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INVITED EDITORIAL

Male Fertility

Afterword to varicocele and male infertility: current concepts and future perspectives

Sandro C Esteves¹, Ashok Agarwal²

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We summarize and comment on the topics discussed by the contributors to this Special Issue of *Asian Journal of Andrology*. The scope of varicocele covers a wide spectrum, including proteomics and metabolomics, hormonal control, interventional therapy, and assisted reproductive technology (ART). The selection of topics demonstrates the exciting breadth of this thematic area and the opportunity research holds for both increasing the understanding and improving the reproductive health of males with varicocele.

The first article of our special issue reviewed the epidemiology of varicocele and critically analyzed the reasons why its actual prevalence remains incompletely understood.¹ Whereas the prevalence of varicocele is low among boys aged 2–10, it becomes relatively high in adolescents and adults, thus suggesting that venous incompetence primarily occurs during testicular growth. Alsaikhan *et al.* discussed hereditary aspects, study population analyzed and influence of diagnostic methods, all of which may affect the variable prevalence of varicocele. Overall, varicoceles have been identified in approximately 15% of all men. It means that with a male population of approximately 3 billion within reproductive age, a gross estimate indicates that approximately 450 million men worldwide have varicoceles. The authors suggested some methodological aspects to be considered in future studies, including a clear definition of study participants and diagnostic methods. In this regard, Belay *et al.*

reviewed the evolution of diagnostic methods for varicocele identification.² The authors discussed the subjective nature of the clinical examination and the marked inter-observer variability in varicocele grading. Although physical examination still represents the gold standard for diagnosing clinically significant varicoceles, which are those with a clear indication for repair, the aforementioned authors commented how the less invasive radiologic methods have replaced the more invasive ones. The authors discussed the advantages and limitations of each diagnostic modality to detect and/or confirm varicocele and highlighted that advanced imaging methods such as magnetic resonance has potential applicability to detect early signs of testicular dysfunction that could lead to better selection of patients for varicocele repair.

The following three articles provided provocative insights into the pathophysiology of varicocele^{3–5} Although several pathophysiological mechanisms have been proposed, current evidence supports oxidative stress as a key element in the pathophysiology of varicocele-related infertility. Three components have been shown to release reactive oxygen species (ROS) in men with varicocele under heat and hypoxic stress: the principal cells in the epididymis, the endothelial cells in the dilated pampiniform plexus and the testicular cells (developing germ cells, Leydig cells, macrophages, and peritubular cells). Excessive ROS has been associated with sperm DNA fragmentation (SDF), which may mediate the clinical manifestation of poor sperm function and infertility related to varicocele. Intrinsic mechanisms are available to counteract the actions of ROS that might explain why most men retain their fertility in the presence of varicocele. However, disruption of these protective antioxidant mechanisms may lead to impairment in sperm

function and consequent infertility. Following the theme, major advances in biomolecular techniques along with the development of mass spectrometers of greater accuracy and sensitivity has led to an unprecedented growth in the knowledge of sperm function. The spermatozoon is an excellent target for proteomics because the functional transformation of this cell during its journey from the seminiferous tubules to the surface of the oocyte takes place in the absence of contemporaneous gene transcription. Camargo *et al.* reviewed the current knowledge concerning the seminal plasma proteomic profiles of adolescents and adults with treated and untreated varicoceles.⁴ The authors pointed out that varicocele leads to a deviation from homeostasis toward a dynamic equilibrium in an altered state, characterized by enrichment of functions such as immune response and apoptosis, somewhat competing with important sperm functions (such as fertilization, motility, and zona binding). They presented evidence indicating that repairing varicocele in adolescents shifts the seminal plasma proteome back to its regular state, enriching expected sperm functions associated with the preserved reproductive health. In adults, a general dysfunction is observed in the seminal plasma proteome whereas functions important for fertilization are underrepresented. The authors also discussed the importance of defining endpoints for proteomics analysis with regards to the target organ, namely testicle and epididymis. In this sense, understanding the role of epididymal microvesicles and exosomes is opportune because epididymal fluid is an important environment to transfer proteins participating in key sperm events. The review of Camargo *et al.* was further expanded by the study of Agarwal *et al.* who identified and validated novel proteomic signatures associated with

