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Usefulness of Prader's Orchidometer and Correlation with Inhibin B Level, In the Evaluation of Infertile Male with Hypogonadism Followed in a Low Resource Setting

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Abstract

Background: Testicular volume is a good marker of sertoli cell count, which correlates with male fertility. The orchidometer is a tool for measuring testicular volume. But it is not widely used in our infertility clinics. Our objective was to investigate the agreement between the measurement of testicular volume by the orchidometer and that obtained by testicular ultrasound in infertile men with hypogonadism and to correlate it with the level of inhibin B.

Materials and Methods: We carried out a descriptive and analytical cross-sectional study in 3 reference hospitals in Cameroon. We proceeded with consecutive sampling. We included all consenting patients followed up or consulting in the host department for non-obstructive infertility. Patients with bilateral cryptorchidism were excluded. Testicular volume was measured with an orchidometer and ultrasound and then compared. Following this, a blood sample was taken for measurement of serum inhibin B levels.

Results: Twenty-six patients with hypogonadism were examined. They were aged between 18 and 49 years with a mean age of 32.23 ± 10.35 years. We examined 49 testes. The average testicular volume found on the orchidometer was 6.13 ± 7.70 ml. On testicular ultrasound, we found an average testicular volume of 5.60 +/- 7 ml. There was an almost perfect agreement between the testicular volume on the orchidometer and that found on the ultrasound (kappa =0.81; p<0.001). There was also a correlation between the level of inhibin B and testicular volume measured by both the orchidometer (r=0.67; p=0.03) and scrotal ultrasound (r=0.60; p=0.04).

Conclusion: The evaluation of the markers of the Sertoli cell function by 3 methods that was clinical, ultrasound and biochemical methods, showed a perfect agreement between them. This confirms the validity and reliability of the Prader's orchidometer in the evaluation of testicular growth in infertile men.

Keywords: Prader's orchidometer; Infertility; Hypogonadism; Testicular ultrasound; Inhibin B

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Introduction

Couple infertility is by its frequency and its impact on quality of life, a public health problem. In Cameroon, the prevalence of infertility among couples is estimated to be between 20 and 30% depending on the region [1]. The male's contribution to couple infertility is highly variable, with a male component being involved in 20% to 70% of cases depending on the series [2]. The male component in couple infertility is often defined by spermogram abnormalities. However, many other male factors may be present, even with an apparently normal spermogram. According to the optimal evaluation of the infertile male, the examination of the infertile man must be systematic complete and meticulous, so as not to omit certain elements [3]. Testicular volume is known to be a good marker of the number of Sertoli cells. Sertoli cells are essential for spermatogenesis: they provide support, protection, and nutrition for germ cells. Thereby, the testicular volumes with Sertoli cells are correlated with male fertility [4]. There are simple, inexpensive and validated clinical tools for estimating testicular volume alongside testicular ultrasound. Prader's orchidometer is one of the tools, but it is not widely used in our infertility clinics. Its reproducibility is good if it is practiced by trained examiners, and studies suggest an agreement of the results obtained with those of the scrotal ultrasound [5,6]. Our main objective was to establish the agreement between the measurement of testicular volume by the orchidometer and that obtained by ultrasound in infertile male with hypogonadism and, to establish the correlation with inhibin B serum level.

Materials and Methods

Study design

We carried out a descriptive and analytical cross-sectional study in 3 reference hospitals. In the city of Yaoundé, the endocrinology services of the Yaoundé Central Hospital and Yaoundé General Hospital and in the city of Douala, the endocrinology service of the Douala General Hospital. Biological analyses, hormonology was carried out in the laboratory of the Center for Research and Application in Endoscopic Surgery and Human Reproduction (CHRACERH). The work was carried out over a period of 1 year from 01 January to 31 December 2017.

Study population

Source population: The population consisted of all patients consulting for the first time for male infertility in the host department during the study period.

Inclusion criteria: We included men aged 18 years or older who consented to participate in the study and who had a complaint:

- Couple infertility
- Signs related to hypogonadism.
- Spermogram abnormalities

Exclusion criteria: Patients with bilateral cryptorchidism were excluded.

Sampling: Our sampling was consecutive and exhaustive.

Sample size: The sample size was determined as followed [7]:

$$N = \frac{1+8Z^2_{1-\alpha/2}(1-p)^2[1+(k+1)p]^2}{k(k+1)\beta^2}$$

N: Minimum sample size to obtain significant results for an event and set a level of risk

Z: Confidence level (the typical value of the 95% confidence level will be 1.96)

K: represents the coefficient intra-class (ICC). Previous study showed a perfect agreement between testicular volume at ultrasound and orchidometer: r=0.94 [6] so, we settled ICC at 0.95

α Margin of error (usually, it is 0.05)

The power of the study was fixed at 90% so, type 2 error (β) was 0.10

β shows type II error, Z21-α/2

N=16

The minimum sample size is 16 patients.

