Male Infertility: The Clinical Aspects of Evaluation and Management

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Introduction

At a time when limiting family size has become of national interest, increasing numbers of married couples are moving in a different direction—to overcome infertility and conceive children. Reasonably reliable statistics indicate that approximately 3.5 million couples, or nearly 15% of those of childrearing age, are subfertile. If one adds the cases of secondary infertility, in which a pregnancy or a miscarriage has already occurred in the marriage but is followed by years of difficulty conceiving another child, the magnitude of the infertility problem is indeed impressive. At the personal level, involuntary childless couples may suffer doubts about their own sexuality and are often caught in intense emotional, family, and societal pressures emanating from their inability to conceive.

Furthermore, the incidence of infertility seems to be slowly increasing due to a number of factors including the increased risk of prolonged anovulation following the use of birth control pills and to adnexal infections associated with the use of intrauterine devices. Additionally, there is a definite trend by women to delay having children until later in life and thus to bypass the time of their optimal fertility potential between 22 and 26 years of age.

Whether or not the true incidence of infertility is increasing, there is a definite and substantial increase in the demand for treatment. This reflects a growing awareness by childless couples that treatment for infertility in many instances can be effective and that the number of babies available for adoption have been sharply reduced by birth control, liberalized abortion laws, and an increasing tendency of unwed mothers to keep their babies.

Until recently, most physicians were not particularly enthusiastic about treating patient infertility. The reasons for this attitude centered around a general pessimism about being able to help the patient, combined with the fact that the physicians' training ill-prepared them for evaluating and managing these patients with the result that male infertility has probably been the most misunderstood item since the IRS short form. Presently, a more optimistic view is warranted as therapy is now effective in achieving pregnancy for about 45% of these couples.

The objective of this article is to present the most recent information regarding the clinical aspects of male infertility and subfertility. The information will be practical and directed to understanding both the causes of male infertility and the various methods of evaluating and managing male patients with this problem.

Definition of Male Infertility and Subfertility

Based on semen analysis, a precise definition of male infertility and subfertility is difficult because the quality of semen that will achieve a pregnancy for one couple and not another will vary due to the relative fecundity of the female partner and the variable interaction of infertility co-factors. In other words, data suggest that there are degrees of fertility for both sexes, depending on the partner.[1] Nevertheless, given a female partner who is fertile by most standards, lower limits for semen quality have been established

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under which a pregnancy is likely to occur.[2-4] These *minimal* values are as follows:

Total ejaculate volume: 1.5-5.0 ccs
Sperm count: 20 m/cc
Sperm motility: 60% motile
Sperm speed: 2+ (Scale 1-4)
Sperm morphology: 60% normal forms

These minimal values must be considered as part of the overall semenogram and may be adjusted if one index is of particularly high quality, for example, a patient with a 10 m/cc sperm density may well be fertile if his sperm motility is excellent.

History and Physical Examination

Beyond obtaining a basic medical and marital history, the infertility history should be directed at uncovering the specific factors that are known to contribute to subfertility. These factors can be conveniently divided into four groups: childhood illnesses; adult illnesses; drugs; and environmental-occupational hazards.

Specific childhood illnesses that can adversely effect fertility include cryptorchidism, mumps, spermatic cord torsion, direct trauma, and the timing of puberty as well as specific surgical procedures including herniorrhaphy, orchiopexy, hypospadias repair, urethroplasty, and Y-V plasty of the bladder neck to relieve "obstruction."

Adult illnesses that are similarly important include tuberculosis of the genital tract, mumps, orchitis, prostatitis, epididymitis, gonorrhea, diabetes, vaginitis in the female partner, and such surgical procedures as noted under childhood illnesses plus retroperitoneal surgery (lymphadenectomy, sympathectomy, and so forth), vasectomy, and prostatic surgery.

Drugs that are known to interrupt or alter spermatogenesis include the nitrofurantoins, amebicides, hormones (for example, testosterone, estrogens, corticosteriods), as well as most of the anti-cancer chemotherapeutic drugs.