¹ANDROFERT, Center for Male Reproduction, Av. Dr. Heitor Penteadó 1464, Campinas, SP 13075-460, Brazil; ²American Center for Reproductive Medicine, Cleveland Clinic, 10681 Carnegie Avenue, X-11, Cleveland, OH 44195, USA.
Correspondence: Guest Editors for this Special Issue: Dr. SC Esteves (s.esteves@androfert.com.br) or Dr. A Agarwal (agarwaa@ccf.org)

mitochondrial dysfunction and infertility in men with clinical varicoceles.⁵

These breakthrough discoveries on varicocele pathophysiology help us to understand why varicocele cannot be forced to fit into a single framework. It also helps us to appraise the limitations of conventional semen analysis, reviewed by Kruger,⁶ to the study of the effects of varicocele on gonadal function. In the early days, semen abnormalities observed in men with varicocele led to the impulse of accepting a universal causative association between varicocele and poor sperm quality. It soon became clear that this framework was not appropriate because semen analysis results of most men with varicocele actually fit within the so-called “normal” reference values. Concomitantly, laboratory methods for the evaluation of human semen have also evolved as shown by the periodic release of updated manuals by the World Health Organization (WHO). In its latest (fifth) edition, the WHO has presented markedly lower reference ranges for human semen, according to population-based studies, and changed some of the methods for conducting the semen analysis. We were, therefore, fortunate to have a systematic review and meta-analysis to answer the question of whether or not varicocele affects conventional semen parameters in the face of the latest WHO manual.⁷ The authors concluded that varicocele is a significant risk factor for reduced semen quality irrespectively of the WHO laboratory manual edition used for semen analysis. Subgroup analyses indicated, however, that the magnitude of effect was influenced by the type of control enrolled in individual studies (fertile men or normozoospermic men with unproven fertility). Given most of the studies published after 2010 still utilize the 1999 manual (fourth edition) for semen analysis, further research is required to fully understand the clinical implication of the latest 2010 WHO laboratory manual on the association between varicocele and semen parameters.⁷

In science, novelty emerges only with difficulty, and this holds true for the translation of sperm function tests from bench to bedside. Notwithstanding, conventional semen analysis is slowly giving space to sperm function tests that measure oxidative stress and sperm DNA fragmentation. Majzoub *et al.* reviewed the past and current advanced laboratory evaluation of human semen in the context of varicocele and provided a glimpse toward the future of laboratory seminology.⁸ Collectively, the methods for measuring reactive oxygen species and other markers of oxidative stress, including

sperm DNA fragmentation, have evolved and became recognized as important biomarkers for assessing fertility potential in men with varicocele. Test results can provide valuable information on the extent of sperm damage and may guide therapeutic management strategies. As far as SDF is concerned, abnormal test results identify couples at higher risk of remaining childless if an expectant management is taken. Testing is also useful to monitor the results of varicocele repair. Persistent abnormal results after interventions could help couples in the decision of pursuing ART. The use of advanced sperm function tests is likely to aid in the understanding of the underlying pathophysiology of varicocele and in suggesting options for treatment and prevention.

With regards to management strategies to males with varicocele, this Special Issue is rich with authoritative reviews. Dabaja and Goldstein provided clear recommendations to when varicocele repair is indicated and discussed the dilemma of hypogonadism and erectile dysfunction.⁹ The authors summarized the evidence which suggests that varicocele is a risk factor for androgen deficiency, and added that microsurgical varicocelectomy improves testosterone levels in the affected men. Samplaski and Jarvi reviewed the prognostic factors for a favorable outcome after varicocele repair in adolescents and adults.¹⁰ Higher testosterone levels, lower age, and larger testis were the factors associated with improvements in semen postvaricocelectomy. The authors also showed that the greatest reductions in sperm DNA fragmentation rates occurred in men with higher baseline levels of SDF, and added that varicocele repair might reduce the need for more invasive modalities of ART. Marmar followed the theme and presented a “must-read” historical review on the evolution and refinements of varicocele surgery.¹¹ In the early years, treatment was offered for the management of pain. After the report by Tulloch in 1952 that varicocele could affect fertility, surgical repair started to gain worldwide interest in the treatment of male infertility. However, not all men improved after varicocele repair and the more contradictions accumulated, the more convoluted the rationalizations became. But as noted by Bruner and Postman in their seminal work on the perception of incongruity, crisis leads to insight and the old framework gives way to a new one.¹² This was achieved by both refinements in surgical technique, which dramatically reduced recurrence rates, and the identification of subfertile men most

likely to benefit from treatment, namely those with clinically detectable varicoceles. Marmar himself greatly contributed to this evolution by presenting in 1985 the first microsurgical varicocelectomy with an operating microscope and microsurgical instruments.¹³ The so-called “Marmar technique” became so popular that nowadays most infertility specialists apply his approach for the treatment of varicoceles.