Procedure

1st visit: Each patient meeting the inclusion criteria was systematically enrolled in the study after signing an informed consent. For each patient, we noted:

- Age, ethnic group, profession, marital status, reason for consultation or referral, referring physician's specialty.
- History of pubertal delay, inguinal surgery or neurosurgery, gonadotoxic treatment, mumps infection with or without clinical orchitis, tobacco and/or alcohol intake as measured by the alcohol index or the number of packets per year for tobacco; we were also looking for clinically patent hyposmia or anosmia.
- During clinical examination we specified the abdominal circumference, the body mass index. The external genitalia were assessed: The size of the penis was measured with a tape measure and the value obtained was projected onto the Schonfeld -Feldman curve [8]. The presence of the testes in the bursae was checked. The position of the urinary meatus was also noted and specified.
- Testicular volume was measured by a single examiner. The testes were palpated in an upright position with the scrotal skin stretched over the testes to isolate the testicular contours from those of the epididymis. We palpated one testis after the other, with one hand while the reference model "being tested" (orchidometer ovoid) was held in the other hand. The ellipsoidal perception closest to the testicular dimensions was retained and its identification number was recorded on our data sheet.

Concerning laboratory workup we requested the following tests: Spermogram, serum FSH, LH, Prolactin, Total Testosterone and serum Inhibin B.

We then booked a second appointment with each patient, at their time of convenience, to perform a testicular ultrasound.

2nd visit: All testicular ultrasounds were performed by the same radiologist. This examination was completed if necessary with a trans-abdominal and endorectal ultrasound. We used a MINDRAY ultrasound scanner with a sectorial probe with a frequency varying between 7.5 Mhz and 13 Mhz. The ultrasound transmitting and receiving probe was lubricated before being delicately placed and moved over the scrotum and then around it, allowing us to visualize its interior. The joint use of color (or energy) Doppler was necessary to appreciate the vascular mapping of the testes. The radiological examination was done in a comparative manner, assessing their topography, size (length, width, height), echostructure, position, and the appearance of the epididymis and vas deferens. The testicular volume was automatically calculated by the ultrasound scanner according to the set formula: 0.71 × Length × Width × Thickness. The findings of this imaging examination were recorded on our charts and a copy was given to the patient.

All our data was collected using anonymous data sheets to ensure confidentiality.

Data processing and statistical analysis

We used the statistical analysis tools: SPSS version 20.0 and Microsoft Excel version 2013. The data collected and processed anonymously were stored in SPSS version 20.0. The results were presented in the form of tables and graphs. Quantitative variables were described as mean and standard deviation or median and interquartile range. Qualitative variables were described as counts and percentages. The comparison of means was analyzed using a Student's test. The correlations between the different quantitative variables were studied using the Pearson correlation coefficient. Agreement between the different quantitative variables was checked using the intra-class correlation coefficient.

For agreement between categorical variables, we used Cohen's Kappa coefficient. The interpretation of the power of the agreement from the Kappa coefficient was made according to the Landis and Koch reference values (Table 1). The degree of statistical significance was set at 5%.

Ethical considerations

Our study was conducted in strict compliance with the fundamental principles of the Helsinki Declaration. We obtained clearance from the Institutional Committee of Ethics and Research of the FMSB of the University of Yaounde I.

Result

During the study, we enrolled 26 patients.

Socio-demographic and clinical characteristics

The average age of our patients was 32.23 years ± 10.35 with extremes between 18 and 49 years. Most of our patients were in a couple at the time of the study: 23 or (88.5%). More than half of our patients (19/26 or 73.07%) were overweight or obese (BMI>25). The average BMI observed was 28.48 ± 6.09.

Gynecomastia was clinically found in 17 (65.38%) of the patients.

The average length of the penis (at rest) was 6.11 ± 2.25 cm. Seven (26.92%) of our patients had a micropenis when the penis size was reported on the Schonfeld curves.

Biological characteristics of the study population

All of our patients had hypogonadism. Hypogonadotropic hypogonadism was found in 21 (80.8%) of our patients. The average inhibin B level was 68.40 ± 18.80 ng/ml with extremes between 34 and 99 ng/ml. A level of inhibin b <34 ng/ml was found in 21 (80.80%) of our patients.

Oligoasthenoteratospermia was the most frequent abnormality found on sperm examination, with a proportion of 21 (80.76%) of patients.

