ORIGINAL RESEARCH

Serum reproductive hormone profiles and semen characteristics of infertile men with clinical varicocoeles before and after varicocoelectomy in Lagos, Nigeria: A prospective cohort study

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Abstract

Background

Varicocoeles have been shown to affect fertility by inducing Leydig cell and Sertoli cell dysfunction in the testes, leading to abnormal reproductive hormone values and impairment of spermatogenesis. Varicocoeles are a significant risk factor for androgen deficiency and infertility. This study aimed to evaluate the early effects of open subinguinal varicocoelectomy on serum hormonal levels and semen parameters in infertile men.

Methods

Forty-five infertile men with varicocoeles had serum hormone levels and seminal fluid analysed preoperatively, as well as at 3 and 6 months after varicocoelectomy.

Results

The mean age was 34.6±3.1 years. The known duration of inability to achieve conception ranged from 1 to 7 years, with a median interval of 3 years (interquartile range, 2-4 years). Most of the patients (n=37, 82.2%) had primary infertility. Thirty-three men (73.3%) had bilateral varicocoeles. Although the reproductive hormone levels were all within normal limits, the testosterone levels significantly increased at 6 months after varicocoelectomy ($P<0.001$). A significant increase in the testosterone level was found in males with low-normal testosterone levels (<4 ng/mL). There was a significant decrease in serum follicle-stimulating hormone after varicocoelectomy ($P<0.001$). Sperm concentration and progressive motility increased significantly 6 months after varicocoelectomy ($P<0.001$ respectively). Neither the preoperative varicocoele laterality nor the grade was associated with changes in serum reproductive hormone levels or semen characteristics.

Conclusions

Open subinguinal varicocoelectomy was associated with significantly increased serum testosterone, particularly among men with preoperative low-normal testosterone levels. Varicocoelectomy also improved the spermatogenic function of the testes.

Keywords: male infertility, reproductive hormones, varicocoele, varicocoelectomy, Nigeria

Introduction

Infertility is the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.[1] The prevalence of varicocoeles among men is approximately 15%, though reports indicate that 19% to 41% of infertile males have palpable varicocoeles.[2]-[4] Varicocoeles have been shown to induce Leydig cell and Sertoli cell dysfunction in the testes, leading to abnormal reproductive hormone values and concomitant impairment of spermatogenesis.[4],[5] These dysfunctions are caused by factors such as testicular hyperthermia, increased testicular blood flow and venous pressure changes, reflux of renal or adrenal products, oxidative stress, and reduced activity of the enzymes 17,20-desmolase and 17-alpha-hydroxylase.[6] Studies in high-income countries have demonstrated improvements in spermatogenesis and serum reproductive hormone levels, which increase the probability of conception following varicocoelectomy.[7] Few studies conducted in Nigeria have analysed the serum reproductive hormone levels of infertile men with varicocoeles and other causes of male infertility, as well as the concomitant impact of varicocoelectomy.[8] Therefore, this study aimed to investigate the early effects of varicocoelectomy on serum reproductive hormone levels and semen characteristics at the Lagos State University Teaching Hospital (LASUTH).

Methods

The study was a prospective single cohort study conducted at the Urology division of LASUTH over 1 year, from April 2017 through March 2018, and the participants were infertile men with varicocoeles.

Patients

The research protocol was approved by the Health Research and Ethics Committee of LASUTH. The study included all consecutive consenting men with infertility, abnormal sperm count, and varicocoeles diagnosed at the LASUTH urology clinic within the study period. Detailed histories were documented, which included age, occupation, home address, mobile phone number, known duration of infertility, and type of infertility. Following this, a comprehensive physical examination was conducted to diagnose and evaluate varicocoele presence, laterality, and grade. Using the criteria outlined by Dubin and Amelar,[9] the study graded clinical varicocoeles as follows: grade I, varicocoele that is palpable only with the patient standing and performing a Valsalva manoeuvre; grade II, varicocoele that is palpable with the patient standing, without a Valsalva manoeuvre; and grade III, varicocoele that is palpable and visible through the scrotal skin with the patient standing. The study classified patients with bilateral varicocoeles as grade III.

