Varicoceles: prevalence and pathogenesis in adult men

Raul I. Clavijo, M.D., Robert Carrasquillo, M.D., and Ranjith Ramasamy, M.D.

Department of Urology, University of Miami Miller School of Medicine, Miami, Florida

Varicocele, or dilation of the pampiniform venous plexus, affects up to 15% of men. However, few of these men encounter problems with fertility. This discrepancy between men with varicocele and the number of adversely affected men has led to abundant research to identify the mechanisms for formation of varicocele as well as the pathologic mechanisms by which varicoceles affect fertility potential. In this review, we discuss the prevalence of varicocele in adults, the anatomic features of varicocele, the leading theories as to how varicocele can negatively affect fertility potential, and finally, the current literature on the impact of varicocele on testosterone production. (Fertil Steril® 2017;108:364–9. ©2017 by American Society for Reproductive Medicine.)

Key Words: Infertility, varicocele, spermatic vein, reactive oxygen species, testosterone

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Varicocele is defined as dilation of the pampiniform venous plexus draining the testicle. It is typically diagnosed during a physical exam of the scrotum and graded according to the following scale: grade I varicocele (palpable only during Valsalva maneuver), grade II (palpable in the standing position), and grade III (visible without palpation) (1). In one of the earliest reviews on varicoceles, written more than 30 years ago, the incidence of varicoceles in healthy men ranged from 4.4% to 22.6%, with an average of 15% (2). Interestingly, the prevalence is similar (15.7%) in a contemporary study of 7,035 military recruits (all over 18 years of age) from six European countries. Among men with varicocele, only 1.1% had bilateral disease and 0.2% had isolated right-sided varicocele on physical exam (3). On the other hand, the prevalence of varicocele can be as high as 45% among men seeking care for primary infertility and 80% among men seeking care for secondary infertility (4, 5).

ANATOMY: DEFINING THE VARICOCELE AND MECHANISMS FOR ITS FORMATION

Blood from the testicle drains into a network of veins referred to as the pampiniform plexus. With the use of cast preparations, light-microscopic examination, and computer-aided three-dimensional reconstruction, Ergun et al. demonstrated that the veins directly draining the testicle can be separated into two bundles, one of which is a collection of veins tightly wrapped around the testicular artery, and the other in the adjacent fatty tissue (Fig. 1) (6). These two bundles of veins eventually coalesce into the internal spermatic vein at the level of the internal inguinal ring. Dilation of the internal spermatic vein with reflux of blood down into the pampiniform plexus, is thought to be the primary pathologic process for varicocele formation. Rarely, varicoceles can be a result of external compression of the ipsilateral renal vein, or the spermatic vein itself, impeding testicular venous drainage.

The dilation and reflux in primary varicocele is thought to occur because of several reasons. First, several venography and cadaver studies confirm that the left, and sometimes right, internal spermatic vein drain into the renal vein, or a suprarenal vein, in a perpendicular fashion (7). This drainage pattern, along with observations that the left spermatic vein has a longer overall drainage tract and experiences greater venous differences in pressure, may explain the preponderance of left-sided varicoceles and relative scarcity of clinically palpable bilateral and isolated right-sided varicoceles (3,8–10). With these anatomic observations it is not surprising that the development of varicoceles has been associated with somatometric parameters that theoretically should alter the length of venous drainage and hydrostatic pressures. In fact, several studies have consistently associated increasing height as a factor associated with the presence of varicoceles, with taller men having a greater prevalence of varicoceles (11, 12). However, those studies did not define distinct height cutoffs that could predict the presence of varicocele.

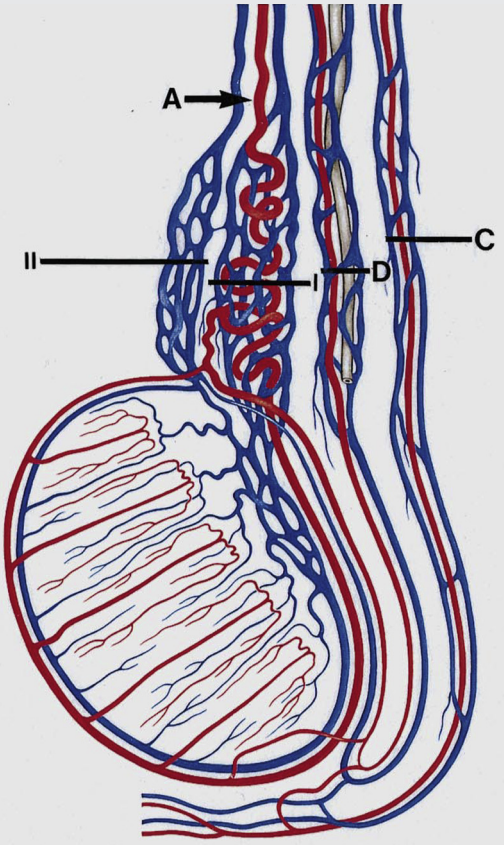
Second, incompetence of venous valves and variation in internal

Received April 30, 2017; accepted June 29, 2017.
R.I.C. has nothing to disclose. R.C. has nothing to disclose. R.R. has nothing to disclose.
Reprint requests: Ranjith Ramasamy, M.D., Department of Urology, University of Miami Miller School of Medicine, 1120 NW 14th Street, Miami, Florida, 33136 (E-mail: ramasamy@miami.edu).

