Peer Review File

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Reviewer A

The purpose of this manuscript was to review the guidelines for evaluation and treatment of azoospermia for the 2023 Canadian Urological Association. This is an editorial commentary.

1. Could the authors re-write their introduction? It is hard to follow the flow of thought, and not sure what the exact reason for their commentary is in this editorial. From the abstract I think they want to discuss the 2023 CUA's guidelines on azoospermia.
2. The rest of the manuscript is superficial and difficult to follow. I would like to see more detail in the various sections.

Reply A: The abstract section has been revised to include your contributions.

Changes in the text: This Commentary delineates the 2023 Canadian Urological Association's directive for the appraisal and therapeutic approach to azoospermia, a clinical syndrome marked by the non-presence of spermatozoa within the seminal fluid. This condition afflicts around 1% of the male demographic and is dichotomized into obstructive or non-obstructive categories, contingent on etiological factors.

The directive underscores the necessity of an exhaustive anamnesis and somatic examination to discern potential reversible etiologies of azoospermia. It advocates for laboratory inquiries, inclusive of hormonal profiling and genotypic assays, to augment the understanding of the disorder. Moreover, diagnostic imaging, such as scrotal sonography, may elucidate obstructive mechanisms.

Therapeutic strategies for azoospermia are predicated upon its categorization. In obstructive azoospermia, surgical restorative procedures like vasovasostomy or vasoepididyostomy are deliberated to reestablish spermatogenic flow. Conversely, non-obstructive azoospermia may necessitate intricate techniques such as testicular sperm extraction (TESE) to procure viable gametes for assisted reproductive technologies.

Furthermore, the guideline accentuates the pivotal role of counseling and ancillary support for those impacted by azoospermia, advocating for an interdisciplinary consort of urologists, reproductive endocrinologists, and genetic counselors to ensure all-encompassing management.

In summation, the 2023 Canadian Urological Association's guideline for azoospermia offers methodically substantiated counsel for the discernment and management of the ailment, endeavoring to facilitate prognostic outcomes for individuals and dyads grappling with sterility as a consequence of azoospermia.

Reviewer B

This Editorial Comment is in response to the Canadian Urological Association guidelines.

As an editorial comment on a guideline, it is appropriate, and we do not see anything in particular that needs to be modified.

Reply B: Thanks.

Reviewer C

Summary of content:

Hossein Azizi et al. provide an Editorial Commentary on the recently published Canadian guidelines for the evaluation and treatment of azoospermia.

Overall opinion of the manuscript:

This work outlines the information contained in the guidelines for the evaluation and treatment of patients with azoospermia.

These guidelines are the most recent Canadian guidelines. However, this paper is more a summary of the content of the guidelines than an editorial commentary in the sense that no comments or criticisms are made against the guidelines. We expected problems or errors to be raised, supported by literature and results.

What message did the author want to convey in this commentary, apart from summarizing the guidelines?

In addition, references 2 and 3 are the same.

Reply C: We delete reference two and add a related study.

Changes in the text: Recent research suggests that while the recommended treatments for obstructive azoospermia have remained consistent, with microsurgical vasal reconstruction being a suitable treatment, there has been a reinforcement of the superiority of micro-dissection testicular sperm extraction over sperm aspiration in men with nonobstructive azoospermia. This is significant because nonobstructive azoospermia involves a dysfunction in sperm production, which requires different management strategies, such as sperm retrieval techniques combined with in vitro fertilization (IVF) [10]. The evaluation of azoospermia involves a detailed assessment of the individual's medical history, physical examination, and diagnostic tests, such as hormone evaluations and genetic testing. For men with low-volume azoospermia, the diagnostic process may involve assuming normal follicle-stimulating hormone (FSH) levels and conducting further tests if abnormalities are detected. In all cases, counseling for alternative options like sperm donation, adoption, or living without children is an integral part of the process.

Reviewer D

The authors provide a well-written commentary on the upcoming Canadian Urological Association 2023 Guidelines for the evaluation and treatment of azoospermia. Indeed, these guidelines will assist urologists and non-urologist clinicians alike in managing this condition. By providing definitions, classifications, and a summary of the existing literature and expert recommendations, these guidelines will improve the quality of care for patients with azoospermia.

Additionally, please provide a citation for the percentage of men with azoospermia (line 27).

Reply D: Thanks. We add the references.

