International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Gupta S et al. Int J Reprod Contracept Obstet Gynecol. 2025 Oct;14(10):3487-3494
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20253097

Original Research Article

Clinical implications of the second and fourth digit ratio in male infertility: associations with semen parameters and sex hormone levels - a cross-sectional study

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Received: 09 August 2025
Revised: 14 September 2025
Accepted: 16 September 2025

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ABSTRACT

Background: Oligospermia and hypogonadism are synonymous with infertility in males. Data regarding its correlation with hand digit length and ratio are inconsistent and scarce. The aim was to study the ratio of second (2D) and fourth (4D) fingers of both hands in 236 infertile oligospermic men and their comparison with various clinical and laboratory parameters related to infertility.
Methods: In this cross-sectional study, the 2D and 4D length and ratio of both hands of 236 infertile oligospermic men were measured. Semen analysis and hormonal assessment, including serum total testosterone (T), estradiol (E), luteinizing hormone, and follicle-stimulating hormone, were performed and correlated with the 2D: 4D ratio and severity of oligospermia. Participants were further subdivided into two groups according to serum T levels.
Results: A significant difference in the 2D: 4D ratio of the right hand was observed between both cohorts and in patients with low T levels. The mean serum T level was significantly lower in infertile oligospermeic males (349.76±115.4 ng/dl; $p<0.001$) than healthy controls ($p<0.001$). The testosterone-to-estradiol (T/E) ratio was also significantly lower in the patient group (8.36±4.84; $p<0.001$). A decline in semen quality, including reduced sperm counts and progressive motility, was observed in patients with low T levels.
Conclusion: The 2D: 4D ratio might directly correlate with testosterone levels and, thus, semen quality and fertility potential of a subject. Thus, providing a cost-effective and time-saving method for indirect estimation of androgenization in male patients.

Keywords: Oligospermia, Testosterone, Infertility, Semen, Hypogonadisms

INTRODUCTION

Infertility and subfertility are often associated with defective sperm production and low testosterone levels. It is defined as failure to achieve a clinical pregnancy after at least one year of regular, unprotected sexual intercourse.[1] Male infertility remains a critical yet frequently neglected aspect of medical practice. Male partners are equally responsible for infertility worldwide.[2] Data from the National Family Health Survey-5 (2019–21) indicate that

the prevalence of primary infertility is highest within the first year of marriage (42.9 per 1,000) in India.[3] Semen analysis is considered as gold standard for the evaluation of male infertility. Oligospermia, defined as sperm concentration of less than 16 million/ml of ejaculate, is seen in up to one-third of infertile patients in the Indian population.[4,5] It is a well-proven fact that low prenatal and adult testosterone levels lead to defective sperm counts and motility, eventually leading to subfertility.[6]

The role of routine physical examination, including anthropometry and genital examination, is often undermined in male partners. Gamete creation, fertilization, and bringing a pregnancy to term are all linked to foetal development and foetal sex hormone levels.[7] The sexual differentiation and digit length are under the control of the expression of Hox genes. Out of the four genes, Hox A and Hox D are essential for length and digital ridge pattern, along with genital ridge differentiation.[8] Studies have supported the hypothesis that low androgen levels in prenatal life are linked to alterations in these anthropometric parameters.[9] In males, the index finger (second digit) is usually shorter than the ring finger (fourth digit), whereas in females, it tends to be of the same length or longer. As a result, the second-to-fourth digit ratio (2D: 4D) is typically less than 1 in men and around 1 or higher in women.[10,11] Few studies have observed a relationship between 2D: 4D ratio and reproductive function in infertile men.[12,13] In the Chinese population, a lower 2D: 4D ratio was linked to reduced sperm count and motility, whereas no significant association was observed in fertile men.[14] Such findings gave rise to theories linking finger morphology and parameters of gonad function, such as sperm and testosterone production.

However, there is limited research on the relationship between the 2D: 4D ratio and primary infertility within the Indian population, where the prevalence of primary infertility exceeds 40% within the first year of marriage.[3] These findings and our observations led to this study, where we measured the 2D and 4D length of both hands and sex hormone levels of oligospermic infertile males and compared them with semen parameters. Similarly, the anthropometric readings and testosterone levels were also recorded in a fertile male group for comparison.

