The association between varicocele, premature ejaculation and prostatitis symptoms: possible mechanisms.

The Association between Varicocele, Premature Ejaculation and Prostatitis Symptoms: Possible Mechanisms

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ABSTRACT

Introduction. No study has ever systematically evaluated the impact of varicocele on sexual function.

Aim. Two cross-sectional studies were performed in patients attending an andrology unit either for male sexual dysfunction (study 1) or couple infertility (study 2). In study 1, we evaluated the impact of varicocele on sexual function. In study 2, we retrospectively evaluated a possible association between varicocele and prostatitis signs and symptoms.

Methods. Study 1 refers to a consecutive series of 2,448 (mean age 52.0 ± 12.9 years) subjects. Study 2 consists of a consecutive series of 139 male subjects (mean age 37.3 ± 6.3).

Main Outcome Measures. In study 1, varicocele was clinically classified into three grades according to Dubin criteria. Different hormonal parameters were also evaluated. All the patients of study 2 underwent simultaneous scrotal and transrectal color-Doppler ultrasonography (CDU) along with seminal characteristics and interleukin-8, a surrogate marker of prostatitis.

Results. After adjusting for age, subjects with severe varicocele (N = 284, 11.6%; Dubin grade 2 and 3) showed a reduction of testicular volume ($P < 0.01$), higher luteinizing hormone (LH) ($P < 0.05$), follicle stimulating hormone (FSH) ($P < 0.0001$) and prolactin ($P < 0.05$) levels, and also an enlarged or tender prostate at digito-rectal examination ($P < 0.05$). Premature ejaculation was the only sexual symptoms significantly associated with varicocele (29.2% vs. 24.9% in subjects with or without varicocele, respectively; $P < 0.05$). In study 2, subjects with severe echographic-defined varicocele (basal venous reflux increasing or not after Valsalva's maneuver; N = 28, 20.1%) showed CDU features of prostatitis and higher seminal inteleukin-8 levels. The presence of any degree of varicocele (N = 40, 28.8%) was also associated with prostatitis symptoms, as measured by the National Institutes of Health Chronic Prostatitis Symptom Index scoring ($P < 0.05$), and in particular with the pain domain ($P < 0.05$).

Conclusions. In conclusion, signs and symptoms of prostatitis are more common in varicocele patients, who more often complain of premature ejaculation. **Lotti F, Corona G, Mancini M, Biagini C, Colpi GM, Innocenti SD, Filimberti E, Gacci M, Krausz C, Sforza A, Forti G, Mannucci E, and Maggi M. The association between varicocele, premature ejaculation and prostatitis symptoms: Possible mechanisms. J Sex Med 2009;6:2878–2887.**

Key Words. Varicocele; Premature Ejaculation; Prostatitis

Introduction

Varicocele, defined as the abnormal dilatation of testicular veins and pampiniform plexus, is characterized by retrograde flow in the affected veins [1]. Depending on the screening method, the estimated incidence of clinically palpable varicocele is 15% in the general male population and 21–39% in subfertile men [2,3]. The possibility to revert infertility through varicocele treatment is under debate [1,3–6]. In fact, although a possible improvement of seminal parameters after

surgical varicocele treatment has been reported [see for review 4,7], a recent meta-analysis does not demonstrate any evidence that varicocele treatment in men from couples with otherwise unexplained subfertility improves the couple's chance of conception [6]. Beyond infertility, traditional indications for varicocele treatment include complaining of symptoms such as scrotal pain, painful swelling, dull scrotal or inguinal heaviness, and perineal discomfort [3,8,9]. However, it should be recognized that all of these symptoms are vague and nonspecific. In fact, they are in someway overlapping with symptoms of different clinical conditions including prostatitis, lower urinary tract symptoms, and/or chronic pelvic pain syndrome [10]. Quite unexpectedly, the relationship between these clinical conditions and varicocele has been poorly studied [11,12]. Lower urinary tract symptoms have been demonstrated to be an independent risk factor for erectile dysfunction (ED) [13], while prostatitis is a well-recognized cause of acquired premature ejaculation [14–18; for review, see 19,20]. Although a few authors have reported an association between ED and varicocele in a limited series of subjects [21,22], no study has systematically evaluated the impact of varicocele on sexual function.