Fertility and Sterility® Vol. 108, No. 3, September 2017 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2017.06.036

FIGURE 1



Testicular venous drainage. A: Testicular artery; C: cremasteric venous drainage with artery; D: deferential venous drainage with artery; I: testicular drainage veins tightly wrapped around testicular artery; II: testicular drainage veins separate from testicular artery. Used with permission from Ergün S, Bruns T, Soyka A, Tauber R. Cell Tissue Res 1997;288:391–8 (6).

Clavijo. Varicocele prevalence and pathogenesis. Fertil Steril 2017.

spermatic vein drainage is postulated as a contributing factor to the development of varicoceles. Early studies in men on postmortem examinations revealed that there was incompetence or absence of internal spermatic vein valves in one-half of the men that were studied (13). More recent studies have shown the complete absence or incompetence of valves in patients with varicoceles (14), particularly adolescents (15). Along these lines, it has been observed that varicoceles may also be caused by the presence of accessory or alternate connections between the internal spermatic vein and systemic venous circulation that lack antirefluxing mechanisms (15, 16). This anatomic variety must be considered when treating patients at a level far from where testicular veins coalesce (17). In fact, this anatomic variety regarding drainage of the internal spermatic vein may be a reason why there is a significantly higher rate of varicocele recurrence after procedures such as laparascopic selective internal spermatic vein ligation and percutaneous venous embolization of the internal spermatic vein (18, 19).

Third, a relatively rare mechanism for varicocele formation is compression of the left renal vein or internal spermatic vein (20). Classically, the nutcracker syndrome, where the renal vein is compressed between the aorta and superior mesenteric artery, has been postulated as a possible source of internal spermatic vein insufficiency, some studies associating this condition with the development of varicoceles more in adolescents than in adults and those with lower body mass indexes (15, 21). Importantly, given the possibility of a varicocele being caused by external compression from a tumor or anatomical malformation, such as situs inversus, it is advised that isolated right-sided varicoceles, and potentially new left-sided varicoceles in older men, be worked up with the use of abdominal imaging (20, 22).

Anatomically distinct from testicular veins, extrafunicular veins are made up of the cremasteric, external pudendal, gubernacular, and deferential veins, all of which drain into the iliac vein. Although it is advocated that one spare the deferential veins during varicocelectomy (23), ligation of the remaining extrafunicular veins is controversial. Venography provides evidence that makes it unlikely that the extrafunicular veins contribute to pathologic (refluxing) primary or recurrent varicoceles (24). However, based on the theory that varicoceles represent an example of a venous retrograde circuit where venous blood flow starts at the incompetent internal spermatic vein and then travels through the pampiniform plexus and out to the pelvic veins, ligation of some these extrafunicular (eg cremasteric) veins may aid in closing this pathologic venous circuit (25). Clinically, it seems that attempting to ligate all extrafunicular veins except for the deferential vein by delivering the testicle provides no benefit in terms of improvement of hormonal and semen parameters (25).

PATHOLOGIC MECHANISMS OF THE VARICOCELE

Despite the extensive literature on varicoceles, the precise mechanism by which they can potentially affect spermatogenesis remains elusive. It has been well established that varicoceles are associated with impaired semen parameters even in those not seeking care for infertility (3). However, no single theory conclusively explains how varicoceles directly affect spermatogenesis, and most plausible mechanisms have been extrapolated from nonhuman models (26).

Here we review the data on the pathologic mechanisms that have been evaluated, including oxidative stress, local hormonal imbalances, stasis of blood (toxin accumulation), testicular hypoperfusion, and heat stress (Fig. 2).

Oxidative Stress

Reactive oxygen species (ROS) are highly reactive oxygen-containing chemical species that are unavoidable byproducts of metabolic pathways, such as mitochondrial respiration, which have been observed to impair spermatogenesis (27). Mitochondria are thought to be the main source of sperm-produced ROS, particularly in the formation of superoxide in the electron transport chain (28). Excessive ROS production has been associated with reduced sperm motility, abnormal