

2023 Canadian Urological Association guideline: Evaluation and management of azoospermia

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INTRODUCTION

Male infertility affects 15% of couples, with azoospermia diagnosed among 1% of the general male population and 10-15% of males presenting with infertility. Use of well-defined diagnostic tools enable clinicians to reliably classify the etiology of azoospermia as pre-testicular, testicular or post-testicular causes. Shared decision-making is recommended in navigating potential therapeutic options for couples wishing to pursue fertility. The purpose of this guideline is to equip the Canadian clinician with a diagnostic and management approach for males presenting with azoospermia. To achieve this, we provide a narrative overview and highlight three priority clinical questions which were identified through a needs assessment among Canadian Urologic

Association (CUA) members. For these priority topics, we performed a critical evaluation of the literature using Evidence to Decision (EtD) GRADE framework to arrive at transparent evidence-based recommendations.

1.0 SUMMARY OF RECOMMENDATIONS

The committee identified three specific clinical circumstances in the management of non-obstructive azoospermia (NOA) by which to apply the GRADE evidence to decision (EtD) framework for a transparent and systematic approach to make well informed healthcare choices and recommendations. See Section 6 for detailed explanation of each recommendation.

Among males with NOA, does cryopreservation of surgically retrieved sperm lower IVF-ICSI live birth rates in comparison to fresh sperm and oocytes?

- **Recommendation 1:** We suggest cryopreservation of surgically retrieved sperm for most couples with NOA and subsequent IVF-ICSI (*Conditional recommendation, very low certainty of evidence*).

Among males with testicular failure NOA and a varicocele, does varicocele repair prior to surgical sperm retrieval and IVF-ICSI improve live birth rates compared to observation?

- **Recommendation 2:** We suggest observation of varicoceles for most couples with testicular failure NOA and a varicocele considering surgical sperm retrieval and IVF-ICSI as compared to pre-treatment with varicocelectomy (*Conditional recommendation, very low certainty of evidence*).

Among males with testicular failure NOA, does neo-adjuvant hormonal therapy improve IVF-ICSI live birth rates compared to conservative management?

- **Recommendation 3:** We do not suggest adjuvant hormone therapies for males with testicular failure NOA for the purpose of improving IVF-ICSI live birth rates (*Conditional recommendation, very low certainty of evidence*).

2.0 METHODOLOGY

The guideline can be considered at two parts. One in which the panel attempted to assess priority areas of controversy in a systematic way using GRADE EtD framework. The second as a narrative summary of background information for learners that is essential to understanding the topic area.

The work in this guideline was carried out by a panel of 17 subspecialty urologists. This panel was selected to represent a broad geographic representation of Canadian male reproductive experts. At the onset, each panel member contributed to the scope, audience and topics of interest

to cover in the guideline. In parallel, 10 community urologists were contacted across the country to perform a needs assessment for the content and topics they would like discussed in the guideline (*Appendix 1*). Virtual meetings were then conducted among all members of the guideline committee to further define scope, topics for discussion, and topics to evaluate through Evidence to Decision (EtD) GRADE methodology^{1,2}.

The expert panel assessed available literature and existing guidelines from the American Urologic Association (AUA)³ and previous Canadian Urologic Association (CUA)⁴ guidelines and incorporated expert opinion from the 17 members of the panel with input from 10 community urologists to arrive at a list of 26 general topics felt to be important to include in the guidelines. The expert panel reviewed the 26 topics and determined, through expert opinion and literature review, that there were 8 controversial topics where a more in-depth assessment using the GRADE EtD framework might provide a more informed review and benefit the urologic and reproductive communities. Given the time intensive nature of using the GRADE EtD framework and available resources, the panel decided that only 3 high-priority, controversial questions could practically be addressed in these guidelines. The selection of the three topics to study using the GRADE EtD framework was then decided by a consensus of the expert panel. The panel recognizes that there may be additional important questions that merit systematic evaluation and can be addressed in subsequent iterations of this guideline. The selected topics are listed below.

1. Among males with NOA, does cryopreservation of surgically retrieved sperm lower IVF-ICSI live birth rates in comparison to fresh sperm and oocytes?
2. Among males with NOA and a varicocele, does varicocele repair prior to surgical sperm retrieval and IVF-ICSI improve live birth rates compared to observation?
3. Among males with hypergonadotropic-hypogonadism (testis failure) NOA, does neo-adjuvant hormonal therapy improve IVF-ICSI live birth rates compared to conservative management?

The second narrative component of this guideline intends to provide an overview of the background, evaluation and standard management of males with azoospermia for a general Canadian urologist. This section is largely based upon clinical principles and expert opinion which is listed throughout for clarity but should not be mistaken for a systematic assessment of evidence. Other goals derived from the panel's discussions and needs assessment were to define clinical scenarios requiring referral to a fertility subspecialist to support the general Canadian urologist and provide optimal patient care.

2.1 About GRADE

The GRADE approach facilitates assigning certainty of evidence for each outcome. Using this methodology, the level of certainty was categorized as very low, low, moderate or high^{2,5}. The EtD framework facilitated a systematic approach to make clinical recommendations based upon a balance of critical components that underly clinical decision making. These include desirable effects, undesirable effects, balance of these effects, certainty in estimates of effect, cost effectiveness, equity, resources required, patients' values and preferences, feasibility and acceptability⁵. The summary of findings (SoF) and EtD framework tables were generated using the GRADEpro GTD application and are available in the Appendix at cuaj.ca^{6,7}.

Since the GRADE and EtD framework were used to answer three questions in the management of non-obstructive azoospermia (NOA), live birth rates, clinical pregnancy rates and sperm retrieval rates were considered as outcomes when available. The effect estimates for these three questions were derived from the most recent and comprehensive existing meta-analyses and systematic reviews, by reproducing some stages of the review to ensure accuracy of the effect sizes. These stages included overall appraisal of the systematic reviews and meta-analyses, review and evaluation of additional literature to locate missing studies, evaluating risk of bias from the original studies, then re-performing the meta-analyses again.

