Journal of Advances in Medicine and Medical Research

33(16): 23-29, 2021; Article no.JAMMR.70852
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Comparative Study on the effect of Varicocelectomy on Infertile Patients with Normal and Low Serum Testosterone Level

Mohammed Saad Mohammed Sherif[1*], Ayman Mohammed Hagras[1], Mohammed Hassan Radwan[1] and Mohammed Abo El-enen Khalwash[1]

[1]Department of Urology, Faculty of Medicine, Tanta University, Tanta, Egypt.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2021/v33i1630997
Editor(s):
(1) Dr. Emin Umit Bagriacik, Gazi University, Turkey.
Reviewers:
(1) Elena Kistanova, Bulgarian Academy of Sciences, Bulgaria.
(2) Maryam Shamsi, Arak University of Medical Sciences, Iran.
Complete Peer review History: https://www.sdiarticle4.com/review-history/70852

Original Research Article

Received 05 May 2021
Accepted 10 July 2021
Published 13 July 2021

ABSTRACT

Introduction: Varicocele is a dilation of the pampiniform venous plexus and the internal Spermatic vein. It is detected approximately in 15% to 20 % of the general male Population; with the prevalence increasing to 40% in infertile men.
Methodology: This prospective, comparative study was conducted on 134 male patients with primary infertility who attended the outpatient clinic of Urology Department, Tanta University Hospital during the period between April 2017 to April 2019. The patients were divided into two groups: Group A (56 patients) with low testosterone level. Group B (78 patients) with normal testosterone level.
Results: In group A, the mean ± SD of testosterone level improved significantly to 2.93 ± 0.77 and 3.36 ± 0.86 after 3 and 6 months respectively (p1-value=0.001* and p2-value=0.001* respectively). In group B, the mean ± SD of testosterone level improved significantly to 6.22 ± 1.51 and 6.82 ± 2.25 after 3 and 6 months respectively (p1-value=0.026* and p2-value=0.001* respectively).
Conclusion: varicocelectomy could improve semen parameters, serum testosterone level and pregnancy rate.

**Corresponding author: E-mail: drmemomode010182@gmail.com;*

Keywords: Infertile; testosterone; varicocele; varicocelectomy.

1. INTRODUCTION

Varicocele is a dilation of the pampiniform venous plexus and the internal Spermatic vein. It is detected approximately in 15% to 20 % of the general male Population; with the prevalence increasing to 40% in infertile men [1]. The presence of varicocele has been associated with impaired testicular function, often causing abnormalities in semen parameters, including sperm count, motility, morphology and pregnancy rate. In addition, it might decrease testicular size, and impaire blood hormone levels [2]. Infertility is considered one of the main public health issues, as it affects about 15% of the couples of reproductive ages. The male factor is involved in 40% - 50% of infertility cases. [3]. The most common type of male infertility is idiopathic infertility, which is characterized by the presence of one or more abnormal semen parameters with no identifiable cause. Another common cause of male infertility is varicocele, which in a European study was found to affect 16.6% of 7.802 men referred for infertility [4]. Theories related to the negative effect of varicocele on testicular functions include testicular hyperthermia, hormonal dysfunctions, increased testicular blood flow due to venous engorgement, reflux of renal or perirenal metabolites, and hypoxia [5]. *Weiss et al.* reported impaired testosterone synthesis in patients with varicocele [6]. Other studies have suggested Leydig cell dysfunction and impaired testosterone synthesis [7]. The effect of varicocelectomy on serum testosterone level is not yet fully established. While some studies found no significant effect, others reported a normalization of the testosterone level following surgical repair of the varicocele [8-10]. Recently, Tanrikut C *et al*. reported that data are still conflicting, although the evidence shows an adverse effect of varicocele on testosterone production and the possible benefit of varicocelectomy. [11] We carried our study to assess the effect of surgical repair of varicocele on testosterone production and male infertility.

2. METHODOLOGY

We conducted this prospective research on 134 infertile men with clinical varicocele grades I, II and III who attended the outpatient of andrology and infertility clinic of Urology Department, Tanta University Hospital during the period between April 2017 to April 2019. The patients were divided into two groups: Group A (56 patients) with low testosterone level. Group B (78 patients) with normal testosterone level. The subjects were men with primary infertility, ages 20-40 years, who were not affected by diabetes and did not take medications known to elicit imbalanced androgen levels. We excluded patients with untreated bleeding disorders, active urinary tract infection (UTI), history of undescended testis, mumps orchitis and torsion testis, patients with secondary varicocele and morbid obesity. Prior to performing the study, consent letters were received from the patients which informed them of all the study procedures.

