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Original Article

Association between digit length ratio (2D:4D) and polycystic ovarian syndrome (PCOS)—A study among eastern Indian population

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ABSTRACT

Introduction: Human finger lengths demonstrate constant ratios amongst themselves throughout life. The ratio between 2nd and 4th digit length (2D:4D ratio) is found to be indicative of intrauterine effect of testosterone and oestrogen upon growing foetus. 2D:4D is usually <1 in male and ≥1 in females. With this anatomical expression of sex-hormonal predominance during intrauterine life, we tried to find any possible association with developing polycystic ovarian syndrome (PCOS) in adulthood.
Methods: 251 women of reproductive age group (15–45 yrs) attending the G&O OPD of I.P.G.M.E&R, Kolkata & R.G.K.M.C.H, Kolkata, who had fulfilled the Rotterdam criteria (2003), was taken as cases. Age matched 285 healthy female were examined for control data. Finger lengths of 2nd and 4th digit were measured using digital vernier caliper.
Results: After obtaining a statistically significant difference ($P < 0.05$) between 2D:4D ratio of cases and controls, a cut off value of 0.9928 for left hand with sensitivity 68.92 and specificity 72.98 and for right hand a cut off value of 0.9846 with sensitivity 66.53 and specificity 83.51 were determined, by interpreting 2D:4D of cases and controls using the ROC curve analysis. Thus we can say that those with a lower ratio than the determined cut off values have high probability of developing PCOS in adult life.
Discussion: This anatomical expression can be used as a tool for early prediction of PCOS and hence substantiates the need for suitable lifestyle modification to counteract this syndrome at its nascent stage.

1. Introduction

Human fingers, like many other body parts, increase in length after birth; but the ratio among them remains fixed since around 14th week of foetal Life.[1] The ratio of length of the index finger (second digit or 2D) to the ring finger (fourth digit or 4D), i.e., the second-to-fourth digit length ratio (usually described as 2D:4D), is sexually differentiated in human as well as across a wide range of non-human species, such as other primate, rodent, avian, lizard, and amphibian species.[2] Other digit ratios had also been investigated and some also show sex differences. But all importance is on the 2D:4D ratio because it has been most extensively studied and consistent significant sexual dimorphism had been observed. Men on average show a lower 2D:4D ratio than women.[3] This particular characteristics of human hand had been already noted by anatomists, physical anthropologists, and forensic physicians of the late 19th century.[4,5]

The development of this ratio had been hypothesized to be affected by testosterone, which increases in level from 8th week to 24th week of prenatal life.[6] The 2D:4D ratio, according to previous studies, does reflect status of prenatal sex hormones and could provide a simple and widely-available method for examining hormonal effects on different human behavioural and physical expressions. The evidence supporting this assumption is mostly indirect.[7] Moreover it was found that the ratio between the 2nd and 4th digit length is dependent not only on the effect of androgen but also to some extent on estrogen.

Abbreviations: 2D4D ratio, ratio of length of second and fourth digit; PCOS, polycystic ovarian syndrome; G&O, Gynaecology & Obstretrics; OPD, out patient department; IPGMER, Institute of Post Graduate Medical Education & Research; RGKMCH, Radha Gobinda Kar Medical College & Hospital; ROC, Receiver Operating Curve; Hox, Homeobox; C, PCOS cases; FC, female control; MC, male control; Anova, Analysis of variance; CI, confidence interval; RH_2D, length of second digit of right side; LH_2D, length of second digit of left side; RH_4D, length of fourth digit of right side; LH_4D, length of fourth digit of left side; RH_2D:4D, 2D:4D of right hand; LH_2D:4D, 2D:4D of left hand.