Aim

The aim of the present study is to assess the impact of varicocele on sexual function in a large series of patients consulting for sexual dysfunction in a clinical facility. Results obtained demonstrated a significant association between varicocele, premature ejaculation, and enlarged prostate at digito-rectal examination. Because premature ejaculation has been described more often in subjects with prostatitis [14–18; for review, see 19,20], we retrospectively evaluated, in a second population of subjects attending our unit for male infertility, a possible association between varicocele and prostatitis signs and symptoms.

Patients and Methods

Two cross-sectional studies were performed in patients referring to an andrology unit either for male sexual dysfunction (study 1) or couple infertility (study 2). In study 1, a consecutive series of 2,448 patients attending our outpatient clinic for sexual dysfunction for the first time (from January 2001 to September 2008) was retrospectively studied. Only patients not fluent in Italian were excluded from the analysis. All patients enrolled underwent the usual diagnostic protocol applied to newly-referred subjects at the andrology outpatient clinic. All the data provided were collected as part of the routine clinical procedure. All patients provided an informed consent to the study. The socio-demographic and clinical characteristics of the sample are summarized in Table 1. Patients were interviewed prior to the beginning of any treatment, and before any specific diagnostic procedures, using the Structured Interview on Erectile Dysfunction (SIEDY) [23]. This is a 13-item interview made up of three scales, which identify and quantify components concurring with sexual dysfunctions. Scale 1 deals with organic disorders, Scale 2 with disturbances in the relationship with a partner, and Scale 3 with psychological traits. Premature ejaculation was defined as ejaculation within 1 minute of vaginal intromission (as reported by the patient) according to previously described criteria [24,25]. Delayed ejaculation was defined as "slowness to ejaculate" (as reported by the patient) according to previously described criteria [25,26]. Hypoactive sexual desire was assessed with question number 14 of SIEDY as previously described [2,27–30]. Patients were asked to complete the Middlesex Hospital Questionnaire, modified (MHQ) [31], a brief self-reported questionnaire for the screening of mental disorders, which provides scores for free-floating anxiety (MHQ-A), phobic anxiety (MHQ-F), obsessive-compulsive traits and symptoms (MHQ-O), somatization (MHQ-S), depressive symptoms (MHQ-D) and hysterical traits and symptoms (MHQ-H).

Main Outcome Measures

All patients underwent a complete physical and andrological examination. The presence of clinical varicocele was bilaterally evaluated by palpation of the venous vessels in the scrotal sac and the observation of each spermatic cord with the patient standing before and during Valsalva's maneuver. Varicoceles were clinically classified into three grades according to Dubin criteria [32]. In particular, grade 1 was defined when varicocele was palpable only during Valsalva's maneuver; grade 2 when varicocele was palpable without Valsalva's maneuver and grade 3 when varicocele was both visible and palpable without Valsalva's maneuver.

Blood samples were drawn in the morning, after overnight fast, for determination of total testosterone (normal range: 10.4–34.6 nmol/L), prolactin,