New data identifying molecular markers related to oxidative stress in men with varicoceles prompted clinicians to explore the usefulness of oral antioxidants as an adjuvant therapy. Garg and Kumar reviewed the role of medical therapy in the management of varicoceles and concluded that current evidence does not support the use of medication alone to infertile males with abnormal seminal parameters and clinically palpable varicocele.¹⁴ The authors acknowledged that surgery remains the treatment of choice, but indicate that men with treated varicocele may benefit from adjuvant therapy with antioxidants. While results of subinguinal microsurgical varicocelectomy are overall satisfactory, other nonmicrosurgical procedures have been associated with recurrence rates of up to 35%. The problematic management of recurrence after varicocele repair and the complex venous drainage patterns of the internal spermatic vein were reviewed by Rotker and Sigman.¹⁵ The authors pointed out that clinical skills of the examining clinician may affect the diagnosis of recurrent varicocele and that the major reason for varicocele recurrence is the persistence of branched spermatic veins not ligated during the initial repair. Many of these branches subdivide above the subinguinal level, thus explaining why microsurgical subinguinal varicocelectomy generally yields the lowest recurrence rates. Varicocele recurrence can be treated by either microsurgical subinguinal varicocelectomy or percutaneous embolization of varicose veins. One advantage of embolization over surgery is the ability to perform intra-operative venography that can identify venous anatomic variants. Theoretically, this can help prevent a recurrence because most surgical failures result from undiagnosed gonadal vein duplications. Halpern *et al.*¹⁶ provided a comprehensive review of the techniques, indications and results of percutaneous embolization of varicocele. Percutaneous approaches, including antegrade sclerotherapy of internal spermatic veins, have been the varicocele treatment method of choice advocated by some authors, including Ficarra's

group in Italy who contributed an article detailing the technique and its results.¹⁷

The outcome of varicocele repair was also analyzed by a multitude of angles. Tiseo *et al.* summarized the evidence on the effects of varicocele treatment to improve natural fertility in subfertile men.¹⁸ The authors pooled data from a variety of study designs and concluded that varicolectomy improved semen parameters in the majority of the treated men with clinical varicocele and abnormal semen parameters regardless of the chosen surgical method. They added that some conflicting results on the effect of varicocele treatment on natural fertility seem to be due to heterogeneous study designs and, more importantly, patient selection criteria. When these issues are controlled, current evidence indicates that while treatment of subclinical varicocele is not warranted, treatment should be offered to infertile patients with palpable varicocele and abnormal semen parameters. Notwithstanding, indication of varicocele repair to other patient populations, including men with nonobstructive azoospermia (NOA) and male partners of infertile couples embarking on ART, are more equivocal. To shed light on these controversial topics, we were fortunate to have two systematic reviews and meta-analyses in this Special Issue.^{19,20} In one of them, sperm retrieval rates by microdissection testicular sperm extraction were increased in men with NOA subjected to varicolectomy compared to those without prior varicocele repair (OR = 2.65; 95% CI: 1.69–4.14; $P < 0.001$). Pregnancy rates after intracytoplasmic sperm injection (ICSI) with the use of testicular sperm retrieved from men with NOA also favored the varicolectomy group, as shown by marginally significant results on live birth rates (OR = 2.19; 95% CI: 0.99–4.83; $P = 0.05$). The authors of the aforementioned study expanded on the topic and conducted a qualitative analysis of 15 studies that reported postoperative semen analysis after varicocele repair in men with NOA. In 43.9% of the patients sperm were found in postoperative ejaculates, indicating that sperm retrieval may be avoided. Natural and post-ICSI pregnancy rates were 13.6% and 18.9%, respectively, in the group of men with sperm in postoperative ejaculates.¹⁹ In the second study involving nonazoospermic men undergoing ICSI, there was a significant increase in clinical pregnancy rates (OR = 1.59, 95% CI: 1.19–2.12) and live birth rates (OR = 2.17, 95% CI: 1.55–3.06) when the male partners had been subjected to varicolectomy before ICSI compared to the group subjected to ICSI without previous

varicolectomy.²⁰ Nonetheless, given the paucity of studies included in these reviews and their retrospective design the quality of evidence was overall low to allow conclusive remarks.