To confirm the clinical varicocoele diagnoses, we performed Doppler scrotal ultrasonography using the LOGIQ C5 Premium machine with its 7.5-MHz linear array probe (GE Medical Systems, Jiangsu, China). The prolate ellipsoid formula was used, employing greyscale imaging, to determine testicular volume.

Operative procedure

Open nonmicrosurgical subinguinal varicocoelectomy was performed under local anaesthesia using 0.5% plain lignocaine solution. A 2- to 4-cm groin crease incision was made over the external inguinal ring and deepened into the subcutaneous layer. The index finger dissected through Scarpa's fascia, and the spermatic cord was grasped with a Babcock clamp and delivered through the wound. A careful dissection of the cord layers was done. The vas deferens was identified, retracted, and encircled with gauze. The dilated veins were meticulously freed from all surrounding tissues, doubly ligated with Vicryl 3-0 sutures, and divided. The spermatic cord and its structures were placed back, and the wound was closed in layers with a dressing applied.

Serum hormone assay

The serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone, and prolactin assays were conducted using Architect chemiluminescence immunoassay kits (Abbott Diagnostics, Lake Forest, IL, USA) for each hormone. The normal ranges are 1.24 to 8.62 mIU/mL for LH, 1.79 to 19.2 mIU/mL for FSH, 2.5 to 8.0 ng/mL for testosterone, and 2.64 to 13.13 ng/mL for prolactin. The preoperative and postoperative measurements were from early-morning samples (8 AM to 10 AM). Hormone assays were conducted preoperatively and at 3 and 6 months postoperatively.

Seminal fluid analysis

Semen samples were collected by masturbation, after 3-day periods of sexual abstinence, in a private room near the microbiology laboratory. The seminal fluid analysis was conducted within 1 hour of collection in compliance with the World Health Organization guidelines.[10] The measured variables were pH, liquefaction time, volume, sperm morphology, sperm concentration, sperm count, and sperm motility (including progressive and total motility, the latter of which is the sum of progressive and nonprogressive motility values). The estimation of sperm count was done using a Neubauer haemocytometer counting chamber (Paul Marienfeld GmbH & Co. KG, Lauda-Königshofen, Germany). The semen analyses were conducted preoperatively and at 3 and 6 months postoperatively.

Statistical analysis

Categorical data (laterality and grade of varicocoele) are presented using frequencies and percentages. Continuous data (LH, FSH, testosterone, prolactin, sperm concentration, sperm count, ejaculate volume, motility, morphology, and testicular volume) are presented using means and standard deviations when normally distributed; data with skewed distributions are reported as medians and interquartile ranges (IQRs). The patients were categorized according to their preoperative serum testosterone levels, using ≤4 ng/mL as a low-normal level, while <2.5 ng/mL denoted low testosterone. They were also classified into 3 subgroups of oligospermia: mild (10 to <15 million sperm/mL), moderate (5 to <10 million sperm/mL), and severe (1 to <5 million sperm/mL).[11] The chi-square test or Fisher's exact test was used to determine associations between categorical variables. Mean comparisons of semen and reproductive hormone levels at different intervals were carried out using repeated measures ANOVA (analysis of variance) or the Friedman test. The analyses were conducted using SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY, USA). P values <0.05 were considered statistically significant.

Results

The study included 45 infertile men diagnosed with varicocoeles. Their ages ranged from 29 to 40 years, with a mean age of 34.0±3.1 years. All study participants were married, with known durations of inability to achieve conception ranging from 1 to 7 years (median, 3 years).

Primary infertility predominated, occurring in 37 men (82.2%), while 8 men (17.8%) had secondary infertility. The duration of infertility in those with primary infertility ranged from 1 to 6 years, whereas it was longer—from 2 to 7 years—in participants with secondary infertility.

Thirty-three participants (73.3%) had bilateral varicocoeles, and 12 (26.7%) had unilateral varicocoeles. Eleven unilateral varicocoeles (24.4%) were on the left side, and 1 (2.2%) was on the right side.