The patient's occupation may have a bearing on his fertility status if he is under a great deal of stress or if the testicles are exposed to undue heat or radiation.

The physical examination should include a thorough examination of the external genitalia and prostate. Testicular size and consistency are particularly important; measurement is facilitated by the use of calipers. The normal adult testis measures approximately 4.6 cm in greatest diameter (range 3.6-5.5 cm) and 2.6 cm in width (range 2.1-3.2 cm). Because the germinal epithelium comprises about 80% of the normal testicular mass, atrophy of the seminiferous tubules will be reflected in a smaller than normal testicle. On the other hand, normal testicular size does not assure normal semen quality. If the patient's body habitus appears abnormal, laboratory investigation should be directed at determining any abnormality of the hypothalmic-pituitary-gonadal axis.

The Semen Analysis

The semen analysis is without doubt the single most important step in the evaluation of male infertility. It is to male infertility what cystoscopy is to bladder tumors, that is, it is the most critical item in the initial evaluation process and is important in therapy follow-up.

The semen analysis, or semenogram, is a study of the characteristics of the spermatozoa that are clinically important in assessing fertility. While noncellular components of the semen also contribute to fecundity, for clinical purposes the semenogram will reflect their influence on the spermatozoal characteristics that are decisive in determining fertility potential, and a separate biochemical analysis of these components is neither necessary nor practical.

Because of its importance, a minimum of two and preferably three semen analyses should be obtained. Additionally, multiple collections are necessary because of physiological variations in the same patient and because of technical variations in analyzing the specimen, for example, acceptable counting errors vary from 10% to 20% with the same specimen.

Preferably, the semen specimen should be collected by masturbation into a clean, wide-mouthed glass or plastic container. The container, such as a standard urine specimen bottle or ointment jar, should be supplied by the physician to avoid factitious results secondary to the container's previous contents or cleaning agents. The specimen should be kept warm and delivered to the laboratory for analysis within 60-90 minutes. The timing of specimen collection should reflect the couple's usual coital frequency pattern, or if that is variable, an abstinence period of 2-4 days is recommended. Personal or religious beliefs may require the use of a silastic seminal fluid collecting device. It is critical that the specimen represents the entire ejaculate since there are significant variations in the seminal values from one portion to the other with regard to motility, sperm den-

sity, and viscosity as compared with the total ejaculate.

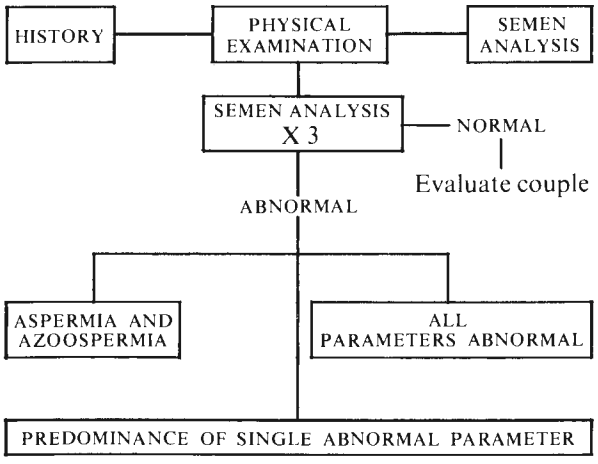
The specific techniques of analyzing the semen will not be discussed because they are beyond the space limitations of this presentation and, additionally, are available in recent texts.[5] Five principal indices should be reported on the semen analysis. Representative values for fertile men are as follows:

1. Total ejaculate volume: 2-5 ccs
2. Sperm count (density in millions/cc): greater than 50 m/cc
3. Sperm motility (% motile cells): 65% to 85%
4. Sperm speed (forward progression speed): 3-4 (scale 0-4)
5. Sperm morphology: 60% to 85% normal oval forms

Additionally: The specimen is normally viscous and opalescent with a grayish-white color. There should be no hyperviscosity, pyospermia, or significant sperm agglutination.