Testicular volume measurement with Prader's orchidometer and testicular ultrasound

Testicular volume on the orchidometer: We examined a total of 49 testes in 26 patients (26 left and 23 right). Cryptorchidism was found on clinical examination in 3 (11.53%) of our patients, it was a unilateral (mainly right) cryptorchidism. The mean testicular volume was 6.13 ± 7.70 ml with a median of 1.5 (0.97 ml to 9.75 ml). Testicular volume <4 ml was found in more than 50% of patients.

Left orchidometry: We examined 26 left testes. The mean testicular volume on the left was 6.32 ± 7.70 ml, with values between 0.9 and 25 ml and a median of 1.5 ml (1; 9.75). Most of our patients, 15/26 or 57.70%, had a left testicular volume <4 ml according to Prader's orchidometer.

Right orchidometry: We examined 23 testes. The mean testicular volume on the right was 5.90 ml +/-7.45 ml with volumes ranging from 1 ml to 25 ml and a median at 2 ml (0.9; 9.75). For 13/23 (56.52%) of these patients, we found a right testicular volume <4 ml according to Prader's orchidometer.

Table 1: Interpretation of Fleiss' kappa (k) from Landis and Koch [9].

Interpretation	Kappa (κ)
Almost perfect	0.81-1.00
Substancial	0.61-0.80
Moderate	0.41-0.60
Fair	0.21-0.40
Slight	0.00-0.20
Poor	<0.00

Table 2: Table of agreement between ultrasound and orchidometer while measuring left testicular volume.

Orchidometry (left testis)	(Left testis) ultrasounds			Total
	<4 ml	[4-15]	[15-25]	
<4 ml	15	0	0	15
[4-15]	1	4	0	5
[15-25]	0	1	5	6
Total	16	5	5	26

Coefficient of agreement: κ=0.86 p<0.001

Table 3: Table of agreement between ultrasound and orchidometer while measuring right testicular volume.

Orchidometry (Right testis)	(Right testis) ultrasounds			Total
	<4 ml	[4-15]	[15-25]	
<4 ml	16	0	0	16
[4-15]	0	4	0	4
[15-25]	0	3	3	6
Total	16	7	3	26

Coefficient of agreement: κ=0.79 (p<0.001)

Table 4: Table of agreement between ultrasound and orchidometer while measuring right and left testicular volume.

Orchidometry	Ultrasound			Total
	<4 ml	[4-15]	[15-25]	
<4 ml	31	0	0	31
[4-15[ml	1	8	0	9
[15-25]ml	0	4	8	12
Total	32	12	8	52

Coefficient of agreement: κ=0.81 p<0.001

There was no significant difference according to laterality (p=0.86).

Testicular volume on ultrasound: Scrotal ultrasonography allowed the study of 26 testes on the left *vs.* 25 on the right (1 test is not visualized). The mean testicular volume observed overall was 5.60 ± 7.0 ml with a median of 1.90 (0.70 ml to 8.60 ml).

The abnormalities found on scrotal ultrasound were exclusively

- Testicular hypotrophies, in 22 patients (84.61%). The mean left testicular volume was 5.75 ml ± 7.17 ml, with a median of 1.80 (0.80 ml to 8.55 ml), and volumes between 0.2 ml and 23 ml.

The mean right testicular volume was 5.44 ml ± 6.96 ml, with volumes between 0.2 and 24.6 ml, and a median of 1.98 (0.65 ml to 8.70 ml).

- Varicocele, in 2 patients (7.7%). These patients all had a hormonal profile of hypergonadotropic hypogonadism.

Scrotal ultrasonography did not reveal microcalcifications, nodules or obstruction of the spermatic excretory tract in any of the patients in our series.

Degree of agreement between clinical orchidometry and scrotal ultrasonography in the estimation of testicular volume

We found good agreement between the two methods of testicular volume measurement: Clinical orchidometry (Prader's orchidometer) and scrotal ultrasound. The coefficients of agreement kappa =0.86 for left testicular volumes, and kappa =0.79 for right testicular volumes, make it possible to affirm this (Table 2 and 3).

For all the testes examined, if we consider the testicular volume in orchidometry for cryptorchid testes to be zero, we find the same degree of agreement between the two methods of measurement, with a kappa =0.81, reflecting an almost perfect agreement (Table 4). We also observed that agreement is better for testicular volumes of prepubertal stage (<4 ml) and those corresponding to pubertal stages of Tanner's classification (4 ml to 15 ml). Above 15 ml testicular volume, the Prader's orchidometer overestimates the testicular volume.

Moreover, the correlation between these different measurements of testicular volume (taken in absolute values) is excellent. The intra-class correlation coefficient r=0.990 makes it possible to affirm this (p=0.001).

Correlation between testicular volume and inhibin B level

By applying a Pearson correlation test, we found a correlation between the level of inhibin B and testicular volume measured using both a Prader's orchidometer (r=0.67, p=0.03) and testicular ultrasound (r=0.60, p=0.04).

