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## Research Article

# Factors predicting early improvement in semen parameters following varicocele surgery

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## ABSTRACT

**Background:** Varicocelectomy does not improve semen parameters and pregnancy rates in all cases. Various studies have been done to find out factors which predict better outcomes of varicocelectomy so that only such patients may be selected to undergo the surgery. The present study is an attempt to identify such factors by prospective cohort method.

**Methods:** A prospective cohort study was conducted on 25 patients undergoing varicocelectomy for infertility at St John medical college hospital, Bangalore from 01-06-2012 to 31-05-2013. Clinical data, semen analysis, scrotal imaging and hormonal assays were done and postoperatively semen analysis was done after three months. The data was analysed to find out predicting factors for improvement of semen parameters.

**Results:** Twenty five patients underwent varicocele surgery, all of them showed improvement of semen parameters. Fifteen of them had more than 50% of improvement. Serum FSH and testosterone levels were found to be predictive of semen parameter improvement.

**Conclusions:** Preoperative low serum FSH and high testosterone concentration were factors predicting early improvement in semen parameters following varicocele surgery in infertile males.

**Keywords:** Follicle stimulating hormone, Infertility, Scrotum, Semen, Testosterone, Testis, Varicocele, Varicocelectomy

## INTRODUCTION

A varicocele can be defined as an abnormal tortuosity and dilation of the veins of the pampiniform plexus. In the general population of healthy males the overall incidence of varicocele (all grades) is 10% to 15%.<sup>1-4</sup> Approximately 30-50% of males with primary infertility have a varicocele.<sup>5-8</sup> There is a clear association between varicocele, infertility and testicular growth arrest.<sup>10-12</sup> It is also known that varicocelectomy can reverse testicular growth arrest.<sup>13-16</sup> Not all patients with varicocele will improve following surgery.<sup>16</sup>

Recent literature reveals much interest in identifying predictive indicators to assess which male patients would most benefit from varicocele repair.

To evaluate improvement of seminal characteristics in the patient by low ligation (Inguinal or subinguinal approach), we investigated factors predicting early improvement in semen parameters following varicocele surgery in male patients with infertility due to varicocele using logistic regression analysis with age, duration of infertility, testicular volume, pampiniform veins diameter, laterality of varicocele, pre-operative serum hormone levels and pre-operative seminal parameters.

## METHODS

Prospective observational cohort study conducted on 25 prospective patients undergoing varicocele surgery for infertility at St. John's medical college hospital, Bangalore from 01-06-2012 to 31-05-2013.

### ***Inclusion criteria***

- A. A male patient presenting with infertility due to varicocele only who gives consent for participating in the study
- B. An infertile adult, when all of following condition are met:
  1. The couple has known infertility (failure to initiate a pregnancy after at least one year of unprotected coitus at a normal frequency with adequate technique).
  2. The female partner has known fertility or a potentially treatable cause of fertility.
  3. The varicocele is palpable on physical examination, or if suspected, the varicocele is corroborated by ultrasound examination.
  4. The male partner has abnormal semen analysis.

### ***Exclusion criteria***

Adult fertile men with incidentally detected varicocele, adolescent varicocele, persons meeting inclusion criteria but not willing to give informed consent, Patients using any form of contraception during the study, Patients who had/ have been taking medications for infertility, Patients who have taken in the past/taking medications which affect semen parameters.

### ***Method of collection of data***

Twenty five patients were included in the study, all of whom fulfilled protocol requirements. Patients underwent standard evaluation consisting of clinical examination, two semen analyses, scrotal ultrasonography and hormonal evaluation. The following parameters were recorded:

1. Age of patient,
2. Duration of infertility,
3. History of smoking,
4. History of drug intake,
5. Varicocele laterality,
6. Grade of varicocele - diagnostic classification of the WHO-1993
  - i. Grade I - palpable only during the Valsalva manoeuvre,
  - ii. Grade II - palpable without the Valsalva manoeuvre,
  - iii. Grade III - visible without palpation,

7. Two semen analysis reports at least 2 months apart - mean value was adopted,
8. Testicular volume (by ultrasonography),
9. Pampiniform Plexus vein diameter (by Ultrasonography),
10. Preoperative serum FSH, LH and Testosterone levels.

Twenty five consecutive cases underwent varicocele surgery (subinguinal approach) for infertility after giving informed consent and fulfilling criteria mentioned above. Patients were advised not to use any form of contraception and abstain from smoking for the duration of the study (as smoking is an independent risk factor for infertility). The patients were reassessed between 90 and 120 days post-operatively with the following:

1. History to confirm that patient is not smoking,
2. Clinical examination to confirm absence of genital infection,
3. Two Semen analyses were done - mean value was adopted.