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The characteristic of the sexual dimorphism of this ratio (2D:4D) is usually expressed as the mean male 2D:4D ratio is lower than mean female 2D:4D ratio. It was suggested that lower 2D:4D ratio is observed in case of male persons in whom the prenatal testosterone takes upper hand during development of male foetus. In case of female foetuses, low prenatal testosterone and high estrogen are observed and the 2D:4D ratio is usually found to be higher than the mean male 2D:4D ratio. So in other words, higher the effect of testosterone in intrauterine life, lower the 2D:4D ratio. Sexually antagonistic genes determine the pattern of expression of 2D:4D ratio; Manning et al. in 1998 in one of the earliest studies on this topic depicted the sexually dimorphic nature of the 2D:4D ratio and its association with gonadal hormones.[3] Later on, many studies supported this characteristic of the 2D:4D ratio. Although 2D:4D ratio in male is less than that of female, absolute value of this ratio varies slightly among different races.[8] The control of differentiation of the digits is mainly by Homeobox or Hox genes (mainly by the posterior-most Hox-D and Hox-A genes), which also controls the differentiation of the testes and ovaries.[9] Vertebrate Hox-D genes are essential determinants of limb morphogenesis.[10] Loss of fertility, digits and genital bud derivative are seen when the components of posterior Hox gene functions are removed progressively.[11] This shows the common control of the distal limbs and genital bud development by Hox genes.

Patterns of 2D:4D ratios may therefore reflect significant aspect of gonadal function such as the production of testosterone and estrogen or its imbalances. There are many syndromes and diseases which have genetic influence and predisposition of sexual hormones. Among these, polycystic ovarian syndrome (PCOS) is a clinical condition, which has a high incidence of about 10% among women of reproductive age group and also a major cause of infertility in present days.[12–14] In PCOS it is an established fact that the main disease pathology is due to the loss of normal equilibrium between androgen and estrogen in adult life. So, considering the influence of androgen and estrogen level in adult life in PCOS cases, we can assume that there might be possible relationship between PCOS cases with some of the physical expressions which are also affected by the level of the same hormones at the very early stage of life, say in the intrauterine period.

Now it is an established fact that 2D:4D ratio is an indicator of the intrauterine effect of the androgen and estrogen upon the foetus. Thus we tried to identify retrospectively, whether the effect of testosterone or estrogen was more during the intrauterine life of an individual who is suffering from PCOS at present, by determining the 2D:4D ratio of that person. Cattrall[15] and Lujan[16,17] explored the association between 2D:4D ratio and PCOS previously on Australian and Canadian population with conflicting results. Recently another study by Pandit et al.[18] in central Indian population demonstrated positive correlation between 2D:4D ratio and PCOS cases. Apart from these we didn't find any literature related to this kind of study.[18]

In this study we tried to find any possible association of 2D:4D ratio and PCOS in Eastern Indian population. Any association between PCOS and 2D:4D ratios in our study could guide us to identify in young girls, the possibility of developing PCOS in future life by undertaking a simple anthropologic measurement of the length of 2nd and 4th digit.

2. Materials and methods

The study mainly focused on measurement of the length of the 2nd digit (index finger) and 4th digit (ring finger). The ratio of these measured lengths was compared among different study groups. The study was mainly based on anthropometric measurements.

2.1. Type of the study

Case control type.

2.2. Study setting

Gynaecology & Obstetrics (G & O) outpatient department (OPD) of the Institute of Post Graduate Medical Education & Research (IPGME&R), Kolkata and Radha Gobinda Kar Medical College and Hospital (RGKMCH), Kolkata.

2.3. Timelines

12 months from the start of the study i.e. July 2014–June 2015.

2.4. Definition of population

251 women of reproductive age group (15–45 yrs) attending the G&O OPD of I.P.G.M.E&R, Kolkata & R.G.K.M.C, Kolkata, who had fulfilled the Rotterdam criteria (2003), taken as cases.

Age matched 285 healthy female for control data were analysed. Whereas, 2D:4D ratio of 285 healthy male persons was also measured for baseline data.

2.5. Study variables

Finger length and polycystic ovarian syndrome (PCOS).

2.6. Inclusion criteria

Women of reproductive age group (between 15 and 45 yrs age) having established polycystic ovarian syndrome according to Rotterdam (2003)[19,20] criteria. The criteria state that PCOS is said to be present if any 2 out of 3 following criteria are met.

i) Oligoovulation and/or anovulation,
ii) Excess androgen activity and
iii) Polycystic ovaries (by gynecologic ultrasound).

