reproductive period.

Results: A significant negative correlation was detected between both right and left hand 2D: 4D ratio and length of urethrovaginal space (p=0.007 and p=0.003, respectively). The thickness of urethrovaginal space at proximal, middle and distal segment was also correlated negatively with 2D:4D ratio for both hands.

Conclusion: The findings of the current study have shown a negative correlation between 2D: 4D ratio and urethrovaginal space measurements. The insights gained from these data will serve as a base for future research about the relationship between intrauterine androgen exposure and female genital anatomy. The present study has also provided additional evidence with respect to anatomical features of UVS.

Keywords: digit ratio, female, genital anatomy, urethrovaginal space

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INTRODUCTION

In the late 1950s, a conglomerate of sensitive nerve endings within the anterior vaginal wall was described and referenced as a pleasure-mediating area by anatomists (1,2). Afterwards, nuclear magnetic resonance, two-dimensional (2-D) and three-dimensional (3-D) ultrasonography (US) have been used to evaluate urethrovaginal space (UVS)(2-6). Gravina et al. used 2-D US to demonstrate a direct correlation between the thickness of the urethrovaginal space and female sexual function (7). The area defined as the female prostate claimed to composed of numerous glands, ducts of pseudo-stratified columnar epithelium and myofibrous tissue, and secretes an ejaculate rich in acid phosphatase and prostate-specific antigen (8,9). The view that this tissue is identical to the male prostate, makes UVS possible to be regulated by steroid hormones (10). Urethrovaginal thickness has been shown to correlate with the real-time androgen levels of women, but the relationship between inutero exposure and UVS has not yet been elucidated (6). Hyperplasia in urethrovaginal cells has been demonstrated by doppler analysis in women with polycystic ovary syndrome, which is one of the conditions associated with androgen metabolism (6). It is also known that intrauterine androgen levels affect hand bone development in the fetus (11).

Second (index finger) to fourth (ring finger) digit ratio (2D: 4D) is used as an indicator of androgen exposure in fetal life (11). It has been shown that the ratio of 2:4 digits of the hand is associated positively with prenatal estrogen and negatively with prenatal testosterone hormone exposure (12). In previous studies, athletic skills, sexual orientation, language development, reproductive success and 2:4 finger ratio has been shown to be related in men and women (11). It is known that the differentiation of urogenital tract and finger length are both controlled by Homeobox genes (HoxA and HoxD) (13). Therefore, factors that are connected with finger characteristics are expected to be in relation with urogenital anatomy on genetic and hormonal basis. In a study investigating the relationship between penile and digit lengths in children, a positive correlation was shown between 2 and 4 digit lengths and penile length (14). Although there are studies investigating the correlation between finger ratios and general/reproductive health, the relationship between female genital anatomical features and 2D:4D ratio has not yet been examined (14, 15).

In our study, we investigated whether there is a correlation between 2D:4D ratio and measurements of UVS.

MATERIALS AND METHODS

Ninety- eight healthy, eumenorrheic (menstrual cycle of 25-35 days), female volunteer who admitted for routine gynecological examination between 20th March and 20th July 2021 were included to initial evaluation for this prospective cohort study. The study protocol was in accordance with the Helsinki II declaration and was approved by the Intuitional Review Board (No: 26379996/09). None of the participants received any monetary compensation and informed consent was obtained from all participants.

Women in reproductive period (18-35 years old), who were in a stable heterosexual relationship, reported at least two acts of sexual intercourse per week and with a normal range of body mass index (weight in kg/height in m2; BMI = 19–25) were enrolled in study. All participants were non-pregnant (confirmed by serum human chorionic gonadotropin) and nulliparous. All subjects had no intercourse in the 12 hours prior the study, they were nonsmokers, did not take psychoactive drugs or recreational substances. Participants also reported no regular intense exercise or hormonal therapy for at least 6 months prior to the study. Women with neurological, psychiatric, cardiovascular, endocrine disorders, renal or hepatic illness, uterine malformations, dyspareunia, endometriosis, ovarian functional cyst, oophorectomy, urologic and proctologic diseases, and history of perineal surgery, previous anti-incontinence surgery or any stage of vaginal prolapse (according to Pelvic Organ Prolapse Quantification System, POP-Q) were not included. Women with decreased serum androgen levels were excluded after initial evaluation[19]. Finally, a total of 31 subjects were enrolled in study. Demographic characteristics (age, BMI), anthropometric measurements of fingers and ultrasonographic measurements of UVS of participants were recorded.

