



Clinical management, differential diagnosis, follow-up and biomarkers of infertile men with nonobstructive azoospermia

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To make well-informed healthcare choices and recommendations in the management of nonobstructive azoospermia (NOA), the GRADE EtD (Grading of Recommendations Assessment, Development, and Evaluation evidence to decision) framework was applied to three specific clinical circumstances. For detailed explanations of each recommendation, see “Management of azoospermia” (1).

Do surgically retrieved sperm cryopreserved during in vitro fertilization-intracytoplasmic sperm injection (IVF-ICSI) result in lower live birth rates than fresh sperm and oocytes among males with NOA?

In most couples with NOA and subsequent IVF-ICSI, cryopreservation of surgically retrieved sperm is recommended (conditional recommendation, very low certainty of evidence).

How does varicocele repair before surgical sperm retrieval and IVF-ICSI affect live birth rates in men with testicular failure and a varicocele?

For most couples with testicular failure and a varicocele, we recommend observation of varicoceles rather than pretreatment with varicocelectomy (conditional recommendation, low certainty of evidence).

When compared to conservative management, does neoadjuvant hormonal therapy improve IVF-ICSI live birth rates among males with testicular failure NOA?

Azoospermia, the absence of sperm in the ejaculate, is a significant challenge in reproductive medicine, affecting approximately 1% of the male population and 10–15% of men who seek infertility treatment (2). It can be categorized as either obstructive or nonobstructive, with distinct paths for evaluation and management. A conditional recommendation with very low certainty of evidence is not made for neoadjuvant hormone therapy in males with testicular failure NOA (3). Based on the available evidence, a conditional recommendation cannot be made for neoadjuvant hormone therapy in males with testicular failure NOA. The certainty of evidence supporting this recommendation is very low. Testicular failure NOA is a condition characterized by the absence of sperm in the ejaculate due to testicular dysfunction. Neoadjuvant hormone therapy, which involves the administration of hormones before a medical intervention, is sometimes considered a treatment option for this condition.

However, the current evidence regarding the effectiveness and safety of neoadjuvant hormone therapy in males

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with testicular failure NOA is limited and of very low certainty. This means the available studies have significant limitations, such as small sample sizes, lack of long-term follow-up, and inconsistent results. Due to the lack of high-quality evidence, it is not possible to make a definitive recommendation regarding the use of neoadjuvant hormone therapy in this population. Additional research with larger sample sizes and rigorous study designs is needed to understand better the potential benefits and risks associated with this treatment approach (4).

In summary, based on the current evidence, a conditional recommendation with very low certainty of evidence is not made for neoadjuvant hormone therapy in males with testicular failure NOA. Healthcare providers and patients need to consider the limitations of the available evidence when making treatment decisions for this condition.

Management

Obstructive azoospermia

For patients with obstructive azoospermia, surgical interventions may be considered. Options include vasovasostomy or vasoepididymostomy to restore sperm flow. The choice of procedure depends on the site and extent of obstruction. The initial step in managing obstructive azoospermia involves a thorough diagnostic evaluation to identify the underlying cause. This includes a detailed medical history, physical examination, and laboratory tests. Semen analysis, hormonal assessment, genetic testing, and imaging studies such as scrotal ultrasound and magnetic resonance imaging (MRI) may be performed to determine the location and extent of the obstruction. The management of obstructive azoospermia depends on various factors such as the site and cause of the obstruction, the patient's fertility goals, and any associated conditions.

Non-obstructive azoospermia

In cases of non-obstructive azoospermia, treatment options are limited. Assisted reproductive techniques, such as testicular sperm extraction (TESE) followed by ICSI, may be considered. The success rates of these procedures vary depending on the underlying cause. A thorough diagnostic workup is crucial in identifying the underlying cause of NOA. This includes a comprehensive medical history, physical examination, hormone analysis, genetic testing, and

testicular biopsy. An accurate diagnosis helps determine the most appropriate management approach for each patient.

Counseling and support

Patients diagnosed with azoospermia should receive appropriate counseling and support. It is essential to discuss the implications of the diagnosis, available treatment options, and the emotional impact of infertility. Referral to a mental health professional or support group may be beneficial. Emotional support: dealing with a diagnosis of non-obstructive azoospermia can be emotionally overwhelming. Individuals and couples need to receive emotional support throughout their journey. Counseling services can provide a safe space for individuals to express their feelings, fears, and concerns. Trained counselors can offer guidance on coping strategies and help navigate the emotional rollercoaster that often accompanies infertility. Understanding treatment options: counseling sessions can also provide information on the various treatment options for non-obstructive azoospermia. These may include assisted reproductive technologies such as IVF with ICSI, TESE, or sperm retrieval techniques. Understanding these options can empower individuals and couples to make informed decisions about their fertility treatment. Joining support groups specifically tailored for individuals and couples dealing with non-obstructive azoospermia can be highly beneficial. These groups provide a platform for individuals to connect with others experiencing similar challenges, share experiences, and exchange advice. Peer support can help alleviate feelings of isolation and give a sense of belonging within a community facing identical fertility struggles.

Follow-up

Regular follow-up is necessary to monitor treatment outcomes and adjust management strategies. Repeat semen analyses, hormonal evaluation, and imaging studies may be indicated to assess treatment response and identify new developments.

Priorities for future research

Regarding research, azoospermia remains a significant area of male reproduction largely underserved. Several clinical, translational, and primary science research areas have been identified as future priorities by the committee.

A clinical study

It is rare for clinical data to come from prospective studies or clinical trials, but most clinical data comes from retrospective case reports. Evaluation and management of azoospermia would be enhanced by future multicenter, randomized clinical trials (2). In men with NOA, varicocele repair has not been definitively proven to affect sperm retrieval, clinical pregnancy, or live birth rate. Males with testicular failure NOA may benefit from neoadjuvant medical treatment, such as selective estrogen receptor modulators (SERMs), gonadotropins, aromatase inhibitors, and other strategies (5). 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 site influences the choice between these procedures and the cause of the obstruction to restore the flow of sperm to the ejaculate, thus enabling natural conception (6).

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 TESE over sperm aspiration in men with NOA. This is significant because NOA involves a dysfunction in sperm production, which requires different management strategies, such as sperm retrieval techniques combined with IVF (7).

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.

Biomarkers and diagnostic

Biomarkers and diagnostic tests that predict sperm retrieval in males with NOA should be identified. The field of male reproduction would benefit from technologies that would identify rare sperm for patients with NOA. There is a challenge in stimulating sperm production in patients with NOA through medical or regenerative approaches (8-11). The cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, known for its role in the pathogenesis of cystic fibrosis, 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, 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.

Basic science

Both scientists and clinicians struggle to understand NOA's mechanisms. In addition, the field of reproductive medicine would benefit significantly from well-characterized studies evaluating the pathogenesis and mechanistic genomic and molecular biological events contributing to NOA. Men with maturation arrest and sperm abnormalities that may be treatable may benefit from such knowledge to restore spermatogenesis (12).

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