Table 1 Characteristics of the sample

	All N = 2,448	No varicocele N = 1,819 (74.3%)	Any varicocele N = 629 (25.7%)
Age (years)	51.8 ± 13.1	50.7 ± 13.6	52.2 ± 12.9*
Marital status (%)			
Stable relationship living together	72.9	73.8	70.3
Stable relationship not living together	15.5	15.4	15.9
No stable relationship	11.5	10.8	13.8
Education (%)			
None/primary school	16.1	16.2	15.7
Secondary school	30.5	30.4	30.9
Secondary high school	34.6	34.9	33.6
University	18.8	18.4	19.8
Morbidities (%)			
Current smoker	32.9	33.3	31.8
Hypertension	25.5	25.8	24.8
Diabetes mellitus	25.4	25.8	24.3
Cardiovascular diseases	11.9	12.3	10.8
Clinical and laboratory parameters			
Body mass index (kg/m^2)	26.5 ± 4.1	26.5 ± 4.1	26.6 ± 4.1
Mean testis volume	19.3 ± 4.1	19.4 ± 4.3	19.1 ± 3.7
$Log_{.10}$ [FSH] (U/L)	0.68 ± 0.35	0.67 ± 0.35	0.68 ± 0.33
$Log_{.10}$ [LH] (U/L)	0.58 ± 0.28	0.57 ± 0.29	0.59 ± 0.25
Total testosterone (nmol/L)	16.1 ± 6.5	16.1 ± 6.3	16.2 ± 6.9
$Log_{.10}$ [prolactin] mU/L	2.21 ± 0.26	2.20 ± 0.27	2.22 ± 0.25
Sexual symptoms: number (%)			
Erectile dysfunction	2,211 (90.3)	1,615 (88.8)	596 (94.7)
Hypoactive sexual desire	903 (36.9%)	688 (37.8)	216 (34.4)
Premature ejaculation	637 (26%)	453 (24.9)	184 (29.3)†
Delayed ejaculation	157 (6.4%)	118 (6.5)	39 (6.2)
SIEDY scale score			
Scale 1 (organic domain of ED)	3.3 ± 2.5	3.3 ± 3.5	3.2 ± 2.5
Scale 2 (relational domain of ED)	1.9 ± 2.0	1.8 ± 2.0	2.1 ± 2.1†
Scale 3 (intrapsychic domain of ED)	3.4 ± 2.1	3.4 ± 2.2	3.3 ± 2.1

Data are expressed as mean ± SD and as percentages when categorical.
*$P < 0.05$.
†After adjustment for age.
LH = luteinizing hormone; ED = erectile dysfunction.

FSH, and LH (by elettrochemioluminescent method, Modular Roche, Milan, Italy).

In study 2, a consecutive series of 139 male patients seeking medical care for couple infertility at our outpatient clinic (from January 2008 to March 2009) was retrospectively studied. Only patients not fluent in Italian were excluded from the analysis. All patients enrolled underwent the usual diagnostic protocol applied to newly-referred subjects at the andrology outpatient clinic. All the data provided were collected as part of the routine clinical procedure. All patients provided an informed consent to the study. The socio-demographic and clinical characteristics of this sample are summarized in Table 2. All the patients underwent simultaneous scrotal and transrectal color-Doppler ultrasonography (CDU). In order to prevent bias on the part of the examiner, scrotal and transrectal CDU were performed intermittently by 2 experienced physicians (F.L. and M.M.) unaware of the clinical data.

Varicocele was diagnosed according to Sarteschi criteria [see in 33,34]. In particular, a severe echographic-defined varicocele (corresponding to Dubin grade 3; [34]) was defined when venous vessels appeared enlarged in the supine position and CDU demonstrated a basal venous reflux increasing or not after Valsalva's maneuver (Sarteschi grade 4 or 5).

All patients attending our outpatient clinic underwent semen analysis according to the World Health Organization criteria (1999) [35]. Furthermore, seminal interleukin-8, a surrogate marker of prostatitis [36] was also measured. Finally, all patients were asked to complete the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) [10] in its validated Italian version [37], a brief self-reported questionnaire for the screening of prostatitis symptoms, which provides scores for pain, voiding symptoms, and quality of life.

Data were expressed as mean ± SD when normally distributed, when distribution could be normalized through logarithmic transformation, logarithmically transformed data have been reported. Correlations were assessed using Spear-

