Diagnosis and Treatment of Infertility in Men

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GUIDELINE TITLE Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline, Parts I and II
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DEVELOPER AND FUNDING SOURCE American Urological Association (AUA) and American Society for Reproductive Medicine (ASRM)
TARGET POPULATION Individual men or couples with potentially impaired reproductive potential
MAJOR RECOMMENDATIONS Semen analysis should guide management, and clinicians should obtain hormonal evaluation including follicle-stimulating hormone and testosterone for men with impaired libido, erectile dysfunction, oligozoospermia (<15 million sperm/mL) or azoospermia, atrophic testes, or evidence of hormonal abnormality on physical evaluation (expert opinion)
- Infertile men and men with abnormal semen parameters should be advised of the relevant, associated health risks and conditions (moderate recommendation [MR], level of evidence [LOE]: B)
- Surgical correction of palpable varicocele(s) should be considered for infertile men with sperm in the ejaculate and abnormal semen parameters (MR, LOE: B)
- For men with nonobstructive azoospermia who are undergoing sperm retrieval, microdissection testicular sperm extraction should be performed (MC, LOE: C)
- Men should be informed about the adverse effects of cancer treatments (chemotherapy, radiation therapy, surgery) on fertility and offered sperm cryopreservation before initiation of these therapies (MR, LOE: C)
- Testosterone monotherapy should not be prescribed for men interested in current or future fertility, but other therapies (aromatase inhibitors, human chorionic gonadotropin, selective estrogen receptor modulators) can be used in these men to treat low testosterone (conditional recommendation, LOE: C)

Summary of the Clinical Problem
Infertility affects about 15% of couples and is due to a male factor alone in 20% and combined male and female factors in 30% to 40%.1 In 25% of couples, no clear cause for infertility can be identified. This guideline addresses the evaluation of male infertility, which can arise from a wide array of conditions, and discusses issues that may affect infertility treatment or the health of the patient and offspring.

Characteristics of the Guideline Source
The guideline was jointly developed by the AUA and ASRM and funded by the AUA. It was written by a volunteer development panel of 15 individuals with expertise in urology, male infertility, primary care, laboratory medicine, reproductive endocrinology, and public health, with representation from patient-based organizations (Table).1,2 Panel members disclosed potential financial and nonfinancial conflicts of interest.

Evidence Base
An Emergency Care Research Institute Evidence-based Practice Center team evaluated observational studies, randomized clinical trials (RCTs), and meta-analyses to provide an evidence base for the guideline.1,2 Initial guideline statements support basic screening of both male and female partners, with detailed evaluation (endocrine, genetic) of men with 1 or more abnormal semen parameters, or for couples with failed assisted reproductive technology (ART) cycles or recurrent pregnancy losses.1 They note consistent associations between abnormal semen parameters and conditions such as testicular cancer, cystic fibrosis, and Klinefelter syndrome. Associations between infertility and other conditions (such as diabetes, hypothyroidism, elevated prolactin, and multiple sclerosis) have been suggested in some studies. These statements are based on retrospective and population-based cohort studies, and as such, they are appropriately characterized as having a moderate evidence base.1

The guideline emphasizes the potential harms of exogenous testosterone on male fertility due to possible azoospermia after negative feedback on the hypothalamus and pituitary, citing a multicenter trial of testosterone enanthate for male contraception, which resulted in at least oligospermia (or azoospermia) in 97.8% of participants.3 Multiple guideline statements address the gonadotoxic effects of cancer treatments, such as chemotherapy and radiation therapy, referencing a series of observational studies finding decline in semen parameters, often to the point of azoospermia, within months of initiating these therapies.4