Along the same lines, there are few studies addressing cost-effectiveness of varicocele surgery compared to ART, as reviewed by Chiles and Schlegel.²¹ The authors highlighted that the cost of the various procedures is an important consideration for couples and society given that private and public insurance providers do not routinely provide coverage for all interventions. Cost-effectiveness analyses are generally hampered because there is a wide variation of cost and effectiveness of various procedures in different institutions. Furthermore, indirect costs related to complications and multiple gestations are not usually taken into account. Quoting Thomas Jr. in his brilliant foreword to this Special Issue, “Success in the ART area has led some reproductive endocrinologists to suggest that given a few live normal appearing sperm is all they need for intracytoplasmic sperm injection and, therefore, it doesn’t matter if there is a varicocele or not in the male partner with suboptimal sperm quality. Disregarding the excessive costs, which are not inconsequential, and potential risks borne by the female partner undergoing ovarian stimulation and IVF, the need for repeated cycles and the inherent risks related to the greater incidence for multiple gestations, it would seem a grave disservice to a couple not to offer the option of a potentially curative solution to their infertility if the male partner has a varicocele and associated suboptimal semen quality.”²²

The aforementioned evidence suggesting the beneficial effect of varicocele repair to improve natural fertility in men with clinical varicocele and abnormal semen parameters support the current guidelines issued by the American Urological Association (AUA), American Society for Reproductive Medicine (ASRM) and European Association of Urology (EAU). As a matter of fact, the clinical practice guidelines and best practice statements for the diagnosis and management of varicocele in adults, children and adolescents were critically reviewed in this Special Issue by Shridharani *et al.*²³ and Roque and Esteves.²⁴ At present, the EAU Guidelines on Male Infertility and the European Society of Pediatric Urology (ESPU) are the only guidelines that offer recommendations along with levels of evidence and include an implementation schema. In general, guidelines concur that treatment should be offered to male partners of

infertile couples presenting for evaluation with clinical varicocele and semen abnormalities. However, guidelines differ on how varicocele should be diagnosed. While all guidelines recommend physical examination as the cornerstone of varicocele diagnosis, the EAU guidelines state that it should be complemented with color duplex ultrasonography. In addition, guidelines differed on the importance of performing multiple semen analysis for detecting semen abnormalities, and none of them have undertaken cost-effectiveness or risk-benefit analyses.²³ As far as children and adolescents are concerned, importance is given to testicular hypotrophy detected during physical examination (defined as a testis that is smaller by >2 ml or 20% compared to the other testis) with regards to treatment indication.²⁴ Of note, due to the paucity of robust data, most of the recommendations were derived from nonrandomized clinical trials, retrospective studies, and expert opinion. This data may reinforce the sentiment that guidelines should be used to provide a framework of standardized care while maintaining clinical autonomy and physician judgment. The limitations identified across all guidelines suggest ample opportunities for research and future incorporation of higher quality standards in patient care.

A section of this Special Issue was fully dedicated to contentious issues in varicocele management in which experts with vast clinical experience provided distinct and precise commentaries. Questions that haunt urologists/androgologists and patients alike, including the management of asymptomatic postpubertal males with equally sized normal testicles with palpable varicocele,²⁵ asymptomatic postpubertal males with a palpable varicocele and a contralateral subclinical varicocele,²⁶ asymptomatic males with large palpable varicocele and previous paternity desiring vasectomy in the scenario of low testosterone levels,²⁷ and symptomatic and asymptomatic males with subclinical varicocele found on ultrasound evaluation have been addressed in opinionated but honest and well-balanced appraisals on the topics we have chosen for them.^{28,29} As indicated by Edmund Ko and colleagues in their interesting commentary, with more prospective studies with improved methodology varicocele repair will no longer remain “much ado about nothing.”³⁰

As with any area of medicine, many issues remain unresolved. Lamb and Lipshultz’s group enlightens us on what remains controversial and which future paths to take.³¹ Molecular markers seem the way to go to a better selection of patients to treat. More

than 160 years since the first publication about varicocele, our knowledge greatly evolved with regards to the understanding of this enigmatic condition. Countless researchers and clinicians have spent a great deal of their time in investigating and providing the best care possible to males affected by varicocele. All of them, listed or not in the references of the articles pertaining to this Special Issue, should be wholeheartedly congratulated. This Special Issue of *Asian Journal of Andrology* aimed to be a landmark treatise on varicocele. The authors we have selected to highlight several important concepts have worked diligently and provided a realistic and critical appreciation of the challenges posed to them. Some years will pass until we can measure the impact of this publication lead by the outstanding initiative of the Editors of *Asian Journal of Andrology*. The closing article of our Special Issue brings about a perspective on how to measure the impact of scientific publication using metrics.³² This paper provided a broad overview of the wide array of metrics currently in use in academia and research and recommended the combined use of quantitative and qualitative evaluation using judiciously selected metrics for a more objective assessment of scholarly output and research impact. We hope the contents of this Special Issue of AJA will educate readers on varicocele and motivate further research that may shape not individual perceptions but entire fields of inquiry.

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