Table 2 Characteristics of the sample

	All n = 139	No varicocele n = 99 (71.2%)	Any varicocele n = 40 (28.8%)
Age (years)	37.3 ± 6.3	36.5 ± 5.9	37.9 ± 6.0
Education (%)			
None/primary school	5.4%	6.2	6.4
Secondary school	21.1%	22.1	23.1
Secondary high school	42.3%	45.2	43.4
University	31.2%	26.5	27.1
Morbidities (%)			
Current smoker	42.7%	43.1	41.2
Hypertension	2.2%	1.1	1.1
Diabetes mellitus	1.1%	0.6	0.5
Cardiovascular diseases	1.1%	0.5	0.6
Clinical and laboratory parameters			
Body mass index (kg/m^2)	25.7 ± 3.5	25.3 ± 2.7	25.7 ± 3.8
Log.$_{10}$ [systolic blood pressure] mmHg	2.01 ± 0.04	2.10 ± 0.03	2.11 ± 0.04
Log.$_{10}$ [diastolic blood pressure] mmHg	1.91 ± 0.04	1.90 ± 0.04	1.91 ± 0.03
Mean testis volume	17.0 ± 4.6	13.3 ± 4.4	12.7 ± 3.7
Log.$_{10}$ [interleukin 8] ng/ml	3.5 ± 0.5	3.4 ± 0.4	3.6 ± 0.3
Seminal parameters			
Sperm volume ml	3.0 ± 1.7	2.8 ± 1.6	3.2 ± 1.9
Sperm concentration, ×10^6/ml	38.8 ± 65.6	37.6 ± 90.9	27.8 ± 51.5
Sperm motility %motile (a + b)	35.5 ± 23.1	26.3 ± 21.2	25.0 ± 18.6
Sperm morphology, % normal forms	12.7 ± 10.5	8.9. ± 8.6	6.7 ± 6.3
NIH-CPSI score			
Total score	3.9 ± 5.9	3.3 ± 5.2	6.0 ± 7.6*
Pain domain (0–21)	1.6 ± 2.9	1.4 ± 2.8	2.9 ± 3.7*
Void domain (0–10)	1.0 ± 1.7	0.6 ± 1.3	1.2 ± 1.9
Quality of life impact (0–12)	1.4 ± 2.3	1.3 ± 2.2	2.0 ± 2.9

Data are expressed as mean ± SD, and as percentages when categorical.
NIH-CPSI = National Institutes of Health Chronic Prostatitis Symptom Index. *$P < 0.05$.

man's or Pearson's method whenever appropriate. Differences between more than two groups were assessed with one-way ANOVA or Kruskal–Wallis test, whenever appropriate. Unpaired two-sided Student's *t*-tests were used for comparisons of means of normally distributed parameters. In all other cases, Mann–Whitney *U*-test was used for comparisons between groups. Stepwise multiple linear or logistic regressions were applied for multivariate analysis, whenever appropriate. All statistical analysis was performed on SPSS for Windows 15.0.

Results

Study 1

Among the patients studied, clinical evidence of varicocele was found in 629 (25.7%) subjects. In particular, a mild varicocele (Dubin grade 1) was detected in 345 (14.1%) patients, while a severe form (Dubin grade 2 and 3) was found in 284 (11.6%). Subjects with any form of varicocele were younger when compared with the rest of the sample (Table 1). In addition, subjects with mild varicocele were younger, while those with the severe form were older than the rest of the sample (47.6 ± 13.8, 54.5 ± 12.3, 52.2 ± 12.9 years old for mild, severe, or no varicocele, respectively; $P < 0.0001$ at ANOVA). Hence, all the following associations were adjusted for age.

Among all the patients studied, subjects with mild varicocele did not show any difference in testis volume when compared with those without varicocele (19.1 ± 3.1 vs. 19.4 ± 4.3 cc; P = NS). Conversely, testis volume was significantly lower in subjects with severe varicocele, even after adjustment for age (Hazard ratio = 1.04[1.01–1.07]; $P < 0.01$ for each millimeter reduction of testis volume). Accordingly, subjects with severe varicocele showed higher LH (Hazard ratio = 1.63[1.01–2.63], $P < 0.05$ for each LH log. unit increment) and FSH (Hazard ratio = 2.84[1.86–4.32]; $P < 0.0001$ for each FSH log. unit increment) when compared with the rest of the sample. In addition, severe varicocele was also associated with higher prolactin levels, when compared with the rest of the sample (Hazard ratio = 1.60[1.03–2.50] for each prolactin log. unit increment; $P < 0.05$). Conversely, testosterone levels were not different in subjects with or without severe varicocele (Figure 1).

