The WHNP's guide to evaluating male infertility

By Hayley E. Rapp, DNP, APRN, WHNP-BC

Male factor is a primary or contributory cause of infertility in up to 50% of couples, making it an important health issue. WHNPs can perform an initial comprehensive workup to evaluate for male factor infertility, which aids in the prompt referral to male reproductive specialists. This review provides the necessary framework to understand male factor infertility and guide the initial evaluation prior to referral.

KEY WORDS: male infertility, sperm, reproduction, azoospermia, semen analysis, male factor

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Women's health nurse practitioners (WHNPs) are uniquely suited to provide for the sexual and reproductive health needs of both women and men. WHNPs may practice in settings with male patients such as family planning clinics, health departments, family practice offices, and reproductive endocrinology and infertility specialty offices. Providing care for men and their fertility concerns is within the WHNP's scope of practice, and recognition of male factor infertility is vital for prompt referral and treatment.[1] Male infertility is diagnosed by the presence of abnormal sperm parameters or other endocrine, anatomic, functional, or genetic malfunctions of the reproductive system.[2] Male infertility is associated with poorer health indices including an increase in cardiovascular disease and chronic disease.[3] The semen analysis (SA) parameters are indicative of overall health status, and men diagnosed with infertility and abnormal sperm parameters have a much higher incidence of testicular cancer, making it important to interpret correctly due to these implications that reach well beyond fertility.[3–5]

The National Association of Nurse Practitioners in Women's Health (NPWH) position statement on the role of the WHNP in caring for the sexual and reproductive health of men affirms the importance of fertility care for all gender identities.[1] The purpose of this article is to provide background information on male factor infertility and to discuss the basic tools of an initial evaluation that facilitate appropriate referrals to a male reproductive specialist or urologist.*

*Throughout this review, the term "male" or "men" is used to refer to biologic or genetic men.

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Etiology

Similar health issues and risk factors that affect women's fertility also can impact men. The causes of male infertility can be broadly categorized as congenital, acquired, or idiopathic. Some conditions are reversible, while others are not.[2]

To understand the various causes of male infertility, it is necessary to have basic knowledge about the formation of sperm (spermatogenesis). Genes located on the Y chromosome of the male are key in this complex and lengthy process.[6] Within the testes are seminiferous tubules that act as the site of spermatogenesis.[7] Sperm must then be transported from the testicle through the epididymis to the ejaculatory duct. Sperm mature in the epididymis, although the final maturation occurs after ejaculation into the female reproductive tract. Because of the length of the spermatogenic process, the results of an SA are reflective of what occurred months earlier—an important counseling point for the patient. Optimal conditions for spermatogenesis include a lower scrotal temperature and appropriate hormone levels.[6] Disruption at any point in the spermatogenic process leads to alterations in male fertility.

Congenital causes

Among the congenital causes of male factor infertility are karyotype abnormalities such as Klinefelter syndrome and Y chromosome microdeletions (YCMD), hypothalamic-pituitary disorders such as Kallmann syndrome, and congenital bilateral absence of the vas deferens (CBAVD).[8] Klinefelter syndrome is the most common sex chromosome abnormality seen in male infertility.[2] The majority of cases are caused by the male having an extra X chromosome (karyotype 47, XXY). Patients with Klinefelter syndrome present with small testicles and low testosterone levels.[9] YCMDs are the second most common cause of genetic infertility in men.[2] Because the Y chromosome is essential for sperm function, deletions cause varying degrees of impaired spermatogenesis depending on the region affected.[10] Kallmann syndrome is another congenital condition, characterized by the deficiency of gonadotropin-releasing hormone secretion, delayed or absent puberty, and accompanied by a poor or absent sense of smell.[2] CBAVD is a disorder of sperm transport that is strongly associated with cystic fibrosis gene mutations and results in obstructive azoospermia discussed later in this article.[5,11]

Acquired causes

The list of acquired factors implicated in male infertility is long, the most common of which is varicocele.[8] A varicocele is a dilation of the pampiniform plexus of veins within the spermatic cord. It can cause abnormal semen parameters and damage to sperm DNA due to an increase in the production of reactive oxygen species.[12] Hypothalamic or pituitary tumors can affect testosterone production leading to cessation of sperm production.[2]