2.7. Exclusion criteria

Those with local hand deformities were excluded from the studies.

2.8. Sample size

We had calculated the sample size for an unmatched case control design. Considering the prevalence of polycystic ovarian syndrome to be 10% in woman of reproductive age group,[12–14] it was estimated that 283 cases and 283 control would be required to determine whether 2D:4D ratio above or below a particular cut off was associated with doubling of risk of developing polycystic ovarian syndrome with 80% power and 95% confidence level. Rounding of, we kept the target numbers at 285 cases and 285 controls. But during the study period we were able to examine 251 cases instead of 285 as had been planned at the beginning of the study.

2.9. Control group

Control group was required for the study. For control group, clinically healthy female persons accompanying the patients in G&O OPD, fulfilling the criteria and willing to participate, were included in the study and their digit lengths were included.

Digits of adult healthy male persons, accompanying the patients in G&O OPD, students and staff volunteers fulfilling the criteria and willing to participate, were included for baseline data.

2.10. Methods of data collection

The hands were placed over a hard flat surface after removing any ornaments, with the palmer surface facing upwards and digits fully stretched with the 2nd to 5th digits adducted and the thumb slightly extended. Then the 2nd digit and 4th digit length of both right and left hands were measured using digital Vernier Caliper (Made by Mitutuyo, Japan with measurement resolution up to 0.01 mm) from midpoint of the proximal most crease at the base of the fingers to the tip of the corresponding digit and then their ratio was calculated. Necessary steps were taken to nullify any bias or observer's variation. Appropriate protocol was followed in obtaining consent from the subjects prior to data collection.

2.11. Statistical analysis plan

Data was summarized by routine descriptive statistics, namely mean and standard deviation for numerical variables; counts, percentage for categorical variables. The 2D:4D ratio was compared among three groups, namely cases (C), female control (FC) and male control (MC) groups. Association of 2D:4D ratio above and below of a certain cut off with risk of developing polycystic ovarian syndrome was quantified by calculating with odd's ratio with 95% confidence level, provided a cut off value could be identified. A receptor operator characteristic (ROC) curve analysis was attempted to identify such a cut off.

2.12. Softwares used

Statistica version 6 [Tulsa, Oklahoma: StatSoft Inc. 2001].

MedCalc version 11.6 [Mariakerke, Belgium: MedCalc Software 2011].

GraphPad Prism version 6.07 [Software Mackiev 2015].

3. Results

Statistically significant difference was present between 2D:4D ratio of PCOS cases and female control group; between 2D:4D ratio of PCOS cases and male control group in hands of both sides as analyzed by Student's unpaired *t*-Test. A one-way Analysis of variance (ANOVA) test also showed that there were statistically significant differences among the mean 2D:4D ratios of the three study groups in hands of both sides. The mean values of different groups are described in [Table 1 & Fig. 1]. The mean of the 2D:4D ratios in PCOS group was lower than that of female control group but greater than male control group, so we could say, that those with PCOS have more male pattern of 2D:4D ratio than the control female groups. Comparative analysis of different parameters involving PCOS cases and female control group was done [Table 2].

A statistically significant cut-off value for right and left hand had been obtained using Receiver Operating Curve (ROC) analysis with moderate sensitivity and specificity after analysing the 2D:4D ratio of cases and female control groups [Fig. 2].

For right hand the cut off value was 0.9846 with sensitivity 66.53% and specificity 83.51%.

For left hand the cut off value was 0.9928 with sensitivity 68.92% and specificity 72.98%.

The odds ratio showed increased statistically significant chance of developing PCOS in those, whose 2D:4D ratios was less than the obtained cut-off value. In cases of right side there was 10.07 times and In cases of left side there was 5.991 times higher chance of developing PCOS if 2D:4D ratio was below the cut off level [Table 3].

