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Digit ratio (2D:4D): A Potential Anatomical Biomarker for Predicting the risk of development of Polycystic Ovarian Syndrome

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Abstract:
Introduction: *Variable exposure to prenatal androgens may be responsible for the spectrum of endocrine and metabolic disturbances characteristic of Polycystic ovarian syndrome. Perinatal androgen level has been proved to play pivotal role in establishing finger lengths in foetus. It has been suggested that the 2D:4D ratio is a negative correlate of prenatal testosterone and a positive correlate of prenatal estrogens. Once established in early neonatal life digit ratio assumed to be stable in later life.*
Aims: *To find out any possible association between digit ratio and developing PCOS*
Methodology: *400 females (200 cases and 200 controls) of age group 18-40 were studied. The length of the index (2D) and ring finger (4D) were measured and 2D:4D ratio were calculated and statistically analyzed.*
Results: *There was a significant difference ($p<0.0001$) in 2D:4D ratio between women with PCOS and the* ***control group.*** *Also 2D:4D relationship is strong for right hand.*
Conclusion: *This anatomical expression can be used as a tool for early prediction of PCOS and hence substantiates the need for lifestyle modification to counteract this syndrome at its nascent stage*
Keywords: *Digit ratio, In-utero androgen exposure , Polycystic Ovarian Syndrome, 2D:4D.*

I. INTRODUCTION

The digit ratio and its association to the phenotypic characteristics has been the focus of much research in recent years [1]. Digit ratio has been seen to show sexual dimorphism in relative and absolute lengths of index (2D) and ring finger (4D). The index to ring finger ratio has been reported to be smaller in males as compared to females [2-3]. The concept of digit ratio is popularized by an evolutionary psychologist Prof John Manning. He describes the digit ratio as a living fossil and a record of factors the foetus was exposed to at a critical time for the development of many other things [1].

The 2D:4D ratio is thought to be determined by testosterone exposure during early intrauterine life. High concentration of foetal testosterone indicates a low 2D:4D which therefore indicates high prenatal testicular activity [3-6]. It has been suggested that the 2D:4D ratio is a negative correlate of prenatal testosterone and a positive correlate of prenatal estrogens [7]. The androgen receptors are present in the bones of hands and high androgen receptor activity has been associated with reduced 2D:4D ratio [1,8-9]. Also high androgen receptor activity, reflected by low numbers of CAG repeats [12-13]. The differentiation of the digits is under the control of Homeobox or Hox genes, which also controls the differentiation of testes and ovaries. This common control of the differentiation of the gonads and digits may therefore indirectly influence the prenatal production of testicular androgen and the development of the digits [1,5,11]. Once established in early neonatal life digit ratio assumed to be stable in later life [1,8]. Similarly in women conditions with elevated androgen concentration during foetal development can result in a masculine finger length pattern [4,10].

Polycystic ovarian syndrome (PCOS) also called Hyperandrogenic Anovulation [14] or Stein-Leventhal syndrome is one of the most common endocrine disorders among females. PCOS has a diverse range of causes. The precise aetiology of PCOS is unknown, but there is strong evidence that it is largely a genetic disease [15]. However variable exposure to prenatal androgens may be responsible for the spectrum of endocrine and metabolic disturbances characteristic of this syndrome [16-17]. PCOS produces symptoms in approximately 5-10% of women of reproductive age. It is thought to be one of the leading causes of female sub fertility [18-23]. The most common immediate symptoms are Anovulation, excess androgenic hormones and insulin resistance. Anovulation results in irregular menstruation, amenorrhea and ovulation related infertility [18-24].

In 2003 a consensus workshop sponsored by ESHRE (European Society of Human Reproduction and Embryology)/ASRM (American Society for Reproductive Medicine) in Rotterdam refined definition of PCOS [25]: namely the

1. Oligomenorrhea/or Anovulation
2. Hyperandrogenism (clinical or biochemical)
3. Polycystic ovaries, with the exclusion of other etiologies [24-25].