Other acquired conditions that may affect male fertility include genital infections or inflammation, systemic diseases, trauma to the testicles, sexual dysfunction, and certain medications.[8] Sexually transmitted infections (STIs) that induce inflammation in the genital tract can negatively alter the male reproductive system. Viruses such as mumps, HIV, and Zika can impact male fertility by infecting the reproductive tract and inducing inflammation.[13] The Covid-19 virus also has been shown to negatively impact sperm quality in the short term, but parameters appear to recover some months later.[14] It should be noted, however, that long-term follow-up studies are not available at this time. Sperm cells can be inadvertently damaged during chemotherapy or radiation therapy, causing these cancer treatments to result in severely low sperm counts or azoospermia, which may or may not rebound.[15,16] It is crucial that a male patient receive fertility preservation counseling prior to undergoing any gonadotoxic treatment.[2]

Exogenous testosterone, taken by some men as a nutrition supplement, suppresses pituitary secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) with a resultant decrease in testosterone production within the testicles and thus spermatogenesis. Other medication classes known to contribute to iatrogenic male infertility include opioids, selective serotonin reuptake inhibitors, and 5-alpha reductase inhibitors.[15]

For transgender women who desire medical gender-affirming therapy, androgen deprivation can be used to lessen endogenous testosterone levels, thereby reducing the appearance of male secondary

sexual characteristics. Although it allows transgender women to achieve their desired body image, this approach risks loss of reproductive potential, making it important to counsel these patients on fertility preservation options prior to undergoing medical (or surgical) gender-affirming treatments.[15]

Sexual dysfunction is an important acquired cause of male infertility and can present as erectile dysfunction, ejaculatory dysfunction, low libido, or a combination of factors.[8] Because proper functioning of the male reproductive system is a necessary component for fertility, evaluation and treatment of sexual dysfunction are of great importance. Unfortunately, male sexual dysfunction is significantly worsened by the added stress of infertility. Careful history taking, use of validated questionnaires, and reassurance are all key in evaluating the male with sexual dysfunction.[17]

Idiopathic or unexplained causes

Idiopathic or unexplained male factor infertility often results from exposure to risk factors and is seen in approximately 30% of cases. It is recommended that WHNPs discuss risk factors as these relate to male fertility, but an important caveat is that data on many of them are limited or the existing evidence is low quality.[2]

Alcohol negatively impacts semen volume and morphology but is not shown to affect concentration or motility. Tobacco smoking and poor diet are associated with reduced fertility. Environmental factors are inherently difficult to study, but lead, cadmium, pesticides, and phthalates have been associated with male infertility.[2] The data on marijuana use and male fertility are noted to be heterogeneous, as it has been shown to contribute to poor quality sperm in some studies, with no effect seen in other studies.[5,18,19] Overall, the literature points to a negative impact of marijuana on sperm morphology, while the effect on other semen parameters remains uncertain.[18] The influence of obesity on female fertility is well known, although the impact of obesity on male fertility receives less attention possibly due to less conclusive data.[20] Certain studies have shown lower counts and less motile sperm and azoospermia in men with obesity.[20,21] Male obesity is associated with lower testosterone levels and may also unfavorably alter sperm function.[20,22]

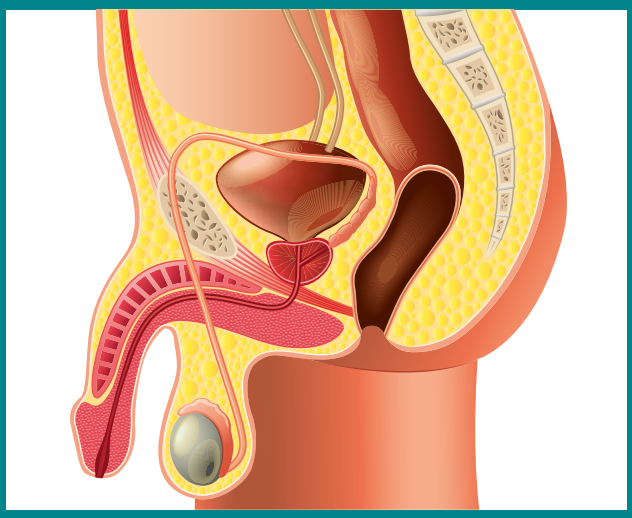
Although male fertility does decline to some extent with age, there is no cessation of sperm production comparable to menopause in females.[23] Advanced paternal age (APA) is often defined as 40 years of age or older.[24] Studies have shown an association between advancing paternal age and an increased risk for structural chromosomal aberrations, psychiatric conditions (eg, autism, schizophrenia), and some de novo autosomal dominant conditions in offspring.[24,25]