Shared decision making between the clinician and patient is key to interpreting recommendations from the GRADE framework, where patient values and preferences are central. Recommendations are categorized by direction, for or against, and by strength, strong or conditional. A strong recommendation implies that the panel believes that a significant majority of patients would be in alignment with the recommendation when aware of the available evidence. A conditional recommendation indicates that the panel believes most patients would agree with the recommendation, but a significant proportion would not. Thus, for a minority of patients it may be appropriate not to proceed with the conditional recommendation. Therefore, for conditional recommendations it is critical for the clinician and patient to engage in shared decision-making consider available evidence, patient values and preferences to arrive at the “best” course of action.

3.0 INCIDENCE & DEFINITION OF AZOOSPERMIA

Male infertility affects 15% of couples globally, with male factors contributing to 50% of cases⁸⁻¹⁰. The most severe form of infertility is termed azoospermia and is defined by the complete absence of sperm after microscopic evaluation of 2 separate semen samples after centrifugation at 3000g for 15 minutes^{11,12}. Azoospermia is found in 1% of the general population and 10-15% of males presenting for fertility evaluation¹³.

4.0 CLASSIFICATION & AETIOLOGIES OF AZOOSPERMIA

Azoospermia may be classified through several approaches, Figure 1. Anatomical classification includes division by pre-testicular, testicular and post-testicular aetiologies.

- **Pre-testicular azoospermia** accounts for 2% of males with azoospermia^{4,14-16}. It is defined as a failure of sperm production (non-obstructive azoospermia) due to a hypothalamic or pituitary abnormality, presenting as hypo-gonadotropic-hypo-gonadism (HH). This may be due to congenital abnormalities (i.e. normosmic idiopathic HH, or anosmic HH i.e. Kallman syndrome), or acquired (i.e. pituitary tumor, pituitary or hypothalamic trauma, or through exogenous testosterone or hormone therapies)¹⁷.
- **Testicular failure azoospermia** (non-obstructive azoospermia [NOA]) accounts for 49-93% of males with azoospermia^{4,14-16}. It is defined as a failure of sperm production due to testicular failure, presenting as hyper-gonadotropic-hypo-gonadism. This may be due to congenital abnormalities (i.e. Klinefelter Syndrome, Y-chromosome microdeletions) or may be acquired (i.e. chemotherapy, radiation therapy, etc). Histopathologic classification is often used to sub-characterize testis failure NOA. This includes *hypospermatogenesis* where rare spermatozoa are identified, *maturation arrest* where germ cell differentiation stops at any immature stage, or *Sertoli cell only syndrome* where no germ cells are identified on histology.
- **Post-testicular azoospermia** accounts for 7-51% of cases with azoospermia^{4,14-16}. It is due to either obstruction of the male reproductive tract, that may be acquired or congenital, such as absence of vas deferens, or an ejaculatory abnormality in the presence of otherwise normal spermatogenesis.
 - **Obstruction** may occur at the level of the epididymis, vas deferens, or ejaculatory duct. Epididymal obstruction may be acquired following epididymitis, idiopathic, or secondary to blockage associated with vasectomy or incidentally with scrotal surgery in up to 10-15% of cases. Vas deferens obstruction may be acquired during vasectomy, inguinal hernia repair or pelvic surgeries. Congenital obstruction of the epididymis or vas deferens may be associated with mutations of the cystic fibrosis transmembrane regulatory gene (CFTR). Ejaculatory duct obstruction may be due to Mullerian or ejaculatory duct cysts or secondary to urethral instrumentation.
 - **Ejaculatory abnormalities** may include retrograde ejaculation, anejaculation or failure of emission. Retrograde ejaculation may be associated with benign prostatic hyperplasia, prostate ablating surgeries (e.g. transurethral resection of prostate), or medications altering the bladder neck (e.g. alpha blockers). Anejaculation is most often associated with selective serotonin reuptake inhibitors (SSRIs) but may also be associated with hyperprolactinemia and low testosterone or psychogenic. Failure of emission can occur from similar causes as retrograde ejaculation but is often associated with neurologic dysfunction as seen in spinal cord injury and pelvic nerve injuries (e.g. retroperitoneal lymph node dissection).¹⁸

5.0 EVALUATION OF THE MALE WITH AZOOSPERMIA

Investigation of the male with azoospermia through a systematic and algorithmic approach will result in accurate diagnosis in most circumstances as demonstrated in Figures 2 and 3. Some investigations may be initiated by general practitioners and general urologists, while final diagnosis and management is best offered through a male infertility expert connected to appropriate clinical facilities with a full breadth of clinical and surgical expertise.

Standard of care

Males found to have azoospermia on semen analysis, should undergo a second semen analysis with microscopic evaluation of the centrifuged pellet. In addition to thorough history and physical exam, patients should undergo serum follicle stimulating hormone (FSH), morning total testosterone testing and luteinizing hormone (LH) (note: LH is not required if total testosterone (TT) is normal; however, if TT low, then LH, estradiol and prolactin testing are indicated). These patients should undergo further evaluation by a male reproductive expert for specialized testing, medical and surgical management. Their partner should also undergo a complete female fertility evaluation with a reproductive endocrinology/infertility specialist. (Clinical Principle)

History

The aim of the infertility history is to identify underlying aetiologies and potentially modifiable factors to enhance their chances of fertility. It is also important to understand and tailor management to the couple's fertility goals. Table 1 summarizes areas of importance when taking an infertility history in addition to open ended questions. (Expert Opinion)

Physical examination

Physical exam is extremely important in helping distinguish the etiology of azoospermia. Key features on physical exam are summarized in Table 2. An emphasis of importance is placed on testis size, epididymal fullness, and presence of vas deferens. (Expert Opinion)

Standard investigations (based on expert opinion):

- **Mandatory:** These include 2 semen analyses, serum morning TT and serum FSH.
 - Semen analyses should be centrifuged at 3000g for 15 minutes with microscopic evaluation of the pellet for rare sperm^{11,12}. Semen volume is critical in guiding further azoospermia evaluation.
 - Serum morning TT, LH and FSH help differentiate pre-testicular, testicular and post-testicular aetiologies of azoospermia. Undetectably low FSH and low TT suggest pre-testicular azoospermia. Normal FSH and TT suggest post-testicular azoospermia. Elevated FSH with normal or low TT suggest azoospermia associated with testicular failure.