Patients, who had more than 50% improvement in sperm count postoperatively, as compared to preoperative sperm count, were considered as responders.

### ***Statistical analysis***

Data are presented as means  $\pm$  Standard Deviation (SD) or percentages. All statistical analysis was performed using SPSS V18.0 (SPSS Inc., Chicago, IL). The categorical variables were compared between the responders and non-responders groups using Chi-square test and continuous variables by Mann-Whitney U test. Factors predicting early improvement in semen parameters following varicocele surgery were assessed using logistic regression analysis. A  $P < 0.05$  was considered statistically significant.

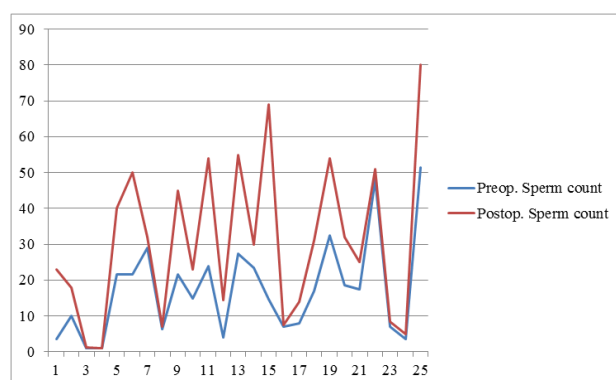
## **RESULTS**

Twenty five patients met the inclusion criteria and underwent subinguinal varicocele ligation and were followed up as per protocol.

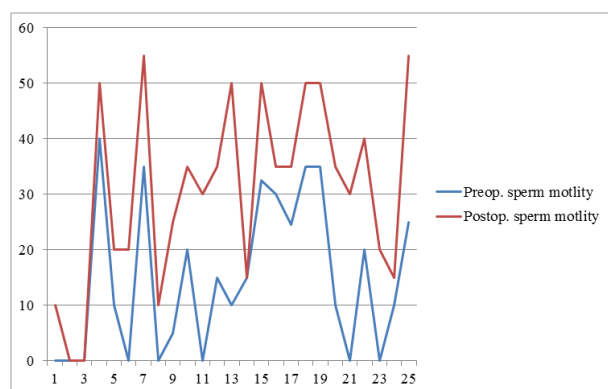
The most frequent age group analyzed in our study was between 31-40 years of age (56%). Mean age of patients studied was 31.92 yrs. with a range of 21-46 years of age. Twenty one (84%) patient had duration of infertility less than 5 year. Mean duration of infertility was 4.66 years with a range of 1 to 28 years. Eighteen patients (72%) had bilateral varicocele while 7 patients (28%) had left side varicocele. Out of 25 patients only 18 patients had right side varicocele among which 4 patients had grade I

varicocele, 14 patients had grade II varicocele and, none of the patient had grade III varicocele. All the patients had left side varicocele among which none had grade I varicocele, 22 patients had grade II varicocele while only 3 patients had grade III varicocele. On right side maximum testicular volume was 16 ml, minimum 7 ml, median 11 ml and mean was  $11.12 \pm 2.16$  ml. While on the left side maximum testicular volume was 14.1 ml, minimum 6 ml, median 11.2 ml and mean was  $10.61 \pm 2.30$  ml. On right side maximum pampiniform vein diameter was 4 mm; minimum 1.6 mm, median 3.2 mm and mean was  $2.87 \pm 0.80$  mm. While on the left side maximum pampiniform vein diameter was 4 mm, minimum 3.3 mm, median 3.7mm and mean was  $3.65 \pm 0.22$  mm.

After surgery, sperm concentration significantly increased from  $17.38 \pm 13.38$  to  $30.83 \pm 21.90$  and sperm motility significantly increased from  $14.88 \pm 13.84$  to  $30.80 \pm 16.88$  (Figure 1, 2).



**Figure 1: Preoperative and postoperative sperm count.**



**Figure 2: Preoperative and postoperative sperm motility.**

Fifteen patients (60%) responded to treatment (varicocelectomy) i. e. had more than 50% improvement in sperm count after surgery, while 10 patients (40%) had not responded to treatment. Table 1 shows comparison of various variables in responders and nonresponders. On comparing the various variables in responders and

nonresponders, significant differences were seen in preoperative serum FSH ( $P = 0.001$ ), testosterone ( $P = 0.027$ ) and postoperative sperm concentration ( $P = 0.006$ ). In univariate analysis, preoperative serum FSH ( $OR=0.41$ ; 95% CI: 0.21-0.81) and testosterone ( $OR=2.02$ ; 95% CI: 1.05-3.88) were the factors predicting improvement in semen parameter after varicocele surgery (Table 2). Multivariate analysis could not be done because of small sample size.