Assessment of male fertility

Male and female fertility should always be evaluated in parallel as male factors are a primary or contributing cause of infertility in up to 50% of couples.[2,8] The two most important aspects of beginning an evaluation of male fertility are a comprehensive history and the SA.[2] Other components of the male fertility evaluation may include physical examination, hormonal assessment, genetic testing, imaging, or specialized tests such as sperm DNA fragmentation testing if indicated.[8] Any abnormal SA findings or abnormal reproductive health history, physical examination, or hormonal test findings on initial evaluation should prompt referral to a male reproductive health specialist such as a reproductive endocrinologist or urologist.[2]

Reproductive history

A comprehensive medical history is paramount in unveiling potential contributors to a male's reproductive status. An important first step is to establish whether the male has primary (no previous clinical pregnancy achieved) or secondary (history of clinical pregnancy with current or former partner) infertility.[2] A sexual history should be elicited, including the presence of any sexual dysfunction (hypoactive sexual desire, delayed or premature ejaculation, erectile dysfunction), history of STIs,



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and coital timing.[8,13] The medical history can provide significant clues about the cause of the infertility including history of cryptorchidism (undescended testicle); delay or absence of puberty; poor or absent sense of smell; any history of testicular torsion, trauma, or surgery; viral or bacterial orchitis (inflammation of one or both testicles); Covid-19; or presence of any neurologic conditions or diabetes.[2,8,14] Any exposures to environmental or occupational hazards should be queried carefully. Use of tobacco, recreational drugs, alcohol, medications, and anabolic steroids should be assessed.[8]

Semen analysis

The purpose of the SA is to evaluate a male's reproductive health and to guide treatment.[26] The male is instructed to collect an ejaculated sperm sample after a minimum of 2 days' abstinence and maximum of 7 days.[27] Evaluation of the SA is based on the World Health Organization parameters. The SA provides information on volume, concentration, motility, and morphology of sperm.[2] Results falling lower than the reference ranges do not necessarily indicate infertility as semen parameters are notoriously variable and a repeat analysis (typically done 2 weeks after initial SA) is often recommended if the first is abnormal. Similarly, a normal SA result does not always mean that the sperm is reproductively competent to achieve pregnancy. Multiple abnormalities in semen parameters are a greater predictor of fertility potential. Abnormal results warrant prompt referral to a male reproductive health specialist. Importantly, abnormalities in the SA may be a sign of another disease such as testicular cancer or underlying chronic medical conditions.[2,3]

Azoospermia is the complete absence of sperm in the ejaculate and can have obstructive (OA) or nonobstructive (NOA) causes. The absence of sperm must be confirmed in two separate semen samples.[10] Evaluation of azoospermia should initially include a thorough history, volume of semen, physical examination, and hormone levels to determine if it is OA (40% of cases) or NOA (60% of cases).[2,11] An obstruction could be from a prior vasectomy, CBAVD, or severe inflammation. Individuals with OA as a cause of infertility typically have normal testicular volumes, FSH levels, and spermatogenesis. Nonobstructive causes include primary and secondary testicular failure, as well as those with an unclear picture of testicular failure. This type of azoospermia may be due to abnormal development, varicoceles, prior gonadotoxic therapies, or a result of a genetic condition. In contrast to OA, men with NOA typically have small- to normal-sized testes, and high or low FSH levels.[11]

The volume of ejaculate also can give clues to the etiology of the problem. Low ejaculate volumes should alert the WHNP to the possibility of retrograde ejaculation. A post-ejaculate urinalysis showing significant numbers of sperm in the urine is diagnostic.[10]

A semen analysis also can detect low sperm counts (oligozoospermia), abnormal shape (teratozoospermia), poor motility (asthenozoospermia), and white blood cells in the sample (leukocytospermia), all of which relate to a potential issue in the male's reproductive system.[8]

Physical examination

A careful physical examination is an important part of the evaluation of male infertility. The overall body habitus, sexual characteristics, and

genitalia of the patient should be examined.[8] Gynecomastia may indicate an endocrinopathy such as testosterone deficiency. [8] Small testicular size and tall stature may raise suspicion for Klinefelter syndrome.[9] Lesions or discharge from the penis suggest a sexually transmitted infection.[2]

Hormonal assessment

Hormone analyses to examine the hypothalamic-pituitary-gonadal axis of the male are warranted when abnormal sperm parameters are found or when a physical examination reveals atrophic testes.[10] These hormones may include FSH, LH, estradiol, testosterone, and/or prolactin.[10] Based on the initial testing results, further laboratory analyses beyond what is described here may be warranted. A fasting total testosterone level drawn in the morning less than 300 ng/dL is considered abnormal.[2] Elevated FSH levels (typically > 7.6 mIU/mL) indicate that there is a spermatogenesis abnormality.[10]