Only grades II and III clinical varicocoeles were found among the participants. Among the left varicocoeles, 15 (33.3%) were grade II, and 29 (64.4%) were grade III. Among the right-sided varicocoeles, 25 (73.5%) were grade II, and 9 (26.5%) were grade III.

The mean right testicular volume was 12.09±3.0 mL (range, 6.08-18.00 mL), and the mean left testicular volume was 10.76±2.3 mL (range, 6.00-16.27 mL). The mean total testicular volume was 22.85±5.3 mL.

The mean LH level was 5.27±1.9 mIU/L (range, 1.59-8.50 mIU/L). The mean testosterone level was 4.85±1.6 ng/mL (range, 2.50-9.11 ng/mL). The mean prolactin level was 6.77±2.5 ng/mL (range, 2.70-11.60 ng/mL). The median FSH level was 6.20 mIU/L (IQR, 4.40-9.60 mIU/L; range, 2.07-18.40 mIU/L).

The changes in the assayed hormone levels among preoperative measurements and those at 3 and 6 postoperative months are presented in Table 1.

Of 18 men with preoperative serum testosterone levels ≤4 ng/mL (low normal), 12 (66.7%) had their testosterone levels increase to >4 ng/mL. The mean change in serum testosterone level was from 3.34±0.5 ng/mL preoperatively to 4.24±1.2 ng/mL at 3 postoperative months and 4.55±1.4 ng/mL at 6 postoperative months (*P*=0.001). The mean total testicular volume was 26.6 mL among the 12 men whose testosterone levels increased to >4 ng/mL, compared with 20.5 mL among the 6 men whose testosterone levels did not increase.

Among 27 patients with preoperative testosterone levels >4 ng/mL, the mean total testicular volume was 21.7 mL, and none experienced a decline in testosterone levels to <4 ng/mL. The mean change in serum testosterone level was from 5.86±1.2 ng/mL preoperatively to 6.09±1.3 ng/mL at 3 postoperative months and 6.39±1.5 ng/mL at 6 postoperative months (*P*=0.045).

The sperm concentrations ranged from 1.00 × 10^6/mL to 13.00 × 10^6/mL (median, 6.40 × 10^6/mL; IQR, 2.00 × 10^6/mL to 10.00 × 10^6/mL). The total sperm count ranged from 1.00 × 10^6 to 44.00 × 10^6 (median, 16.00 × 10^6; IQR, 5.00 × 10^6 to 25.50 × 10^6).

Preoperatively, 13 (28.9%), 14 (31.1%), and 18 (40.0%) men had mild, moderate, and severe oligospermia, respectively. At 3 and 6 postoperative months, 11 (24.4%) and 18 (40%) sperm concentrations improved to normal levels (≥15 million sperm/mL). Increased sperm concentrations were noted for 41 men (91%) at 6 postoperative months.

Of the 45 patients with oligospermia, 28 (62.2%) had asthenospermia. Progressive motility ranged from 5% to 50% (median, 30%; IQR, 20%-40%). Total motility ranged from 10% to 90% (median, 50%; IQR, 45%-60%). At 3 and 6 postoperative months, asthenospermia was observed in 21 (46.7%) and 14 (31.1%) men, respectively. Postoperatively, progressive sperm motility improved to a normal level (>32%) in 14 of the asthenospermic men (50%).

An examination of spermatozoa morphology revealed no teratospermia, as the normal forms ranged from 10% to 90% (mean, 62.71±21.7%).

The changes in seminal fluid parameters are summarized in Table 2. Table 3 and Table 4 show that there was no significant variation in the changes in hormone levels or seminal parameters associated with varicocoele laterality or grade, respectively.