4. Discussions

In the current study, we observed that there were statistically significant differences between the PCOS cases and female control group exists in 2D:4D ratio of both the hands. The mean of right hand 2D:4D ratio of PCOS cases and female control group were found to be 0.9736 (±0.033) and 1.004 (±0.03) respectively, and in left hand it was 0.9798 (±0.033) and 1.007 (±0.036) respectively. The difference was statistically significant with p value measuring <0.0001 in both hands. The difference of the mean was 0.0304 in right and 0.0272 in left hand. Similar results were depicted by Cattrall et al.[15] They noted a difference of 0.016 in right hand 2D:4D ratio and 0.08 in left hand 2D:4D ratio in their study where 70 PCOS cases and 70 apparently healthy female were taken into account. They found statistically significant lower 2D:4D ratio in right hand only. Whereas in a recent study involving central Indian population, 2D:4D ratios of both hands were found to be lower in the PCOS cases with statistically significant differences bilaterally.[18] They had analysed 200 cases and 200 female controls but no male groups were analysed. The mean of right hand 2D:4D ratio of PCOS and female control group were found to be 0.96 (±0.021) and 1.0 (±0.028) respectively, and in left hand it was 0.99 (±0.038) and 1.0 (±0.028) respectively.[18] They found the difference in right hand more than the left hand, similar to the present study.

In this present study the data of 2D:4D ratio was analysed between PCOS cases and healthy female using receiver operating characteristic (ROC) curve and cut off values for both hands were obtained. In right hand the cut off value was 0.9846 with 66.53% sensitivity and 83.51% specificity. In left hand the cut off value was 0.9928 with 68.92% sensitivity and 72.98% specificity. The odds ratio calculation showed that women with 2D:4D ratio less than 0.9846 in right hand had 10.07 times higher chance of developing PCOS with 95% confidence interval (CI) being 6.693–15.14. In case of left hand, those with 2D:4D ratio less than 0.9928 had 5.991 times higher chance of developing PCOS with 95% Confidence Interval (CI) being 4.122 to 8.709. Neither Cattrall nor Pandit et al. perform ROC curve analysis for the data obtained in their study; hence they could not depict any cut off value, so we were unable to compare the cut off value obtained in the current study with any previous one. By obtaining cut off values in the present study, we can provide a baseline cut-off for specific prediction at very early in life, involving risk of developing PCOS in adult life.

Table 1
Mean values of the length of 2D & 4D and 2D:4D ratio of both hands in MC, FC & C groups.[a]

Study Population	RH_2D (mm)[b]	RH_4D (mm)	RH_2D:4D	LH_2D (mm)[c]	LH_4D (mm)	LH_2D:4D
Male Control	71.12	73.82	0.9638	71.53	73.74	0.9706
Female Control	66.44	66.2	1.0042	66.43	66.03	1.007
PCOS Cases	65.35	67.17	0.9736	66.03	67.42	0.9798

[a] MC – Male Control; FC – Female Control; C – PCOS Cases.
[b] RH – Right Hand.
[c] LH – Left Hand.