Systematic Approach to Male Infertility

A systematic approach to male infertility can be facilitated with the use of the following diagnostic flow sheet (modified after Lipshultz[6]):



The flow sheet is based on the semen analysis and the identification of the three broad seminal categories of: 1) aspermia and azoospermia, 2) predominance of a single abnormal parameter, and 3) all parameters abnormal.

Aspermia and Azoospermia

Somewhat less than 5% of male infertility patients will present with either aspermia or azoospermia. In the aspermic patient there is failure of any ejaculate to appear at the time of orgasm. On the other hand, the azoospermic patient experiences both ejaculation and orgasm, but the ejaculate contains no spermatogenic elements.

The absence of ejaculation in aspermic patients is generally due to neurogenic causes[7] and, less commonly, to retrograde ejaculation. The neurogenic causes include pituitary tumors, olfactogenital dysplasia (Kallman syndrome), and absent contraction of the seminal vesicles and vasa differentia following retroperitoneal lymph node dissection for the treatment of testicular tumors (and not due to retrograde ejaculations as previously thought).

The neurogenic causes can be successfully treated in most cases by specific replacement therapy.

The common causes of retrograde ejaculation include those in which the anatomy of the internal sphincter is disrupted as in transuretheral resection (TUR) of the prostate or vesicle neck surgery, or where the nerve supply of the internal sphincter is distrupted as in spinal cord injury, surgical sympathectomy, chemical sympathectomy [guanethidine (sulfate) (Ismelin)], and diabetes visceral neuropathy.

Apart from a history of a previous elective vasectomy, the azoospermic patient's differential diagnosis rests between obstruction or atresia of the epididymal or vasal ducts and testicular failure as seen in germinal cell aplasia, marked spermatogenic arrest, chromosomal defects, severe peritubular fibrosis, and Klinefelter syndrome.

The seminal specimens of all azoospermic patients should be tested for the presence or absence of fructose: this is quantitatively determined by adding the reducing reagent resorcinol to a small portion of the seminal specimen and bringing it to a boil.[5] If fructose is present, an orange color will appear within half a minute of boiling. The presence of fructose, a product of the seminal vesicles, effectively rules out congenital bilateral absence of the vasa as the presence of the seminal vesicles depends on the existence of the vasa which embryologically give rise to the former. On the other hand, the presence of fructose only rules out bilateral obstruction of the ejaculatory ducts but does not assure ductal patency throughout the vasa and epididymi. Therefore, in a setting of azoospermia and a normal testicular biopsy, vasograms should be obtained to identify the site of ob-

struction which can be corrected surgically by microsurgical techniques, depending on its location.

Predominence of a Single Abnormal Parameter

Approximately a third of subfertile male patients will have a semen analysis characterized by the predominence of a single abnormal parameter, most commonly sperm viability/motility. Asthenospermia, a decrease in sperm motility below 60%, can be caused by a number of factors including sperm immobilizing antibodies, infection, endocrinopathy, varicocele, and epididymal dysfunction.

It is now widely appreciated that testicular spermatozoa acquire their fertilizing capacity and motility as they pass through the epididymis. Important for these considerations is the fact that testosterone is transported, bound to androgen-binding-protein, from the seminiferous tubular fluid to the epididymis in concentrations about 20 times that of serum. In the epididymis, the antigen-binding-protein disappears and the free testosterone diffuses into the epididymal cell. Therefore, the functional integrity of the epididymis may be compromised either by failure of the Leydig cells to produce high enough local concentrations of testosterone, by failure of the Sertoli cells to produce adequate amounts of androgen-binding-protein, or by failure of the epididymal epithelium to utilize effectively the free testosterone. In any event, the end result is a local epididymal environment not optimal for the normal development of sperm motility. Therapy is directed at improving the local epididymal environment by the administration of gonadotropins which stimulate Leydig cell production of testosterone and androgen-binding-protein by the Sertoli cells. Therapy has been effective in somewhat less than half the patients so treated. Low-dose androgen therapy in the form of fluoxymesterone (Halotestin) 2-5 mg, b.i.d., has not been effective.

