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Varicoceles affect semen quality of infertile men in Southern China

A cross-sectional study of 5447 cases

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Abstract

The association of varicoceles with infertility is well established, but the exact effect of varicoceles on semen quality among patients with infertility is still poorly known. The study aimed to examine the prevalence of varicoceles among Chinese men with infertility and to examine the factors associated with semen quality.

This was a cross-sectional study of 5447 male patients treated for infertility at the Affiliated Hospital of Guangdong Medical University from October 2012 to December 2015. The patients were divided on the basis of the presence of varicoceles. Examinations of the amount of semen and sperm morphology were performed according to seminal parameter detection methods recommended by the World Health Organization.

Patients with varicoceles (n = 1429/5447, 26.2%) were slightly younger ($P = .046$), and had smaller testis ($P = .019$), higher frequency of abnormal epididymis ($P < .001$), slightly shorter infertility duration ($P = .046$), and lower frequency of smokers ($P = .012$). There was no difference in the distribution of occupations ($P = .777$). Using multiple linear regression analysis, varicoceles were shown to be independently associated with semen volume [B = −0.153, 95% confidence interval (95% CI): −0.245 to −0.062, $P = .001$], sperm concentration (B = 9.633, 95% CI: 7.152–12.114, $P < .001$), proportion of sperms with normal morphology (B = 0.951, 95% CI: 0.623–1.278, $P < .001$), motility (B = 3.835, 95% CI: 2.675, 4.995, $P < .001$), total sperm count (B = 22.481, 95% CI: 13.333–31.629, $P < .001$), and forward movement sperm count (B = 15.553, 95% CI: 9.777–21.329, $P < .001$). Varicoceles were present in 26% of Chinese male patients with infertility.

Varicoceles were independently associated with sperm volume, sperm concentration, proportion of sperms with normal morphology, motility, total sperm count, and forward movement sperm count.

Abbreviations: B = beta value, CI = confidence Interval, SCA = sperm class analyzer, SD = standard deviation.

Keywords: forward motility sperms, male infertility, sperm morphology, varicocele

1. Introduction

Infertility is the inability to conceive after 1 year of unprotected sexual intercourse.[1–4] Male factor infertility alone accounts for about 30% to 50% of the infertile couples.[1] In Beijing (China), the prevalence of couple infertility is around 4.2%.[5] Risk factors for male infertility are many and include obstructive, genetic, endocrine, and occupational risk factors, as well as age, diet, and ejaculatory disorders.[4]

A varicocele is a vascular lesion characterized by dilation of gonadal veins in the scrotum, sometimes described as having a "bag of worms" appearance.[6] Varicoceles are most frequent at the beginning of puberty and are found in 14% to 20% of adolescents and adults.[4,6] Varicoceles may lead to elevated scrotal temperature, which impairs spermatogenesis, for which optimal temperature is typically 33°C to 34°C.[7] Varicoceles are easily corrected by surgery, restoring proper scrotal temperature and fertility.[6,8,9]

The prevalence of varicoceles is about 15% to 20% in the general population, but the prevalence is 30% to 40% among patients with infertility.[10] The prevalence of varicoceles increases with age and the risk of varicoceles increases by about 10% for each decade of life.[11] Nevertheless, even if the association of varicoceles with infertility is well established, the exact effect of varicoceles on semen quality among patients with infertility is still poorly known and studies are limited by a small sample size.[12,13] In addition, far from all, men with a varicocele are infertile.[14] The incidence of varicocele ranges from 35% to 40% in men with primary infertility, but increases to 80% in men with secondary infertility, suggesting a progressive decline in male fertility.[9,15] A recent European meta-analysis showed that

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there is an adverse effect of varicoceles on semen quality among men unselected for fertility status.[16] Nevertheless, data in a Chinese population are lacking.