This study aimed to explore the association between the 2D: 4D ratio and reproductive parameters in infertile men within the Indian population. Measuring digit length and ratios may offer a cost-effective method for indirectly estimating androgenization in male patients, particularly in resource-constrained developing countries such as India.

METHODS

Study design and participants

This prospective cross-sectional study was conducted based in a tertiary health care centre of South Rajasthan, India.

This cross-sectional study involved 262 men aged 20–55 visiting the infertility clinic of Pacific Medical College and Hospital, Udaipur, South Rajasthan, India between December 2022 and July 2024.

Participants were diagnosed with primary infertility based on their medical history and semen analysis (sperm concentration and motility) or were being evaluated for *in vitro* fertilization (IVF).

Furthermore, 265 fertile men who had fathered at least one child were included as healthy controls.

Semen analysis adhered to World Health Organization (WHO) 2021 standards.[15]

Participants were categorized into two groups, group I comprised 141 infertile men with normal testosterone levels (≥241 ng/dl), whereas group II included 95 infertile men with low testosterone levels (<241 ng/dl). Each group was further subdivided according to severity of oligospermia (sperm concentration): mild (10–15 million/ml), moderate (5–10 million/ml), and severe (<5 million/ml).[16,17] In group I, there were 141 men, of whom 133 were assigned to subgroup I (mild to moderate oligospermia with 05 to 15 million/ml)), and 8 were placed in subgroup II (severe oligospermia). Group II comprised 95 individuals; 78 infertile men were classified into subgroup I, while the remaining 17 were assigned to subgroup II. The terms "sperm count" and "sperm concentration" are often used interchangeably in our study. The study design, illustrated in figure 1, further categorizes the patient and control populations.

Inclusion exclusion

The study participants were enrolled according to inclusion and exclusion criteria according to a previous study conducted by Di Guardo and colleagues.[17] Participants were identified as having primary infertility through a review of their medical history and results from semen analysis, including assessments of sperm concentration and motility, or were undergoing evaluation for IVF at our tertiary care centre.[17]

Exclusion criteria

The study excluded infertile male patients who had normal semen parameters but presented with amputated or deformed index or ring fingers on one or both hands. Also excluded were men currently using external testosterone supplements, hormonal medications, or drugs such as aromatase inhibitors that could influence study outcomes. Additional exclusion criteria included a history of secondary infertility, chronic alcohol use, severe obesity, prostate-related conditions (benign or malignant), or surgical factors impacting semen quality—such as varicocele, hydrocele, abnormalities or infections of the genitourinary tract, obstructive azoospermia, and previous exposure to testicular radiotherapy or chemotherapy.[17]

Sample collection and hormone analysis

The participants underwent anthropometric measurements. An early morning sample of 5 ml venous blood was collected for hormonal assays including serum total testosterone (T), luteinizing hormone (LH), and follicular stimulating hormone (FSH), estradiol (E) to minimize diurnal variation per American Society for Reproductive Medicine (ASRM) guidelines.[18] Semen samples were collected in sterile containers after 2–5 days of abstinence.[19] Semen samples were analysed after liquefaction in a standard microscope Neubauer chamber for sperm concentration and motility. Serum samples were processed in the COBAS E411 immuno analyzer using the Electrochemiluminescence immunoassay (ECLIA) method for hormone levels. Participants who have not given consent, were excluded from the study. All the samples were processed at Department of Lab Medicine of our tertiary care centre. Normal reference ranges for various lab parameters were used in our study as described; serum LH 1.5-9.3 mIU/ml, serum FSH 1.4-18.1 mIU/ml, serum testosterone 241- 827 ng/dl, and serum estrogen level 10-52 pg/ml.

