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INVITED REVIEW

Male Fertility

Epidemiology of varicocele

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Varicocele is a common problem in reproductive medicine practice. A varicocele is identified in 15% of healthy men and up to 35% of men with primary infertility. The exact pathophysiology of varicoceles is not very well understood, especially regarding its effect on male infertility. We have conducted a systematic review of studies evaluating the epidemiology of varicocele in the general population and in men presenting with infertility. In this article, we have identified some of the factors that can influence the epidemiological aspects of varicoceles. We also recognize that varicocele epidemiology remains incompletely understood, and there is a need for well-designed, large-scale studies to fully define the epidemiological aspects of this condition.

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INTRODUCTION

A varicocele is defined as an abnormal venous dilatation and/or tortuosity of the pampiniform plexus in the scrotum. Although varicoceles are almost always larger and more common on the left side, up to 50% of the men with varicocele, have bilateral varicoceles.¹ The rare, isolated right sided varicocele generally suggests that the right internal spermatic vein enters the right renal vein, but it should prompt further investigation as this finding may be associated with situs inversus or retroperitoneal tumors. It is generally reported that varicoceles are present in 15% of the general male population, in 35% of men with primary infertility, and in up to 80% of men with secondary infertility.^{2–4}

The etiology of varicocele is thought to be multi-factorial. The anatomic differences in venous drainage between the left and right internal spermatic vein (accounting for the predominance of left sided varicocele), and, the incompetence of venous valves resulting in reflux of venous blood and increased hydrostatic pressure are the most quoted theories for varicocele development.^{5,6} Physical exertion during puberty may lead to the development of varicocele whereas physical exertion at a later age can aggravate the condition but does not modify the prevalence of varicocele.^{7,8}

Investigators have proposed several mechanisms to explain the pathophysiology of varicocele. Scrotal hyperthermia likely represents the primary mechanism by which a varicocele affects endocrine function and spermatogenesis, both sensitive to temperature elevation.^{9–12} The reflux of adrenal and renal metabolite (supported by early anatomic radiographic studies) is another potential mechanism.^{13–16} Increased hydrostatic pressure in the internal spermatic vein from renal vein reflux may also be responsible for varicocele-induced pathology.¹⁷

The exact pathophysiology of varicocele, specifically, the influence of varicoceles on male fertility potential has not been established conclusively. To date, several studies have demonstrated an association between varicocele and reduced male fertility

potential (e.g., poor semen parameters, infertility). However, most varicocele studies involve highly selected populations (e.g., infertile men) and rarely examine unselected men, representing an important reason for the difficulty in relating varicoceles with male fertility.¹⁸

Clinical (palpable) varicoceles are detected and graded based on physical examination: a grade 1 clinical varicocele is one that is only palpable during the Valsalva maneuver, a grade 2 varicocele is easily palpable with or without Valsalva but is not visible, while grade 3 refers to a large varicocele that is easily palpable and detected by visual inspection of the scrotum.¹⁹ Despite having a varicocele grading system¹⁹ it is important to recognize that epidemiological studies may report variable results due to variations in the detection of varicocele.

The focus of this chapter is to examine and report on the epidemiology of varicoceles in the general male population and in infertile men.

METHODS

Initially, a MEDLINE search was performed including articles from 1992 to 2015. The MEDLINE search terms included: “varicocele,” “epidemiology,” and “infertility.” To widen the search scope, EMBASE and Google Scholar search engines were used, as well as, major references of reviewed articles. Abstracts of more than 140 articles were identified, and a total of 82 articles were reviewed. The main focus was on articles discussing the epidemiological aspect of clinical varicoceles and their relationship to male infertility/subfertility.

EPIDEMIOLOGY OF VARICOCELE – CLINICAL FACTORS

Prevalence of varicocele in the general male population

Most of the early epidemiological studies on varicocele evaluated the prevalence of this condition in young men (military recruits, adolescent school boys, prevasectomy). These early studies reported that the prevalence of varicocele in the general male population is

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about 15%.^{2,20–24} These early observations did not suggest that age was an important determinant of varicocele prevalence.

Subsequent epidemiological studies have demonstrated that varicoceles develop at puberty. Oster observed that no varicoceles were detected in 188 boys 6–9 years of age, but were detected with increasing frequency in boys 10–14 years of age, strongly suggesting that varicoceles develop at puberty.²⁵ More recently, Akbay *et al.*²⁶ evaluated the prevalence of varicoceles in 4052 boys aged 2–19. They reported that the prevalence of varicoceles was <1% in boys aged 2–10, 7.8% in boys aged 11–14 years and 14.1% in boys aged 15–19 years. These epidemiological observations suggest that the venous incompetence that is characteristic of varicocele primarily occurs during testicular development.

