

Improvement of seminal parameters and pregnancy rates after antegrade sclerotherapy of internal spermatic veins

Antonio Galfano, M.D.,^a Giacomo Novara, M.D.,^b Massimo Iafrate, M.D.,^a
Vincenzo De Marco, M.D.,^a Marco Cosentino, M.D.,^a Carolina D'Elia, M.D.,^a Walter Artibani, M.D.,^a
and Vincenzo Ficarra, M.D.^a

^a Department of Oncological and Surgical Sciences, Urology Clinic; and ^b I.R.C.C.S. Istituto Oncologico Veneto, University of Padua, Padua, Italy

Objective: To evaluate the impact of antegrade scrotal sclerotherapy on seminal parameters and pregnancy rates in varicocele patients who have impairment of seminal parameters and/or couple infertility.

Design: Longitudinal, noncomparative study.

Setting: Tertiary university hospital.

Patient(s): Three hundred sixty-four consecutive varicocele patients with seminal impairment, including 173 (47.5%) patients who were not interested in fertility and 191 (52.5%) who were infertile.

Intervention(s): Modified antegrade scrotal sclerotherapy.

Main Outcome Measure(s): Increase in sperm count, motility, and/or normal forms in all patients. Pregnancy rates 12 months after treatment in infertile men.

Result(s): The median patient age was 32 years. Twelve months after treatment, persistent reflux was present in 45 (12.4%) cases. In 188 (51.6%) patients with low sperm number, sperm count statistically significantly improved, from 12 to 19.5×10^6 per milliliter. In the 336 (92.3%) patients with asthenospermia, progressive motile forms statistically significantly improved, from 25% to 45%. In the 147 (40.4%) patients with teratospermia, normal forms increased from 17% to 35%. In infertile patients without persistent varicocele, 65 (37.4%) patients fathered offspring. Patients obtaining a pregnancy presented a significantly higher sperm motility than did infertile patients (46% vs. 35%).

Conclusion(s): Antegrade scrotal sclerotherapy significantly improves sperm count, motility, and morphology. Patients with couple infertility achieved a pregnancy in 37% of cases. Patients achieving pregnancy present a better progressive motility after treatment than patients who did not father any child. (Fertil Steril® 2009;91:1085–9. ©2009 by American Society for Reproductive Medicine.)

Key Words: Varicocele, antegrade scrotal sclerotherapy, semen analysis, pregnancy rate

A pathologic dilatation of the veins of the pampiniform plexus is present in 15%–20% of the general population and in 30%–40% of patients with couple infertility (1). Moreover, a high number of young men with a varicocele who are not yet interested in conceiving offspring have an impairment of the main semen analysis parameters. The improvement of seminal parameters after varicocele correction has been reported by several investigators in clinical series (2–5), nonrandomized comparative studies (6–8), and randomized clinical trials (9, 10).

More controversies exist concerning the role of varicocele treatment to obtain pregnancy in infertile couples (11, 12). Nevertheless, the results of recent nonrandomized controlled studies confirm a significant improvement in the number of pregnancies obtained by patients who have undergone a varicocele correction, in comparison with patients who have not received any treatment for varicocele (7, 8, 13, 14).

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Reprint requests: Vincenzo Ficarra, M.D., Department of Oncological and Surgical Sciences, Urology Clinic, University of Padua, Via Giustiniani, 2, 35100 Padua, Italy (FAX: 39-049-821-8757; E-mail: vincenzo-ficarra@unipd.it).

Most of the results reported in the literature come from studies in which varicoceles have been treated with a surgical, microsurgical, or laparoscopic ligation or with a retrograde scleroembolization. Few studies have reported data related to the improvement of seminal parameters and pregnancy rates in patients treated with antegrade scrotal sclerotherapy of internal spermatic veins (15, 16).

The objective of this study is to evaluate the results of antegrade scrotal sclerotherapy for varicocele treatment in terms of improvement of seminal parameters and pregnancy rates in patients with impairment of seminal parameters and/or couple infertility.

