

Original article

Spontaneous Pregnancy Outcome after Surgical Repair of Clinically Palpable Varicocele in Young Men with Abnormal Semen Analysis

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ABSTRACT

Objective: The beneficial effect of varicocele repair in male infertility remains unresolved. The aim of this study was to identify the benefit from varicocele treatment based on pregnancy rate rather than improvement of semen quality.

Subjects and Methods: This study included 141 infertile men with varicocele detected by clinical examination and confirmed by venous reflux on continuous wave Doppler ultrasonography (US). Measurement of Body Mass Index (BMI) and hormonal assays were performed in all patients. A total of 233 sub-inguinal varicocele repairs were done. Couples were followed up with semen analysis and pregnancy detection for 6, 12 and 18 months. Statistical analysis was performed using the chi-square, t-test and Mann-Whitney test where appropriate ($p < 0.05$ accepted as statistically significant).

Results: The spontaneous pregnancy rate was significantly greater in men with low or normal BMI. There were statistically significant differences between postoperative mean sperm count (64.7 ± 6.8 and 10.5 ± 1.8 million/ml) and progressive motility (38.3 ± 2.4 and $17.7 \pm 1.8\%$) for spontaneous pregnancy and non-pregnancy, respectively. There were also significant changes from pre- to postoperative mean sperm concentration (21.5 ± 2.1 and 64.7 ± 3.8 million/ml), progressive motility (12.9 ± 1.8 and $31.7 \pm 1.4\%$) and normal morphology (54 ± 1.3 and $81.3 \pm 4.6\%$) in the spontaneous pregnancy cohort. Comparing pre- and postoperative serum hormone levels, FSH and prolactin decreased significantly in spontaneous pregnancy (6.57 ± 0.65 to 4.6 ± 0.53 IU/L and 166.2 ± 11.8 to 149.3 ± 10.4 pmol/L, respectively) and increased in non-pregnancy (9.05 ± 0.71 IU/L and 187.8 ± 13.3 pmol/L, respectively).

Conclusion: Spontaneous pregnancy after sub-inguinal varicocelectomy is significantly affected by BMI, sperm concentration, progressive motility and morphology. The decrease of FSH may predict the spontaneous pregnancy outcome.

Key Words: Male infertility, Pregnancy, Varicocelectomy, Semen

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INTRODUCTION

Infertility affects 10-15% of couples and in 30-40% of cases both partners have impaired reproductive function, with male infertility contributing to nearly 50% of cases¹. Varicocele is the most common surgically correctable disorder and the most prevalent abnormal physical finding in infertile men, with prevalence up to 41% of men with primary infertility and 45-81% of men with secondary infertility^{2,3}. Varicocele is often, but not always, associated with impaired fertility. Even men with undisturbed sperm function can show latent hypogonadism⁴.

Although varicocele repair has been extensively practiced over several decades in cases of male infertility, their beneficial effect on male fertility remains unresolved. Numerous conflicting reports on the outcome of varicocele treatment have been published, with many studies reporting improvements in pregnancy rates and semen characteristics³, while others reported no benefit⁵.

There is a need for reproducible criteria to identify men who will benefit from varicocele treatment. In this study the spontaneous pregnancy rate in relation to the baseline clinical characteristics and semen parameters were used to identify men who will benefit from varicocele treatment.

PATIENTS AND METHODS

Study design

This prospective study was conducted between August 2007 and January 2010. The study received ethical committee approval and informed consent was obtained from all patients prior to enrollment. After initial assessment of 334 patients and exclusion of 193, 233 varicocele repairs were performed in 141 men, with 36 being left-sided, 13 right-sided and 92 bilateral.

Inclusion criteria

Married, healthy men 18 to 40 years of age with infertility after more than one year of unprotected intercourse, clinically palpable unilateral or bilateral varicoceles (grades I to III) and impaired semen quality (at least one of the characteristics: Sperm concentration less than 15 million/ml, progressively motile sperm less than 50%, or morphologically normal sperm less than 30%) were considered eligible for the study.

Exclusion criteria

The reasons for exclusion in 193 patients were subclinical varicocele (21), normal semen (11), azoospermia (17), atrophic testicles (3), chronic medical diseases (9), occupational heat exposure (6), smoking (34), female partner >35 years old (19), female factor infertility (23), unstable marriage (7), refusal to undergo surgery (12), additional infertility causes (24), cryptorchidism (4) and previous scrotal surgery (3).

Evaluation

The varicocele was diagnosed by examination of the patient in the standing position, its size was determined by visual inspection and palpation and venous reflux was confirmed by Continuous Wave (CW) Doppler ultrasonography (US). All varicoceles were graded according to the Dubin grading system (I-III)¹⁶.

Hormonal assays were performed in all patients, including serum prolactin, thyroid stimulating hormone, Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), testosterone and estradiol.

All patients underwent two semen analyses preoperatively within a three month baseline period, after 3-5 days of sexual abstinence. Patients were

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instructed to avoid using any medications that might affect their semen quality or fertility throughout the baseline and study periods. Semen analyses were performed according to WHO guidelines.