Therefore, the aim of the present study was to examine the prevalence of varicoceles among Chinese men with infertility and to examine the factors associated with semen quality. The findings of this study provided clear data on the risk factors for poor seminal fluid quality in Chinese males, which could help identify the risk factors that could be modulated to improve semen quality.

2. Methods

2.1. Study design and patients

This was a cross-sectional study of male patients treated for infertility at the Reproductive Medicine Department of the Affiliated Hospital of Guangdong Medical University from October 2012 to December 2015. A total of 8648 patients were initially screened. The inclusion criteria were duration of infertility ≥ 1 year; abstinence of 2 to 7 days; and no fertility drugs in the past 6 months. The exclusion criteria were azoospermia; or incomplete outpatient data. A total of 8648 patients were screened and 5447 were included.

This study was approved by the Reproductive Ethics Committee of the Affiliated Hospital of Guangdong Medical University. All subjects signed the informed consent forms.

2.2. Data collection

A detailed medical history inquiry and physical examination were performed. Semen analysis and microbiological culture of semen were examined. Demographic information and physical examination results of the patients were collected. The patients were divided into 2 groups based on the presence of varicoceles. Occupational hazards were evaluated and classified into 4 groups: high temperature and heat exposure (e.g., cooks and drivers); toxic substance exposure (e.g., building and decoration workers, crews, farmers, hairdressing workers, factory workers, and petroleum workers); computer radiations (e.g., designers and civil service staffs); and no obvious risk factor (e.g., teachers, medical personnel, business personnel, breed personnel, self-employed businessmen, soldiers, and policemen). Abnormal epididymis referred to enlargement of the head or tail of the epididymis.

2.3. Semen collection

The semen was collected after an abstinence of 2 to 7 days. Urine was collected, and the hands and penises were washed using soap. After rinsed off the soap, the hands and penises were dried using new disposable towels. Semen was collected by masturbation and injected into a sterile container. Aseptic incubation was immediately performed for 100 μL of semen in *Mycoplasma urealytium* and nonspecific bacterial culture. Remaining semen in the container was used to perform semen analysis after liquefaction.

2.4. Seminal parameters

Examinations of the amount of semen and sperm morphology were performed according to seminal parameter detection methods recommended by the World Health Organization.[17] Concentration of sperms (10^6/mL) and forward sperm motility (%) were measured using a sperm class analyzer (SCA) (Microptic S.L., Barcelona, Spain). Sperm morphology was examined using Papanicolaou staining. Optimized semen (10 μL) was dropped at one end of a slide glass, and the pull-thin technology was used to coat semen on the surface of the slide. After air drying, staining was performed using Papanicolaou staining.[17] Using oil microscopy, 200 sperms were examined repeatedly and the percentage of normal sperm morphology of each semen sample was calculated. The morphological assessment of the sperm was performed strictly according to the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edition) [18] and 200 sperms were assessed. The parameters of the sperms were determined after 2 examinations.

Sperms included head, neck, connecting piece, tail, and end piece. It is difficult to observe the end piece of sperms through an optical microscope, so it was considered that sperm was constituted by head (and neck) and tail (connecting piece and tail). Only the sperms with normal head and tail were called normal, and all the other sperms were called abnormal. More specifically, according to the classification criteria of abnormal sperm described by the World Health Organization,[19] the abnormalities include head abnormality, including big head, small head, conical head, pear-shaped head, round head, amorphous head, head with vacuole (with 2 or more vacuoles, or the size of unstained vacuole was larger than 20% of the area of the head), vacuole at the postacrosomal region, too big or small acrosome (less than 40% of the head area, or larger than 70% of the head area), 2 heads, or any combination of these abnormalities; neck and middle part abnormality, including asymmetric connecting of the middle part to the head, too thick or irregular, acute-angle bending, abnormally thin middle part, or any combination of these abnormalities; tail abnormality, including short tail, multiple tails, broken tail, hairpin-shaped smooth bending, acute angle bending, irregular thickness, curling, or any combination of these abnormalities; or excessive residual cytoplasm, which is mainly found in sperms from abnormal spermatogenesis; the features of such sperms include containing large volume of irregular stained cytoplasm, of which the volume is over one-third of the head area; defects in the middle part are also very common.