A complete medical history was obtained for each patient, and a physical examination was performed. Examination of scrotal neck for varicocele was done for these patients in the supine and upright positions using Valsalva maneuver and confirmed with color flow scrotal doppler ultrasound examination. According to Dubin and Amelar (1970) varicocele was classified into: Grade 1: varicocele felt only with valsalva maneuver, Grade 2: varicocele felt without valsalva maneuver and Grade 3: varicocele felt and seen through the scrotum.

Low ligation of the left or both spermatic veins was performed in all these patients. Semen analysis was done preoperative, 3 and 6 months later. Serum levels of total testosterone (TT), follicle stimulating hormone (FSH), prolactin and eostrogen were measured preoperative, 3 and 6 months later. Pregnancy rate among patients included in the study was evaluated one year post varicocele repair.

Statistical analysis: Statistical analysis was done by SPSS v25 (IBM Inc., Chicago, IL, USA). Numerical variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing Student's t- test and with three measures with F test. Categorical variables were presented as frequency and percentage (%) and were analysed utilizing the Chi-square test. A two tailed P value < 0.05 was considered significant.

3. RESULTS

A total of 134 infertile men with varicocele participated in the study-56 with low testosterone level and 78 with normal testosterone level. The mean ± SD patient's age was 29.77 ± 3.55 years (range 21 – 39) in the low testosterone group,

while it was 30.46 ± 5.28 years (range 20 – 40) in the normal testosterone group with no statistically significant difference between the two groups (p-value=0.395).

Regarding count, motility and abnormal forms of sperms, there was statistically significant improvement in each of the two groups but, with no statistically significant difference between the two groups. Regarding testosterone level, the degree of improvement was statistically significant different between group A and group B after 3 and 6 months (p-value =0.001* and 0.001* respectively). In group A, the mean ± SD of testosterone level improved significantly from 1.91 ± 0.20 (range 1.59 – 2.2) preoperatively to 2.93 ± 0.77 (range 2.25 – 4.9) and 3.36 ± 0.86 (range 2.25 – 4.9) after 3 and 6 months respectively (p1-value=0.001* and p2-value=0.001* respectively). In group B, the mean ± SD of testosterone level improved significantly from 5.56 ± 1.73 (range 3.5 – 8.9) to 6.22 ± 1.51 (range 3.9 – 8.8) and 6.82 ± 2.25 (range 3.2 – 11) after 3 and 6 months respectively (p1-value=0.026* and p2-value=0.001* respectively). Regarding FSH level, the degree of improvement was statistically significant different between group A and group B after 3 and 6 months postoperatively (p-value =0.001* and 0.001* respectively). In group A, the mean ± SD of FSH level decreased significantly after 3 and 6 months postoperatively (p1-value=0.001* and p2-value=0.001* respectively). In group B, the mean ± SD of FSH level decreased insignificantly after 3 and 6 months postoperatively (p1-value=0.085 and p2-value=0.065 respectively). Regarding Prolactin and Eostrogen levels, there was neither statistically significant improvement in each group nor statistically significant difference between the two groups after 3 and 6 months. Regarding pregnancy rate, the number of patients' wives who got pregnant after 1 year was 40 wives (71.4%) in group A. While, it was 58 wives (74.4%) in group B. The number of patients' wives who did not get pregnant after 1 year was 16 wives (28.6%) and 20 wives (25.6%) in group A and group B respectively. There was no statistically significant difference between the two groups (p-value=0.706).

Table 1. Testosterone level (postoperative)

Testosterone		Group A	Group B	t. test	p. value
Pre	Range	1.59 – 2.2	3.5 – 8.9	313.804	0.001*
	Mean ± S. D	1.91 ± 0.20	5.56 ± 1.73		
3 m.	Range	2.25 – 4.9	3.9 – 8.8	224.766	0.001*
	Mean ± S. D	2.93 ± 0.77	6.22 ± 1.51		
6 m.	Range	2.25 – 4.9	3.2 – 11	119.421	0.001*
	Mean ± S. D	3.36 ± 0.86	6.82 ± 2.25		
F. test		68.197	9.095		
p. value		0.001*	0.001*		
P1		0.001*	0.026*		
P2		0.001*	0.001*		
P3		0.001*	0.044*		

P1: Pre & 3 m. P2: Pre & 6 m. P3: 3m. & 6 m.