Body Mass Index (BMI) or Quetelet index was calculated for each patient. BMI of less than 18.5 kg/m² was regarded as underweight, 18.5 to 24.9 as normal, 25-29.9 as overweight, 30-34.9 as obese class I, 35-39.9 as obese class II and above 40 as obese class III.

Patients underwent sub-inguinal varicocelectomy within one month following the last baseline semen analysis. Patients were followed for 18 month after the date of surgery. Any pregnancy that occurred during the study period was documented. Semen analysis was performed at 6, 12 and 18 month postoperatively, using the same laboratory to eliminate inter-laboratory variation. All participants were assessed for adverse events throughout the follow-up period, physical examination and scrotal ultrasound to assess varicocele recurrence, hydrocele formation and testicular size. All patients received a 6-12 month course of medical supplementation with ProXeed® Plus containing L-carnitine fumarate, acetyl L-carnitine, fructose, citric acid, selenium, coenzyme Q10, vitamin C, zinc, folic acid and vitamin B12 (Sigma-Tau Health Science International BV Groenewoudsedijk, Netherlands).

Exclusion of female factor infertility was done by a gynecologist, including full menstrual and obstetric history, mid-luteal serum progesterone as a test of ovulation with cut-off > 10 ng/ml and hysterosalpingography too exclude tubal obstruction.

The primary outcome measure was spontaneous pregnancy during the 18-month period after the surgical intervention. The secondary outcome measure was improvement in semen parameters.

Statistical analysis

Statistical analysis was performed using SPSS v.19.0 software (Statistical Package for Social Sciences, SPSS, Chicago, IL, USA). All values are expressed as mean±Standard Deviation (SD). Univariate analysis (chi-square test) was performed to detect any significant association between the occurrence of spontaneous pregnancy and the patient's age, age of the wife, varicocele side, varicocele grade, infertility type or BMI. Linear regression was performed to identify any independent association of the studied co-variables with the occurrence of spontaneous pregnancy. Student's t-test was used to compare continuous numerical values ($p \leq 0.05$ was considered statistically significant).

RESULTS

Baseline patient characteristics relative to the occurrence of spontaneous pregnancy are shown in (Table 1). Spontaneous pregnancy was significantly associated only with the BMI of the participant ($p < 0.001$) (Table 1).

Spontaneous pregnancy had a significant relationship to the mean postoperative sperm count and progressive motility but not sperm morphology or semen volume (Table 2).

Comparison of pre- and postoperative sperm parameters showed a significant increase in mean sperm concentration, progressive motility and normal morphology in men whose wives achieved pregnancy (Table 3).

DISCUSSION

Varicocele is a progressive lesion that leads to primary and secondary infertility because of progressive damage to the testicular structures⁶. Hammoud et al⁷ reported that men with untreated varicocele who previously had fathered children had progressive

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Table 1: Spontaneous pregnancy in relation to baseline patient characteristics

Parameter	N (%)	Pregnancy achieved (n= 88)	No pregnancy achieved (n= 53)	P-Value
Patient's age (years)		26.6 ± 8.1	27.4 ± 7.3	0.53
Wife's age		21.2 ± 1.2	23.4 ± 2.6	0.71
<u>Varicocele side</u>				0.77
- Left	36	21 (58.3)	15 (41.7)	
- Right	13	9 (69.2)	4 (30.8)	
- Bilateral	92	58 (63)	34 (37)	
<u>Infertility type</u>				0.66
- Primary	98	60 (61.2)	38 (38.8)	
- Secondary	43	28 (65.1)	15 (34.9)	
<u>Varicocele grade</u>				0.12
- Grade I	38	27 (71.1)	11 (28.9)	
- Grade II	77	49 (63.6)	28 (36.4)	
- Grade III	26	12 (46.2)	14 (53.8)	
<u>Body mass index</u>				<0.001
- Data missing	3	2	1	
- Underweight	15	10 (66.7)	5 (33.3)	
- Normal	36	24 (66.7)	12 (33.3)	
- Overweight	42	25 (59.5)	17 (40.5)	
- Obese Class I	23	16 (69.6)	7 (30.4)	
- Obese Class II	14	7 (50)	7 (50)	
- Obese Class III	8	4 (50)	4 (50)	

N = Number, % = Percentage

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Table 2: Spontaneous pregnancy in relation to postoperative semen parameters

Semen parameter	Pregnancy achieved	No pregnancy achieved	P-Value
Concentration ($10^6/ml$)	64.7 ± 6.8	10.5 ± 1.8	<0.001
Motility (progressive)	38.3 ± 2.4	17.7 ± 1.8	<0.001
Morphology (normal)	58.2 ± 7.9	55.0 ± 10.2	0.35
Volume (ml)	3.8 ± 1.2	2.8 ± 1.5	0.39

deterioration of their sperm parameters. Cozzolino and Lipshultz⁸ reported that some men with varicocele, a normal sperm count and normal testicular volume will probably develop impaired testicular function in the future. It is necessary to identify and treat asymptomatic patients with decreased hormonal function as early as possible because it is not clear which men with varicocele will develop impaired fertility. The effect of varicocele repair on pregnancy outcome and semen characteristics has been reported in the literature, but most studies did not provide enough data to draw any valid conclusions³ and further studies are required to provide more information on this topic⁴.