Measurement of 2D:4D ratio and digit length

Finger lengths for the second (index) and fourth (ring) digits were measured from fingertip to the Center of basal crease on the palm, utilising digital vernier callipers.20 Afterward, the 2D:4D ratio was computed based on the formulas provided below.

$$2D{:}\,4D\ ratio\ left\ hand = Left\ hand\ 2D\ measurement\ (inch) / left\ hand\ 4D\ measurement\ (inch)$$

$$2D{:}\,4D\ ratio\ right\ hand = Right\ hand\ 2D\ measurement\ (inch) / right\ hand\ 4D\ measurement\ (inch)$$

Sample size

The sample size of 255 is based on the prevalence of male factor infertility in general population as 21% (50% of the total prevalence of primary infertility).[3] Sample size (n) for a cross-sectional study is calculated using formula as mentioned: Z=confidence level (e.g., 1.96 for 95% confidence), p=prevalence, and d=margin of error.

$$n = (Z^2 \times p \times (1-p))/d^2$$

Statistical analysis

Initially, data was recorded in both categorical and continuous form, and further, the continuous data were checked for normality using the Shapiro-Wilk test. Further data were analysed using descriptive statistics (frequency, percentage, mean, median, interquartile range, and standard deviation), as well as analytical methods (Chi-square, Mann-Whitney, and independent t-test), and odds ratio (univariate logistic regression). P<0.05 was considered statistically significant. The data were analysed using statistical package for the social sciences (SPSS), version 23.0, SPSS Inc., Chicago, Illinois, USA.

RESULTS

Demographic, clinical, and measurable parameters

A total of 262 men with oligospermia were enrolled out of which 236 men and 258 controls were finally included in the study (Figure 1). Patients in the study group were subjected to anthropometry and hormonal assessment. Amongst infertile patients, we found 141 (59.75%) patients with normal testosterone levels (group I) and 95 (40.25%) with subnormal levels (group II). In the control group, only the digit ratio and hormonal assessment were performed. Semen analysis was not conducted in this group due to ethical and practical concerns with established parenthood. An initial comparison of healthy controls and infertile patients across various demographic, clinical, and measurable parameters is presented in Table 1. Serum testosterone levels were significantly low in infertile patients (p<0.001), with a mean level of 349.76±115.4 ng/dl, however, the mean serum estrogen level in infertile patients was 141.84±6.94 pg/ml, approximately two-fold higher than that of healthy controls (p<0.001). The mean body mass index (BMI) was significantly higher in infertile patients compared to healthy controls (p=0.02). Moreover, testosterone-to-estradiol (T/E) ratio was significantly lower in patient's group (8.36±4.84) than in controls (p<0.001). Both LH and FSH levels were higher in the patient group (7.39±4.43 and 10.81±14.38, respectively) than control group (p=0.08 and p=0.01, respectively).

Subsequently, the patient population (n=236) was subdivided into group I (normal testosterone) and group II (low testosterone). Various demographic, clinical, and measurable parameters were compared between the two groups, as elucidated in Table 2. The mean age of patients in group I was slightly lower than in group II (p=0.45). However, the mean BMI of group II was higher (32.04±8.86 kg/m^2; p<0.001) testosterone levels were significantly lower (mean: 229.98±60.93 ng/dl; p<0.001). Conversely, the mean serum estrogen level in group II was 48.86±10.02 pg/ml, 1.4-fold higher than in group I (p<0.001).

The testosterone-to-estradiol (T/E) ratio was also found significantly lower in group II (4.7±1.98; p<0.001). Both serum LH and FSH levels were significantly higher in group II.

2D: 4D ratio

While comparing of mean 2D: 4D ratios, we found that the values for the left hand were lower than right hand in both groups. The 2D:4D ratio in the right hand of infertile patients (0.982±0.028) was significantly higher than that

of healthy controls (p<0.001). However, the 2D:4D ratio in the left hand of infertile patients was not significantly higher compared to healthy controls (p=0.06) as illustrated in Table 3. When comparing both hands of the same patient, 2D:4D ratio for the right hand was higher than that of the left hand across all infertile patients in both group I and group II.