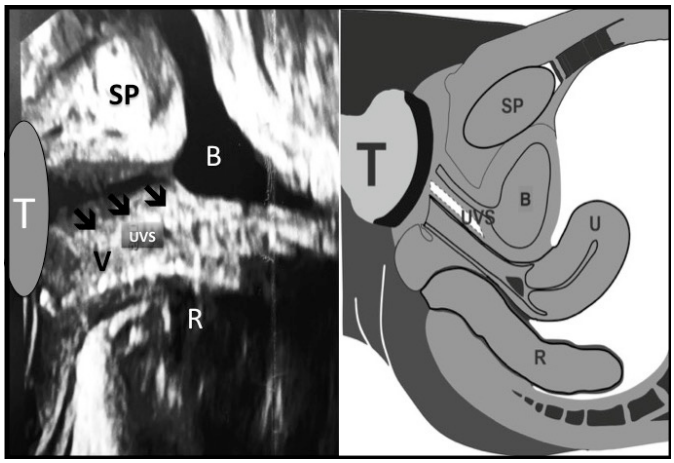
Anthropometric measurements of hands were done directly by using digital stainless-steel vernier caliper. The widest transverse distance between the outer edges of the 2nd and 5th metacarpal bones was recorded as width of hand and the vertical distance from the curve of the wrist to the topmost point of the middle finger was recorded as length of hand. The lengths of second digit (index finger) and fourth digit (ring fingers) were measured from the fingertip to the midpoint of the basal crease, on the ventral surface of the hand [14]. The 2D:4D ratio is obtained by dividing these values.

The ultrasonographic examination was performed with a high-resolution ultrasound transducer (Acuson S2000

HELXTM; Siemens Healthcare GmbH, Munich, Germany). Ultrasonographic approach was obtained by translabial approach with the transducer placed over the external urethral orifice without excessive pressure on the vulva and the bladder was completely voided to avoid any anatomical distortion. Measurements were performed by a single investigator (G.F.Y.) blinded to the anthropometric measurements of patients. UVS described as 'between the border of the smooth muscle and mucosa-submucosa layer of the urethral wall and the border of vaginal wall' by Gravina et al. (7). In the midsagittal plane, the vertical distance between caudal and cranial edges of the referenced area was measured and recorded as UVS length. For standardization and compatibility with previous studies, the internal urethral meatus considered as zero and distal urethral meatus considered as 100th percentile while measuring UVS thickness (2,6,7). In the midsagittal plane, thickness of the urethrovaginal space was measured at the 10th (proximal segment), 50th (middle segment), and 90th percentile (distal segment) of the urethra (7) (Figure 1).

Measurements were taken three times for each and median value was recorded to ensure reliability. Ultrasonographic examination took about 20 minutes for each participant.

Figure 1. Ultrasonographic (a) and graphical (b) presentation of urogenital anatomy and urethrovaginal space



B: bladder, SP: symphysis pubis, T: transducer, U: uterus, UVS: urethrovaginal space, R: rectum

Main outcome of this study was the correlation between 2D:4D ratio and ultrasonographic measurements of UVS. All analyses were performed on SPSS version 21 (SPSS Inc., Chicago, IL, USA). Shapiro- Wilk test was used to determine whether variables are normally distributed. Data are given as mean ± standard deviation or median (minimum - maximum) for continuous variables according to normality of distribution. Pearson or Spearman correlation coefficients were calculated to evaluate relationships between continuous variables. P- values of less than 0.05 were considered statistically significant.