Genetics

Genetic testing may be warranted in the setting of male factor infertility, specifically in cases of severe oligozoospermia (typically sperm concentration < 5 million/mL), to determine the cause.[2] Genetic counseling should be offered whenever there is a suspected genetic issue in either the male or female partner and should be provided whenever such abnormality is detected.[10]

A karyotype and YCMD study aim to detect abnormal chromosomal patterns or microdeletions within the Y chromosome. Congenital bilateral or unilateral absence of the vas deferens requires CFTR [cystic fibrosis transmembrane conductance regulator] testing.[10] The risks of APA should be discussed with the couple if the man is age 40 years or older, and genetic counseling is recommended.[24]

Imaging

A scrotal ultrasound may be done to identify a varicocele or any other abnormalities in the scrotum and spermatic cord. A transrectal ultrasound can evaluate for ejaculatory duct obstruction. This level of imaging is not routinely done but is indicated on a case-by-case basis.

Specialized tests

Although SA is the gold standard for assessing male fertility potential, it has limitations and cannot evaluate all sperm functions, so at times more specialized tests are indicated. Sperm DNA fragmentation testing measures the amount of damage to sperm's DNA. High levels of damage can prevent natural conception.[28] In the presence of a mass, testicular biopsy may be warranted. The presence of antisperm antibodies may hinder the ability of the sperm to penetrate the egg. These antibodies may result from trauma or any disruption to the blood-testis barrier (eg, prior vasectomy or testicular torsion). Antisperm antibody testing should be considered only if it will impact the management of the infertile couple.[2]

Treatment

The treatment options for male factor infertility are aimed at the underlying cause. Examples of treatment options include medications (to correct hormonal imbalances or treat sexual dysfunction), induced ejaculation (for spinal cord injuries), surgical repair of abnormalities (eg, varicocelectomy, vasectomy reversal), intrauterine insemination, assisted reproductive technologies (ART; eg, in vitro fertilization or intracytoplasmic sperm injection [ICSI]), surgical sperm retrieval, donor sperm use, or adoption.[16]

Surgical retrieval of sperm has made fathering a genetic child possible for some patients with male infertility in whom this was previously not believed feasible. Because males with OA typically continue to have normal sperm production in the testes, surgical sperm retrieval may be a good option. Additionally, if the cause of obstruction is a prior vasectomy, a reversal may be considered as a cost-effective option for the couple. The length of time since the vasectomy factors into counseling on the odds of reversal success, as a shorter interval since vasectomy has a better success rate.[2] In men with NOA, sperm retrieval is successful in 50% of cases, but if it is not successful the use of donor sperm or adoption remain options.[8] For elevated percentages of sperm DNA fragmentation, testicular sperm has been found to have much lower percentages of sperm DNA damage as compared to ejaculated sperm. Therefore, the usual treatment for this is surgically retrieved sperm to be used in ICSI.[28]

Among the acquired causes of male infertility, the treatment options are varied and tailored toward the cause. Genital infections should be treated appropriately, and systemic diseases should be addressed. Many cases of erectile dysfunction can be treated with phosphodiesterase type-5 inhibitors such as sildenafil, tadalafil, avanafil, or vardenafil.[17] The presence of antisperm antibodies can be overcome with ICSI.[2] For men who have a palpable varicocele and NOA, there are no definitive data to support repair prior to ART.[2] Lifestyle modifications (eg, weight loss, smoking cessation) and ART are considerations for treatment of idiopathic male infertility.[8]

Implications for WHNPs

WHNPs do not need to specialize in reproductive endocrinology or infertility to complete an initial investigation of male factor infertility. This

investigation includes a thorough reproductive health history and physical examination, SA, and potentially initial hormone tests. This pre-referral evaluation allows for the patient to immediately begin more specialized testing or treatment as indicated when they present to a male reproductive health specialist. The WHNP can provide education about male reproductive function, counseling regarding lifestyle modifications that might improve fertility, and what to expect in a further workup. Additionally, the WHNP should remain up to date on emerging evidence related to male infertility and other health conditions to allow for appropriate risk reduction strategies. ■

Hayley E. Rapp is a women's health nurse practitioner at Reproductive Medicine Associates of New Jersey in Marlton, New Jersey. **The author has no actual or potential conflicts of interest in relation to the contents of this article.**

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