In particular, the ratio in the right hand of group II was 0.986±0.021, significantly higher than that of group I (p=0.02). Although the ratio in the left hand of group II was also higher (0.979±0.025), the difference was not statistically significant (p=0.07), as depicted in Table 3.

Semen analysis

A Chi-square test of independence was conducted to examine the relationship between the severity of oligospermia and serum testosterone levels. The association between these variables was statistically significant (p=0.002, OR=1564; 95% CI: 1293–1978). In subgroup I (mild and moderate oligospermia), 94.3% of group I patients and 82.1% of group II patients were represented among the total infertile subjects. In contrast, a smaller proportion of patients belonged to subgroup II (severe oligospermia), comprising 5.67% of group I patients and 17.89% of group II patients, as illustrated in Table 4.

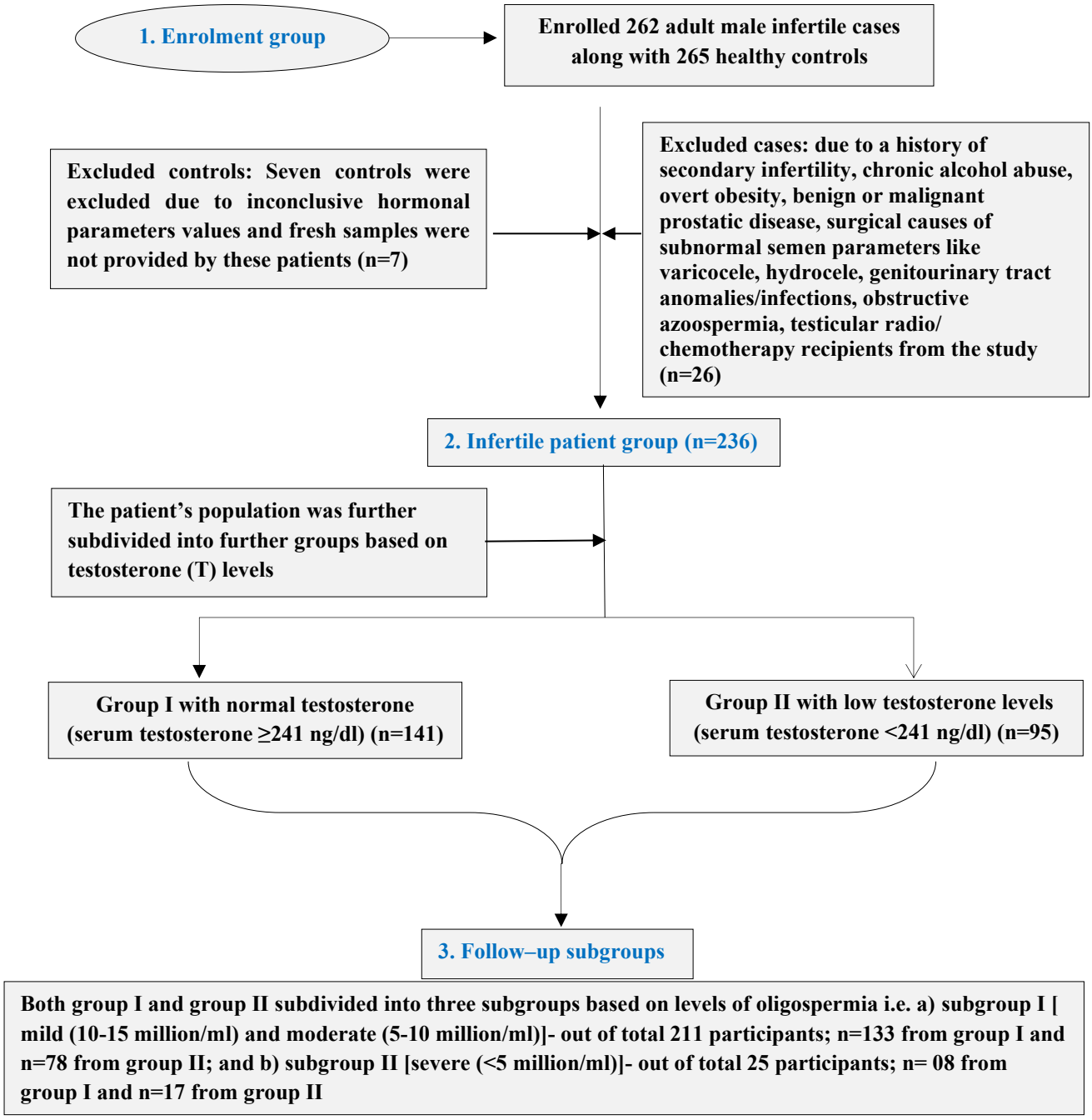

Figure 1: Study design.