RESULTS

The mean age of entire cohort (n=31) was 28.61 ± 3.26 (range 22 - 35). The mean of UVS length was 19.2 (16.7-27.1) mm. The mean of UVS thickness was; 10.8 mm for proximal segment, 10.5 mm for middle segment and 10 mm for distal segment. The mean width and length of right hand were 82.22 mm and 174.38 mm, respectively. Medians of second- and fourth-digit length of right hand were 69.3 m and 72.7 mm, respectively. Mean width and length of left hand was 82.61nmm and 176.09 mm, respectively. Medians of second- and fourth-digit length of right hand were 71.1 mm and 70.1 mm, respectively. 2D: 4D ratio was 0.99 ± 0.04 for right and 0.99 ± 0.05 for left hand. Summary of participants' characteristics, anthropometric and ultrasonographic measurements are given in Table 1.

Table 1. Summary of characteristics

Age (y)	28.61 ± 3.26
Height (cm)	161.13 ± 5.00
Weight (kg)	68.00 ± 9.70
Body mass index (kg/m^2)	26.15 ± 3.22
UVS measurements (mm)	
UVS length	19.2 (16.7 - 27.1)
UVS thickness- Proximal segment	10.8 (9.3 - 14.5)
UVS thickness- Middle segment	10.5 (8.5 - 14.3)
UVS thickness- Distal segment	10.0 (8.3 - 14.1)
Right hand measurement (mm)	
Width	82.22 ± 8.43
Length	174.38 ± 10.88
2nd digit length	69.3 (60.2 - 84.9)
4th digit length	72.7 (60.0 - 83.0)
2D:4D ratio	0.99 ± 0.04
Left hand measurement (mm)	
Width	82.61 ± 8.06
Length	176.09 ± 12.52
2nd finger length	71.1 (61.3 - 86.5)
4th finger length	70.1 (60.7 - 93.7)
2D:4D ratio	0.99 ± 0.05

Data are given as mean ± standard deviation or median (minimum - maximum) for continuous variables according to normality of distribution.

UVS: urethrovaginal space, 2D:4D: second to fourth digit ratio, y: year, m: meter, cm: centimeter, mm: millimeter, kg: kilogram

Right 2D: 4D ratio was negatively correlated with UVS length (p= 0.007, r= -0.478). Left 2D:4D ratio was negatively correlated with UVS length (p= 0.003, r= -0.511). Right 2D: 4D ratio was negatively correlated with the thickness of UVS proximal, middle and distal segment (p= 0.004, p= 0.007 and p= 0.009, respectively). Left 4th digit length was positively correlated with proximal segment of UVS thickness (p= 0.024, r= 0.404).

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Table 2. Correlation between hand and urethrovaginal space measurements

		UVS measurements			
		Length	Thickness Proximal segment	Thickness Middle segment	Thickness Distal segment
Right hand measurements					
Width	r	0.154	0.290	0.115	0.003
	p	0.408	0.114	0.537	0.988
Length	r	0.012	0.139	-0.018	-0.019
	p	0.948	0.454	0.923	0.917
2nd finger length	r	-0.008	0.135	-0.076	-0.155
	p	0.967	0.469	0.683	0.406
4th finger length	r	0.145	0.268	0.035	-0.014
	p	0.437	0.145	0.854	0.941
2D:4D ratio	r	**-0.478***	**-0.503***	**-0.474***	**-0.462***
	p	**0.007**	**0.004**	**0.007**	**0.009**
Left hand measurements					
Width	r	0.163	0.228	0.123	0.045
	p	0.380	0.217	0.511	0.812
Length	r	0.124	0.298	0.140	0.098
	p	0.507	0.104	0.452	0.601
2nd finger length	r	0.053	0.211	-0.020	-0.102
	p	0.776	0.254	0.915	0.586
4th finger length	r	0.232	**0.404***	0.151	0.083
	p	0.209	**0.024**	0.419	0.656
2D:4D ratio	r	**-0.511***	**-0.557***	**-0.511***	**-0.509***
	p	**0.003**	**0.001**	**0.003**	**0.003**

UVS: urethrovaginal space, 2D:4D: second to fourth digit ratio

* Correlation is significant at the 0.05 level (2-tailed).