The current study attempted to ensure greater homogeneity and comparability of baseline characteristics to better identify and quantify the effect of each variable on the outcome. The study was limited to males between 18 and 40 years old and females younger than 35 years to eliminate age as a confounder. All patients received postoperative supplementation with ProXeed® Plus for 6-12 months, which is given routinely to improve semen quality in many centers. The treatment of all patients eliminated possible bias due to the effect of ProXeed® Plus.

In this study, the mean age of men whose wives did or did not achieve spontaneous pregnancy was 26.6 and 27.4 years, respectively

(no statistically significant difference), comparable to the mean ages of 22, 28.4 and 34.9 years, respectively, reported by Bach et al⁹, Abdel-Meguid et al¹⁰ and Baazeem et al¹¹. The mean age of the wives who did or did not achieve spontaneous pregnancy was 21.2 and 23.4 years, respectively (not statistically significant), comparable to the mean ages of 25.8 and 33.1 years, respectively, in the studies of Abdel-Meguid et al¹⁰ and Baazeem et al¹¹.

Baazeem et al¹¹ reported spontaneous pregnancy rates of 48% for bilateral and 31% for unilateral varicocelectomy, with no statistically significant difference. In our study, the spontaneous pregnancy rates were not significantly different between unilateral and bilateral varicocele, or between left-sided, right-sided and bilateral varicocelectomy. There was no statistically significant difference between varicocele grades in our study, similar to the finding by Abdel-Meguid et al¹⁰.

Jensen et al¹² concluded that sperm quality was poorer in obese men, with lower sperm count and fewer progressively motile sperms, possibly because an excess of fat affects the metabolism of sex hormones and disrupts sperm production by overheating. Du Plessis et al¹³ concluded that obesity is associated with a higher incidence of male factor infertility by causing sleep apnea, reduced inhibin B and androgen levels accompanied by elevated estrogen levels and increased scrotal temperature. In our

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Table 3: Spontaneous pregnancy in relation to pre- and postoperative semen parameters

	Pregnancy			Pregnancy		
	Baseline	Follow-up	P-Value	Baseline	Follow-up	P-Value
Concentration (10⁶/ml)	21.5±2.1	64.7±3.8	0.000**	6.9±1.2	10.5±1.8	0.390**
Motility (Progressive)	12.9±1.8	31.7±1.4	0.000**	15.9±1.9	17.7±1.8	0.500**
Morphology (Normal)	54±1.3	81.3±4.6	0.013**	53.5±2.6	52.1±2.3	0.896**
Volume (ml)	2.9±0.9	3.4±1.2	0.616**	2.8±0.8	3.0±1.1	0.489**

Table 4: Spontaneous pregnancy in relation to hormone levels

	Baseline	Pregnancy +	Pregnancy -	P-Value (Mann-Whitney test)
FSH (IU/L)	6.57 ± 0.65	4.6 ± 0.53	9.05 ± 0.71	0.023
LH (IU/L)	5.8 ± 0.66	5.9 ± 0.86	5.7 ± 0.9	0.387
Testosterone (nmol/L)	4.1 ± 0.36	4.2 ± 0.32	4.0 ± 0.22	0.294
Prolactin (pmol/L)	166.2 ± 11.8	149.3 ± 10.4	187.8 ± 13.3	0.026

FSH = Follicle stimulating hormone, LH = Luteinizing hormone

study there was a statistically significant difference in spontaneous pregnancy rates related to BMI (Table 1).

Bazeem et al¹¹ reported significant changes in sperm concentration and motility, but not in volume and morphology, after unilateral varicocelectomy. They also reported significant changes in sperm concentration, motility and morphology, but not in volume, after bilateral varicocelectomy. Abdel-Meguid et al¹⁰ reported significant changes in sperm count,

motility and morphology in men whose wives achieved natural pregnancy, but no significant change in semen parameters in men whose wives did not achieve natural pregnancy. Our study showed significant changes from baseline to follow-up in sperm concentration, progressive motility and normal morphology only in men whose wives achieved natural pregnancy (Table 3). Postoperative sperm concentration and progressive motility (but not normal morphology and semen

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volume) were significantly greater in men whose wives achieved natural pregnancy compared to those who did not (Table 2).

Schreiber et al¹⁴ reported a negative correlation between FSH level and sperm count, Bach et al⁹ concluded that a high normal FSH level indicates disturbance of spermatogenesis. In our study, FSH levels at baseline and follow-up were within normal limits, but FSH levels decreased significantly in men whose wives achieved natural pregnancy (Table 4).

CONCLUSION

The spontaneous pregnancy rate after sub-inguinal varicocelectomy is significantly associated with BMI, sperm concentration, sperm progressive motility and serum FSH level.

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