- **Optional tests:** These include LH, prolactin and estradiol if TT is low. Scrotal ultrasound is not routinely ordered, but may be considered if physical examination is difficult, or testicular mass is suspected. (Expert Opinion)

Specialized investigations (based on expert opinion):

- **Karyotype** is routinely ordered for all males with azoospermia with suspected testicular failure. While numerous abnormalities have been associated with azoospermia, Klinefelter Syndrome, defined as the presence of at least one additional X chromosome (i.e. 47, XXY), is the most common genetic abnormality in males with azoospermia and is identified in 10.8% of males with azoospermia due to testicular failure¹⁹. Other chromosomal abnormalities may include, but are not limited to, inversion, translocations, and other sex chromosome abnormalities^{19,20}. Couples with karyotypic abnormalities may benefit from referral for genetic counselling.
- **Y chromosome microdeletion (YCM)** is routinely ordered for all males with azoospermia with suspected testicular failure. This test evaluates for DNA deletions of the azoospermia factor region on the Y chromosome. Commonly evaluated YCMs include the AZFa, AZFb, and AZFc deletion and are found in 7.5% of azoospermic males²¹. Complete deletions of AZFa and AZFb regions have not been associated with successful sperm retrieval, and thus sperm retrieval should not be attempted. Thirty three percent of men with complete AZFc deletions have been found to have sperm present in the ejaculate, while 47% of men with azoospermia with complete AZFc deletions have successful surgical sperm retrieval²². Couples with YCMs may benefit from referral for genetic counselling.
- **Cystic fibrosis transmembrane conductance regulatory gene (CFTR)** is indicated for males with absent vas deferens (unilateral or bilateral), idiopathic epididymal obstruction or absent/hypoplastic seminal vesicles on transrectal ultrasound (TRUS). Numerous mutations have been described and commonly used assays report on frequently identified mutations. CFTR pathogenic variants are identified in 80-97% of men with congenital bilateral absence of vas deferens (CBAVD)^{23,24}. When CFTR mutations are identified, the female partner should also be evaluated for CFTR mutations, and the couple referred for genetic counselling to discuss the risk of cystic fibrosis in the offspring.
- **Post-ejaculate urine analysis** is indicated in low volume azoospermia (<1.5 milliliter) to evaluate for presence and quantity of sperm in the urine reflective of retrograde ejaculation.
- **Transrectal ultrasound** is indicated in low volume azoospermia (<1.5 milliliter), when semen pH is <6.8, fructose is negative and retrograde urine analysis is negative. CFTR testing is indicated in cases with absent or hypoplastic seminal vesicles and abdominal vas deferens as the male will have 80% risk of carrying a CFTR mutation²⁵. Enlarged seminal vesicles (>1.5cm wide) typically reflect ejaculatory duct obstruction which may be accompanied by a cystic structure in the prostate²⁶.

- **Testis biopsy** is not routinely performed in the evaluation of azoospermia. Testis biopsy is reserved for male reproductive experts and can be used to confirm a presumptive diagnosis of obstructive azoospermia, typically in situations where history, physical exam findings and investigations (serum FSH) point to a post testicular aetiology of azoospermia but are unclear. If testis biopsy is indicated, unilateral biopsy should be performed if symmetrical testis volume. If asymmetrical testis volumes, the larger of the two testes should be biopsied.
- **Abdominal ultrasound** is indicated in the presence of unilateral or bilateral non-palpable vas deferens. The purpose is to evaluate for embryologic mesonephric (Wolffian) duct anomalies (e.g. renal agenesis, malformation or malposition).
- **DNA sequencing.** While reports of single gene defects have been reported in the literature^{27,28}, routine whole genome sequencing, whole exome sequencing, or gene arrays are not currently indicated for routine clinical testing.
- **Biomarkers for NOA** have been investigated for decades. Anti-mullerian Hormone (AMH) and inhibin B have been investigated but do not meaningfully predict chances of sperm retrieval for men with testis failure NOA²⁹⁻³³. Recent reports of AMH:testosterone appear intriguing; however, additional data is required prior to application to widespread clinical practice.

In summary, history, physical and investigations will help the clinician delineate the underlying classification and cause of azoospermia. Azoospermia evaluative algorithms are divided into low volume azoospermia, Figure 2, and normal volume azoospermia, Figure 3.

6.0 MANAGEMENT OF AZOOSPERMIA

Couples should be counselled that their fertility options may include child-free living, adoption, donor sperm or attempts to have children genetically related to the male. The following management approaches are directed toward having children genetically related to the male. Figures 2 and 3 summarize the diagnostic and treatment algorithms for males with azoospermia. Management of males with azoospermia should be performed by urologists with expertise in male reproduction with access to advanced fertility centre services.

Pre-testicular azoospermia

The treating clinician should reverse any identified causes of pre-testicular azoospermia. Advanced hormonal manipulation should be done under the supervision of a fertility specialist comfortable with prescribing the medications and monitoring these patients (*Expert opinion*).