MATERIALS AND METHODS

We longitudinally collected clinical data of patients who underwent antegrade scrotal sclerotherapy for varicocele in the period between December 1997 and October 2005. All patients had been informed about the possible surgical, microsurgical, and radiointerventional alternatives to treat varicocele. At the same time, all patients signed an informed consent, in which the antegrade scrotal sclerotherapy technique was explained step-by-step. Considering that the

study did not cause any change in our clinical practice, an internal review board evaluation was not required.

We included in the study all patients >18 and <40 years of age, with clinically palpable hydropathic varicocele and impairment of at least one seminal parameter (sperm count, percentage of sperms with progressive motility 1 h after sample collection, or percentage of normal forms).

We excluded patients who were <18 or >40 years old, patients with subclinical varicocele, patients with normal semen analysis, and patients with further pathologies that were associated to varicocele and potentially were responsible for an alteration of semen analysis.

For each single patient, we evaluated the following parameters: age at surgery, marital status, partner age, cigarette smoking, varicocele side and clinical grade, severity of spermatic reflux using the color Doppler examination, the number and motility of spermatozoa, and the percentage of normal sperms.

The population was subdivided into two groups: group A, which included patients ≥ 18 years of age who were not yet interested in fertility, and group B, which included patients who had had couple infertility for ≥ 2 years. In the last subgroup, possible causes of female infertility had been investigated and excluded.

According to physical examination, varicocele was categorized as grade 1 if it was detectable during Valsalva maneuver only, as grade 2 if it was palpable at rest, and as grade 3 if it was visible at rest (17). The reflux detected during color Doppler ultrasound was classified into three grades: [1] slight and brief reflux, ending before the Valsalva maneuver was completed; [2] severe reflux, lasting throughout the Valsalva maneuver; and [3] severe reflux, already present with the patient supine at rest.

In all patients, semen analysis was conducted according to the World Health Organization recommendations (18). Specifically, the abstinence period was ≥ 48 hours and <7 days in all cases. Preoperative evaluation included the execution of two semen analyses. The interval between the two sample collections had to be ≥ 7 days or ≤ 3 weeks. The sample was collected inside the laboratory; alternatively, it was delivered by the patient within 1 hour from its collection. For the statistical analysis, the latest exam before surgery was considered.

Accordingly, semen analysis was considered impaired if at least one of the following features was present: a sperm count of $<20 \times 10^6$ per milliliter, a percentage of progressive motility ($a =$ rapid progressive motility + $b =$ slow progressive or irregular motility) at 1 hour of <50%, and a percentage of normal sperms of <30%.

All patients underwent antegrade scrotal sclerotherapy, according to a technique originally described elsewhere (19).

All patients underwent physical examination 1 month after surgery and underwent spermatic color Doppler 6 and 12 months after surgery. Varicocele was defined as persistent if

it was detected by color Doppler ultrasonography 6 months after surgery and was defined as recurrent if it was detected by color Doppler ultrasound 12 months after treatment in patients with a negative 6-month follow-up.

Moreover, the follow-up schedule was based on two semen analyses 12 months after surgery. The mean value of the post-operative seminal parameters was considered for statistical analyses. Spontaneous pregnancies were evaluated at a minimum of 12 months after treatment.

Statistical Analysis

Frequencies of nonparametric continuous variables are reported as median and interquartile range (IQR). For the statistical comparison of nonparametric continuous variables, we used the Mann-Whitney U test for two independent samples or the Wilcoxon test for related samples. To compare categorical variables we used the Pearson's χ^2 square test. All *P* values were two sided and a *P* of <.05 was considered significant. The analysis was conducted by one of the investigators using the Statistical Package for Social Sciences software (version 15; SPSS, Chicago, IL).