Discussion

We conducted a study to investigate the level of concordance between two methods of testicular volume assessment (orchidometer and testicular ultrasound) in infertile patients with hypogonadism and to establish the correlation between measured testicular volumes and the level of inhibin B in these patients. Testicular ultrasonography is the most commonly used test to assess testicular volume in our practice. Although increasingly available in our hospitals, it is still an expensive and operator-dependent test. On the other hand, the Prader Orchidometer is an old instrument for clinical measurement of testicular volume. It has the advantage, when available, of being non-invasive, easy to perform, with good reproducibility [6,9], and it does not generate additional costs. However, the estimation of testicular volume with the Prader orchidometer can be a source of error in the hands of unaccustomed clinicians. Moreover, it gives a rough estimate especially for volumes between 2 consecutive ovoids. This could constitute measurement bias. In order to limit these biases, the orchidometric examinations were performed by a single examiner and the testicular ultrasounds were all performed by the same operator using the same ultrasound scanner each time.

At the end of our work we observed that the measurement of testicular volume using a Prader orchidometer was consistent with the ultrasound measurement. Testicular volume was correlated with the level of inhibin B regardless of the measurement method used; and the agreement was better for testicular volumes in the prepubertal stage (<4 ml) and those corresponding to testicular volumes between 4 ml to 15 ml. Above 15 ml testicular volume, Prader's orchidometer overestimates testicular volume.

In clinical orchidometry, we found an average testicular volume of 6.13 ml ± 7.70 ml corresponding to a stage of pubertal development according to Tanner G3. The median testicular volume observed within this wide distribution was 1.5 (0.97 ml to 9.75 ml). It should be noted that all our patients had hypogonadism. These observed differences in testicular volume values in our series could be justified by the fact that some of our patients were already on androgen replacement therapy at study entry and others had acquired hypogonadism in the post-pubertal period with normal testicular volume.

On testicular ultrasound, we found a mean testicular volume of 5.60 ± 7 ml, with a median of 1.90 (0.70 ml to 8.60 ml). This median is lower than the mean testicular volume of 3.9 ml found by Anne Barbotin on testicular ultrasound in patients with Klinefelter's syndrome [11], and the mean of 3.32 ml found by Canale et al. in patients with hypogonadotropic hypogonadism [12]. No studies found in literature report a variation in testicular volume according to ethnic origin. This low average testicular volume observed in our patients may in fact reflect the delay in diagnosis and consequently the delay in initiating hormone replacement therapy. Indeed, an early treatment allows a better pubertal maturation. Moreover, testicular hypotrophy was the most frequently found abnormality on testicular ultrasound, followed by varicocele in proportions of 65.38% and 7.7% respectively. The importance of testicular hypotrophy attests the longer duration of hypogonadism in our patients.

We found varicocele in 7.7% of our patients. This finding is consistent with the data published in the literature, according to which a varicocele is found in 4.30% to 13.30% of azoospermic patients depending on the series [13]. This abnormality of the pampiniform venous plexus is the most frequent cause of surgically treatable male infertility and the first cause of male infertility in the world [4,14]. However, hypogonadism is only found at extreme and/or complicated stages of varicocele [15]. The frequency of this abnormality in our hypogonadic patients suggests once again the delay in the management of male fertility related conditions in our localities.

Comparative analysis of testicular volumes by the 2 methods shows an excellent correlation, r=0.99 (p<0.001), between measurement of testicular volume by the Prader's orchidometer and testicular ultrasound. Studies had also described this correlation of testicular volumes in infertile patients (r=0.94), and also in a pediatric population [6,10,16]. Also, the inhibin B level in our patients averaged 68.40 ± 18.80 ng/ml. More than 80% of our patients had low inhibin levels. Normal values in adult males ranged from 92 to 316 ng/ml, a result similar with the hypogonadic state of all our patients [11]. The level of inhibin B correlated with testicular volume as measured by both the Prader orchidometer and testicular ultrasound (r=0.67; r=0.60). The correlation between these two markers (testicular volume and inhibin B level) and therefore of fertility, can be explained by physiology. In fact, almost all of the inhibin B is secreted by Sertoli's cells, and the latter make up almost 80% of testicular volume. These correlations had also been reported by Klingmuller et al. [17] in patients with both impaired and normal spermatogenesis (r=0.79); as well as Kumanov et al. [18] in a study of infertile patients (r=0.57).

Conclusion

The evaluation of the markers of the sertolian function by 3 methods: clinical, ultrasound and biochemical methods, showed an excellent concordance and correlation between them. This concordance between the ultrasound and clinical measurements confirms the validity and reliability of the Prader orchidometer in the evaluation of testicular growth. However, testicular ultrasonography retains a prominent place in the management of infertility during hypogonadism as it provides additional information.

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