2.5. Statistical analysis

Continuous data were checked using the Kolmogorov–Smirnov test to see if they met the normal distribution. Normally distributed data were presented as mean ± standard deviation (SD) and analyzed with the Student *t* test. Non-normally distributed data were presented as median (range) and analyzed using the Mann–Whitney *U* test. Categorical data were presented using frequencies and analyzed with the Chi-square test or the Fisher exact test, as appropriate. Multiple linear regression analyses were used to examine the factors independently associated with the seminal parameters (dependent variables). Results were presented using the B value (the coefficient of the model) and the 95% confidence interval (95% CI) for the B value. Statistical analysis was performed using SPSS 22.0 (IBM, Armonk, NY). Two-sided $P < .05$ were considered to be statistically significant.

3. Results

3.1. Characteristics of the patients

Table 1 presents the characteristics of the patients. Patients with varicoceles were slightly younger ($P = .046$), had smaller testis

Table 1

Characteristics of the patients.

	All n = 5447	Varicocele n = 1429	No varicocele n = 4018	P
Age, y	31.7 ± 5.4	31.4 + 5.4	31.8 ± 5.4	.046
Testis size, mL				.019
≤3.0	1 (0.0%)	0	1 (0.0%)	
3.1–8.0	372 (6.8%)	110 (7.7%)	262 (6.5%)	
8.1–10.0	877 (16.1%)	262 (18.3%)	615 (15.3%)	
10.1–15.0	4178 (76.7%)	1054 (73.8%)	3124 (77.8%)	
>15.0	19 (0.3%)	3 (0.2%)	16 (0.4%)	
Epididymis				<.001
Normal	1574 (28.9%)	319 (22.3%)	1255 (31.2%)	
Left abnormal	1327 (24.4%)	437 (30.6%)	890 (22.2%)	
Right abnormal	444 (8.2%)	86 (6.0%)	358 (8.9%)	
Both abnormal	2102 (38.6%)	587 (41.1%)	1515 (37.7%)	
Vas deferens				.218
Normal	5437 (99.8%)	1426 (99.9%)	4011 (99.8%)	
Unilateral impalpable	7 (0.1%)	1 (0.0%)	6 (0.2%)	
Bilateral impalpable	3 (0.1%)	2 (0.1%)	1 (0.0%)	
Infertility duration	2.33 ± 2.28	2.22 ± 2.08	2.36 ± 2.35	.046
Etiology				.02
Primary	3429 (63.0%)	948 (66.3%)	2481 (60.9%)	
Secondary	2018 (37.0%)	481 (33.7%)	1569 (39.1%)	
Cigarettes				.012
No	3089 (56.7%)	851 (59.5%)	2238 (55.7%)	
Yes	2358 (43.3%)	578 (40.5%)	1780 (44.3%)	
Smoking duration, y (smokers only)				.434
≤5	231 (9.8%)	63 (10.9%)	168 (9.4%)	
5–10	1169 (49.6%)	290 (50.3%)	879 (49.4%)	
>10	958 (40.6%)	224 (38.8%)	734 (41.2%)	
Occupation				.738
High temperature and heat exposure	739 (13.6%)	206 (14.4%)	533 (13.3%)	
Toxic substance exposure	1722 (31.6%)	448 (31.4%)	1274 (31.7%)	
Computer radiation exposure	868 (15.9%)	229 (16.0%)	665 (16.6%)	
No obvious risk	1637 (30.1%)	429 (30.0%)	1208 (30.1%)	
Inoccupation	481 (8.8%)	117 (8.2%)	364 (9.1%)	

($P = .019$), had a higher frequency of abnormal epididymis ($P < .001$), had a slightly shorter infertility duration ($P = .046$), and had a lower frequency of smokers ($P = .012$). There was no difference in the distribution of the occupations ($P = .777$).