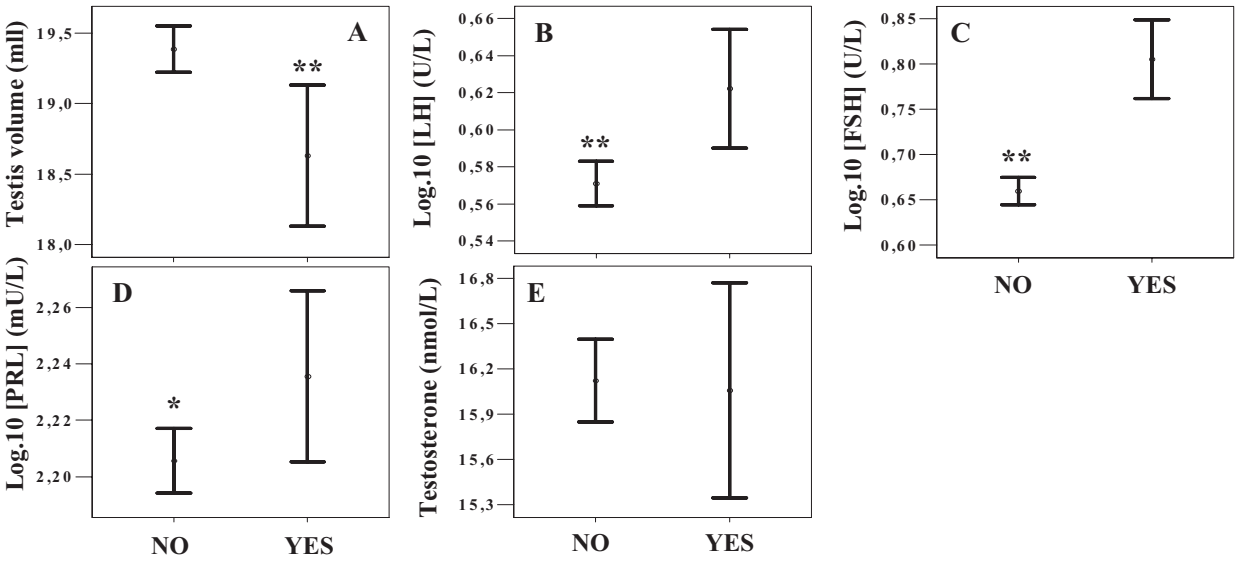

Figure 1 Testis volume (panel A) and hormonal parameters (panels B–E) in subjects with (YES) or without (NO) severe clinical varicocele (Dubin grade 2–3). PRL = prolactin. $^{*}P = 0.05$; $^{**}P < 0.005$; $^{***}P < 0.0001$.

Premature ejaculation was the only sexual symptom significantly associated with the presence of clinical varicocele after adjustment for age (Table 1). In particular, the prevalence of premature ejaculation was significantly higher in subjects with any degree of varicocele when compared with the rest of the sample without any differences regarding premature ejaculation severity. In addition, subjects with varicocele more often reported orgasmic impairment in their partner (60.7% vs. 53.3%, $P < 0.005$). All of these associations were confirmed at logistic multivariate analysis after adjustment for confounding factors such as age, anxiety symptoms (as derived from MHQ-A score), and prolactin levels (Hazard ratio = 1.33[1.02–1.74], $P < 0.05$; 1.47[1.15–1.88], $P < 0.005$, respectively for premature ejaculation and partner's climax). In line with these observations, the relational domain of ED, as explored by SIEDY Scale 2 score, was more compromised in subjects with varicocele (Table 1; hazard ratio = 1.06[1.01–1.12]; $P < 0.05$ for each increment of SIEDY Scale 2 score).

Finally, an abnormal (enlarged or tender) prostate was found more often at digito-rectal examination in subjects with severe varicocele (31.8%, 31.6%, 42.5% for no, mild, or severe varicocele, respectively; Adj $r = 0.06$; $P < 0.05$ after adjustment for age).

The presence of bilateral varicocele did not modify the results obtained (data not shown)

Study 2

In a separate clinical setting (male patients attending our andrology unit for couple infertility), we simultaneously studied prostatic, vesicular, and testicular features, and blood flow by color-Doppler-ultrasound, along with seminal characteristics and interleukin-8. Echographic-defined varicocele was found in 40 (28.8%) subjects, while a severe form (continuous spermatic venous reflux at rest increasing or not during Valsalva maneuver; Sarteschi grade 4 and 5) was observed in 28 (20.1%). No difference between patients with or without severe echographic varicocele was detected in sperm count, motility, and morphology (data not shown). Subjects with severe echographic varicocele showed higher seminal interleukin-8 ($P < 0.05$); in addition they presented a higher prevalence of ultrasound signs of prostatitis, such as hypoechoic prostatic texture ($P < 0.02$), prostatic calcifications ($P < 0.001$), higher seminal vesicle anterior-posterior diameter before ejaculation ($P < 0.05$), and higher prostatic venous plexus diameter ($P < 0.0001$) (Figure 2). All of these associations were confirmed at multivariate analysis after adjustment for age (Hazard ratio = 4.73[1.81–12.41], $P < 0.005$, 3.95[1.62–9.64], $P < 0.005$, 1.17[1.03–1.33], $P < 0.05$ and 1.53[1.27–1.84], $P < 0.0001$, for the presence of prostatic calcification, hypoechoic prostatic texture and for each millimeter increment of anterior-posterior seminal vesicle diameter or prostatic venous plexus