Prenatal testosterone exposure is known to decrease the 2D:4D ratio and as it is also associated with endocrine and metabolic disturbances in Polycystic ovarian syndrome. With this anatomical expression of sex-hormonal predominance during intrauterine life, we tried to find out any possible relation of digit ratio with the developing PCOS in adulthood.

Since the 2D:4D ratio was first proposed as a marker for prenatal androgen action in 1998, many studies have been published that have either further tested the association between the digit ratio and prenatal androgens, or employed digit ratios as a marker to investigate the association between prenatal androgens and a variety of outcomes. So far only a few studies [13,16-17] have attempted to correlate PCOS and 2D:4D ratio. Numerous methods are used in the assessment of 2D:4D, however, some are not reliable enough and others are difficult to perform in large epidemiological studies [26]. According to Costas L *et al.* [26], the main source of variation was differences between subjects (real variation). His results suggest that reliability is influenced by participants' characteristics. Digit ratios determined directly with calipers are reliable when repeated measurements are averaged. Results with less number of sample population were prone to a number of drawbacks which may be major or minor errors which result in outlier values of 2D:4D ratio. These drawbacks can be countered if large numbers of participants are recruited. Therefore we have taken 400 of population with 200 cases and 200 controls. This study focus on relation of digit ratio with PCOS about which little is known. Also to document bilateral variability in digit ratio if present and to determine the handedness which relates more with PCOS.

II. MATERIALS AND METHODS

The present study was conducted in Gynaecological OPD of MY hospital and M.G.M. Medical College, Indore (M.P.) India.

2.1. Inclusion criteria:

It included 200 women of age group 18-40 years which were diagnosed cases of PCOS either by a reproductive endocrinologist or gynaecologist on the basis of clinical history to determine menstrual irregularities or duration of infertility and Ultrasonography to detect the presence or absence of polycystic ovaries. These cases were compared with 200 regular cycling women of the same age group without PCOS.

2.2. Exclusion criteria:

- Subjects below 18 years and above 40 years
- Subjects with injuries or deformities of digits
- Subjects with other aetiologies of androgen excess and anovulatory infertility such as hyperprolactinemia, thyroid dysfunction and congenital adrenal hyperplasia
- Subjects with pathological causes of oedema, hypertension and patients on drugs like diuretics, steroids which can affect vascular and extra vascular volume were also excluded.

2.3. Methodology:

The digit ratio is the ratio of the length of different digits or fingers typically measured from the mid-point of proximal crease of the digit to their tip[27,5]. Measurement of index (2D) to ring finger (4D) length ratio (2D:4D) were made on the ventral surface of the right and left hand from the most proximal basal crease of the digit to the tip of the finger in the mid line (Fig.1) and protruding finger nails were excluded. Volunteers were asked to remove any jewellery or rings that would interfere while obtaining finger lengths measurements. The procedure, aims and objectives of the study were explained to each subject. A written consent was taken from each subject. All the measurements were taken in a well-lighted room with overhead light.

Physical measurements were made on the ventral aspect by using Vernier Calipers without exerting pressure by a single experienced investigator to remove inter observer error. The left hand index finger were measured first followed by left ring, right index and then right ring finger. Measurements were taken twice for accuracy and to take out mean.The 2D:4D ratio for each hand were calculated by dividing the length of index finger by the length of ring finger. The 2D:4D ratio <1 has been considered as a "male finger pattern" and >1 has been considered as a "female finger pattern" [3].

2.4. Statistical evaluation:

Data thus collected was compiled, tabulated and analysed statistically on word excel and SSP softwares**.** Descriptive statistics (Mean± SD) of the 2D:4D for the left and right hands were tabulated for all women with PCOS and female controls. Data obtained was analysed using student 't-test' and 'p-values' were calculated**.**