Changes in the text: A conditional recommendation with very low certainty of evidence is not made for neoadjuvant hormone therapy in males with testicular failure NOA [2]. Based on the available evidence, a conditional recommendation cannot be made for neoadjuvant hormone therapy in males with testicular failure NOA [3].

Reviewer E

The authors provide an editorial for the recently published Canadian Azoospermia guidelines. The authors provide a summary of each of the sections. To strengthen this submission, I would recommend the following to consider:

-Including some discussion surrounding highlighting some of the nuanced or controversial points and discussing how to use this in a clinician's practice would be helpful. Some of this is performed in the counselling section, which is an expansion beyond the guideline itself.

-Other points from the guideline that would be helpful right now include only performing vasectomy reversal's, if the surgeon has the skill set for both vasovasostomy and vasoepididymostomy.

-It would be helpful to be more specific with comments such as 'investigations', authors could highlight that FSH is the most important hormone when distinguishing NOA from OA, or y micro deletions and karyotype are important for the evaluation of azoospermia if no obvious obstructive aetiology, or CFTR for unilateral or bilateral absence of vas deferens.

-Re MRI comments, I think TRUS should be highlighted upon identifying if EDO, MRI can be used as an adjunct therapy, but isn't typically used up front.

-In the spirit of an editorial, adding some professional opinion to the content i.e., emphasizing key highlights from the guideline that may not have been addressed in other guidelines would be helpful (e.g., using the EtD GRADE framework, uses a very multi-dimensional and rigorous approach in attempt to address controversial or challenging questions in our field). Similarly, emphasizing the need for higher quality data could be helpful, -perhaps having a 'call to action', could or organizations work to facilitate multi-site research? etc.

Reply E: Thank you so much. We corrected and added some studies related to these topics.
Changes in the text:
(To further understand patient perspectives on treatment pathways and their multidimensional impacts, value-based research is needed on patients with NOA and their partners. In cases of obstructive azoospermia, where the blockage in the male reproductive tract prevents the presence of sperm in the ejaculate, reconstructive surgery is a primary treatment option. Vasovasostomy and vasoepididymostomy are microsurgical procedures that restore the passage of sperm. Vasovasostomy is the reconnection of the vas deferens, which is the duct that transports sperm from the epididymis to the ejaculatory ducts. Vasoepididymostomy is a more complex surgery that attaches the vas deferens directly to the epididymis when a closer connection is needed, often due to a blockage closer to the testis. The choice between these procedures is influenced by the site and cause of the obstruction, to restore the flow of sperm to the ejaculate, thus enabling natural conception.
Recent research suggests that while the recommended treatments for obstructive azoospermia have remained consistent, with microsurgical vasal reconstruction being a suitable treatment, there has been a reinforcement of the superiority of micro-dissection testicular sperm extraction over sperm aspiration in men with nonobstructive azoospermia. This is significant because nonobstructive azoospermia involves a dysfunction in sperm production, which requires different management strategies, such as sperm retrieval techniques combined with in vitro fertilization (IVF) [10].
The evaluation of azoospermia involves a detailed assessment of the individual's medical history, physical examination, and diagnostic tests, such as hormone evaluations and genetic testing. For men with low-volume azoospermia, the diagnostic process may involve assuming normal follicle-stimulating hormone (FSH) levels and conducting further tests if abnormalities are detected. In all cases, counseling for alternative options like sperm donation, adoption, or living without children is an integral part of the process.)
The cystic fibrosis transmembrane conductance regulator (CFTR) gene, known for its role in the pathogenesis of cystic fibrosis (CF), has been implicated in the etiology of azoospermia, particularly congenital bilateral absence of the vas deferens (CBAVD). Variants in the CFTR gene can result in the malfunctioning of the CFTR protein, affecting the ion transport in the epithelial cells of the reproductive tract, leading to the obstruction and atrophy of the vas deferens. On the other hand, follicle-stimulating hormone (FSH) plays a crucial role in spermatogenesis, and alterations in FSH levels or signaling can also lead to azoospermia, a condition characterized by the absence of sperm in the ejaculate. Guidelines for the evaluation and treatment of azoospermia typically include genetic screening for CFTR mutations, especially in cases of CBAVD, and assessment of FSH levels to determine the presence of spermatogenic failure. Treatment strategies are tailored based on the underlying etiology, ranging from surgical correction, assisted

reproductive technologies, and hormone therapy, with an interdisciplinary approach involving urologists, genetic counselors, and fertility specialists being paramount for optimal patient care.)