Table 1. Serum reproductive hormone levels at baseline and at 3 and 6 months after varicocoelectomy

Hormone	Baseline	Postoperative interval		*P* value
		3 months	6 months	
Luteinizing hormone, mean ± SD, mIU/L	5.3±1.9	5.4±1.8	5.1±2.1	0.13
Testosterone, mean ± SD, ng/mL	4.85±1.6	5.4±1.5	5.7±1.8	<0.001
Prolactin, mean ± SD, ng/mL	6.8±2.5	6.6±2.2	6.7±2.2	0.64
Follicle-stimulating hormone, median (IQR), mIU/L	6.2 (4.4-9.65)	6.0 (4.55-9.20)	5.9 (4.1-8.85)	<0.001

IQR, interquartile range; SD, standard deviation

Table 2. Seminal fluid parameters at baseline and at 3 and 6 months after varicocoelectomy

Variable	Baseline	Postoperative interval		*P* value
		3 months	6 months	
pH, mean ± SD	7.9±0.2	7.8±0.3	7.72±0.9	0.47
Liquefaction time, mean ± SD, min	40.6±12.3	35.3±12.7	31.2±13.4	0.03
Normal morphology, mean ± SD, %	62.8±21.7	65.8±20.3	66.1±20.0	0.045
Volume, median (IQR), mL	2.5 (2.0-3.5)	3.0 (2.0-4.0)	3.0 (2.4-4.0)	<0.001
Sperm concentration, median (IQR), × 10^6/mL	6.4 (2.0-10.0)	8.0 (4.0-15.5)	10.0 (5.5-19.5)	<0.001
Sperm count, median (IQR), × 10^6/ejaculate	16.0 (5.0-22.5)	24.0 (12.0-39.5)	30.0 (14.5-58.5)	<0.001
Progressive motility, median (IQR), % total motility	30.0 (20.0-40.0) 50.0 (45.0-60.0)	39.0 (30.0-40.0) 60.0 (50.0-70.0)	40.0 (25.0-60.0) 70.0 (50.0-80.0)	<0.001 <0.001

IQR, interquartile range; SD, standard deviation

Table 3. Changes in hormone and semen parameters according to varicocoele laterality

Variable	Unilateral	Bilateral	*P* value
	Mean	Mean	
Luteinizing hormone, mIU/L	−0.25	−0.19	0.87
Testosterone, ng/mL	0.43	0.96	0.22
Prolactin, ng/mL	0.90	−0.15	0.49
Follicle-stimulating hormone, mIU/L	−0.31	−0.49	0.55
pH	0.08	−0.23	0.37
Liquefaction time, minutes	−1.15	−4.22	0.23
Normal morphology, %	0.77	1.06	0.87
Semen volume, mL	0.40	0.44	0.86
Sperm concentration, × 10^6/mL	6.35	7.93	0.56
Sperm count, × 10^6/ejaculate	21.17	29.69	0.42
Progressive motility, %	13.84	14.75	0.82
Total motility, %	13.07	15.15	0.69

Discussion

Clinical varicocoeles have been shown to negatively impact spermatogenesis via the progressive nature of their effects on sperm production. Nonetheless, repair is performed with the aim of improving semen characteristics in infertile men. The associations between varicocoeles and serum reproductive hormone levels have not yet been established in Lagos.

The mean age of the patients was 34.6 years, comparable to the findings of previous studies conducted in southwestern Nigeria that determined mean ages of 35 and 35.6 years among infertile patients with varicocoeles.[12],[13] The median duration of known infertility in this study was 3 years, aligning with the finding of a 7-year review of men with varicocoele-associated infertility at a tertiary teaching hospital in Ibadan.[12]

In this study, bilateral varicocoeles were found in 33 men (73.3%); this was concordant with a retrospective review of male infertility cases managed at a private urology clinic in Lagos, where 36 men (70%) had bilateral varicocoeles.[13] However, other authors have reported lower rates of bilateral varicocoeles, with proportions of 48.7%[5] and 35%.[14] Discrepancies among studies may be attributable to variations in sample sizes.