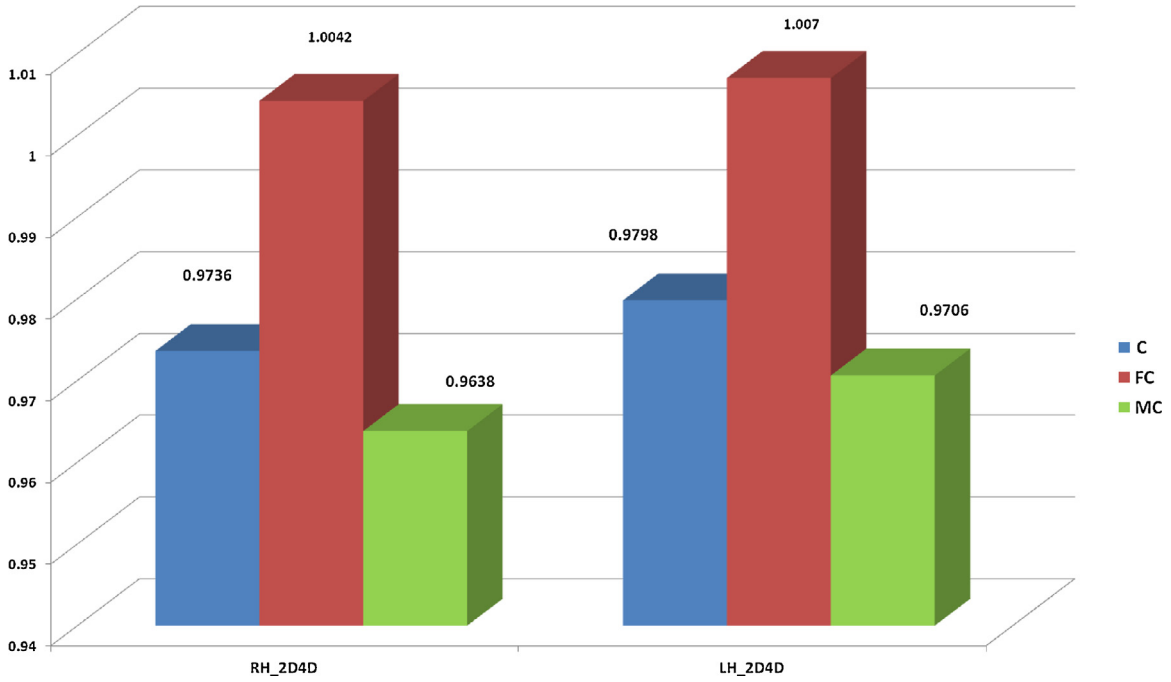

Fig. 1. Bar Diagram Showing Comparison Between Mean of Right and Left Hand 2D:4D Ratio of PCOS Cases (C), Female Control (FC) & Male Control (MC).

Table 2
Comparative value of different parameters involving PCOS cases (C) and Female Control (FC).

Parameters Group	Mean C	Mean FC	t-Value	P value	Valid Number of subjects C	Valid Number of subjects FC	Standard Deviation C	Standard Deviation FC
Age (Yrs)	23.39	23.07	0.776	0.432*	251	285	4.779	4.645
RH_2D (mm)[a]	65.35	66.44	−3.516	<0.0001**	251	285	3.782	3.414
RH_4D (mm)	67.17	66.20	2.983	0.003**	251	285	4.002	4.036
RH_2D:4D	0.9736	1.004	−11.363	<0.0001**	251	285	0.033	0.030
LH_2D (mm)[b]	66.03	66.43	−1.211	0.226*	251	285	4.023	3.536
LH_4D (mm)	67.42	66.03	4.233	<0.0001**	251	285	3.950	3.683
LH_2D:4D	0.9798	1.007	−9.102	<0.0001**	251	285	0.033	0.036

* Non significant.
** Significant.
[a] RH – Right Hand.
[b] LH – Left hand.