Congenital pre-testicular azoospermia

Congenital pre-testicular azoospermia is most commonly managed with gonadotropic therapy. While several different medications and combinations may be used, in most instances, human chorionic gonadotropin therapy (hCG) is routinely used between 1000 and 2500 international units (IU) injected subcutaneously two to three times per week. Addition of recombinant FSH (rFSH) 75 to 150 IU three times per week or human menopausal gonadotropins (hMG) 75 to 150 IU three times per week may be considered after 3-6 months if no sperm is present in the ejaculate. Alternative options may include pulsatile gonadotropin releasing hormone (GnRH) pump. Spermatogenesis may be achieved in 80% by 6 months³⁴ and overall up to 90% of males with gonadotropin therapy. Surgical sperm retrieval using a technique such as microdissection testicular extraction of sperm (mTESE) is only considered after an adequate trial of gonadotropin therapy by a reproductive expert³⁴⁻³⁷ (*Expert opinion*).

Acquired pre-testicular azoospermia

Exogenous testosterone, steroids or hormone therapy should be stopped when safe or augmented with gonadotropins if not otherwise possible. The patient may be followed for natural recovery of the hypothalamic-pituitary-gonadal (HPG) axis by following serum LH, FSH, TT +/- estradiol and semen analyses every 1-3 months. Clinicians may consider use of off-label gonadotropin therapy (i.e. hCG), selective estrogen receptor modulators (SERMs) (i.e. clomiphene), or aromatase inhibitors (AIs) (i.e. anastrozole or letrozole) to augment HPG recovery. If HPG recovery is not possible, the clinician should use gonadotropin therapy as discussed above for *congenital pre-testicular azoospermia*. Elevated prolactin should be repeated, and if remains elevated, patients should have expert endocrine evaluation such as referral to an endocrinologist when the treating reproductive urologist does not have the expertise for further evaluation and management. (*Expert Opinion*)

Testicular failure azoospermia (NOA)

Fertility options for couples where the male has testicular failure NOA includes attempted surgical sperm retrieval combined with in vitro fertilization intracytoplasmic sperm injection (IVF-ICSI), donor sperm, adoption or child free living. Sperm retrieval techniques described have included testicular sperm extraction (TESE)³⁸, fine needle aspiration mapping (FNA)³⁹, and mTESE⁴⁰. mTESE is the most accepted technique among male reproductive experts. While no head-to-head controlled randomized trials exist comparing surgical techniques, among studies controlled for histopathology, mTESE is 1.3 times more likely to retrieve sperm than conventional TESE. This corresponds to a number needed to treat (NNT) of 8, and drops to a NNT of 5 in cases of Sertoli Cell Only (SCO), where sperm retrieval is 2.3 times more likely with mTESE⁴¹. mTESE leverages the ability to take advantage of intratesticular heterogeneity of spermatogenesis. It requires use of an operating microscope to visualize the seminiferous tubules within the testis, allowing the surgeon to select the healthiest appearing tubules potentially containing sites of active spermatogenesis. This tissue is further dissociated and analyzed using a

bench microscope to find rare sperm in 52% of males⁴². Sperm used with IVF-ICSI leads to oocyte fertilization in approximately 57% of attempts and results in clinical pregnancy and live birth rates in up to 39% and 24% of patients that undergo embryo transfers respectively⁴³. No apparent differences exist in congenital malformations for offspring of fathers with NOA compared to OA controls undergoing IVF-ICSI⁴⁴. mTESE procedures may be offered to all males with testicular failure NOA, but should only be undertaken in a centre with expertise in mTESE and where an IVF-ICSI laboratory has expertise in processing the tissue. Males with NOA should also be made aware of options for sperm donation, adoption and child free living (*Expert opinion*).

Unique considerations:

- In males with complete AZFa or AZFb deletions sperm have not been previously identified during retrieval and the utility of retrieval by any technique is negligible.
- While controversy exists among timing of attempted surgical sperm retrieval in males with Klinefelter Syndrome, the committee recommends performing surgical sperm retrieval for males at the time of desired fertility, or post-pubertally prior to initiating exogenous testosterone therapy, among males when they and their families have been adequately counselled and wish to attempt cryopreservation.⁴⁵ (*Expert opinion*).

GRADE EtD recommendations

The panel identified three specific clinical circumstances in the management of NOA by which to apply the GRADE evidence to decision (EtD) framework for a transparent and systematic approach to make well informed healthcare choices and recommendations. These recommendations are summarized at the beginning of this guideline and should be used as guidance and not definitive rules, as shared decision-making is an essential element for personalized patient management.

Among males with NOA, does cryopreservation of surgically retrieved sperm lower IVF-ICSI live birth rates in comparison to fresh sperm and oocytes?

Based upon the available evidence, the panel ***conditionally recommends*** cryopreserving microsurgically retrieved sperm in males with NOA to use for a subsequently staged cycle of IVF-ICSI. This recommendation should be considered as a general guiding principal, where certain patient and couple centered factors may influence the approach of performing fresh mTESE sperm retrievals concomitant with fresh/frozen oocytes for IVF-ICSI, versus staged mTESE sperm retrieval with cryopreservation and subsequent IVF-ICSI cycle. Of particular note, the current health care coverage in Quebec favors the use of fresh sperm retrieval and IVF-ICSI due to substantial cost savings for the couple compared to a cryopreservation protocol. For couples looking for the highest chance of live birth irrespective of all other considerations, then a fresh sperm retrieval and IVF-ICSI cycle may be preferred. *Appendix 2* transparently

summarizes the panel's summary of judgements related to components underlying clinical decision making for this question such as: desirable effects, undesirable effects, balance of these effects, certainty in estimates of effect, cost effectiveness, equity, resources required, patients' values and preferences, feasibility and acceptability⁵.