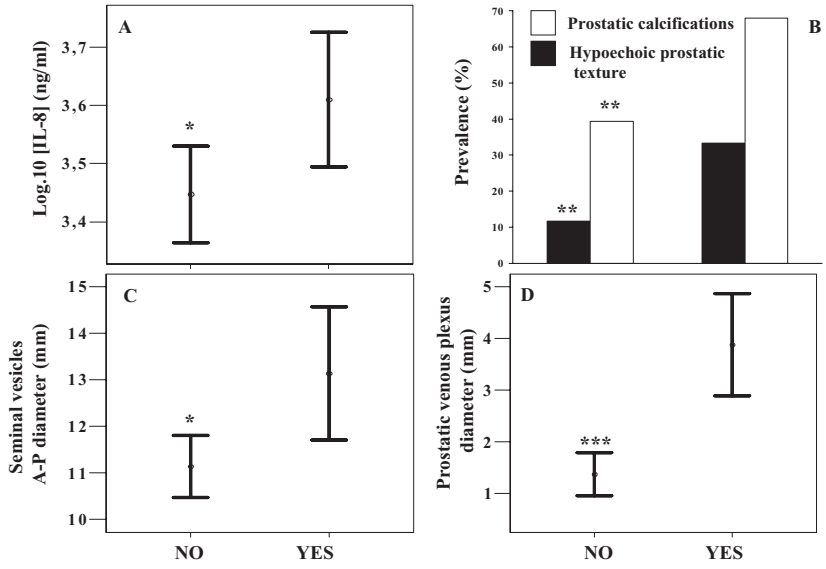

Figure 2 Interleukin-8 (IL-8) levels (panel A), presence of prostatic calcification and hypoechoic prostate texture (panel B), seminal vesicles diameter (panel C) and prostatic venous plexus diameter (panel D), as derived from ultrasound evaluation, in subjects with (YES) or without (NO) severe echographic varicocele (continuous spermatic venous reflux at rest increasing or not during Valsalva maneuver; Sarteschi grade 4 and 5). $^{*}P < 0.05$; $^{**}P < 0.001$; $^{***}P < 0.0001$.

diameter, respectively). Venous reflux velocity in the internal spermatic vein correlated with arterial prostatic blood flow peak velocity ($r = 0.312$; $P < 0.005$). No positive association between prostate volume and varicocele was found (data not shown).

The presence of any degree of echographic varicocele was also significantly ($P < 0.05$) associated with symptoms of prostatitis, as measured by NIH-CPSI scoring and in particular with the pain domain (Table 2). These associations were confirmed after adjusting for age (Hazard ratio = 1.06[1.01–1.13], $P < 0.05$ and 1.12[1.00–1.26], $P = 0.05$ for total score and pain domain, respectively).

The presence of bilateral varicocele did not modify the results obtained (data not shown).