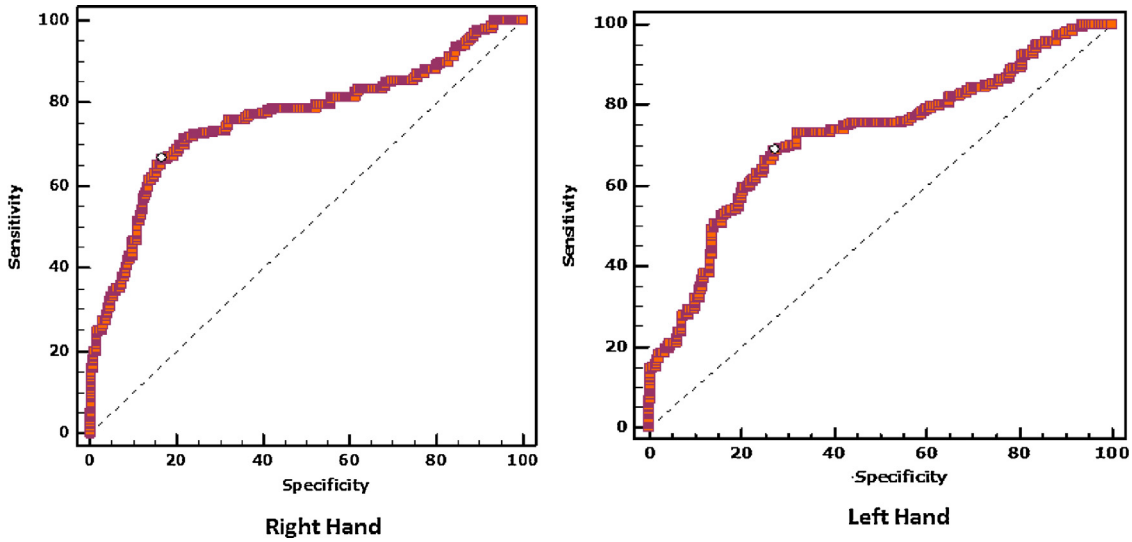

Fig. 2. ROC Curve Analysis for Right and Left Hand 2D:4D Ratio between PCOS cases (C) and Female Control (FC).

Table 3
Odd's Ratio calculated using cut off value obtained from ROC Curve analysis against actual numbers of cases and control.

Data analyzed (For Right Hand)	PCOS CASE	Female Control	Total	Odd's Ratio [(a*d)/(b*C)] = 10.06
Number of positive cases based on ROC curve analysis cut off	167 (a)	47 (b)	214	
Number of negative cases based on ROC curve analysis cut off	84 (c)	238 (d)	322	95% confidence interval: 6.693–15.14
Total	251	285	536	P value: <0.0001**
Data analyzed (For Left Hand)	**PCOS CASE**	**Female Control**	**Total**	**Odd's Ratio [(a*d)/(b*C)] = 5.991**
Number of positive cases based on ROC curve analysis cut off	173	77	250	
Number of negative cases based on ROC curve analysis cut off	78	208	286	95% confidence interval: 2.064–3.120
Total	251	285	536	P value: <0.0001**

** Significant.

In 2010, Lujan et al. did a similar study to find the correlation between PCOS and 2D:4D ratios.[16] They had studied 98 PCOS cases and 51 healthy female controls to measure their finger lengths by direct physical measurement. Both the studies by Lujan et al. & Pandit et al. used Rotterdam criteria (2003) to diagnose PCOS cases similar to this present study. On the contrary the Cattrall et al. used 1990 National Institutes of Health criteria which defined PCOS as the combined presence of: (i) oligo- or chronic-amenorrhea and (ii) clinical and/or biochemical evidence of hyper-androgenism.[21] But the study by Lujan et al. could not find any statistically significant association between 2D:4D ratio and PCOS. They in fact, found higher mean of 2D:4D ratio in case of PCOS cases than healthy female controls in both right and left hand. Their result showed a mean of 0.983 in right hand of PCOS against 0.981 in healthy females. Whereas, in the left side, they showed a mean of 0.991 and 0.981 in PCOS cases and female controls respectively. The unpaired *t*-test data showed insignificant p values for both hands. This result did not corroborate with the present study where we observed statistically significant variations between female control group and PCOS cases. In Table 4 comparative values of some parameters as documented in a few previous studies has been portrayed. Though both the studies used Rotterdam (2003) criteria, which is wider, for diagnosing PCOS, one major difference between the studies was that, in the study by Lujan et al. they used only 51 healthy females as control group. Whereas the present study had included 285 healthy females as a control group, after keeping in mind the prevalence of PCOS with proper statistical plan of achieving a cut off value and also 285 male persons were taken as a reference group. As the differences between the ratios were very small, study with a small amount of data could give very different result when analysed in comparison to that of larger set of data. If they also had taken a healthy male group's 2D:4D ratio then it would have been interesting to see whether the usual sexual dimorphism was present in that result or not. The study was done in Canadian population, where it had already shown to have sexual dimorphism in 2D:4D ratios.[22]