The panel reviewed 24 studies⁴⁶⁻⁶⁹ from Amer & Fakhry 2021 systematic review⁷⁰ and subsequent studies published since this review, where an appropriate comparator arm was available. The panel acknowledges that the evidence has significant limitations as only 7 of 23 cryopreservation studies reported an intention-to-treat-like methodology where patients were included if sperm were found during surgical sperm retrieval, thereby capturing potential unusable sperm after cryopreservation; the remainder of the studies potentially underestimate the negative impact of cryopreservation on primary and secondary outcomes by only reporting IVF-ICSI outcomes with useable sperm in fresh or cryopreserved conditions. We calculate a 92.2% rate of finding useable sperm for IVF-ICSI after cryopreservation and thawing of NOA-derived testicular sperm, among all studies reporting this data, meaning that 7.8% of couples may not have useable sperm following thawing of a cryopreserved sample. In this context, the meta-analysis results for the primary outcome, live birth rate, demonstrated that cases using cryopreserved sperm had a RR of 0.77 (95% CI: 0.67 to 0.89) compared to those cases using fresh sperm; similarly, we performed a sensitivity analysis including only the 7 studies utilizing an intention-to-treat-like methodologically demonstrating that using cryopreserved sperm had a RR of 0.73 (95% CI: 0.60 to 0.88). Collectively, both the primary meta-analysis and sensitivity analyses favor the use of fresh sperm over cryopreserved sperm in patients undergoing surgical sperm retrieval and IVF-ICSI, *see appendix 3, 4a, 4b, 5a, 5b for summary of literature, effect size and summary of findings*. While performing coordinated fresh sperm retrieval and oocyte retrieval for IVF-ICSI appears to have an advantage for overall live birth rates, there are notable potential disadvantages in this approach compared to sperm retrieval and cryopreservation prior to oocyte retrieval and IVF-ICSI, such as increase cost⁷¹ and harms to the female partner when committing to an IVF cycle if back-up donor sperm is not desired, and limitations to accessing such logistics at many centres. Therefore, the panel suggests that most couples would overall benefit from cryopreservation of surgically retrieved mTESE sperm with subsequent IVF-ICSI; however, it is also acceptable to perform coordinated fresh sperm retrieval and oocyte retrieval, to meet the needs of individual couples, such as couples desiring highest chance of live birth rate irrespective of all other considerations, couples willing to use back up donor sperm, or couples living in Quebec.

Among males with NOA and a varicocele, does varicocele repair prior to surgical sperm retrieval and IVF-ICSI improve live birth rates compared to observation?

Based upon the available evidence, the panel *conditionally recommends observing varicoceles* prior to surgical sperm retrieval in patients with NOA. This recommendation should be

considered as a general guiding principal, where certain patient and couple centered factors may influence the approach of performing varicocele repairs prior to attempted sperm retrieval. Couples with younger female age may be amenable to an attempted varicocele repair (VR), where the delay in attempted sperm retrieval and IVF-ICSI doesn't change the statistical IVF-ICSI outcomes. *Appendix 6* transparently summarizes the panel's summary of judgements related to components underlying clinical decision making for this question such as: desirable effects, undesirable effects, balance of these effects, certainty in estimates of effect, cost effectiveness, equity, resources required, patients' values and preferences, feasibility and acceptability⁵.

The panel reviewed 3 studies for sperm retrieval⁷²⁻⁷⁴, 1 study for clinical pregnancy and live birth rates⁷⁴ derived from several recent meta-analyses and systematic reviews⁷⁵⁻⁷⁷, and numerous studies evaluating VR complications and recurrences⁷⁸⁻⁸⁵. The studies by Haydardedeoglu *et al.* 2010⁸⁶ and Kizilkan *et al.* 2019⁸⁷ were excluded, which deviated from previously published meta-analyses due to the comparator group not having a varicocele; thus, preventing the comparison of a treatment effect of a varicocele repair. Based upon the primary outcome of live birth rates, males that underwent VR had a RR of 1.43 (95% CI: 0.34 to 6.11) compared to males that had a varicocele and did not undergo VR. Secondary outcomes of clinical pregnancy rate demonstrated that males undergoing VR had a RR of 1.75 (95% CI: 0.42 to 7.27) compared to males with a varicocele who did not undergo VR, and sperm retrieval rate demonstrated that males undergoing a VR had a RR of 1.19 (95% CI: 0.82 to 1.73) compared to males with a varicocele that did not undergo a VR, *see appendix 7, 8, 9, 10 for summary of literature, effect size and summary of findings*. With a significant paucity of data, further studies with appropriate comparator groups are needed to further evaluate the role of VRs in this group.

Among males with testicular failure NOA, does neo-adjuvant hormonal therapy improve IVF-ICSI live birth rates compared to conservative management?

Based upon the available evidence, the panel *conditionally recommends proceeding directly to microsurgical sperm retrieval* in the context of neoadjuvant hormone therapy for the sole purpose of improving fertility outcomes such as live birth rate. This recommendation should be considered as a general guiding principal, where certain patient and couple centered factors may influence the approach of neoadjuvant hormone therapy prior to attempted sperm retrieval. Patients that are hypogonadal and symptomatic may still benefit from adjuvant therapies such as selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs) and gonadotropins such as human chorionic gonadotropin (hCG). *Appendix 11* transparently summarizes the panel's summary of judgements related to the components underlying clinical decision making for this question such as: desirable effects, undesirable effects, balance of these effects, certainty in estimates of effect, cost effectiveness, equity, resources required, patients' values and preferences, feasibility and acceptability⁵.

The panel reviewed studies derived from the recent meta-analysis by Tharakan *et al.* 2022⁸⁸. These included 3 studies reporting on clinical pregnancy rates and live birth outcomes⁸⁹⁻⁹¹, and 12 studies evaluating sperm retrieval rates⁸⁹⁻⁹⁹. It should be prefaced that the treatment regimens were extremely heterogeneous; sensitivity analyses for specific regimens are included in the *appendix 13, 14, 15*. Similarly, the patient populations were highly heterogeneous including some patients with Klinefelter Syndrome, others with idiopathic NOA, primary mTESEs and some salvage mTESEs. Based upon the primary outcome, the RR of live birth rate for males treated with neoadjuvant hormone therapy was 0.75 (95% CI: 0.52 to 1.08) relative to males who did not. The secondary outcomes of clinical pregnancy rate demonstrated that males treated with neoadjuvant hormone therapy had a RR of 0.94 (95% CI: 0.57 to 1.53) compared to males with no treatment, and surgical sperm retrieval rates demonstrated a RR of 1.40 (95% CI: 1.01 to 1.93) in males treated with neoadjuvant hormone therapy relative to males that did not, *see appendix 12, 13, 14, 15 for summary of literature, effect size and summary of findings*. Therefore, it is emphasized that subpopulations may have potential benefit as additional, higher-quality data is generated and considered; however, at the present time, the patient populations and neoadjuvant hormonal strategies remain poorly understood to support generalized use of neo-adjuvant hormones in all males with NOA.