Discussion

In the present study, we report for the first time an association between varicocele and premature ejaculation in patients consulting for sexual dysfunction. In particular, premature ejaculation appears to be the only sexual symptom significantly associated with varicocele. Mechanisms linking varicocele with premature ejaculation appear to be complex and difficult to explain. We also confirm the previously reported association of varicocele with prostatitis [11,12] which is a well-known risk factor for premature ejaculation [14–18; for review, see 19,20]. Antibiotic treatment is able to delay ejaculation in patients with premature ejaculation associated with chronic bacterial prostatitis [38,39]. The exact pathophysiology linking prostatitis and premature ejaculation is unknown. However, it has been proposed that prostatic inflammation may lead to an altered sensation and modulation of the ejaculatory reflex through a neurophysiologic pathway [19,40]. It can be speculated that varicocele, leading to intrapelvic congestion and prostatic inflammation, could be the primum movens for the onset of premature ejaculation, at least in some subjects. It has been reported that varicocele is associated with an underlying systemic venous abnormality [11,41,42], and with an increased diameter of the prostatic venous plexus in particular [43]. In addition, Gat et al. [44] recently demonstrated the presence of a venous blood reflux from the high pressure testicular venous drainage system to the low pressure prostatic drainage system, through a direct communication represented by the deferential vein and the vesicular plexus. It can be speculated that the presence of communication between the testicular and the prostatic venous system might justify a back-flow of venous blood from the testis to the prostate, which can lead to intrapelvic venous congestion. This could facilitate the onset of symptoms of prostatitis. Accordingly, it has been demonstrated that the selective occlusion of impaired venous drainage in the male reproductive system was associated with a reduction in prostate volume and benign-prostatic-hyperplasia-related symptoms [44]. Our findings are in line with this evidence. In fact, subjects with severe echographic varicocele were characterized by increased seminal interleukin-8 levels (a surrogate marker of non-

bacterial prostatitis; [36]) and a higher prevalence of echographic signs of prostate inflammation. In addition, we found an association between the presence of any degree of echographic varicocele and symptoms of prostatitis, as measured by NIH-CPSI scoring [10,37].

The clinical relevance of premature ejaculation should not be underestimated. In fact, although premature ejaculation is the main reason for referral to andrological consultation only in a minority of cases [19,24,25,45], it is a frequent condition in the general population [19,45,46] and it has a relevant impact on quality of life. In fact, premature ejaculation affects the psychosexual equilibrium of the couple [24,47]. Our findings are in line with the latter evidence, showing that subjects with premature ejaculation more often reported an impairment of relational domain and a partner with climax difficulties.

This study shows that varicocele is a further organic condition associated with premature ejaculation, besides hyperthyroidism [24,25,48–50] and chronic prostatitis [14–18; for review, see 19,20]. Hence, any patient with premature ejaculation should be screened for the aforementioned conditions.

Clinical varicocele has been associated with relative testicular hypotrophy [51]. Varicocele treatment may reduce this negative effect [51]. Our data are in line with these findings. In fact, subjects with severe varicocele showed lower testis volume and increased FSH levels (a marker of testicular damage) when compared with the rest of the sample.

The effect of varicocele on Leydig cell function and testosterone biosynthesis is still controversial [52]. Although some authors have reported that serum testosterone levels could be affected by varicocele [53,54] others did not find any correlation [42,51]. In addition, varicocelectomy did not show any effect on testosterone circulating levels [55,56] although only a limited series of subjects was evaluated. In agreement with the latter observations, we did not find any difference in testosterone levels between subjects with or without varicocele, probably due to the observed compensatory increase of LH, as previously reported [51,57,58]. Larger prospective studies are advisable in order to better clarify the relationship between varicocele and Leydig cell function. Finally, in line with other authors [57–60], an increase of prolactin levels was also observed in subjects with varicocele. The imbalance between androgens and oestrogens, due to the condition of primary hypogonadism derived from the testicular damage could explain, at least partially, this observation [57–60].

Several limitations should be recognized. First of all, it should be clarified that study 1 was performed on patients with sexual dysfunction, and its results cannot be extended to a broader population. In addition, sexual dysfunction, and premature ejaculation in particular, was not investigated in study 2. It should be noted that the patients in study 2 were retrospectively evaluated in order to better clarify the association between varicocele and the enlarged prostate volume observed in study 1. Further prospective studies are advisable to better clarify the relationship between premature ejaculation and varicocele and symptoms of prostatitis. In particular, it should be clarified whether premature ejaculation or signs and symptoms of prostatitis will improve after varicocele repair.

Conclusions

Signs and symptoms of prostatitis are more common in patients with varicocele, who more often complain of premature ejaculation. Premature ejaculation should be considered a marker underlying organic diseases including varicocele, and chronic prostatitis could be the link between the two conditions.

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Conflict of Interest: None.

Statement of Authorship

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Category 3

(a) Final Approval of the Completed Manuscript
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