Serum testosterone levels significantly increased following varicocoelectomy, corroborating findings from other studies.[7],[15],[16] Su et al.[7] noted increased serum testosterone levels after microsurgical varicocoelectomy, more so in bilateral cases; this specific trend, however, was not observed in our study. Hsiao et al.[15] found microsurgical

Table 4. Change in hormone and seminal parameters according to varicocoele grade

Variable	Grade II	Grade III	*P* value
	Mean	Mean	
Luteinizing hormone, mIU/L	−0.40	−0.98	0.43
Testosterone, ng/mL	0.92	0.74	0.67
Prolactin, ng/mL	−0.08	−0.08	0.99
Follicle-stimulating hormone, mIU/L	−0.39	−0.46	0.82
pH	0.03	−0.23	0.41
Liquefaction time, minutes	0.00	−5.17	0.30
Normal morphology, %	1.19	0.86	0.85
Semen volume, mL	0.34	0.48	0.51
Sperm concentration, $\times 10^6$	7.76	7.32	0.865
Sperm count, $\times 10^6$/ejaculate	26.2	27.8	0.88
Progressive motility, %	13.5	15.2	0.215
Total motility, %	13.4	15.2	0.725

varicocoelectomy to be associated with increased serum testosterone, regardless of the clinical varicocoele grades. Similarly, Su et al.,[7] in their study aiming to evaluate the effect of varicocoelectomy on serum testosterone levels among 53 infertile men with varicocoeles, found no significant correlation between preoperative clinical grade and postoperative improvement in serum testosterone level. Our study findings aligned with this observation, as the postoperative changes in serum reproductive hormone levels were not associated with preoperative varicocoele grades. This suggests that factors other than clinical grade determine the extent to which varicocoeles affect testicular function.

Abdel-Meguid et al.[17] reported that patients with low preoperative testosterone values had better postoperative improvements in serum testosterone levels, corroborating the findings in patients with low-normal preoperative serum testosterone levels (<4 ng/mL) in this study. This may be attributable to improvements in Leydig cell function after alleviating the adverse effects of varicocoeles on the testes.

Conversely, Segenreich et al.[18] observed no significant changes in serum testosterone levels after high ligation of the left spermatic vein in 50 subfertile men with left varicocoeles. They investigated a small cohort of infertile men with mixed testosterone values, which may account for the contrasting findings from our study.

In our study, the mean serum FSH level significantly decreased by 5% after 6 postoperative months, which can be attributed to an improvement in Sertoli cell function. This finding aligns with the work of Cayan et al.,[5] who evaluated 78 men who underwent inguinal varicocoele ligation, determining a significant decrease of 10% in serum FSH levels, along with a concomitant significant rise in testosterone levels.

Additionally, our study found that serum levels of LH and prolactin decreased 6 months after varicocoelectomy; however, these changes did not reach statistical significance. These results are consistent with publications by other authors who found an insignificant decrease in serum LH levels in hypogonadal patients, which could have been due to an improvement in Leydig cell function, as there was a concomitant rise in testosterone levels in the same patients.[14]

There were significant improvements in median sperm concentration and total sperm count by 56% and 87%, respectively, 6 months after varicocoelectomy. We also determined significant improvements in median progressive motility and total motility by 10% and 20%, respectively. The mean percentage of normal morphology significantly increased by 3.25%. These findings are in line with previous research.[5],[7],[19]

Various studies have noted significant, albeit smaller, improvements in sperm count and motility relative to those determined by our study. In a retrospective study of 53 infertile patients after varicocoelectomy, there was a 32% increase in sperm count and a 5% increase in motility.[7] Almahdy et al.,[19] evaluating the outcomes of bilateral inguinal varicocoelectomy on spermography patterns, noted significant improvements in mean sperm concentration (by 48%) and mean percentage of progressive sperm motility (by 5.8%), with no significant decrease in the mean percentage of abnormal forms. Cayan and colleagues[5] found no significant improvement in sperm count, although they found a significant increase in sperm motility (by 9.3%), explained by the removal of the hyperthermic effects of varicocoeles and the recovery of testosterone synthesis essential for epididymal function.

Limitations

Our study had a small sample size, and only grade II and grade III varicocoeles were identified. We lacked an operating microscope and micro-Doppler ultrasound. The follow-up period was not sufficient to thoroughly evaluate the persistence of hormonal and semen parameter improvements after varicocoelectomy or to determine the procedure's impact on achieving pregnancy.

Conclusions

Open subinguinal varicocoelectomy leads to a significant increase in serum testosterone levels, with a favourable impact on male testosterone production. Furthermore, there were improvements in the semen parameters, and these improvements occurred regardless of the preoperative varicocoele grade or laterality.

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