Post-testicular Azoospermia (based on expert opinion)

Management of post-testicular azoospermia may be achieved through appropriate surgical reconstruction/correction, medical therapies (ejaculatory failure), or through sperm retrieval and advanced reproductive therapies (ART).

Obstructive azoospermia

- **Epididymal obstruction** may be successfully reconstructed micro-surgically to facilitate motile sperm to be transported into the semen in 48-84% of cases¹⁰⁰, and facilitate a natural pregnancy in approximately 20-50% of cases¹⁰¹. Various surgical techniques have been described for vasoepididymostomies (VEs) with longitudinal intussuscepted vasoepididymostomy (LIVE) being broadly cited with respectable success rates^{100,102}, although microsurgical technique of the surgeon's preference is appropriate. An operating microscope should be used in all epididymal reconstruction procedures. Patients should be offered the opportunity to cryopreserve sperm at the time of the procedure, since a non-trivial number of patients undergoing epididymal reconstruction are not ultimately successful in establishing motile sperm in the ejaculate. Patients may also be offered the opportunity to cryopreserve sperm following successful epididymal reconstruction where sperm is present in the semen post operatively, in case they acquire a late failure of the anastomosis.
- **Vasal obstruction** encountered in the scrotum, inguinal canal or intra-abdominally may be successfully reconstructed micro-surgically to facilitate motile sperm to be transported into the semen to accommodate a natural pregnancy. Numerous

techniques exist with adequate reported success. Multi-layer anastomoses with an operating microscope are recommended. Patency rates have been reported to vary between 70 and 99.5%^{101,103}, with the highest reported rates using multi-layer, microdot techniques¹⁰⁴.

- **Vasectomy reversals** may be performed by surgeons who possess the clinical and microsurgical expertise, operating microscope availability, equipment and environment necessary to perform either a vasovasostomy or vasoepididymostomy at the time of reconstruction. Vasectomy reversals should not be routinely offered if the ability to adequately perform a vasoepididymostomy is not within the skillset of the surgeon as an estimated 13%-60% of vasectomy reversal cases require at least unilateral VE¹⁰⁵⁻¹⁰⁸, including up to 20% within obstructive intervals of 0 to 3 years¹⁰⁶, and no available preoperative definitive diagnostic test can determine the presence of epididymal obstruction. To determine which type of reconstruction is necessary, intra-vasal fluid should be evaluated microscopically at the time of the reconstruction to determine whether a vasal or epididymal reconstruction is necessary. Patients seeking vasectomy reversals should be made aware of sperm retrieval and IVF-ICSI as another viable fertility option for couples desiring biologic children, or the ability to concomitantly perform sperm retrieval at the time of vasectomy reversal.
- **Ejaculatory duct obstruction (EDO)** may be successfully treated through transurethral resection of ejaculatory duct (TURED). This procedure is successful in improving semen parameters among 59% of patients with complete EDO, and 94% with partial EDO, resulting in spontaneous pregnancy rates between 12.5%-31%. TURED is best performed with intraoperative real time TRUS guidance to precisely unroof the ejaculatory duct cyst. Pre-operative counselling of potential surgical complications and the risks of re-stenosis post-operatively is important.¹⁰⁹

Ejaculatory failure

- **Failure of emission** may be overcome through electroejaculation (EEJ) in nearly all men to successfully obtain sperm.
- **Retrograde ejaculation** may be managed through use of oral sympathomimetics such as pseudoephedrine 60-120mg prior to ejaculation. In refractory cases, a retrograde urine sample may be collected for subsequent ART. Urine alkalization using NaHCO₃ should be performed prior to retrograde sample collection to optimize sperm quality.
- **Anejaculation** may be managed through modifying any reversible factors (e.g. SSRI discontinuation), or through psycho-sexual education and counselling when appropriate. Limited data exists for off-label medication use such as cabergoline¹¹⁰. In refractory cases, sperm may be retrieved through EEJ or directly from the testicle or epididymis.

In cases where spinal cord injuries (SCI) are present, penile vibratory stimulation (PVS) may be performed with success in eliciting antegrade ejaculation among 86% of males whose level of injury is T10 or cranial, and in 17% of males whose level of injury is T10 or caudal¹¹¹. In refractory cases, EEJ may be considered which elicits ejaculation among 97% of males¹¹¹. It is important to monitor and be prepared to treat males with SCI receiving PVS or EEJ for autonomic dysreflexia.

Sperm retrieval for post-testicular azoospermia

Sperm may be retrieved from the epididymis percutaneously (percutaneous epididymal sperm aspiration; PESA) or microsurgically (microsurgical epididymal sperm aspiration; MESA). Sperm may also be retrieved directly from the testicle percutaneously (testicular sperm aspiration; TESA) or through a small incision (testicular sperm extraction; TESE). Sperm retrieved through these techniques require pairing with IVF-ICSI to achieve pregnancy. PESA, TESE or TESA may be performed in an outpatient setting; while MESA may result in higher quantity of sperm retrieved, it requires an operating microscope typically associated with sedation or a general anesthetic and is more costly. Common practice among Canadian practitioners is to offer PESA, TESA, or TESE to limit costs with acceptable rates of success. However, each of the aforementioned methods of sperm retrieval in this population are appropriate¹¹².

Future priorities of research

Azoospermia remains an important area of male reproduction that has been vastly underserved with respect to research. The committee has identified several clinical, translational and basic science areas of research as future priorities.