Lujan et al.[17] in a follow up study of their previous one[17] took the digital scan image of the same subjects of PCOS group and female control group selected for the purpose of their previous study. They analysed new set of data of the same subjects with 96 cases and 48 controls (2 cases and 3 control subject did not turn up for re-evaluation) from their previous study; but this time finger lengths were measured in computer after scanning the hands of the subjects, rather than by direct physical measurement. Also for the second study they took measurement of 50 male subjects. This time too they could not find any statistically significant variation between PCOS cases and female controls. Right hand means 2D:4D ratio of PCOS and female control were found to be 0.981 and 0.972 respectively with male ratio observed 0.949. In left hand the ratios were 0.982, 0.974 and 0.949 for PCOS cases, female controls and male controls respectively. Thus they observed statistically significant difference between PCOS cases and male controls ($p < 0.0001$) & between female controls and male controls ($p < 0.001$) similar to the present study, but failed to depict any statistically significant differences between PCOS cases and female controls. The mean 2D:4D ratios of PCOS females were higher than both that of control female groups and male groups, which was again, not in agreement with the present study. The second study by Lujan et al. though incorporated a male group, but again did not have a larger control group. Mitsui et al.[23] in a prospective study showed that 2D:4D ratios were lower in males than in females due to leydig cell function by analysing stored cord blood hormone level and 2D:4D ratios of the same children in a latter life.[23] Abbott et al.[24] showed that when foetuses of monkeys were subjected to high testosterone during intrauterine life, they showed PCOS like syndrome in adult life.[24] This supports the fact, that high intrauterine testosterone (which is reflected by lower 2D:4D ratio in the present study) increases the chance of developing PCOS. Thus studies by Lujan et al.[16,17] not only contradicted the previous study by Cattrall et al.,[15] but also questioned the use of 2D:4D ratio as a marker of pre natal androgen exposure. So at the end of the discussion it can be commented from this study that statistically significant differences exist between 2D:4D ratios of PCOS cases and control females and lower 2D:4D ratio is being more associated with the emergence of PCOS; hence sufficient further scopes are there to find out that why there were discrepancies between the results of similar studies regarding PCOS and 2D:4D ratio.

Table 4
Comparison among Various Studies Involving Some Parameters.

Parameters	Present Study [Eastern Indian Subject]		Study by Cattrall et al.[15] [Australian Subjects]		Study by Lujan et al.[16] [Canadian Subjects]		Study by Pandit et al.[18] [Central Indian Subject]	
	PCOS	Control	PCOS	Control	PCOS	Control	PCOS	Control
No of Cases	251	285	70	70	98	51	200	200
Difference of mean 2D:4D (Control-Case)	[a]R = 0.0304 [b]L = 0.0272		R = 0.016 L = 0.08		R = −0.002 L = −0.01		R = 0.04 L = 0.01	
P Value in unpaired *t*-Test	P Value <0.0001 (Both R & L)		P Value <0.05 (For R only)		R = 0.634 L = 0.093		P Value <0.0001 (Both R & L)	

[a] R – Right hand.
[b] L – Left hand.

Thus we depicted that the women with PCOS had a lower 2D:4D ratio than healthy females in eastern Indian population. As higher intrauterine testosterone level is associated with lower 2D:4D ratio, it can be summarized that those with higher intrauterine testosterone level have higher chance of developing PCOS. Using this simple tool of measuring finger length ratio (2D:4D), up to a certain level of accuracy, we can predict vulnerability to develop PCOS and then can take precautionary and preventive measures and lifestyle modification to tackle this clinical syndrome.

5. Conclusion

Though the present study showed lower 2D:4D ratio being associated with developing PCOS; there are ample scopes of further studies to find out why there are discrepancies between results of similar studies. Also with study involving larger population and different ethnic groups, the cut off value obtained will be more sensitive and specific and the intended use for early prediction and prevention of PCOS will be more accurate which will help to control PCOS for betterment of health.

Conflicts of interest

None of the authors has anything to declare.

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