RESULTS

During the study period, 697 patients underwent antegrade scrotal sclerotherapy for hydropathic varicocele. We excluded from the study 77 (11%) patients who were <18 and 23 (3.2%) patients who were >40 years of age. One hundred eighty-three patients (26.2%) were excluded because of normal semen analysis. In this last subgroup, 157 patients were treated for symptomatic varicocele, and 26 were treated to prevent a future impairment of seminal parameters in the absence of symptoms. Among the 414 remaining patients with seminal impairment, 11 were excluded because they were affected by subclinical varicocele, and 35, for concomitant scrotal pathologies negatively affecting fertility (previous cryptorchidism or testicular torsion). The remaining 364 patients met the study inclusion criteria.

The median age of the 364 evaluated patients was 32 years (IQR, 26–35 y). There were 149 single (40.9%) and 215 married patients (59.1%). The median age of the partners was 32 years (IQR, 28–34 y). One hundred forty-seven patients (40.4%) were smokers, 201 (55.2%) were nonsmokers, and 16 (4.4%) were former smokers. The varicocele was located on the left side in 307 (84.3%) cases, on the right in 3 (0.8%), and bilaterally in 54 (14.8%). In 65 (17.8%), the varicocele was classified as grade 1; in 178 (48.9%), as grade 2; and in 121 (33.2%), as grade 3. According to Doppler ultrasound, reflux was classified as grade 1 in 55 (15.1%) cases, as grade 2 in 167 (45.9%), and as grade 3 in 142 (39%).

Median sperm number was 19×10^6 per mL (IQR, 12–54 $\times 10^6$ per mL). Sperm count impairment was present in 188 (51.6%) patients. The median value of the percentage of progressive motile sperms ($a + b$) was 26% (IQR, 18%–36%). An alteration of the percentage of sperms with progressive motility was noted in 336 (92.3%) patients. Median value of

TABLE 1**Clinical features of patients undergoing scrotal sclerotherapy, stratified according to patient interest in achieving pregnancy.**

Variable	Group A (n = 173)	Group B (n = 191)	P value
Median age, y (IQR)	26 (22–29)	34 (32–37)	<.001
Marital status, n (%)			<.001
Single	143 (82.7)	0	
Married	29 (18)	191 (100)	
Partner median age, y (IQR)	30 (27–34)	32 (29–34)	.909
Cigarette smoking, n (%)			.01
No	109 (63)	92 (48.2)	
Former	7 (4)	9 (4.7)	
Yes	57 (32.9)	90 (47.1)	
Diagnosis, n (%)			.01
First diagnosis	157 (90.8)	185 (96.9)	
Failure after previous treatment	16 (9.2)	6 (3.1)	
Varicocele side, n (%)			.123
Left	153 (88.4)	154 (80.6)	
Right	1 (0.6)	2 (1)	
Bilateral	19 (11)	35 (18.3)	
Clinical grade, n (%)			.562
Grade 1	27 (15.6)	38 (19.9)	
Grade 2	83 (48)	95 (49.7)	
Grade 3	63 (36.4)	58 (30.4)	
Doppler reflux, n (%)			.211
Grade 1	22 (12.7)	33 (17.3)	
Grade 2	76 (43.9)	91 (47.6)	
Grade 3	75 (43.4)	67 (35.1)	
Median sperm count, $\times 10^6$ per mL (IQR)	22 (11–64)	17 (12–34)	.01
Median motility (a + b), % (IQR)	30 (20–40)	24 (16–33)	<.001
Median normal forms, % (IQR)	33 (18–45)	32 (20–40)	.518

Galfano. Seminal and pregnancy outcomes after antegrade scrotal sclerotherapy. *Fertil Steril* 2009.

the percentage of normal forms was 32% (IQR, 20%–41%). Specifically, the percentage of normal forms was impaired in 147 (40.4%) cases.

Group A (patients with seminal impairment not interested in fertility) included 173 (47.5%) patients. The remaining 191 (52.5%) were infertile (group B). **Table 1** shows the features of the patients, subdivided into the two groups. All treatments were performed under local anesthesia. No intraoperative complication was observed, and all patients were discharged 4 hours after surgery. The return to working activities required 24 hours for sedentary jobs and 48–72 hours for more active jobs. Postoperative complications occurred in 20 (5.5%) patients. These included 2 cases of scrotal hematomas needing surgical drainage, 6 cases of slight hematomas resolved spontaneously, 2 infectious orchiepididymitis cases successfully treated with antibiotics, and 10 cases of occasional scrotal pain (successfully treated with antibiotics and nonsteroidal analgesics).