Table 2. FSH level (postoperative)

FSH		Group A	Group B	t. test	p. value
Pre	Range	10.3 – 18	2.6 – 12.5	68.541	0.001*
	Mean ± S. D	13.46 ± 1.98	7.83 ± 2.89		
3 m.	Range	7 – 13.4	2.4 – 10.7	52.314	0.001*
post	Mean ± S. D	10.47 ± 2.13	7.06 ± 2.66		
6 m.	Range	5.5 – 12.5	2.6 – 10.9	35.217	0.001*
post	Mean ± S. D	9.63 ± 1.83	7.01 ± 2.70		
F. test		57.600	2.151		
p. value		0.001*	0.119		
P1		0.001*	0.085		
P2		0.001 *	0.065		
P3		0.027*	0.901		

P1: Pre & 3 m. P2: Pre & 6 m. P3: 3m. & 6 m.

Table 3. Pregnancy rate

Pregnancy rate			Group (A)	Group (B)	Total
Succeeded		**N**	40	58	98
		%	71.4%	74.4%	73.1%
Failed		**N**	16	20	36
		%	28.6%	25.6%	26.9%
Total		**N**	56	78	134
		%	100.0%	100.0%	100.0%
Chi-square	**X2**	**0.143**			
	P-value	**0.706**			

4. DISCUSSION

Varicocele is the most common identified cause of male factor infertility [12]. Defective testosterone synthesis has been reported to be associated with varicocele [13-14] Varicocele not only has deleterious effects on the hormonal aspects of spermatogenesis but also decreases function through testicular hyperthermia, reflux of toxic metabolites and seminiferous tubular hypoxia secondary to venous stasis. Therefore, every patient will not benefit similarly from varicocelectomy [15]. The detrimental effect on spermatogenesis by varicocele is well documented, but not completely understood [16]. Nonetheless, varicocelectomy has been shown to improve semen parameters in 70% of infertile men and approximately 40% will achieve pregnancy as a result [17].

The effect of varicocelectomy on serum testosterone level is not yet fully established. While some studies found no significant effect, others reported a normalization of the testosterone level following surgical repair of the varicocele [8-10] The results of earlier studies that did not find a statistically significant rise in testosterone following varicocele repair are difficult to interpret. For example, participants in the studies by Di Bisceglie et al., Zheng et al., and Rodriguez et al.) appear to have had normal-to-above-normal baseline testosterone levels, which may have limited the ability of these studies to detect a rise in testosterone level after varicocelectomy [18-20]. Methodological differences in the way testosterone levels were obtained and measured between these studies make interpretation of the reported high baseline testosterone levels difficult to interpret as well [21].

A *2007* study by *Lee et al.* showed a post-varicocelectomy rise in testosterone compared to baseline, but the change did not reach statistical significance [22]. This likely resulted from the relatively small numbers of individuals and the very wide range of testosterone values recorded after varicocelectomy (416±358 ng/dl) [23]. Despite these difficulties of interpretation, a meta-analysis of studies published up until May 2011 concluded that a varicocele causes a disturbance of Leydig cell function resulting in decreased testosterone biosynthesis and surgical repair significantly increases testosterone levels in men with varicocele [24]. Nonetheless, this meta-analysis did not include three more recent articles, all of which found statistically significant increases in testosterone levels following varicocelectomy in men with below-normal baseline levels [23],[25-26] These studies strengthen considerably the evidence base about the positive relationship between varicocele repair and testosterone levels [21]. In the present study, there was a statistically significant improvement in sperms count, motility and abnormal forms in each group after 3 and 6 months. But there was no statistically significant difference between the two groups after 3 and 6 months regarding these parameteres. Serum testosterone levels elevated significantly in both groups, and FSH decreased significantly in group A after 3 and 6 months postoperatively, but we detected no significant change in prolactin and eostrogen in each group and between groups after 3 and 6 months postoperatively. Regarding serum testosterone and FSH levels, the degree of improvement was statistically significant different between the two groups after 3 and 6 months. Pregnancy rate improved in each group, but with no statistically significant difference between the two groups (p-value=0.706).