DISCUSSION

The principal implication of the current results is that a significant negative correlation was detected between both right and left hand 2D: 4D ratio, and UVS measurements. It was claimed that not only in postnatal life but also fetal androgen exposure has an effect on female genital anatomy. Thus, this study also provides a data to the growing body of research, which supports the effects of intrauterine hormonal status to final characteristics of urogenital anatomy.

The second to fourth digit ratio (2D: 4D) is a sexually dimorphic trait and variations have been reported in different ethnic and geographic groups (11,18). Lutchmaya et al. have shown that high levels of fetal sex hormones derived from samples of amniotic fluid are correlated with 2D:4D at age two, with low 2D:4D associated with high fetal testosterone relative to fetal estradiol (12). Finger length and the differentiation of the urogenital tract are both controlled by the Homeobox genes Hox A and D, thus, 2D:4D is thought to be a somatic marker of prenatal sex hormone exposure (13). In the light of this evidence, a correlation may be reasonable between anatomical characteristics of urogenital system and anthropometric measurements of fingers. In a study designed in a group of patients undergoing urological surgery, a significant correlation was found between stretched penile length and 2:4 digit ratio (15). From gynecologic point of view, in a study examining the relationship between finger lengths and women reproductive health, later age at menarche, heavier menses bleeding and dysmenorrhea found to be associated with 2:4-digit ratio (19). Several studies found 2D:4D to be associated with reproductive cancers (20,21).

In the past, the female prostate was considered as a non- functional gland remaining immature throughout life from fetal life to the advanced stage (22). Afterwards, many anatomical and vascular studies, which detailed functional and structural characteristics of urethrovaginal space, have been conducted and reference this area with different terms such as skene's gland, female prostate and G- spot. Wimpissinger et al. have used perineal 2-D US to study the female prostate in subjects and showed a hyper echoic structure spanning the entire length of the urethra along the anterior wall of the vagina (23). In 2008, Gravina et al. described the objective measurement method of urethrovaginal space thickness with 2-D US (7). Zaviacic et al. demonstrated that the female prostate was histologically similar to the male counterpart but different in morphology and function (8,9). Battaglia et al. demonstrated the hyper echoic structures contained in the urethrovaginal space with small volumes, a gland-like aspect and no rich vascularization or blood flow by 3-D US (2). These findings exactly correspond to the histological description of the female prostate. Although, it has not claimed clearly yet, a functional correlation was found between thickness of urethrovaginal space and ability to experience the vaginal orgasm (10,24,25). The anatomic region including distal urethra, vagina and clitoris described by O'Connell et al. as the 'locus of female sexual function' and these tissues around the distal urethra become engorged with sexual arousal (25). Additionally, there is evidence that sexual functions are affected

after urogenital surgeries involving this region (25). These data strengthen the relationship between UVS and sexual function. In the perspective of these evidences, it is concluded from our results that 2D:4D may be also associated with sexual function, but further studies are needed to support this hypothesis.

The main strength of the present study is the elimination of possible confounders that might affect the anatomical features of urethrovaginal space. To improve objectivity of urethrovaginal space measurements, we included only nulliparous patient with normal BMI and we excluded patients with any stage of vaginal prolapse, history of previous perineal/ anti-incontinence surgery, increased androgen levels and decreased ovarian function due to their potential effects on UVS. Although the strict selection criteria create a unique study population, broadening of exclusion criteria caused small sample size as the main potential limitation of the present study. On the hand, to best of our knowledge, the relationship between 2D:4D and any anatomical region in the female genital tract has never been evaluated, yet. Notwithstanding the limited sample, the study adds new insights to the growing body of research regarding clinical implications of 2D:4D. Although, the fact that UVS is still under investigation, can be considered as a weakness of the study, the data gained from this study may be of assistance to elucidate this region which is of recent interest to researchers.

The findings of the current study have shown a significant negative correlation between both right and left hand 2D: 4D ratio, and UVS measurements. Digit ratios have been used as a marker of intrauterine hyperandrogenism and UVS measurements have been shown to be greater in individuals with androgen exposure in fetal life. Based on the relationship between UVS and sexual function; insights gained from these data will serve as a base for future research investigating whether fetal androgen exposure affects sexual function in reproductive life. The present study has also provided additional evidence with respect to anatomical features of UVS.

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