More recent studies suggest that the prevalence of varicoceles in adult men is age-related. Levinger *et al.* evaluated the age-related prevalence of varicoceles in men above the age of 30.²⁷ Out of 504 healthy men, 34.7% were found to have a varicocele on physical examination (with all examinations performed by the same investigator). On further analysis, they observed that the prevalence of varicocele increases by approximately 10% for each decade of life. Varicocele prevalence was 18% at age 30–39, 24% at age 40–49, 33% at age 50–59, 42% at age 60–69, 53% at age 70–79 and 75% at age 80–89.²⁷ Canales *et al.* reported a relatively high prevalence (42% prevalence) of varicocele in older men presenting to a prostate cancer screening program (mean age 60.7 years).²⁸ However, unlike the study of Levinger *et al.* the report of Canales *et al.* did not demonstrate an age-related increase in varicocele prevalence in their cohort likely because most men in their study were elderly. These epidemiological observations suggest that testicular venous incompetence increases with age, likely a result of the aging of venous valves. These data are in keeping with the age-related increase in the prevalence of lower limb varicose veins.²⁹

Prevalence of varicocele in a population of infertile men

The prevalence of varicocele in men presenting for infertility is in the range of 25%–35%, and in that subset of men with secondary infertility it is 50%–80%.^{3,30} In 1992, the World Health Organization (WHO) conducted a large study in 34 centers over a 12-month period.³⁰ Men consulting for infertility evaluation were screened using a standardized protocol common to all participating centers. The WHO investigators evaluated 9034 men and reported that 25.4% of the men with an abnormal semen analysis had a varicocele. In contrast, in the same study, the prevalence of varicocele in men with a normal semen analysis was 11.7%.³⁰

Gorelick and Goldstein evaluated 1001 infertile men and reported that the prevalence of varicocele is 35% in men with primary infertility and 81% in men with secondary infertility.³ Similarly, Witt and Lipshultz evaluated 2989 infertile men and reported that a varicocele is identified in 69% of men with secondary infertility.⁴ These two groups of investigators concluded that in some men, a varicocele is a progressive and not a static lesion resulting in the loss of previously established fertility. However, given the subsequent observations of Levinger *et al.*²⁷ it is also possible that the increased prevalence of varicocele in some men with secondary infertility is a result of the age-related increase in the prevalence of a varicocele as these men tend to be older than men with primary infertility.^{3,31}

Venous insufficiency

An association between varicose veins of lower extremities and varicoceles has been suggested. Yasim *et al.* reported on 100 patients undergoing surgical repair of varicose veins, of which 72% had

varicoceles with multiple degrees of severity, suggesting a common origin, likely incompetent venous valves.³² As suggested by Levinger *et al.*²⁷ in their study on the age-related increase in varicocele prevalence, systemic venous insufficiency may be at the root of both lower venous incompetence and testicular venous incompetence.

Body mass index (BMI)

Most studies on the subject of BMI have reported an inverse relationship between the prevalence of varicocele and BMI. Although some studies have found no significant differences in BMI between men with and without varicocele,^{33,34} other studies have reported that men with varicocele have lower BMI than men without varicocele,^{35,36} or that the prevalence of varicocele decreases as BMI increases.^{37–43}

The inverse relationship between the prevalence of varicocele and BMI may be due to detection bias. It is possible that the proper detection of a varicocele may be more difficult in obese patients (due to a thicker spermatic cord) and this may lead under-detection of varicocele in these men. However, investigators have also suggested that the “nutcracker” phenomenon (thought to be responsible for compression of the spermatic vein) may be dampened in obese men due to increased intra-abdominal adiposity.^{37,38}

Hereditary factors

Raman *et al.* reported on the hereditary patterns of varicoceles.⁴⁴ They concluded that 56% of first-degree relatives of patients with varicoceles had a palpable varicocele, which was 8-fold higher than their control group (men presenting for vasectomy reversal).⁴⁴ Mokhtari *et al.* also showed a 45% prevalence of varicoceles among first-degree relatives, compared to 11% in their control group (population of healthy men serving as kidney donors).⁴⁵ More recently in 2010, Gökçe *et al.* reported a prevalence of 34% among first-degree relatives and this was significantly different than their control group (population of healthy men).⁴⁶ These studies strongly suggest that the prevalence of varicocele can be influenced by hereditary factors. The specific genetic factors associated with the increased prevalence of varicocele among family members remains to be elucidated.

Limitations of existing studies

The published studies on varicocele prevalence in fertile and infertile men have provided us with a good insight into the epidemiological aspects of this condition. However, there are several limitations that need to be recognized regarding the available studies on varicocele epidemiology. One of the main limitations of these epidemiological studies is that comparison of the general male population and the infertile male population is mostly indirect because few studies examine varicocele prevalence in both of these groups. This is important because the diagnosis of varicocele greatly depends on the expertise of the clinician performing the physical exam and establishing the diagnosis may vary from center to center. Failure to carefully define the study populations (e.g., age, semen parameters, hereditary factors, co-existing venous insufficiency, BMI) is another important limitation of the available studies. These limitations would best be addressed by performing studies that carefully define the study population(s), physical examination findings (with inter-observer variability) and control for important clinical parameters (e.g., age, semen parameters, hereditary factors, co-existing venous insufficiency, BMI).

CONCLUSION

Varicocele epidemiology remains incompletely understood. We need well-designed, large-scale studies that include evaluation of important clinical factors to comprehend fully the epidemiological aspects of this

condition. Future studies must carefully define the study population(s), physical examination findings (with inter-observer variability) and all pertinent clinical parameters (age, semen parameters, hereditary factors, co-existing venous insufficiency, BMI) to further advance our knowledge in this field.

COMPETING INTEREST

All authors declare no competing interests.

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