3.2. Seminal parameters

Table 2 presents the seminal parameters. The varicocele group showed larger semen volume ($P = .01$), lower sperm concentration ($P < .001$), lower total sperm count ($P < .001$), lower proportion of spermatozoa with normal morphology ($P < .001$), lower total count of normal spermatozoa ($P < .001$), and lower proportion of motile spermatozoa ($P < .001$).

3.3. Multiple linear regression analyses

Table 3 presents the multiple linear regression analyses of factors associated with the seminal parameters. Each semen quality parameter was tested separately with the potential risk factors. Age was independently associated with semen volume (B = −0.023, 95% CI: −0.031 to −0.016, $P < .001$), semen concentration (B = 0.486, 95% CI: 0.277–0.695, $P < .001$), proportion of sperms with normal morphology (B = −0.030, 95% CI: −0.059 to −0.002, $P = .033$), motility (B = −0.437, 95% CI: −0.537 to −0.338, $P < .001$), and forward movement sperm count (B = −1.064, 95% CI: −1.561 to −0.566, $P < .001$).

Primary/secondary infertility was associated with semen volume (B = 0.177, 95% CI: 0.089–0.264, $P < .001$), proportion

Table 2

Seminal parameters.

Parameters	All, n = 5447	Varicocele, n = 1429	No varicocele, n = 4018	P
Semen volume, mL	3.40 (2.50–4.50)	3.50 (2.60–3.50)	3.30 (2.40–4.40)	.01
Sperm concentration, 10^6/mL	44.00 (24.20–73.90)	36.20 (19.70–62.20)	47.30 (26.18–77.90)	<.001
Total sperm count ($\times 10^6$)	147.66 (74.10–253.68)	127.40 (61.11–219.76)	156.86 (78.94–264.99)	<.001
Normal morphology (%)	6.00 (2.00–10.00)	5.00 (1.50–9.00)	6.00 (2.50–10.00)	<.001
Forward movement sperm count ($\times 10^6$)	53.77 (20.81–114.81)	41.68 (15.40–93.12)	56.98 (23.35–120.42)	<.001
Motility (%)	38.00 (23.8–52.8)	33.50 (21.00–49.23)	39.60 (24.90–53.70)	<.001

Table 3

Multiple linear regression of factors associated with seminal parameters.

Dependent variables	Independent variables	B	95% CI for B		P
			Lower limit	Upper limit	
Semen volume					
	Age	−0.023	−0.031	−0.016	<.001
	Primary/secondary	0.177	0.089	0.264	<.001
	Cigarettes	−0.090	−0.171	−0.009	.029
	Testis size	0.085	0.018	0.153	.013
	Vas deferens	0.623	0.092	1.153	.021
	Varicoceles	−0.153	−0.245	−0.062	.001
Sperm concentration					
	Age	0.486	0.277	0.695	<.001
	Infertility years	−0.543	−1.036	−0.050	.031
	Occupation	−3.478	−5.704	−1.252	.002
	Cigarettes	−3.294	−5.500	−1.088	.003
	Testis size	16.580	14.749	18.410	<.001
	Epididymis status	−3.996	−6.418	−1.574	.001
	Varicoceles	9.633	7.152	12.114	<.001
Normal morphology					
	Age	−0.030	−0.059	−0.002	.033
	Primary/secondary	0.411	0.098	0.725	.010
	Testis size	0.953	0.704	1.202	<.001
	Varicoceles	0.951	0.623	1.278	<.001
Motility					
	Age	−0.437	−0.537	−0.338	<.001
	Primary/secondary	2.323	1.211	3.434	<.001
	Cigarettes	1.384	0.355	2.413	.008
	Testis size	4.985	4.105	5.866	<.001
	Varicoceles	3.835	2.675	4.995	<.001
Total sperm count					
	Infertility years	−1.781	−3.547	−0.016	.048
	Primary/secondary	17.223	8.903	25.543	<.001
	Occupation	−10.537	−18.748	−2.326	.012
	Cigarettes	−13.495	−21.597	−5.394	.001
	Testis size	58.807	52.062	65.553	<.001
	Epididymis status	−12.804	−21.676	−3.932	.005
	Varicoceles	22.481	13.333	31.629	<.001
Forward movement sperm count					
	Age	−1.064	−1.561	−0.566	<.001
	Primary/secondary	9.488	3.971	15.005	.001
	Occupation	−7.026	−12.202	−1.849	.008
	Testis size	30.686	26.322	35.051	<.001
	Epididymis status	−6.579	−12.201	−0.956	.022
	Varicoceles	15.553	9.777	21.329	<.001