Table 1: Baseline characteristics and hormone assay levels of healthy controls and infertile patients.

Parameters	Healthy controls (n=258) mean±SD (median, IQR)	Infertile cases (n=236) mean±SD (median, IQR)	P value	Odd ratio$ (OR) with CI
Age (years) #	28.8±5.7 (28, 6)	28.78±5.34 (27, 6)	0.25	1.00 (0.78-1.28)
BMI (kg/m²) #	24.85±4.24 (25, 5)	29.39±7.15 (30, 7)	0.02*	2.32 (1.02-3.04)
Serum LH level @	6.33±1.43 (6.98, 2.13)	7.39±4.43 (7.87, 5.13)	0.08	3.46 (0.82-4.39)
Serum FSH level@	9.37±4.69 (9.87, 5.14)	10.81±14.38 (11.14, 15.98)	0.01*	3.01 (1.99-4.00)
Serum testosterone level @	644.5±177.47 (689.3, 201.8)	349.76±115.4 (389.7, 121.4)	<0.001 *	8.01 (7.78-9.67)
Serum estrogen level @	28.32±6.61 (29.31, 7.14)	41.84±6.94 (42.34, 7.31)	<0.001 *	14.89 (12.78-15.89)
Testosterone/ estrogen ratio (T/E ratio) @	22.75±9.97 (23.14, 10.14)	8.36±4.84 (9.31, 5.14)	<0.001 *	93.61 (91.8-95.5)

SD: Standard deviation, BMI: body mass index, LH: luteinizing hormone, FSH: follicle-stimulating hormone; central tendency and dispersion were compared using #-independent t-test and @-Mann-Whitney test, $ Univariate binary logistic regression assessed odds ratios of independent variables on the outcome. *The result is considered significant at p<0.05

Table 3: Baseline characteristics and hormone assay levels of both groups of infertile patients.

Parameters	Group I (normal testosterone) (n=141) mean±SD (median, IQR)	Group II (low testosterone) (n=95) mean±SD (median, IQR)	P value	Odd ratio$ (OR) with CI
Age (years) #	28.5±6.65 (27, 7)	29.08±4.43 (28, 5)	0.45	1.00 (0.89-1.34)
BMI (kg/m²) #	26.78±5.74 (27, 6)	32.04±8.86 (33, 9)	<0.001*	2.76 (1.03-3.12)
Serum LH level @	6.59±6.73 (6.31, 8.91)	8.19±3.23 (8.07, 4.65)	0.03*	5.234 (3.12-6.89)
Serum FSH level @	9.37±4.70 (9.12, 6.6)	12.57±8.56 (13.65, 9.10)	0.003*	10.02 (8.01-12.69)
Serum testosterone level @	478.3±168.53 (512.1, 203.6)	229.98±60.93 (251.70, 65.80)	<0.001*	34.78 (32.12-36.78)
Serum estrogen level @	35.67±4.39 (41.80, 5.08)	48.86±10.02 (52.21, 12.13)	<0.001*	10.78 (8.34-12.34)
Testosterone/estrogen ratio @ (T/E ratio)	13.20±7.93 (13.39, 8.12)	4.7±1.98 (4.9, 2.23)	<0.001*	98 (64-112)

SD: Standard deviation, BMI: body mass index, LH: luteinizing hormone, FSH: follicle-stimulating hormone; central tendency and dispersion were compared using #-independent t-test and @-Mann-Whitney test, $ Univariate binary logistic regression assessed odds ratios of independent variables on the outcome. *The result is considered significant at p<0.05

Table 3: Mean 2D and 4D (2D: 4D) length ratio of both hands in various study groups.

