Chapter 32
How is male infertility defined? How is it diagnosed?
Epidemiology, causes, work-up

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An estimated 1 in 7 couples experience difficulties with conceiving. While societal and cultural biases tend to focus on the female side of fertility, male factor is present in up to 50% of infertile couples. Generally, the diagnosis and workup of male infertility is prompted by abnormal semen parameters or inability to transport semen, although novel research has brought to light markers of sperm quality which also contribute to fertility. Any pathology which prevents transport or production of sperm can be attributed as male infertility. The term "subfertility" has also been used to describe this and can be used interchangeably with infertility. A thorough evaluation of the male partner, along with concurrent female evaluation, is essential in infertile couples to aid in counseling and treatment. Male infertility has also been shown to be a harbinger for future diseases, hospitalization, and early mortality (Chapter 64). The male partner workup provides a unique opportunity for the andrologist to perform an early overall health evaluation in a young population unlikely to have regular medical visits.

The causes of male factor infertility are varied, ranging from issues of sperm quality and/or production to abnormal transport (emission, ejaculation, or obstruction). Primary infertility is defined as the inability to conceive with any partner, while secondary infertility is defined as prior ability to conceive but subsequent fertility difficulties. Varicoceles are the most common cause of male infertility, being present in 40% of men with primary infertility and over 80% of men with secondary infertility. Approximately 25% of patients will have idiopathic or unexplained infertility, although recent guidelines reclassify many of these patients as having hypogonadism, which was previously present in 9% of patients. Other causes include primary testicular failure (9%), obstruction (6%), and cryptorchidism (5%). Anejaculation and retrograde ejaculation make up approximately 2% of male infertility.

The basic evaluation of a male presenting with infertility begins with a thorough history. Male infertility has been associated with higher overall mortality, and thus patients should have a detailed history to assess for concomitant diseases. Duration of infertility, past fecundity, and any infertility treatments should be noted. Past and current medical problems such as genitourinary infections, malignancies, medications and congenital or developmental issues should be evaluated. Special attention is given to past surgeries including genitourinary instrumentation, hernia repairs, orchidopexies, and scrotal surgeries, which may increase the risk of infertility. Female partner age, past fertility, cycle information, and fertility workup are also important factors. Sexual function, change in erections or ejaculation, and timing and frequency of intercourse should be discussed. Family history should focus on infertility, endocrine disorders, malignancy, and cystic fibrosis. The patient's social history can elucidate any modifiable substance use or exposures. Other patient specific information, such as exogenous testosterone use, past trauma, or prior infertility workup can be useful and should be considered in all patients.

A physical exam should be performed both standing and lying down, with focus on general examination of body habitus and development of secondary sex characteristics. Additional characteristics associated with infertility include anosmia (Kallman syndrome) and situs inversus (Kartagener's syndrome). Abdominal exam should focus on the presence of any healed incisions, as patients may have had surgery as a child that they are unaware of. The phallus should be examined for hypospadias, lesions, or other urethral defects. Careful palpation of the testes, vas deferens, epididymides and cords should be performed. Testicular size can be estimated with the use of an orchidometer. Testis size and texture can offer insight into pathology, with small and soft testicles being associated with hypogonadism. Small (3-6cc), firm testicles are associated with Klinefelter's disease, the most common genetic cause of male infertility. Congenital bilateral absence of the vas deferens should prompt cystic fibrosis transport receptor (CFTR) testing in both the patient and the female partner. Unilateral absence should be followed by a renal ultrasound, as wolffian duct development alterations can lead to renal agenesis. Although virtual consultations have become more popular in recent years, it is still recommend that an in-person visit be done for all new infertility patients as a physical exam is invaluable to establishing a diagnosis. At least two semen analyses should be performed, preferably with at least 3 weeks between samples. In

patients with less than 2mL of semen, post-ejaculate urine analysis evaluates is needed for retrograde ejaculation. Interpretation of the semen analysis relies on the andrologist's expertise. Total sperm count, rather than concentration, should be used for determination of oligozoospermia. Concentration does not account for volume and thus men with normozoospermia may have a low concentration and a high semen volume. Total motile sperm has been suggested as a better predictive parameter for male infertility. Sperm morphology, although included in the WHO classification, has been shown to have no impact on natural conception, IUI or IVF outcomes, and thus should not be used solely as a diagnostic criterion for male infertility. It is notable that while abnormal semen parameters can suggest a male factor, the presence of normal values does not guarantee fertility, nor does it rule out modifiable male factors.

Additional laboratory evaluation with a hormonal workup should include a determination of concentration of morning serum follicle-stimulating hormone (FSH) and testosterone, with or without an estradiol depending on the patient's body habitus/BMI. Luteinizing hormone (LH) and prolactin can be considered for men with low testosterone. Hypogonadotropic hypogonadism should be further evaluated with a prolactin level, and a pituitary MRI should be performed for an elevated prolactin level. Empirical medical management with anti-estrogenic compounds such as clomiphene citrate or anastrozole can be considered in patients with inappropriately normal FSH and low or borderline low testosterone levels. Genetic testing with a karyotype and Y chromosome microdeletion should be performed for patients with severe oligozoospermia or azoospermia. Latest Guidelines jointly published by the American Society of Reproductive Medicine and the American Urological Association recommend a cutoff of 5 million sperm/mL, but these authors' clinical practice is to test any patient with less than 5 million total sperm. Scrotal ultrasound and transrectal ultrasound should not routinely be performed. Scrotal ultrasound is reserved for patients with unexplained testicular asymmetry or palpable masses, as well as select patients with progressive decline in semen parameters. Transrectal ultrasound can be offered for patients with low volume, low pH semen azoospermia and palpable vasa. Diagnostic testis biopsy is not indicated in most patients with azoospermia, but can be used to determine the extent of spermatogenesis if the patient is counseled on its role in predicting sperm retrieval and desires further information prior to microsurgical testicular sperm extraction (microTESE).

Assessment of DNA fragmentation has become increasingly utilized, with terminal deoxynucleotide transferase-mediated dUTP nick end labeling (TUNEL) and sperm chromatin structure assay (SCSA) being the most widely accepted assays. Sperm DNA can be affected by free radicals and lead to poor sperm quality, affecting conception as well as increasing miscarriage rates. Instances in which DNA fragmentation testing may be useful include recurrent miscarriages, unexplained fertility, or multiple failed intrauterine insemination (IUI) cycles. Varicoceles are also known to cause DNA fragmentation, and evaluation of DFI can be useful in certain patients who have normal semen parameters and grade 2 or grade 3 clinical varicoceles. Microfluidic sperm sorting devices can be used in patients with a high DFI for in vitro fertilization (IVF) or IUI, with data suggesting it can improve clinical pregnancy rates.

The workup of male fertility requires a thorough history, physical examination and laboratory evaluation, While an etiology may not always be determined, it is important to have a fertility specialist involved for adequate counseling and treatment options. As genomic and proteomic tests emerge, new diagnostics and treatment options may follow.

Suggested reading

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