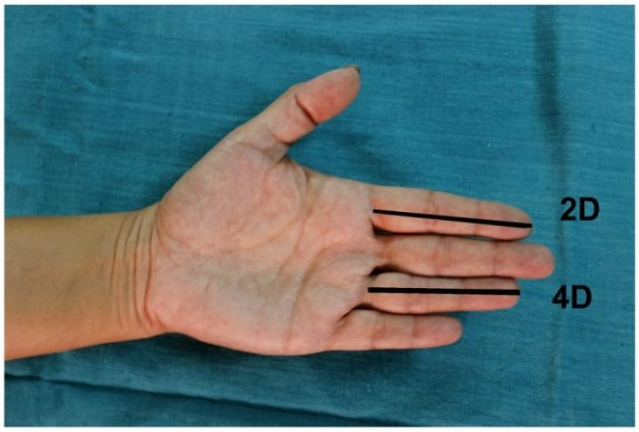


Fig. 1: Diagrammatic representation of digit ratio

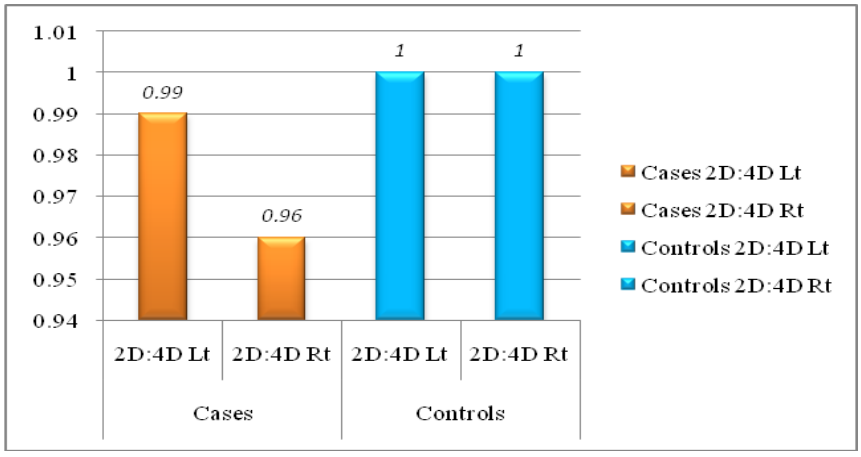
III. OBSERVATIONS AND RESULTS

Clinical features of all women meeting the criteria for PCOS and female controls have been summarized in Table 1. Collectively, women with PCOS had higher incidence ($p < 0.0001$) of acne, hirsutism and irregular menses. 70% of women with PCOS were reported to demonstrate a delayed age of menarche when compared with a reference cohort of women without PCOS. In fact, some of control subjects (15%) tend to demonstrate lower 2D:4D ratio and demonstrated delayed menarche.

Table 1: Distribution of Clinical symptoms in Cases and Controls

Groups	**Cases**		**Controls**	
	N=200	**%**	**N=200**	**%**
Acne	128	64%	44	22%
Hirsutism	124	62%	16	08%
Irregular Menses	168	84%	06	03%
Delayed Menarche	140	70%	30	15%

Women with PCOS had higher ovarian volume measurements ($p < 0.0001$) with the mean volume of ovary of right side with 11±02 cc and that of left side with 11±2.2 cc (as calculated through USG by the radiologists) compared to female controls which have bilaterally equal volumes of ovary within normal range of 7.94±2.34 cc [28].



Graph 1: Comparison of digit ratio in Lt and Rt hand of cases and controls

Table 2: Statistical calculations in Cases and Controls

	Cases							Controls						
	2D:4D Lt	**2D:4D Rt**	**Age**	**Wt (kg)**	**Ht (m)**	**BMI**	**Age at menarche**	**2D:4D Lt Co**	**2D:4D Rt Co**	**Age**	**Wt (kg)**	**Ht (m)**	**BMI**	**Age at menarche**
Min	0.93	0.93	19	45	1.5	17	12	0.94	0.94	19	43	1.5	17	11
Max	1.1	1.0	35	82	1.7	32	17	1.1	1.1	36	76	1.7	30	16
Mean	0.99	0.96	24	66	1.6	26	14	1.0	1.0	24	60	1.6	24	13
SD	0.038	0.021	3.7	8.7	0.036	3.2	1.1	0.028	0.028	3.9	7.0	0.031	2.7	1.2
Std. Error	0.0027	0.0015	0.26	0.62	0.0026	0.22	0.077	0.0020	0.0020	0.27	0.49	0.0022	0.19	0.088
CV%	3.81	2.19	15.60	13.29	2.29	12.28	7.69	2.80	2.74	15.89	11.57	1.98	11.29	9.89