Li and colleagues concluded that surgical treatment of varicocele significantly increases testosterone production and improves testicular Leydig cell function. Their combined analysis

showed that mean serum testosterone levels after surgical treatment increased by 97.48 ng/dL (95% confidence interval 43.73–151.22, P = 0.0004) compared with preoperative levels [24]. These results were going on hand with the results of our study regarding testosterone level in group B (normal testosterone group). Since, Li and colleagues, meta-analysis included only infertile men with grade I, II and III varicocele, the period of follow up was at least 3 months, and the mean age of patients was (31.4 years), This explains the nearly similar results between them and our study. In another meta-analysis, Chen and colleagues compared the pre-operative and postoperative serum testosterone, eight studies and 712 patients were included. They found that, the combined analysis of seven studies discovered that the mean serum testosterone of patient's post-operation improved by 34.3 ng/dl (95% CI: 22.57–46.04, p < .00001, I^2 = 0.0%) compared with their pre-operative levels. In their subgroup analysis, testosterone improvements in the hypogonadal treated subgroup were more significant (improved by 123 ng/dl, 95% CI: 114.61–131.35, p < .00001, I2 = 37%) than in the eugonadals, or the untreated controls. In an analysis of surgery versus untreated control (three studies included), their results showed that mean testosterone among hypogonadals increased by 105.65 ng/dl (95% CI: 77.99–133.32), favouring varicocelectomy, as the differences were significant (p < .00001), however, there were insignificant differences in eugonadals. They concluded that, varicocelectomy significantly improved testosterone in hypogonadal men with subfertility. Surgical treatment of varicocele might have a benefit of maintaining healthy androgen levels in subfertile men [25]. These results were going on hand with the results of our study regarding testosterone level in both groups, and this because the inclusion and exclusion criteria of the studies of Chen and colleagues' meta-analysis were more or less similar to those of our study. In another study, Cayan and colleagues retrospectively evaluated 78 infertile patients who underwent microsurgical inguinal varicocelectomy, with documented serum FSH, testosterone, free testosterone levels, sperm concentration and sperm motility before and after surgery. In addition, serum hormonal values of 10 fertile men in whom physical examinations and Doppler ultrasonography revealed no evidence of varicocele were recorded and used as a control group. They concluded that varicocelectomy promotes Sertoli and Leydig cell function. The significant increase in serum free testosterone level results in a significant improvement in sperm concentration and motility [26]. Close to our study, they found that serum testosterone levels increased significantly from 5.63 (1.40) to 8.37 (2.2) ng/mL (P=0.01), the mean (sd) serum FSH levels of all patients significantly decreased from 15.21 (3.34) before surgery to 10.82 (2.93) mIU/mL afterward (P=0.01). Also, a significant difference in sperm motility was found before and after surgery of all patients (P < 0.01), and this is because the inclusion and exclusion criteria were more or less the same as in our study. In contrast to our study, they found that the difference in sperm count was insignificant (P > 0.05), and this is due to the difference in the number of patients and the type of procedure used.

5. CONCLUSION

Varicocelectomy could improve semen parameters (*count, motility and abnormal forms*) and increase the serum testosterone level, and this increase is statistically significant. However, pregnancy rate improved in group B (74.4%) more than group A (71.4%) but, still comparable with insignificant statistical difference.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Witt MA and Lipshultz LI. Varicocele: A progressive or static lesion? urology. 1993;42:541-543.
2. Vazquez-Levin Friedmann P, Goldberg SI, Medley NE, Nagler HM. Response of routine semen analysis and critical assessment of sperm morphology by Kuger classification to therapeutic

varicocelectomy, J Urol, 1997;158(5): 1804-7.

