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THE INVESTIGATION OF THE INFERTILE MALE

by Mickey S. Coffler, M.D.

Infertility affects approximately 15% of couples. The male partner is responsible in about 30-50% of cases. This document will discuss the evaluation of the male partner when male factor infertility is suspected.

The primary test of male reproductive function is the semen analysis. The specimen is obtained by masturbation and collected into a clean container following 2 to 5 days of abstinence. To prevent sperm deterioration prior to analysis, the specimen needs to be kept at body temperature and brought to the lab for evaluation within an hour of production. Many infertility centers, including Huntington Reproductive Center, maintain dedicated facilities for specimen collection in a private setting. This facilitates immediate specimen processing and avoids the exposure of the sperm to potential environmental modifiers.

The basic semen analysis includes an assessment of its volume, sperm concentration, the percent motility, and the percentage of normal shapes (morphology). The presence of immature sperm cells and inflammatory cells is also noted. The normal range can be slightly variable among laboratories and it is typically included with the report. More recently, the sperm morphology is evaluated according to stringent criteria developed by Kruger. This newer method helps to better predict the fertilization potential of sperm when used in fertility treatments. Additionally employed methods for sperm evaluation include assessment of the percentage of DNA fragmentation and testing for anti-sperm antibodies. There are other less commonly

used sperm tests (sperm penetration assay, etc.) that lack specificity and standardization. Those will not be discussed in this document.



An abnormal semen analysis that is confirmed on repeated testing should prompt a complete evaluation of the male partner. The goals of this evaluation are to

- help the patient better understand the basis for his fertility problem;
- distinguish conditions that are correctable when applying specific and less expensive therapies versus those that require advanced assisted reproductive technologies;
- correctly diagnose those situations where critical medical conditions underlie the infertility (pituitary or cranial tumors, testicular cancer);
- identify hereditary aberrations that might be transmitted to the offspring.

Typically, initial screening includes a general medical and reproductive history. Focus is placed on fertility history, past medical and surgical histories, family history, medications, allergies, infections and sexually transmitted diseases. Heavy smoking, alcohol and drug abuse are important factors that negatively affect sperm parameters and function. An occupational history is important in eliciting potential work related and environmental causes for sperm pathology.

(continued)

The exam includes a general physical and a targeted exam of the genitalia. Attention is given to penile and urethral anatomy and scrotal contents. In particular, testicular location, size, and consistency are evaluated, and any pathology of the ducts that conduct the sperm from the testicles (epididymides and vasa) to the penile urethra is carefully assessed. At this time, abnormally dilated scrotal blood vessels (varicocele) may also be noted. The examination may include a rectal exam for the size and consistency of the prostate gland if infection is suspected.

A hormonal evaluation may include serum levels of follicle stimulating hormone (FSH), testosterone and the serum testosterone to estradiol ratio. FSH is produced by the pituitary gland and testosterone is made by the testicles. In the male, most of the estradiol is made by conversion of testosterone in extra-gonadal tissues. A low FSH coupled with a low testosterone may point to secondary testicular failure due to a hypothalamic or pituitary disorder. A high FSH, on the other hand, is a sign of primary testicular failure which is a more challenging problem for management. An abnormal testosterone to estradiol ratio can be corrected with medications that block the conversion of testosterone to estradiol.

In patients with suspected retrograde ejaculation we recommend a post-ejaculatory examination of the urine. This condition is more frequent in diabetics and associated with certain neurological conditions. The semen is abnormally ejected in a backward fashion into the urinary bladder rather than forward out the penis. A typical finding is a large quantity of sperm cells in the post-ejaculatory urine specimen.

Imaging studies are added as indicated based on the initial findings. Scrotal ultrasonography may be used in patients in whom the physical exam of the scrotum is difficult or inadequate or in whom a testicular mass is suspected. Physical findings consistent with a varicocele can be confirmed on a scrotal ultrasound if initially inconclusive.

Transrectal ultrasonography is done in patients with low ejaculate volumes to determine the presence of ejaculatory duct obstruction. Ultrasound findings suggestive of obstruction are dilated seminal vesicles, dilated ejaculatory ducts, or midline prostatic cystic structures.

Men with very low sperm count (severe oligospermia) or total absence of sperm in the semen (azoospermia) are candidates for genetic testing. Genetic abnormalities may cause infertility by affecting sperm production or sperm transport. There are at least three genetic factors known to be related to male infertility:

- cystic fibrosis gene mutations;
- chromosomal abnormalities resulting in impaired testicular function;
- Y-chromosome microdeletions.

Cystic fibrosis (CF) is a genetically transmitted disease that affects multiple organs and particularly the lungs and gastrointestinal system. Its mode of expression varies significantly from patient to patient; while some patients succumb to the disease, others are only minimally affected. Essentially all male patients with CF exhibit congenital bilateral absence of the vas deference (a tubular structure that transports sperm from each testicle to the urethra). The reverse is also correct: most men with congenital bilateral absence of the vas deference have mutations of the cystic fibrosis gene; and azoospermia may be the only clinical expression of the disease in these patients. In those circumstances, it is recommended to test the female partner to determine whether she is CF carrier herself. If both partners carry a CF mutation, the risk of transmitting the disease to the offspring is significantly increased.

Karyotypic abnormalities (abnormal number of genes, translocations, etc.) may be detected in about 7% of infertile men. The frequency of abnormalities is higher in azoospermic men (10%–15%) than in men with oligospermia (5%). For comparison, karyotypic abnormalities are found in less than 1%

of men with a normal sperm count. Klinefelter's syndrome (the presence of an extra X chromosome in a male patient) accounts for about two thirds of the chromosomal abnormalities in infertile men. Transmission of some of those anomalies to the offspring can be prevented by employing PGD (pre-implantation genetic diagnosis).

Deletions of small pieces (microdeletions) of the Y chromosome may be found in 10–15% of men with azoospermia or severe oligospermia. These abnormalities are detected by a highly specific technique named polymerase chain reaction. Sons of individuals with such an abnormality would inherit the microdeletion and may be infertile themselves. At present, a microdeletion of the Y chromosome is not known to be associated with other health disorders.

Conclusions

The sperm count is the first step in the assessment of the male partner. When consistently abnormal, a thorough investigation is recommended. Although most cases of severe male factor are best treated with IVF, a comprehensive evaluation may elicit significant underlying medical disorders. This work-up should include a complete history and physical, specific laboratory testing and imaging, and genetic testing when appropriate. Referral to genetic counseling is recommended when a genetic abnormality is detected.

Reference

2006 Compendium of Practice Committee Reports, *Fertility and Sterility*, November 2006, Vol 86, Supp 4.