Min= Minimum Max= Maximum SD= Standard Deviation CV= Coefficient of variation

Statistical calculations of cases and controls have been summarized in Table 2 and 3. Women with PCOS had low 2D:4D ratio (Graph 1), increased weight, high BMI and delayed age of menarche which were highly significant ($p < 0.0001$). The differences in mean 2D:4D ratio between the PCOS and the control groups (Table 3) was greater on the right hand (-0.051 ± 0.0025) with a t value of 21, compared with that of the left (-0.029 ± 0.0033) with t value of 8.6 which means the 2D:4D relationship is strong for right hand.

Table 3: Unpaired t test and F test Results

Unpaired t test	**Cases**	**Controls**	**Cases vs Controls**						
	2D:4D Lt vs Rt	2D:4D Lt vs Rt	2D:4D Lt	2D:4D Rt	Age	Wt (kg)	Ht (m)	BMI	Age at menarche
p value	P<0.0001	0.9111	P<0.0001	P<0.0001	0.0348	P<0.0001	0.2844	P<0.0001	P<0.0001
p value summary	***	ns	***	***	*	***	ns	***	***
t value	t=7.3	t=0.11	t=8.6	t=21	t=2.1	t=6.9	t=1.1	t=6.8	t=13
Difference between means	0.022 ± 0.0030	-0.00031 ± 0.0028	-0.029 ± 0.0033	-0.051 ± 0.0025	-0.80 ± 0.38	5.4 ± 0.79	0.0036 ± 0.0034	2.0 ± 0.29	1.5 ± 0.12
95% confidence interval	0.016 to 0.028	-0.0058 to 0.0052	-0.035 to -0.022	-0.056 to -0.046	-1.5 to -0.060	3.9 to 7.0	-0.0030 to 0.010	1.4 to 2.6	1.2 to 1.7
R squared	0.12	0.000031	0.16	0.52	0.011	0.11	0.0029	0.10	0.28
F test to compare variances:									
F value	3.2	1.0	1.7	1.7	1.1	1.6	1.3	1.4	1.3
p value	P<0.0001	0.3803	P<0.0001	P<0.0001	0.2312	0.0008	0.0202	0.0103	0.0232
p value summary	***	ns	***	***	ns	***	*	*	*

***Highly Significant *Significant ns= not significant

There was a non significant negative relationship between the right hand finger length ratio and BMI (i.e., as the BMI increased, the finger length ratio decreased; Pearson correlation coefficient = −0.064; P=.37). But in left hand finger length ratio there was a weak significant positive relationship (Pearson r = 0.14; P=.042).

IV. DISCUSSION

The prenatal androgens might contribute to development of PCOS has been retrospectively investigated by Cattrall *et al., 2005* [13] using a putative anatomical marker of in utero androgen exposure. He found a small, yet significant, difference in the right hand 2D:4D of women with PCOS compared to healthy female controls (98.3% of that in the controls) providing support for prenatal androgens in the etiology of PCOS which is consistent with our study. The groups were similar with respect to age and height but differed in BMI. The average age of the PCOS group was 28.7 ± 5.0 years and 28.7 ± 5.6 years in the control group. The average

height of the PCOS group was 163.8 ± 8.2 cm and 164.4 ± 6.1 cm in the control group. He found that 59% of the PCOS women were obese with a BMI more than 30 kg/m^2, compared to 7% in the control group. The mean BMI of the PCOS group was 29.2 ± 6.5 kg/m^2. In the control group the mean BMI was 23.5 ± 4.4 kg/m^2. Similarly in my study groups were similar with respect to age and height but differed in weight and BMI. The average age of the PCOS group was 24.35 ± 5.0 years and 24.35 ± 5.6 years in the control group. The average height of the PCOS group was 159 ± 3.8 cm and 159 ± 3.0 cm in the control group. The mean BMI of the PCOS group was 25.79 ± 3.1 kg/m^2 and that of control group was 23.7 ± 2.5 kg/m^2. Cattrall et al. used NIH criteria to define PCOS which did not included ultrasonic evidence of polycystic ovaries and conducted his studies on 70 women aged between 18-40 years with PCOS and compared it with 70 women of same age group without PCOS. Although we used Rotterdam criteria to define PCOS which also included USG as a measure to diagnose women with PCOS, then also our results are consistent with his study.