Clinical

Nearly all clinical data arises from retrospective case series and in rare circumstances prospective series, or clinical trials. Prospective, multicentered randomized clinical trials would elevate the level of evidence in the evaluation and management of azoospermia. Among men with NOA, evaluating the impact of varicocele repair on sperm retrieval, clinical pregnancy and live birth rate has yet to be definitively answered. Use of neoadjuvant medical therapy including SERMs, gonadotropins, aromatase inhibitors and other strategies for males with testicular failure NOA is of interest and requires further evaluation. Further, value-based research on patients with NOA and their partners are necessary to better understand patient perspectives on treatment pathways and their multi-dimensional impact.

Translational

Identification of reliable biomarkers and diagnostic testing to predict sperm retrieval in males with NOA is of interest. Technologies to identify rare sperm for patients with NOA would be of

value to the male reproductive field. Medical or regenerative approaches to stimulating sperm production in patients with NOA is a challenge problem.

Basic science

Understanding the mechanisms of NOA remain an elusive problem to scientists and clinicians alike. Further well characterized studies evaluating the pathogenesis and mechanistic genomic and molecular biological events contributing to NOA would be of paramount value to the field of reproductive medicine. Such knowledge could lead to effective interventions to restore spermatogenesis, especially for men with maturation arrest and identifiable, but potentially treatable abnormalities affecting sperm development. Similarly, development of regenerative strategies to promote spermatogenesis and spermiogenesis in vivo or in vitro would be valuable for future therapeutic intervention.

Conflicts of interest: Dr. Flannigan has been an advisory board member for Acerus; has received speaker honoraria from Boston Scientific and Paladin; and received product from Theralogix for clinical trial evaluating impact of antioxidant supplements on sperm DNA fragmentation. Dr. Patel has been a consultant for Boston Scientific and Nestle Health; and has received honoraria from Paladin. Dr. Mak has served in advisory boards for Astellas, Bayer, Ferring, Janssen, Sanofi, and TerSera; and has been a presenter for AbbVie, Amgen, Astellas, Duchesnay, Ferring, Janssen, Sanofi, and TerSera. Dr. Fischer owns shares in J&J. Dr. Chow has participated in a speaker training session for Astellas. Dr. Wu participated in an advisory board for TerSera (Zoladex); and has give talks supported by Astellas and Pfizer.

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FIGURES AND TABLES

Figure 1. Classifications of azoospermia. SV: seminal vesicle.

Normal Volume Azoospermia				Low Volume Azoospermia					
Pre-Testicular		Testicular		Post-Testicular					
Non-Obstructive Azoospermia		Obstructive Azoospermia			Ejaculatory Dysfunction				
Pituitary-Hypothalamic Dysfunction		Testicular Failure / Defective Spermatogenesis		Epididymal Obstruction	Vasal Obstruction	Ejaculatory Duct or SV Obstruction	Failure of Emission	Anejaculation	Retrograde Ejaculation

Figure 2. Diagnostic and management flow chart for the evaluation of males with low volume azoospermia. Note: Counselling for sperm donation, adoption or child free living are important options in each clinical scenario. Following low-volume azoospermia workflow is with assumption that follicle-stimulating hormone (FSH) is normal. If FSH is abnormal, consider following normal volume azoospermia workflow. If fructose or pH is not available on semen analyses, consider performing a post ejaculate urine evaluation. CF: cystic fibrosis; IVF-ICSI: in vitro fertilization intracytoplasmic sperm injection; TRUS: transrectal ultrasound; TURED: transurethral resection of ejaculatory duct.

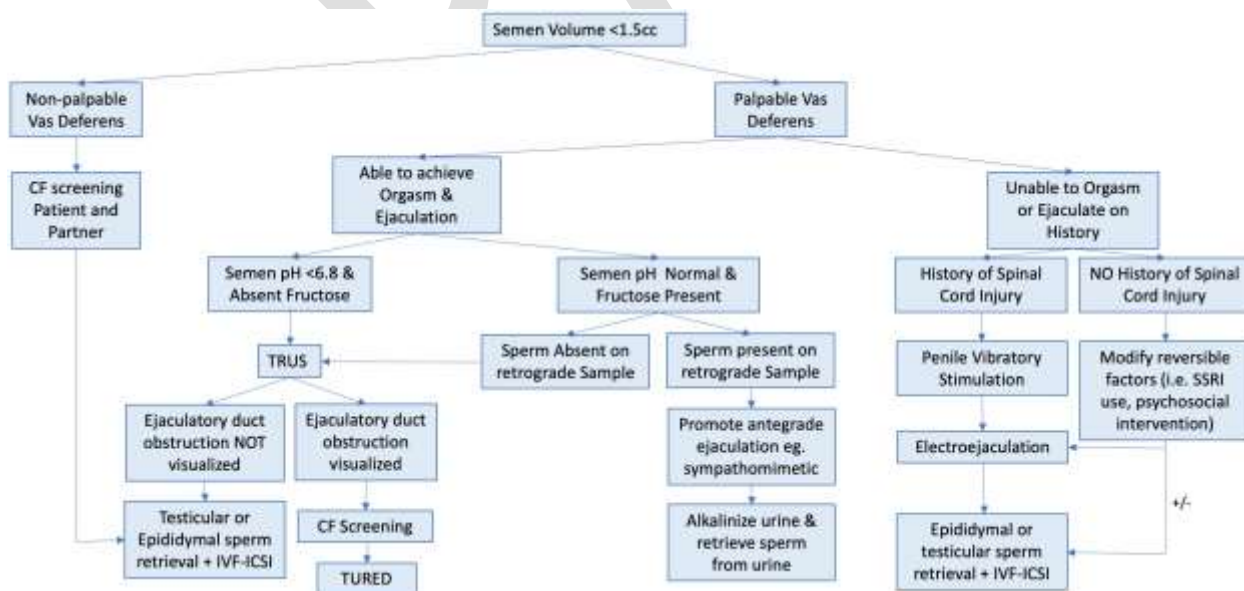


Figure 3. Diagnostic and management flow chart for the evaluation of normal volume azoospermia in males. Note: Counselling for sperm donation, adoption or child free living are important options in each clinical scenario.