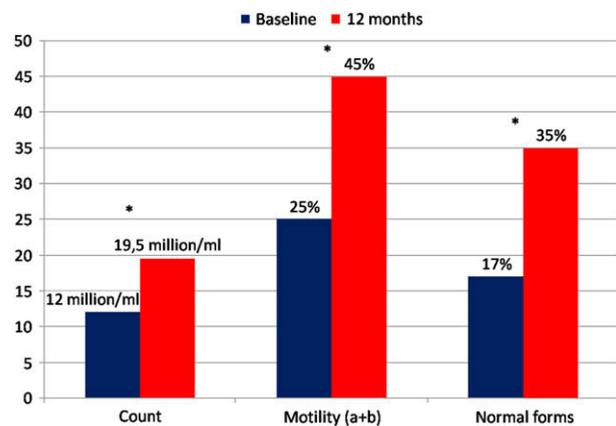
Doppler ultrasound 6 months and 1 year after surgery showed a persistent reflux in 45 (12.4%) cases. No patients

with absence of reflux after 6 months showed a recurrent varicocele 12 months after surgery. In patients with a low sperm number before surgery, sperm count improved from 12×10^6 per milliliter (IQR, $8\text{--}15 \times 10^6$ per mL) to 19.5×10^6 per milliliter (IQR, $14\text{--}30 \times 10^6$ per mL; $P < .001$). In patients with asthenospermia, the median value of the percentage of progressive motile forms at 1 hour (a + b) improved from 25% (IQR, 18%–34%) to 45% (IQR, 34%–54%; $P < .001$). Also, in patients with an alteration of the percentage of normal forms, this parameter had significantly improved. Median values increased from 17% (IQR, 10%–22%) before surgery to 35% (IQR, 26%–45%) 1 year after ($P < .001$; **Fig. 1**).

In the subgroup of the 174 infertile patients who did not present recurrent or persistent varicocele after antegrade scrotal sclerotherapy, 65 (37.4%) patients fathered offspring at a 12-month-minimum follow-up. **Table 2** compares the features of patients who achieved pregnancy with those of patients who did not. Specifically, patients obtaining a pregnancy presented sperm motility 1 year after treatment that was significantly higher than that of patients who did not father any child.

FIGURE 1

Increase in median values of the main seminal parameters, before and 1 year after treatment. * $P < .001$.



Galfano. Seminal and pregnancy outcomes after antegrade scrotal sclerotherapy. *Fertil Steril* 2009.

DISCUSSION

The results of our study demonstrate a significant improvement of the main seminal parameters in patients who have undergone antegrade scrotal sclerotherapy for varicocele. In the

subgroup of patients with couple infertility, we were able to observe spontaneous pregnancies in $>37\%$ of cases.

At an adult age, varicocele can be diagnosed in patients with couple infertility or in patients not yet interested in fertility. In both cases, the treatment of varicocele is indicated only if a seminal impairment is present (20, 21). In these cases, a correction of varicocele can improve testicular gametogenesis and postoperative seminal parameters. A significant seminal improvement in treated vs. nontreated patients has been demonstrated in nonrandomized (6–8, 22) and randomized controlled studies (9, 10).

Recent studies have confirmed a significant increase in sperm number and motility in patients who have undergone surgical or microsurgical treatments or retrograde percutaneous scleroembolization (2–4, 16).