3. Speroff L, Glass RH, Kase NG. Infertility In: Clinical Gynecologic Endocrinology and Infertility (6th Ed). Baltimore USA: Lippincott Williams & Wilkins. 1999;201-246.
4. Nieschlag E. Classification of andrological disorders In: Nieschlag E, Behre HM, eds. Andrology. Berlin, Heildelberg, New York: Spriger-Verlag. 1997;79-83.
5. Romeo C, Arrigo T, Impellizzeri P, Manganaro A, Antonuccio P, Di Pasquale G, Messina MF, Marseglia L, Formica I, Zuccarello B. Altered serum inhibin b levels in adolescents with varicocele. Journal of pediatric surgery. 2007; 42(2):390-394.
6. Weiss DB, Rodriguez-rigau LJ, Smith KD, Steinberger E. Leydig Cell Function in Oligospermicmen with Varicocele. The Journal of urology. 1978;120(4):427-430.
7. Della EM, Fortuna FF, Gerevini G, Lania C, Grasso M. Evaluation of FSH and Leydig cells function in patients with varicocele. Archivio italiano di urologia, andrologia: organo ufficiale [di] Societa italiana di ecografia urologica e nefrologica. 2002;74(3):152-156.
8. Su LM, Goldstein M, Schlegel PN. The effect of varicocelectomy on serum testosterone levels in infertile men with varicoceles. Journal of Urology. 1995; 154(5):1752–1755.
9. Gat Y, Gornish M, Belenky A, Bachar GN. Elevation of serum testosterone and free testosterone after embolization of the internal spermatic vein for the treatment of varicocele in infertile men, Human Reproduction. 2004;19(10):2303– 2306.
10. Ozden C, Ozdal OL, Bulut S, Guzel O, Koyuncu HH, Memis A. Effect of varicocelectomy on serum inhibin B levels in infertile patients with varicocele. Scandinavian journal of urology and nephrology. 2008;42(5):441-443.
11. Tanrikut C and Goldstein M. Varicocele repair for treatment of androgen deficiency. Curr. Opin. Urol. 2010;20:500–2.
12. Marc G. Surgical Management of Male Infertility. Campbells-Walsh Urology. 11th ed. Elsevier Publishing. 2011;580-611.
13. Ando S, Giacchetto C, Colpi G, et al. Plasma levels of 17-OH progesterone and testosterone in patients with varicoceles. Acta Endocrinol. 1983;102:463–9.
14. Takeyama M, Honjoh M, Kodama M, et al. Testicular steroids in spermatic and peripheral veins after single injection of HCG in patients with varicocele. Arch Androl. 1990;24:207–13.
15. Nagler HM, Luntz RK, Martinis FG. Varicocele. In Lipshultz LI, Howards SS, eds. Infertility in the Male, 3rd edn, St Louis, Missouri: Mosby Year Book. 1997;336–59.
16. Choi WS and Kim SW. Current issues in varicocele management: A Review. World J Mens Health. 2013;31:12-20.
17. Marmar JL, Agarwal A, Prabakaran S, et al. Reassessing the value of varicocelectomy as a treatment for male subfertility with a new meta-analysis. Fertil Steril. 2007;88:639-48.
18. Di Bisceglie C, Bertagna A, Baldi M, et al. Varicocele sclerotherapy improves serum inhibin B levels and seminal parameters. Int J Androl. 2007;30:531-536.
19. Zheng YQ, Gao X, Li ZJ, Yu YL, Zhang ZG, Li W. Efficacy of bilateral and left varicocelectomy in infertile men with left clinical and right subclinical varicoceles: a comparative study. Urology. 2009; 73(6):1236-1240.
20. Rodriguez-Rigau LJ, Weiss DR, Zukerman Z, et al. A possible mechanism for the detrimental effect of varicocele on testicular function in man. Fertil Steril. 2009;30:577–585.
21. Fisch H and Hyun G. Varicocele repair for low testosterone. Curr Opin Urol. 2012; 22:495-498.
22. Lee RK, Li PS, Goldstein M. Simultaneous vasectomy and varicocelectomy: indications and technique. Urology. 2007; 70:362-365.
23. Sathya Srini V and Belur Veerachari S (): Does varicocelectomy improve gonadal function in men with hypogonadism and infertility? Analysis of a prospective study. International Journal of Endocrinology. 916380.
24. Li F, Yue H, Yamaguchi K, Okada K, Matsushita K, et al. Effect of surgical repair on testosterone production in infertile men with varicocele: a meta-analysis. Int J Urol. 2012;19:149-54.
25. Chen X, Yang D, Lin G, Bao J, Wang J, Tan W. Efficacy of varicocelectomy in the treatment of hypogonadism in subfertile males with clinical varicocele: A meta-analysis. Andrologia. 2017;49(10): e12778.
26. Cayan S, Kadioglu A, Orhan I, Kandirali E, Tefekli A, Tellaloglu S. The effect of

microsurgical varicocelectomy on serum follicle stimulating hormone, testosterone and free testosterone levels in infertile men with varicocele. BJU International. 1999;84(9):1046 -1049.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/70852