Variables	Healthy controls mean±SD (median, IQR)	Infertile cases mean±SD (median, IQR)	P value#	Odd ratio$ (OR) with CI
Among healthy controls and infertile patients				
Left hand				
2D: 4D ratio	0.962±0.038 (0.961, 0.047)	0.970±0.034 (0.969, 0.046)	0.06	1.12 (1.08-3.04)
Right hand				
2D: 4D ratio	0.968±0.032 (0.967, 0.039)	0.982±0.028 (0.987, 0.032)	<0.001 *	11.01 (10.0-12.56)
Among group I and group II patients:				
	Normal testosterone: (ng/dl) n=141	**Low testosterone: (ng/dl) n=95**		
Left hand				
2D: 4D ratio	0.973±0.026 (0.975, 0.035)	0.979±0.025 (0.986, 0.034)	0.07	1.68 (1.01-3.56)
Right hand				
2D: 4D ratio	0.979±0.024 (0.981, 0.029)	0.986±0.021 (0.991, 0.023)	0.02*	10.12 (9.18-11.87)

2D: Second (index) finger, 4D: fourth (ring) Finger. Central tendency and dispersion were compared using #-independent t-test; $ Univariate binary logistic regression assessed the odds ratios of independent variables on the outcome. *The result is considered significant at p<0.05

Table 4: Distribution of patients according to severity of oligospermia.

Severity of oligospermia (sperm concentration)	Subgroup I (mild and moderate) (05 to 15 million/ml) (%)	Subgroup II (severe) (<05 million/ml) (%)	P value*, odd ratio# (OR) and CI
Number of subjects in group I (normal testosterone), n=141	133 (94.3)	8 (5.67)	P=0.002*, OR=1564 (1293-1978)
Number of subjects in group II (low testosterone), n=95	78 (82.10)	17 (17.89)	

*The chi-square statistic is considered significant at p<0.05; #odds ratio calculated by binary logistic regression

DISCUSSION

Infertility is as prevalent as any other lifestyle disorder in the modern world. Adult-onset hypogonadism is difficult to diagnose and is picked up mostly during detailed evaluation of male partners in dedicated IVF clinics when other causes of infertility are ruled out. Serum testosterone level might serve as a surrogate marker for the same. Although hypogonadism with low testosterone levels is found in less than 15 percent of sub fertile males, its diagnosis and treatment is quite rewarding for both the physician and patient.[21] We discovered a 40% (n=95) prevalence of low testosterone out of 236 oligospermic males. Out of which 24% (n=25) patients had severe oligospermia (sperm concentration <5 million/ml).

Gamete creation, fertilization, and bringing a pregnancy to term are all linked to fetal development and fetal sex hormone levels.[7] Fetal androgen levels in male children rise 8 weeks onwards to peak levels arising between weeks 14 and 16. The ratio between the lengths of the second (index) and fourth (ring) digits known as the 2D: 4D ratio is sexually dimorphic in humans, with males typically exhibiting a lower ratio than females.[22] This ratio is determined during intrauterine development, which aligns with the relevant gonadal developmental time frame. The digit ratio in the right hand is significantly lower in healthy cohorts than in the infertile subjects in our study, consolidating the role of testosterone conditioning in early fetal life. The reason behind the low ratio in males as compared to females in various population studies can also be attributed to higher testosterone levels.[23] Inversely, we found higher mean digit ratios in patients with lower testosterone levels amongst the infertile cohort as described by various researchers previously.[11,24] Examining the situation from a different perspective may be more illuminating to assess the relationship between digit ratios and fertility as to whether there is a relationship between digit ratios and semen quality.