Age referred to increasing age; testis size referred to larger testis. Primary/secondary, occupation, epididymis status, and varicoceles were categorical variables.
95% CI = 95% confidence interval.

of sperms with normal morphology (B=0.411, 95% CI: 0.098–0.752, $P=.010$), motility (B=2.323, 95% CI: 1.211–3.434, $P<.001$), total sperm count (B=17.223, 95% CI: 8.903–25.543, $P<.001$), and forward movement sperm count (B=9.488, 95% CI: 3.971–15.005, $P=.001$).

Occupation was independently associated with sperm concentration (B=−3.478, 95% CI: −5.704 to −1.252, $P=.002$), total sperm count (B=−10.537, 95% CI: −18.748 to −2.326, $P=.012$), and forward movement sperm count (B=−7.026, 95% CI: −12.202 to −1.849, $P=.008$).

Cigarette smoking was independently associated with semen volume (B=−0.090, 95% CI: −0.171 to −0.009, $P=.029$), sperm concentration (B=−3.294, 95% CI: −5.500 to −1.088, $P=.003$), motility (B=1.384, 95% CI: 0.355–2.413, $P=.008$), and total sperm count (B=−13.495, 95% CI: −21.597 to −5.394, $P=.001$).

Vas deferens status was independently associated with sperm volume (B=0.623, 95% CI: 0.092–1.153, $P=.033$).

Epididymis status was independently associated with sperm concentration (B=−3.996, 95% CI: −6.418 to −1.574, $P=.001$), total sperm count (B=−12.804, 95% CI: −21.676 to −3.932, $P=.005$), and forward movement sperm count (B=−6.579, 95% CI: −12.201 to −0.956, $P=.022$).

Testis size was independently associated with semen volume (B=0.085, 95% CI: 0.018–0.153, $P=.013$), sperm concentration (B=16.580, 95% CI: 14.749–18.410, $P<.001$), proportion of sperms with normal morphology (B=0.953, 95% CI: 0.704–1.202, $P<.001$), motility (B=4.985, 95% CI: 4.105–5.866, $P=.008$), total sperm count (B=58.807, 95% CI: 52.062–65.553, $P<.001$), and forward movement sperm count (B=30.686, 95% CI: 26.322–35.051, $P<.001$).

Finally, varicoceles were independently associated with semen volume (B = −0.153, 95% CI: −0.245 to −0.062, $P = .001$), sperm concentration (B = 9.633, 95% CI: 7.152–12.114, $P < .001$), proportion of sperms with normal morphology (B = 0.951, 95% CI: 0.623–1.278, $P < .001$), motility (B = 3.835, 95% CI: 2.675–4.995, $P < .001$), total sperm count (B = 22.481, 95% CI: 13.333–31.629, $P < .001$), and forward movement sperm count (B = 15.553, 95% CI: 9.777–21.329, $P < .001$).

