

# Effect of Varicocelectomy on Serum Follicle-Stimulating Hormone and Testosterone; The Interrelationship Between Hormonal Variables

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**Purpose:** The present study was conducted to analyze the effect of varicocelectomy on serum follicle-stimulating hormone (FSH) and testosterone. The interrelationship between seminal and hormonal variables is also investigated.

**Patients and Methods:** A prospective cohort study was conducted on patients of the urology clinic from 2012 to 2017. The study was conducted in the Security Forces Hospital, in Riyadh, Saudi Arabia. Infertile patients who had already undergone the FSH examination and testosterone twice were included in the study. Statistical Package for Social Sciences (SPSS) version 21.0 was used to analyze the data.

**Results:** A total of 186 patients were studied which reveals that the age group of 21–30 years was higher than other age groups 80 (43%), micro varicocelectomy was performed in 138 (74%) of patients and 79 (47%) patients had one-year infertility. The study assessed the effect of varicocelectomy on sperm count and motility serum FSH, testosterone, luteinizing hormone (LH), and prolactin, and it was found that none of the variables showed significant association after varicocelectomy, except for luteinizing hormone (P-value = 0.014). Testosterone levels in patients who had FSH  $\leq 10$  were also evaluated and it was found that the level of testosterone was increased with a decreased level of FSH (P-value = 0.005).

**Conclusion:** It was concluded from our results that after varicocelectomy, those patients who had FSH levels  $\leq 10$  were found to have increased testosterone levels. LH was also found to be significant; however, other hormones were not found to be significant. This may occur due to the reason that we have the majority of the participants in the age group 21–30. Further prospective studies are needed to evaluate the association with ample sample size.

**Keywords:** varicocelectomy, hormones, testosterone levels, Riyadh, Saudi Arabia

## Introduction

The presence of infertility in males is commonly associated with the presence of varicocele. Almost 15% of the general population has been reported to have varicocele; however, it exists in more than 25% of the male population, emphasizing primary infertility. Moreover, secondary fertility has been emphasized among 80% male population.<sup>1</sup> One of the major concerns regarding this detrimental effect on spermatogenesis by varicocele is the lack of evidence and awareness. It has been validated to be secondary to assorted abuses, which include high scrotal temperature with loss of scrotal counter-cooling mechanism, gonadotropins or autoimmunity, oxidative stress, and reflux of adrenal metabolites.<sup>2</sup> Semen parameters are reported to be enhanced by varicocelectomy in almost 70% of the infertile male population as well as 40% of the population will accomplish pregnancy consequently. It is postulated that Sertoli cell dysfunction and low testosterone might be intertwined concerning the influence of testosterone on spermatogenesis.<sup>3</sup>

According to Yamaçake et al,<sup>4</sup> varicocele is an abnormal dilation of the testicular veins in the pampiniform plexus, which shows an adverse impact on sperm production and increases the testicular temperature and is present in 10–20% of the general population and 19–41% of men with infertility.<sup>5</sup> It is also related to testicular atrophy, reduced fertility rates, and pain. Additionally, the extent of varicocele might heighten up to 80% in the male population with secondary infertility.<sup>6</sup>

Biochemical changes in the epididymal fluid, testicular hypoxia, and stasis of the internal spermatic vein are related to the varicocele.<sup>7</sup> There is inadequate evidence regarding subclinical varicocele and its association with infertility.

There is great significance in the hypothalamic-pituitary-testicular axis in male fertility. Leydig cell dysfunction, hypogonadism, and testicular damage are associated with varicocele in infertile males.<sup>8</sup> The varicocele patients usually reveal anti-sperm antibodies.<sup>9</sup> Higher levels of the FSH are also related to the presence of varicocele. An abnormality in spermatogenesis is indicated by an increased serum FSH concentration.<sup>10</sup> The production of sperm in the testis has been stimulated by the FSH, which is the main hormone, and possesses an adverse outcome from this condition. On the other hand, testosterone is produced in the testis.<sup>2</sup> The alteration of spermatogenesis is associated with an increase in serum FSH and a decrease in testosterone levels. Different categories of sperm concentration in infertile men have been revealed from the FSH concentration, which includes oligozoospermia and azoospermia.<sup>3</sup> There is no clear indication of obstructive and non-obstructive azoospermia as a sub-classification of azoospermia. Moreover, more than 40% of infertile patients have been affected by azoospermia, whereas more than 10% of infertile men were affected by altered spermatogenesis.<sup>5</sup> In this regard, a biopsy of testicular tissue will be advised for patients with non-obstructive azoospermia for artificial fertilization. Based on this discussion, a study was conducted to analyze the effect of varicolectomy on serum FSH and testosterone and to investigate the interrelationship between seminal and hormonal variables.