However, few data concerning the improvement in seminal parameters is available in patients undergoing antegrade scrotal sclerotherapy. Specifically, Tauber and Johnsen (23) in 1994 analyzed 79 patients who had undergone antegrade scrotal sclerotherapy 2 to 4 months before and reported a significant increase in the percentage of sperms with progressive motility and normal morphology. More recently, Zucchi et al. (16) reported the seminal results of 32 patients who had undergone antegrade scrotal sclerotherapy 8 months before, showing a significant improvement in the percentage of sperms with progressive motility after treatment. Our study confirms the

TABLE 2

Comparison of the features of infertile patients with those of patients achieving spontaneous pregnancies 1 year after treatment.

Variable	Not achieving pregnancy (n = 109)	Spontaneous pregnancy (n = 65)	P value
Median age (y) (IQR)	34 (32–36)	34 (32–38)	.77
Partner median age (y) (IQR)	32 (29–33)	32 (29–35)	.54
Cigarette smoking, n (%)			.46
No	50 (45.8)	36 (55.3)	
Former	5 (4.5)	3 (4.6)	
Yes	54 (49.5)	26 (40)	
Doppler reflux, n (%)			.61
Grade 1	18 (16.5)	14 (21.5)	
Grade 2	51 (46.8)	31 (47.7)	
Grade 3	40 (36.7)	20 (30.8)	
Preoperative sperm parameters			
Median sperm count, $\times 10^6$ per mL (IQR)	16 (12–37)	16 (11–29)	.64
Median percentage motility, a + b (IQR)	23 (17–32)	25 (14–36)	.66
Median percentage normal forms (IQR)	33 (23–41)	30 (18–37)	.12
Postoperative sperm parameters			
Median sperm count, $\times 10^6$ per mL (IQR)	25 (13–69)	25 (19–47)	.58
Median percentage motility, a + b (IQR)	35 (25–50)	46 (40–56)	.001
Median percentage normal forms (IQR)	40 (29–46)	40 (34–45.5)	.28

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seminal improvement after antegrade scrotal sclerotherapy in a very large series evaluated 1 year after treatment.

Literature data do not show significant differences in seminal parameter improvements comparing the different surgical, microsurgical, or interventional radiologic techniques. According to the main international guidelines, currently it is not possible to identify a gold-standard treatment, and the most appropriate technique is the one about which the urologist is most confident or that is the easiest to perform in each hospital setting. Antegrade scrotal sclerotherapy is easy, is quick to perform, requires only local anesthesia, has low perioperative complication rates, has low costs, and allows rapid return to working activities (24, 25). Moreover, better results in terms of spermatic veins reflux control and complication rates can probably be obtained only by using inguinal or subinguinal microsurgical techniques. However, these techniques have a more limited diffusion because of the need to have an operating microscope and use it frequently.

More controversies exist concerning the results of varicocele treatment in patients with couple infertility when the endpoint of treatment is the improvement of spontaneous pregnancy rates. In the years of evidence-based medicine, the controversy has been stirred up by the absence of high-quality randomized controlled trials (12). The randomized allocation to a treatment or to a 1-year follow-up observation makes it very difficult to realize such studies (13). Nevertheless, observing the results of recent nonrandomized, controlled studies, the mean percentage of spontaneous pregnancies obtained 1 year after treatment is higher in comparison to the one recorded in patients who remain untreated for 1 year (7, 8, 13, 14). Pregnancy rates after varicocele treatment are between 30% and 60% in the most recent studies (8, 13). In our experience, the only parameter able to distinguish fertile patients from patients not achieving pregnancies is the higher percentage of sperms with progressive motility 1 year after treatment. Considering that the percentage of sperm with progressive motility was overlapping in the two groups before treatment, this difference might be attributed to the efficacy of varicocele correction.

In conclusion, antegrade scrotal sclerotherapy of internal spermatic veins significantly improves sperm count, motility, and morphology in patients with a preoperative impairment of these parameters. In patients with couple infertility, 1 year after antegrade scrotal sclerotherapy, the percentage of spontaneous pregnancies accounts for 35% of cases. Patients achieving pregnancy present a better progressive motility after treatment than do patients who do not father any child. Antegrade scrotal sclerotherapy can be considered a valid option in the treatment of patients with dysspermia related to varicocele.

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