Routine physical examination, including anthropometry and genital examination, is often undermined in male partners of infertile couples. Concept of digit length in males and its significance in the Indian context was first proposed by Voracek and colleagues in 2001.[25] Researchers are still trying to assess the relationship between finger length ratio and distinct aspects of fertility. The answer to this lies in developmental biology. Across all vertebrate species, including humans, the Homeobox a (Hoxa) and Homeobox d (Hoxd) genes regulate limb development, including fingers and toes.[8] These genes are also responsible for development of the urogenital system, including testes, ovaries and penis. Demonstration of Hox gene expression products in spermatozoa after meiotic division has led to the idea that expression of these genes and hence digit characteristics may be related to fertility. Thus, prenatal androgen levels definitely influence the digit length and ratio, which is maintained throughout adulthood.

Data is scarce to prove a relationship between adult testosterone concentrations and 2D: 4D. Manning and co-workers first studied this relationship between the 2D: 4D ratio and sperm count in 1998. They compared 12 males with germ cell failure and 46 males with normal semen parameters in terms of right and left hand 2D: 4D ratios and reported a significant difference in right hand ratios and an insignificant difference in left hand, an outcome similar to our study.[13] Various studies targeting healthy men reported both positive and negative associations between 2D: 4D ratio and total sperm count.[12,26] The results of research by Uchida and colleagues and Firman and colleagues have confirmed the existence of a positive significant correlation of body fluctuation asymmetry and total sperm count, sperm motility, and sperm head length.[27,28] These findings have prompted the hypothesis that the way digits develop could be linked to the functioning of the gonads.

Hormonal assays in males are not the recommended initial test in all patients, as it is a costly affair and might not add benefit in decision making for patients going for IVF.[15] Since our patient group with low sperm counts had significantly low levels of testosterone, it seems logical to do a thorough hormonal evaluation for all oligospermic males without any other cause of primary infertility. The testosterone-to-estrogen ratio (T/E) has been reported to be an important parameter for the male fertility evaluation. Lower ratios indicate less potent spermatogenesis and androgenization.[29] We found similar results with a significantly lower ratio (<10) in hypogonadal infertile males.

It is high time to find the missing link between the digit ratio, semen quality and thus overall fertility. Thus, we can draw a rough conclusion that measurement of anthropometrical parameters is a simple, cost-effective tool for such patients and can grossly seclude those who will need any hormonal intervention, particularly in resource-constrained developing countries such as India.

The strength of our study lies in the patient selection, including a large sample size of infertile males, with direct comparison to fertile male partners. Performing timely hormonal and semen analysis in the same laboratory according to WHO 2010 guidelines alleviates diurnal variations in serum testosterone levels. Despite an adequate study design, we were unable to assess semen morphology and DNA fragmentation index due to financial limitations. Therefore, unrecognized sources of bias may still persist despite controlling for known confounders through multivariable analysis. Conducting pituitary imaging in infertile men could help identify central causes of low testosterone levels. Additionally, measuring sex hormone-binding globulin (SHBG) and calculating free testosterone would have enhanced the precision of our findings. Future research should incorporate these additional assessments, along with comparative studies involving patients with normal sperm parameters and those with unexplained infertility, to address the remaining gaps.

CONCLUSION

The 2D: 4D ratio might directly correlate with testosterone levels and, thus, semen quality and fertility potential of a subject. We reported significantly higher levels of right-hand 2D: 4D ratio in patients with lower levels of testosterone in oligospermic infertile males (p=0.022), and a nonsignificant increase for the left hand in a similar group. Among men, testosterone, LH and FSH play an important role in reproductive function, have also been compared with the 2D: 4D ratio. Similar findings were reflected in our study, where significantly high FSH levels were seen in patients with low testosterone. Thus, finger length and ratio might serve as a cost-effective and time-saving method for indirect estimation of androgenization in male patients.

ACKNOWLEDGEMENTS

Authors would like to thank the support staff and study participants for their valuable contributions.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Gupta S, Tripathi D, Mathew D, Sharma M, Hasmukhbhai KA, Sharma KR, et al. Clinical implications of the second (2D) and fourth (4D) digit ratio in male infertility: associations with semen parameters and sex hormone levels - a cross-sectional study. Int J Reprod Contracept Obstet Gynecol 2025;14:3487-94.