## Materials and Methods

### Patients

A prospective cohort study was conducted. Patients were recruited from a urology clinic in Security Forces Hospital, Riyadh, Saudi Arabia, with major complaints regarding the complexities of having offspring. The sample size was calculated through Open Epi, Version 3, an open-source calculator, and at least 163 were computed by taking the 12% response of increase in testosterone in grade II patients.<sup>11</sup> Patients from 2012 to 2017 from the infertility database as per the inclusion criteria were recruited. The data were collected through a structured questionnaire that comprised study variables at baseline and after 3 months of surgery. The study was approved by the International Review Board (IRB No. KACST, KSA: H-01-R-069, Security Forces Hospital Program, Ministry of Interior, Kingdom of Saudi Arabia), and each patient provided informed consent (verbal or written) as both methods were approved by the IRB Committee. WHO's definition of infertility was considered. It is defined as an inability to achieve pregnancy in 1 year in a sexually active and non-contracepting couple. All the patients who had been diagnosed with varicocele were studied. Varicocele diagnosis was based on examination, therapeutic approach, physical examination of the patients, and sperm analysis. Infertile patients who had undergone the FSH examination and testosterone twice were included in the study. Age, testosterone level, FSH level, testicular volume, and the presence of varicocele were the patient's attributes. The exclusion criteria were based on patients who had not undergone sperm retrieval surgery less than 3 months after the surgery and those patients who had uncontrolled diabetes and hypertension. This study assessed hormonal changes after varicolectomy irrespective of changes in sperm count and motility. Testosterone level in patients who had the FSH level  $\leq 10$  mIU/mL was also evaluated.

Grading was done physically as if the varicocele veins were palpable and visible without the Valsalva maneuver, which was considered grade III. In contrast, if the varicocele veins were palpable and visible without the Valsalva maneuver in normal mode, it was considered grade II. Furthermore, if the varicocele veins were palpable only with the Valsalva maneuver, it was considered grade I. Thus, this research included all the degrees of varicocele.<sup>12</sup>

Testosterone ng/dL, serum FSH mIU/mL, LH mIU/mL, and prolactin  $\mu\text{g/L}$  were measured using the electrochemiluminescence immunoassay (ECLIA). The FSH valued at more than 19.4 mIU/mL will be considered an authentic criterion for retrieving sperm. Testosterone was measured using ECLIA testosterone II with a lower limit of average testosterone level of  $-2.40$  ng/dL in the lab. Cut-off points of testosterone and FSH in this population have been observed from receiver operating attributes.

A surgeon performed microscopic inguinal varicolectomy surgery on all patients, while they were sedated and supine. Microsurgical varicolectomy was performed in patients due to retrograde flow and venous pooling disruption and to conserve lymphatic drain and arterial flow to attain a reduction in the post-operative recurrence of hydrocele and

varicocele complications.<sup>13,14</sup> Thus, following an inguinal incision, the spermatic cord was raised under a microscope, and the dilated veins of the looping chord were closed. After 3 months, levels of testosterone, LH, and FSH were tested and recorded using the same method and kits.

## Ethical Approval

The study was conducted according to the Declaration of Helsinki for medical research involving human subjects, and study approval was taken from the institutional review board before the conduct of the study.

## Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 21.0 was used to analyze the data comprising the inclusion and exclusion criteria. Descriptive statistics such as frequency for qualitative variables and the mean and standard deviation for quantitative variables were computed. The paired sample *t*-test was used to observe the association and to observe the mean difference between pre- and post-surgery study variables. P-value  $\leq 0.005$  was considered significant.

## Results

A total of 186 patients were studied during the study period. Demographic characteristics of the respondents are depicted in Table 1, which reveals that the age group of 21–30 years was higher than other age groups 80 (43%), micro varicocelectomy was performed in 138 (74%) of patients, and 79 (47%) patients had one-year infertility. The mean width and depth of the right and left testis is presented in Table 2. The sperm count (millions/mL) was improved from 12.8 to 13.43 after varicocelectomy.