**Table 1: Comparison of various variables in responders and nonresponders.**

Variables	Responders (n=15)	Nonresponders (n=10)	P value
Age	$31.9 \pm 5.52$	$31.9 \pm 3.67$	0.82
Left testicle vol.	$12.7 \pm 8.2$	$10.1 \pm 2.0$	0.22
Right testicle vol.	$11.5 \pm 2.5$	$10.6 \pm 1.5$	0.39
Bilateral varicocelectomy	11 (61%)	7 (39%)	0.86
Left varicocelectomy	4 (57%)	3 (43%)	
Duration of infertility	$6.07 \pm 6.81$	$2.55 \pm 1.12$	0.066
FSH (mIU/ml)	$6.79 \pm 2.61$	$11.62 \pm 1.73$	0.001*
LH (mIU/ml)	$5.85 \pm 2.80$	$4.45 \pm 3.30$	0.202
Testosterone (ng/ml)	$5.19 \pm 1.52$	$3.39 \pm 1.88$	0.027*
Pre op. sperm conc. ( $\times 10^6 \text{ ml}^{-1}$ )	$19.4 \pm 12.1$	$14.4 \pm 15.2$	0.371
Post op. sperm conc. ( $\times 10^6 \text{ ml}^{-1}$ )	$40.2 \pm 20.2$	$16.8 \pm 16.7$	0.006*
Pre op. sperm motility (%)	$14.8 \pm 13.1$	$15.0 \pm 15.6$	0.932
Post op. sperm motility (%)	$33.3 \pm 16.2$	$27.0 \pm 18.0$	0.370

**Table 2: Predictors of sperm concentration improvement.**

Variables	Odds ratio (95% CI)	P value
Age	1.00 (0.84-1.19)	0.986
Left testicle vol.	1.17 (0.83-1.65)	0.374
Right testicle vol.	1.24 (0.82-1.86)	0.308
Duration of infertility	1.63 (0.88-3.01)	0.120
FSH ( $\text{mIU ml}^{-1}$ )	0.41 (0.21-0.81)	0.011*
LH ( $\text{mIU ml}^{-1}$ )	1.19 (0.88-1.62)	0.259
Testosterone ( $\text{ng ml}^{-1}$ )	2.02 (1.05-3.88)	0.034*
Pre op. sperm conc. ( $\times 10^6 \text{ ml}^{-1}$ )	1.04 (0.91-1.04)	0.36
Pre op. sperm motility (%)	0.99 (0.94-1.06)	0.971

## DISCUSSION

Varicocelectomy has been reported to improve the semen profile significantly in the majority of patients, and to result in a slight decrease in the frequency of aneuploidy in some chromosomes.<sup>17</sup> Several attempts have been

made to predict which varicocele patients are likely to benefit from varicocele repair in terms of an improved seminogram; such prediction has proved to be very difficult.

Marks JL and co-workers in 1986, studied 130 men presenting with oligospermia and varicocele, who were treated surgically and followed for 1 year for pregnancy rate. A significant association with improved pregnancy rates was demonstrated in patient displaying a lack of testicular atrophy, preoperative sperm density of 50 million or more sperm per ejaculate, preoperative sperm motility of 60 per cent or more and FSH value of less than 300 ng/ml. Furthermore, no significant improvement in pregnancy rate was observed in association with change in varicocele size and laterality, sperm morphology or sperm forward progression.<sup>18</sup> Yoshida et al., 2000, in a study to find out predictive indicators of successful varicocele repair in 168 infertile Japanese males, studied 11 indicators viz. age at marriage, duration of infertility, varicocele grade, seminal volume, sperm count, percentage of motile sperm, serum Follicular Stimulating Hormone (FSH), Luteinizing Hormone (LH), prolactin (PRL), and Testosterone levels. No associations were observed between outcome and mean age at marriage, duration of infertility, varicocele grade, seminal volume, serum PRL and testosterone concentrations but testicular volume, sperm count, percentage of motile sperm, and serum FSH and LH concentration were significantly associated with the outcome. Testicular volume and serum FSH were identified as independent factors.<sup>19</sup> The association of age has been studied by many groups and observations vary. Kamaluddin et al. in 2011 found that individuals aged, 25 years demonstrated the greatest improvement in all semen parameters studied.<sup>20</sup> However numerous studies have not shown any such association. Ishikawa and Fujisawa indicated that even in men older than 40 years of age, sperm concentration and motility increased significantly after varicocele ligation.<sup>21</sup> Zini et al. found similar sperm parameters and spontaneous pregnancy rates following varicocelectomy in couples with advanced paternal age ( $\geq 40$  years) compared with younger couples.<sup>22</sup> Reşorlu et al. and Liguori et al. reported no significant alterations in sperm concentration and motility rates after ligation between the different age groups.<sup>23,24</sup> In our study, age was not a predictor in univariate analysis.