4. Discussion

The association of varicoceles with infertility is well established,[6,8,9] but the exact effect of varicoceles on semen quality among patients with infertility is still unclear. Therefore, the objective of this study was to examine the prevalence of varicoceles among Chinese men with infertility and to examine the factors associated with semen quality. Results showed that varicoceles were present in 26% of Chinese male patients with infertility. Varicoceles were independently associated with sperm concentration, proportion of sperms with normal morphology, motility, total sperm count, and forward movement sperm count. The results of the present study provide insightful data about the risk factors for poor semen quality in Chinese male with infertility.

Varicocele are present in 35% to 40% of men with primary infertility, and in 80% of men with secondary infertility.[9,15] A recent study showed that varicoceles were associated with impaired testicular function as shown by lower sperm parameters and decreased testosterone levels.[16] In addition, increasing grade of varicocele seems to be associated with worst sperm parameters.[16] Supporting the association between varicoceles and infertility, surgical repair of varicoceles has been shown to increase sperm concentration and to improve sperm motility.[20–24] A recent meta-analysis showed that varicocele repair improves sperm parameters, probably by reducing sperm oxidative stress and DNA damage.[9] All types of repair improve these parameters, but microsurgical repair seems to produce the best outcomes.[9] In the present study, the multiple linear regression analyses performed with a large number of patients showed that the presence of varicocele was an independent predictor of poorer sperm parameters (i.e., smaller sperm volume, lower sperm concentration, abnormal sperm morphology, lower motility, lower total sperm count, and lower forward movement sperm count) among infertile Chinese men.

The association between age and sperm parameters is controversial. In a general manner, a study showed a decline in the likelihood of pregnancy, independent from the women's age, and increasing with age.[25] On the contrary, age does not seem to affect semen volume, sperm count, and sperm motility in men consulting infertility clinics,[26] but a review of the literature suggests that increasing age is associated with lower semen volume, sperm motility, and sperm morphology, but not with sperm concentration.[27] A study showed that younger age was associated with better improvements in total motile sperm counts after microsurgical varicocele repair compared with older men.[20] In the present study, age was independently associated with semen volume, motility, and total sperm count. Discrepancies among the present study and previous ones[25–27] could be due to a number of factors, including population, genetics, stress, and diet. Additional studies are necessary to examine these factors.

Varicoceles may lead to elevated scrotal temperature, which impairs spermatogenesis.[7] Among occupational hazards, working at high temperatures may also contribute to increased scrotal temperature, contributing to infertility.[28,29] Exposure to toxic substances such as solvents and heavy metals has been reported to impair spermatogenesis.[30,31] Accordingly, in the present study, even if occupations were similar between patients with and without varicoceles, occupations were independently associated with sperm concentration, motility, total sperm count, and forward movement sperm count.

The present study is not without limitations. Albeit the sample size was large, it was from a single center. In addition, because of the retrospective nature of the study, many interesting data (such as hormone levels) could not be included in the analyses. The occupational risk factors were examined on the basis of the occupation of each patient, but we could not rule out other types of environmental exposures (e.g., at home or during recreational activities). The oxidative stress profile of the patients was not assessed. Finally, the effect of varicocele repair was not assessed because of the cross-sectional design of the study. We investigated the effects of varicocele on the quality of semen in the male partner of infertile couples. The spouse also underwent corresponding examinations, but this does not mean that all spouses were healthy and fertile, which introduce a bias. Additional studies are still necessary to determine adequately the contribution of varicoceles and other factors on semen quality among infertile men.

In conclusion, varicoceles were present in 26% of Chinese male patients with infertility. Varicoceles were independently associated with sperm volume, sperm concentration, proportion of sperms with normal morphology, motility, total sperm count, and forward movement sperm count. The present study suggests that the presence of varicoceles could explain many cases of male infertility, but that other factors such as age and occupational risks have to be taken into account. Nevertheless, many issues remain unanswered and additional studies will have to examine the molecular risk factors (such as oxidative stress) associated with male infertility.

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