**Table 1** Demographic Details of the Participants

Variables	Measures	Frequency	Percentage
Age in years (n=186)	18–20	13	7
	21–30	80	43
	31–40	67	36
	41–50	24	13
	51–60	2	1
Type of Procedure (n=186)	Open	48	26
	Micro	138	74
Indication (n=170)	Primary infertility	79	47
	Secondary infertility	50	29
	Pain	25	15
	Swelling	16	9
Testis Bx (n=164)	No	158	96
	Yes	6	4
Varicocelectomy grade – Left (n=82)	Grade I	16	20
	Grade II	39	47
	Grade III	27	33
Varicocelectomy grade – Right (n=52)	Grade I	29	56
	Grade II	20	38
	Grade III	3	6

**Table 2** Mean Width and Depth of Testis

	Mean	Std. Deviation
Left testis length	38.71	6.541
Right testis length	39.95	6.571
Left testis width	22.40	4.666
Right testis width	23.17	5.374
Left testis depth	22.87	5.071
Right testis depth	22.53	4.742

However, it was not found to be statistically significant. Similarly, sperm motility was also found to be non-significant. The study assessed the effect of varicocelectomy on sperm quality (sperm count morphology and motility), and hormones (serum FSH), and it was found that none of the variables showed significant association after varicocelectomy, except for luteinizing hormone (P-value = 0.014) as presented in Table 3. Testosterone levels in patients who had FSH  $\leq$ 10 were also evaluated. It was unveiled that the level of testosterone increased from 6.2 to 13.5 with a decreased level of FSH and showed statistical significance (P-value = 0.005). Moreover, Table 4 exhibits the outcome of taking clomiphene citrate (CC) among the individuals, which showed no significant difference (p-value = 0.52).

**Table 3** Assessment of Serum Quality and Hormonal Parameters in Pre- and Post-Operative Varicocelectomy (MFP)

Variables		Mean MFPI	Mean MFP2	P-value
Volume of Semen (mL)	Pre-Operation	5.3 $\pm$ 1.34	5.7 $\pm$ 1.4	0.59
	Post-Operation	6.1 $\pm$ 1.22	6.3 $\pm$ 1.2	
Total Motility of Sperm (%)	Pre-Operation	33.41 $\pm$ 11.50	30.1 $\pm$ 11.1	0.613
	Post-Operation	47.2 $\pm$ 10.21	40.9 $\pm$ 10.8	
Concentration of Sperm (million/mL)	Pre-Operation	13.89 $\pm$ 6.66	8.89 $\pm$ 4.61	0.878
	Post-Operation	40.12 $\pm$ 15.71	36.24 $\pm$ 10.78	
Cumulative Sperm Count (million)	Pre-Operation	12.1 $\pm$ 7.6	12.9 $\pm$ 7.7	0.510
	Post-Operation	12.8 $\pm$ 7.7	13.43 $\pm$ 8.2	
Normal sperm morphology (%)	Pre-Operation	28.91 $\pm$ 7.1	25.63 $\pm$ 11.5	0.681
	Post-Operation	23.2 $\pm$ 5.6	21.3 $\pm$ 5.1	
Total testosterone count (ng/mL)	Pre-Operation	18.52 $\pm$ 0.4	18.77 $\pm$ 12.6	0.863
	Post-Operation	18.32 $\pm$ 11.3	19.23 $\pm$ 8.05	
FSH Count (mIU/mL)	Pre-Operation	6.16 $\pm$ 6.06	8.95 $\pm$ 9.05	0.735
	Post-Operation	6.77 $\pm$ 6.52	8.95 $\pm$ 8.05	
Total LH count (mIU/MI)	Pre-Operation	5.45 $\pm$ 4.24	6.95 $\pm$ 6.3	0.014
	Post-Operation	6.74 $\pm$ 4.2	7.95 $\pm$ 4.4	
Prolactin count ( $\mu$ g/L)	Pre-Operation	307.14 $\pm$ 220.7	236.45 $\pm$ 195.8	0.426
	Post-Operation	290.55 $\pm$ 190.5	274.18 $\pm$ 213.8	

**Table 4** Comparing Outcomes of Clomiphene Citrate (CC) Intake

	Mean	Std. Dev.	P-value
Pre-operation Clomid	1.55	0.50	0.52
Post-operation Clomid	1.52	0.50	

**Abbreviations:** FSH, Follicle-Stimulating Hormone; SPSS, Statistical Package of Social Sciences; LH, Luteinizing Hormone.