Additionally, epididymal dysfunction may be secondary to complete or partial obstruction, or to changes in the functional integrity of the epididymis itself due to such conditions as epididymitis. Treatment is directed at the specific disorder and involves short-circuiting the obstruction by microsurgical techniques and by appropriate antibiotic treatment of the epididymitis.

The most profound manifestation of a viability-motility/disorder is necrospermia which fortunately is rare as there is no successful treatment.

In patients with high ejaculate volumes (>3.5 ml) and a secondary decrease in sperm count (oligospermia of less than 20 million/ml), sperm density may be improved in about 80% of patients by use of the split-ejaculate technique. To collect a split or fractionated ejaculatory specimen, the patient is given two collection jars which are numbered #1 and #2 and secured together with adhesive tape. The first one third of the ejaculate is collected in jar #1 and the remainder in jar #2. In 80% of patients, the sperm density will be significantly higher in the first portion of the ejaculate. The more favorable first portion may be delivered to the cervical os by a withdrawal coital technique (penis withdrawn from the vagina after the first spurt of ejaculate) or by insemination. In properly selected cases, pregnancy results are about 60%.

Diffuse Abnormality of All Seminal Parameters

The most common (60%) abnormal presentation of the semen analysis is a diffuse abnormality of all seminal parameters, that is, low sperm density, poor sperm viability, and more than 40% abnormal sperm forms. While nonspecific stress, subclinical endocrinopathy, and epididymal dysfunction or block are rare causes of diffuse seminal abnormality, they must nevertheless be considered and treated.

However, the most common cause of diffuse seminal abnormality is a varicocele which accounts for one third of all cases of male infertility. The varicose enlargement of the veins of the spermatic cord (pampiniform plexus) is caused by valvular incompetence of the internal spermatic vein with secondary retrograde flow of venous blood from the left renal vein into the internal spermatic vein. Because of the characteristic anatomy of the internal spermatic vein on the left side, varicoceles clinically occur more commonly on that side, that is, 80% left, 19% bilateral, and 1% right. Even if a varicocele is clinically limited to one side, venous dilatation occurs bilaterally due to the liberal cross-venous circulation of the pampiniform plexus, and the germinal epithelium of both testes is pathologically affected.

Varicoceles are best diagnosed with the patient standing erect as recumbency will decompress the varices. Small varicoceles can be more readily appreciated by having the patient perform a Valsalva maneuver. The diagnosis of small, subtle, and even subclinical varicoceles can be facilitated by use of the Doppler stethoscope[8]; their diagnosis is equally important as there is no correlation between the size of the varicocele and the reduction in spermatogenesis based on testicular biopsies and semen analyses.[9]

The mechanism whereby the varicocele causes

the deleterious effect on the germinal epithelium remains unresolved. But of the two principal postulated causes (venous reflux of adrenal "toxins" vs increased intrascrotal temperatures secondary to venous stasis), the weight of recent evidence favors elevated intrascrotal temperatures as the probable cause of depressed spermatogenesis.

The treatment of varicoceles is surgical and is directed at preventing retrograde venous flow by interrupting the course of the internal spermatic vein at the level of the inguinal canal (Ivanissevich method)[10] or the retroperitoneum (Palomo procedure).[11] Attempts to directly remove the dilated scrotal veins through a transscrotal incision are to be avoided as they are not effective.

The overall results of surgery are excellent with an improvement in semen quality of 70% and a pregnancy rate of 45%.

Conclusion

The prognosis for a previously infertile couple of achieving a pregnancy has improved substantially over the past 5-8 years. This has been made possible by a variety of diagnostic and therapeutic advances based on a greater understanding of testicular and epididymal function and disorder, hypothalamic-pituitary-gonadal interrelationships, and reproductive immunological and physiological factors. This knowledge, combined with a more comprehensive and systematic approach to the evaluation and management of the infertile male patient, has made possible the identification of the cause in 80% of patients as well as effective therapy in approximately 50% of couples under the age of 30 and approximately one third of those who are older.

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