Lujan ME *et al.* [16], concluded that women with PCOS do not demonstrate finger length patterns that are consistent with increased prenatal androgen exposure and precluded that digit ratios measured by Vernier callipers do not serve as anatomical evidence of prenatal androgen exposure in PCOS which contradict our and Cattrall results. In her study collectively, women with PCOS tended to be slightly older ($P = 0.068$), of greater body mass index (BMI; $P < 0.001$), and had larger waist circumferences ($P < 0.001$) and reported longer menstrual cycles ($P < 0.001$) compared with controls. Mean 2D:4D in the left (0.991 ± 0.030 versus 0.981 ± 0.038, respectively; $P = 0.093$) and right (0.983 ± 0.031 versus 0.981 ± 0.031, respectively; $P = 0.634$) hands of women with PCOS did not differ from that of controls.

In another study by Lujan ME *et al.* [17] she showed that women with four clinical phenotypes of PCOS do not demonstrate anatomical evidence of elevated prenatal androgen exposure as judged by a lower 2D:4D ratio. This time finger lengths were not measured using Vernier callipers but their hands were digitally scanned which was considered as a more reliable method by her.

There are several reasons why our and Cattrall *et al.* results differ from that of Lujan *et al.* One of it may be because she used different criteria to define PCOS by categorizing it into four clinical phenotypes. Another reason may be due to the fact that she determined digit ratio in 98 PCOS women and in 51 controls which differ from our study group which included large population groups (400) with equal number of cases and control (200 each). Although we both used the same Rotterdam criteria for diagnosing PCOS but since she conducted her study in different region with different race, genetic constitution and environmental factors which may also have some affect on the results to an extent. There may also be significant hormonal and morphological differences among the control subjects investigated by both studies.

The digit ratio has also been associated by many authors with several characteristics such as congenital adrenal hyperplasia [10,29], developmental psychopathology, Autism and Aspergers syndrome [30], Down's syndrome [1], Physical aggression [31], Sperm counts [7,32], family size [33], age at myocardial infarction [34], good visualspatial ability [35], late menarche and time to pregnancy [36], eating disorders [37], fetal growth and birth weight [38-40], alcohol dependency [41], breast cancer [42-43], and prostate cancer risk [44-45].

Women with congenital adrenal hyperplasia who are genetically programmed to produce in utero androgens have masculine finger length patterns [10], commonly exhibit a PCOS-like syndrome with hypersecretion of luteinizing hormone and ovarian hyperandrogenism, suggesting prenatal testosterone excess as a possible PCOS etiology [46].

We found that the differences in the second to fourth finger length ratios were greater on the right hand compared with the left. Similarly, studies of women with congenital adrenal hyperplasia and homosexual women have also reported lower finger length ratios on the right hand [10,47]. It may be because that the right hand is more sensitive to fetal androgens than the left [6] or it may represent more rapid cell division on the right side of the body during embryological development [48]. In one study, no difference could be found in the left hand finger length ratio in women with congenital adrenal hyperplasia [4]. A number of other studies have also shown the right 2D:4D to be a stronger predictor of index traits than the left; for e.g. testosterone and sperm counts [7], fetal growth [38], athletic ability [35] and MI [34]. These traits could help in the identification of fetal origins of adult diseases, as they reflect the endocrine signaling during the prenatal period [26].

V. CONCLUSION

We concluded that women with PCOS can have masculinized finger length patterns with low 2D:4D consistent with increased prenatal androgen exposure. There was a subtle but significant difference ($p<0.0001$) between women with PCOS and the control group and therefore our findings also suggest a role for in utero androgens in the development of PCOS. We also found that the differences in the 2D:4D ratios were greater on the right hand compared with the left. This anatomical expression can be used as a tool for early prediction of PCOS and hence substantiates the need for lifestyle modification to counteract this syndrome at its nascent stage.

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