Zorba UO et al., 2008, studied the effect of infertility duration on post varicocelectomy sperm counts and pregnancy rates. The medical records of 574 patients with palpable varicocele were retrospectively reviewed. According to the duration of unprotected intercourse without conception (infertility period), the patients were divided into 4 groups: group 1, 0-3 years ( $n = 353$ ); group 2, 3-6 years ( $n = 132$ ); group 3, 6-9 years ( $n = 47$ ); and group 4,  $>9$  years ( $n = 42$ ). The preoperative and postoperative Total Motile sperm Counts (TMCs) and postoperative pregnancy rates among these groups were

compared statistically, including multivariate analysis. The greatest pregnancy rate was achieved in group 1 (43.9%) and the lowest pregnancy rate in group 4 (31.7%;  $P < 0.05$ ). The mean postoperative TMC in these groups was  $34.9 \pm 3.5 \times 10(6)$  and  $24.6 \pm 1.7 \times 10(6)$ , the only statistically significant difference in terms of postoperative TMC and pregnancy among the 4 groups. They concluded that the pregnancy rates and TMCs after varicocelectomy correlate negatively with the infertility period.<sup>26</sup> Present study didn't find any such association.

The varicocele grade, laterality and testicular volume have been assessed in various studies and give conflicting results. Steckel et al. observed improved sperm concentration and motility in those with higher grade.<sup>26</sup> The testicular volume may indicate testicular atrophy, hence reduced volume is not associated with improvement in semen characteristics as observed by Uygur et al.<sup>27</sup> and Merks et al.<sup>18</sup> Scherr & Goldstein (1999) reported that bilateral varicocele repair resulted in significantly greater improvement in post-operative seminal parameters than unilateral repair in patients with high grade varicocele<sup>28</sup> but our study indicated no significant difference.

Few studies have analysed the prediction of preoperative sperm count and sperm motility on improvement of semen parameters. Yoshida et al. found some association of sperm count and motility with outcome of surgery.<sup>19</sup> Matkov et al., 2000, studied 110 cases retrospectively and found that men with moderate oligoasthenospermia [Total Motile sperm Count (TMC)  $>5$  million] had significantly better seminal improvement following varicocelectomy and concluded that patients with TM  $<5$  million may be better initial candidates for IVF.<sup>29</sup> Kamal et al., 2000, in their retrospective study of 159 infertile couples found that significantly higher spontaneous pregnancy rates were observed in couples in whom the man's initial sperm concentration was greater than or equal to 5 million sperm per ml compared to those in whom the man's initial sperm concentration was less than 5 million sperm per ml (61% vs. 8%, respectively).<sup>31</sup> Present study didn't have much patients with severe oligospermia hence such association couldn't be studied.

Varicocele is associated with endocrine abnormalities involving LH, FSH, Testosterone.<sup>31-33</sup> Sertoli cell dysfunction has been observed in varicocele.<sup>34</sup> Varicocele may be a factor in progressive deterioration of testis function (both spermatogenesis and steroidogenesis). High serum FSH and low serum testosterone imply poor testis function and vice versa.<sup>33</sup> Yoshida et al. observed that serum FSH  $<11.7$  mIU/ml preoperatively is an independent predictive factor for sperm improvement following varicocele surgery.<sup>19</sup> Kondo Y et al. also found that low serum FSH and high testosterone are significant factors predicting the improvement of semen characteristics in their study of 97 patients.<sup>35</sup> In our study we have found that preoperative low FSH and high testosterone were factors predicting early improvement in

semen parameters implying that patients with normal Sertoli cell function benefit from varicocele repair.

## CONCLUSION

The present study demonstrated that varicocelectomy results in improvement in sperm concentration and motility. Results also showed that preoperative low serum FSH and high testosterone concentration were factors predicting early improvement in semen parameters following varicocele surgery in infertile males. Age, testicular volume, pampiniform vein diameter, duration of infertility, preoperative serum LH level, preoperative sperm count and motility are not factors predicting early improvement in semen parameter following varicocele surgery according to this study. Studies with large sample size are required for further clarification.

## Abbreviations

et al - and others, FSH - Follicle stimulating hormone, LH - Luteinizing hormone, mIU - milli international units, ml - milliliter, ng - nanogram, TM - total motile sperm count

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