FSH: follicle stimulating hormone; hCG: human chorionic gonadotropin; HMG: human menopausal hormone; IVF-ICSI: in vitro fertilization intracytoplasmic sperm injection; MRI: magnetic resonance imaging; mTESE: microdissection testicular sperm extraction; NOA: non-obstructive azoospermia; rFSH: recombinant follicle stimulating hormone; SERM: selective estrogen receptor modulator; YCM: Y chromosome microdeletion.

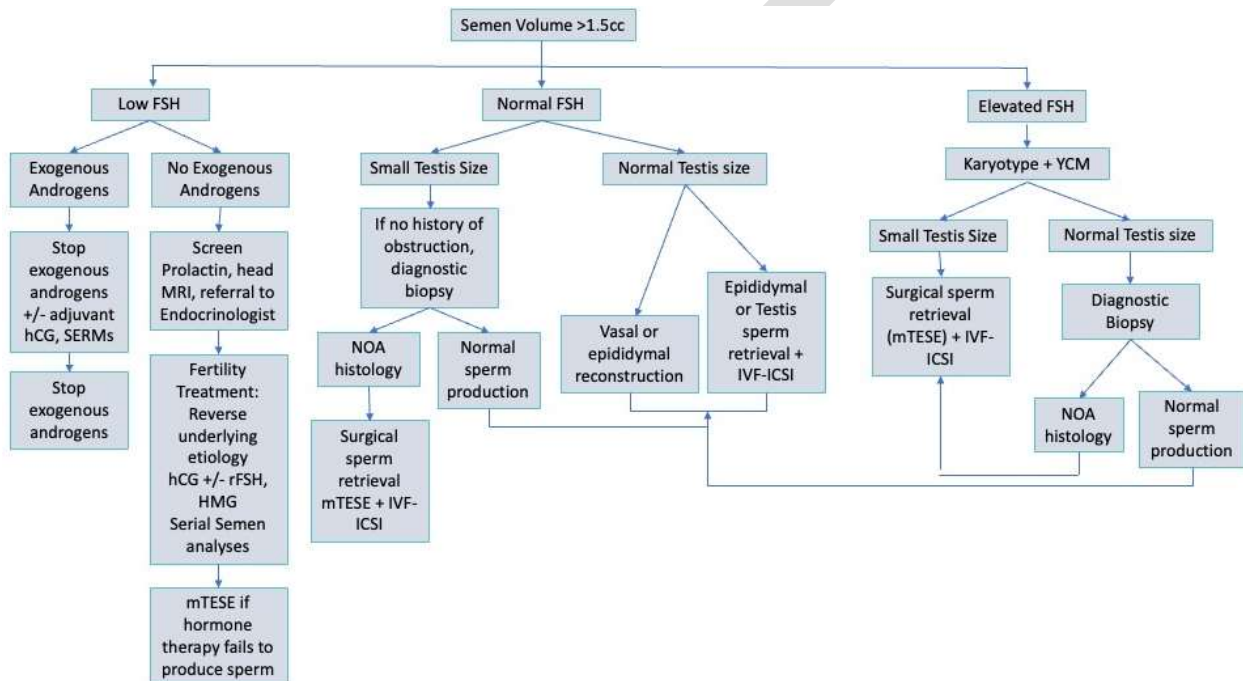


Table 1. History for infertility evaluation	
Medical history	Areas of focus
History of presenting illness (HPI)	<ul style="list-style-type: none"> – Demographics of patient and partner: age and ethnicity – Reproductive history of patient and partner (pregnancies, live births, miscarriages) – Reproductive treatments to date – Sexual function: libido, erectile function, ability to ejaculate, mechanics of intercourse, lubricants, frequency of intercourse, timing with ovulation, tracking of ovulation
Past medical history	<ul style="list-style-type: none"> – Infectious: Epididymitis, orchitis, recent systemic illness/fever – Congenital: Undescended testes, delayed puberty – Malignancies: Treatments received (chemotherapy, radiation, surgery) – Diabetes – Testicular trauma, torsion – Anosmia (i.e., Kallman syndrome) – Bitemporal hemianopsia (i.e., pituitary tumor) – Respiratory issues (i.e., cystic fibrosis)
Past surgical history	<ul style="list-style-type: none"> – Vasectomy – Orchiectomy – Orchidopexy – Hydrocelectomy & spermatocelectomy – Varicocele repair – Transurethral prostatic surgery – Retroperitoneal & pelvic surgery – Inguinal hernia repair – Brain/pituitary surgery
Medications	<ul style="list-style-type: none"> – Testosterone/hormone therapy, anabolic steroids, fitness supplements – Chemotherapeutic agents – Narcotics – Alpha blockers – 5-alpha-reductase inhibitors – Antibiotics (e.g., sulfasalazine) – SSRIs
Social history	<ul style="list-style-type: none"> – Smoking – Excessive alcohol use – Recreational drugs – Environmental exposures (e.g., excessive heat to testes, pesticides, chemicals)
Family history	<ul style="list-style-type: none"> – Infertility – Genetic diseases

Table 2. Key physical exam features for an infertility evaluation	
Location of examination	Areas of focus
General	<ul style="list-style-type: none"> – Virilization – Obesity
Scrotum	<ul style="list-style-type: none"> – Testis size, consistency, and location – Presence of mass – Epididymal fullness – Palpable vas deferens – Presence and grade of varicoceles
Abdomen	<ul style="list-style-type: none"> – Abdominal scars – Inguinal or scrotal scars indicative of hernia repair, orchidopexy, hydrocelectomy, etc.
Chest	<ul style="list-style-type: none"> – Gynecomastia

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