Surgery-related guideline statements address the role of varicocelectomy, microdissection testicular sperm extraction (micro-TESE), and vasectomy reversal in managing male infertility. The guideline cites a meta-analysis that included both RCTs and observational studies and demonstrated approximately 35% and 42% pregnancy rates after inguinal and subinguinal microsurgical varicocelectomy, respectively, vs 17% without intervention.5 Similarly,
when considering men with nonobstructive azoospermia (NOA), the guideline references a meta-analysis that was based mostly on observational studies demonstrating a 1.5-fold higher chance of sperm retrieval with microTESE vs conventional nonmicrosurgical testicular sperm extraction (cTESE) (52% vs 35%; odds ratio, 1.5 [95% CI, 1.4-1.6]). Testicular sperm aspiration was less successful than cTESE.6

Benefits and Harms

The guideline prioritizes treating causes of male factor infertility when possible, while minimizing the harm from invasive procedures. Interventions such as subinguinal microsurgical varicocelectomy can improve spontaneous pregnancy rates from 13.9% to 32.9%.7 However, this procedure has potential risks including injury to the testicle that could jeopardize spermatogenesis and testosterone production.2,5-8 The guideline recommends that men with clinically palpable varicoceles, infertility, and semen parameter abnormalities (except azoospermia) are most likely to benefit from correction.2 By contrast, the guidelines recommend against surgical correction of varicoceles detected only on imaging studies (non-palpable “subclinical varicoceles”), given the lack of demonstrable clinical benefit in semen parameters or pregnancy rates.

Sperm extraction in the setting of nonobstructive azoospermia can potentially lead to hematoma, infection, testicular fibrosis and atrophy, or long-term hypogonadism. To attain the best retrieval rates and minimize the risk of these sequela, the guideline recommends microTESE for men with NOA instead of cTESE or percutaneous approaches,8 with 1 study suggesting only 3% of men develop chronic fibrosis with microTESE vs 30% of men with cTESE.9

The guideline also notes that male factor infertility may be managed using ART (e.g., in vitro fertilization). While this may be an effective and expedient therapeutic approach for some couples, this treatment strategy may result in greater morbidity (e.g., ovarian hyperstimulation) in the female partner vs male partner-directed therapies that may be similarly efficacious. Moreover, ART for male factor infertility is often associated with significantly greater costs vs treatment involving lifestyle modification or simpler medical and surgical approaches.

Discussion

This first guideline on male infertility appropriately stresses the importance of both male and female partner evaluation for all couples attempting to conceive. Given the high prevalence of male factor infertility, and its less frequent evaluation, it is important for all male partners to undergo timely evaluation. A useful appendix describes physical examination findings potentially relevant to male reproductive health.1

The guideline raises awareness regarding the broad health implications of male infertility. Statements 5 and 6 address the higher rates of malignancy and possibly greater mortality in subfertile men, although there is less discussion of the robust observational evidence linking infertility and metabolic syndrome.3 Paternal age is mentioned as a risk factor for adverse health outcomes in offspring, and it likely impacts fertility as well. Additionally, the discussion of oncofertility provides specific time intervals for deferring conception after treatment and obtaining initial semen analysis after therapy. While these statements are predominantly based on expert opinion and older observational studies, they provide important new guidance for men undergoing gonadotoxic therapies.

Areas in Need of Future Study or Ongoing Research

Additional research is needed in reproductive genetics, specifically to further identify and characterize the wide array of genetic causes of infertility. This will be challenging for multiple reasons. Many genetic anomalies can affect reproductive system development and function, and thus impair reproductive potential. To date, more than 3600 gene abnormalities are associated with male infertility and another 3200 linked with genitourinary birth defects. Moreover, given the broad range of genes involved in sperm production, it is not surprising for male infertility to be associated with other health issues, including immune and metabolic disorders, as well as malignancy. The potential role of germ line gene therapy is also controversial and can pose ethical concerns, including that genome editing can cause unintended, potentially deleterious “off-target” effects, that is, unintended cleavage and mutations at untargeted genomic sites similar to the target site. Despite these obstacles, promising research in novel therapeutics is underway, including germ cell transplantation (NCT04452305) and techniques to support in vitro spermatogenesis (NCT02972801).

ARTICLE INFORMATION

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REFERENCES