## Discussion

The dilation of veins in turbulent blood flow and pampiniform plexus is known as varicocele.<sup>15</sup> The knowledge of the association between clinical varicocele and the production of testosterone is not clear. It is known that the level of mean testosterone among hypogonadal patients after surgery increased significantly as compared to patients before surgery. The results of the present study have shown a significant difference in the mean levels of the LH followed by varicocelectomy, unlike the mean FSH levels that showed no significant difference. Although there was a difference in the level of testosterone, it was statistically insignificant. LH and FSH are released from the hypothalamus as a result of the depletion of GnRH from the anterior pituitary gland. These hormones are responsible for regulating testicular function. The negative feedback pathway helps in the regulation of LH through the release of estrogen and androgen hormones. The function of gonadal hormones depends on the release of the LH and the FSH. Steroidogenesis is associated with mitochondrial conversion of cholesterol into pregnenolone and testosterone in the Leydig cells and the banding of the FSH into Sertoli cells and spermatogonia membrane in the testis that is stimulated by the LH. In our study, slightly higher FSH and LH levels were reported with normal semen quality. A meta-analysis reported sperm quality can be improved with antioxidant therapy after varicocelectomy and a reduction in FSH levels could improve living conditions for spermatozoa.<sup>16</sup> Higher levels of FSH and testicular hypertrophy also demonstrate a high degree of spermatic vein reflux.<sup>17</sup>

There is a need to treat varicocele because it is likely to increase internal scrotal temperature resulting in decreased production of testosterone by the Leydig cells. This might even cause hindrance in protein metabolism by germinal cells and decrease the ability to function in Sertoli cells. The cooling temperature required for optimal sperm production is supported through the temperature exchange mechanism carried out between the outflow and the testis from the pampiniform venous plexus and blood. This is termed the normal condition on the scrotum. However, the production of testosterone is negatively affected as a result of the thermal effects caused by varicocele.<sup>18,19</sup> A study used a rat model and reported a reduction in malondialdehyde levels through intratesticular injection hADSC cells ( $1.0 \times 10^6$ ) and improvement in spermatogenesis that got deteriorated by varicoceles.<sup>20</sup> Another approach is clinical varicocele repair before any intracytoplasmic sperm injection, intrauterine insemination, or in-vitro fertilization to improve fertility among males, and increase pregnancy results among couples considering the age of females as well.<sup>21</sup> The present study showed a significant difference in the levels of LH before and after the surgery, whereas there was no significant difference in the level of testosterone levels. On the contrary, a study conducted by Abdel-Meguid et al<sup>22</sup> monitored a group of men for around 6 months that showed significant improvement in levels of testosterone among patients who had undergone the surgical procedure. The study confirmed that levels of testosterone are likely to decrease owing to varicocele, which needs improvement among hypogonadal patients.<sup>22</sup> Another retrospective study showed that there is a significant improvement in levels of testosterone after varicocelectomy.<sup>15</sup>

Based on the physical examination done by Su et al,<sup>23</sup> the males with firm testis, before surgery, experienced an increased level of testosterone after varicocelectomy. However, various groups were presented with a lower level of FSH and LH in the serum after varicocelectomy. The present study has shown a significant difference in the levels of LH that indicates improvement in testosterone levels on account of varicocelectomy. On the contrary, a study conducted by Li et al<sup>24</sup> stated an insignificant decline in the level of LH and FSH after varicocelectomy. The recurrence of varicocele after microscopic sublingual varicocelectomy significantly depends on the varicoceles advanced grade and dilated vein size on the left side.<sup>25</sup> In our study, different surgical methods are used to treat varicoceles, which might impact hormones in

different ways. Literature showed spermatic veins' high-level ligation during laparoscopic varicocelectomy to linea terminalis showed low recurrence and hydrocele rates, irrespective of the technique used.<sup>26</sup> Other surgical interventions including sclerotherapy for varicocele reparation and Spermatic vein embolization is considered an effective and safe treatment for symptomatic varicocele, resulting in improved quality of life through pain management.<sup>27,28</sup> However, limited studies are focusing on the level of these hormones, which requires evaluation of hormonal changes after varicocelectomy in a time shorter than 3 months. One of the contributions of this study is that it undertakes a homogeneous group of patients from Saudi Arabia, while previously, a heterogeneous group of patients was focused on. Additional information regarding the prediction of serum levels of FSH, LH, testosterone, and prolactin is needed among patients with varicocele for better treatment. There are a few limitations in our study. This was a retrospective study, and missing data was available. Therefore, the pregnancy rate in patients could not be postulated.

## Conclusion

The present study concluded that after varicocelectomy, patients with FSH levels  $\leq 10$  indicated increased testosterone levels and improved semen quality. The LH was also found to be significant. However, other hormones were not found to be significant. This study will be a valuable addition to the existing literature as there are scarce data available in this regard. Further prospective studies are needed to evaluate the association with ample sample size.

## Ethical Approval

The study was approved by the International Review Board (IRB No. KACST, KSA: H-01-R-069, Security Forces Hospital Program, Ministry of Interior, Kingdom of Saudi Arabia), and each patient provided informed consent (verbal or written) as both methods were approved by the IRB Committee.

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## Disclosure

The author declares no conflicts of interest in this work.

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