Male Infertility

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TYPICAL MALE EVALUATION

In 40% of infertile couples an isolated female factor will be identified. In 30-40% of the time an isolated male factor will be elucidated. In the remaining 20-30% of cases, the etiology of infertility is shared among partners (combined factors). Therefore it is now indicated to start the male factor evaluation not only simultaneous with the female, but possibly even prior to the partner workup.

1. HISTORY
A thorough history reviews **medical** problems including recent fevers, systemic illnesses, diabetes, cystic fibrosis, cancer and infections. Prior **surgery**, including orchidopexy, herniorraphy, trauma, open retroperitoneal, pelvic or bladder procedures and TURP should be documented. A **family** history of cryptorchidism, midline defects or hypogonadism are important. A **developmental** history of hypospadias, congenital anomalies and hormonal (DES) exposure may also be found. The use of **medications** including nitrofurantoin, sulfasalazine and sulfa drugs, cimetidine and alpha blockers may also impact on fertility. A **social** history may elucidate the habitual use of the gonadotoxins, such as alcohol, tobacco, recreational drugs and anabolic steroids. **Sexual** history such as the use of spermicidal lubricants, and incorrect patterns and timing of intercourse. **Occupational** history is important to determine exposure to ionizing radiation, chronic heat, dyes, pesticides, herbicides and heavy minerals. **Partner** history: A history of prior pregnancies, the regularity of the ovulatory cycle, menstrual flow, and intermenstrual bleeding can provide important clues about the reproductive health of the"other half." By far the most important piece of information to obtain about the female partner is her age, as fertility in women declines unpredictably after age 35 and is almost certainly decreased at age 40.

2. PHYSCIAL EXAMINATION

Inspection of **body habitus** including obesity, gynecomastia and secondary sex characteristics. The **phallus** may reveal evidence of hypospadias, chordee, plaques or venereal lesions. The **testes** should be evaluated for size and consistency and any contour irregularities. Palpation of the **epididymides** should note any induration, fullness or nodules indicative of infections or obstruction. Careful delineation of each **vas deferens** may reveal agenesis, atresia or injury. The **spermatic cords** above the testes should be felt for asymmetry suggestive of a lipoma or varicocele. A **rectal** examination is important in identifying large midline cysts, infections or dilated seminal vesicles all of which may be associated with infertility.

3. SEMEN EVALUATION

Although not a true measure of fertility, the semen analysis, if abnormal, may suggest that the probability of achieving fertility is statistically low. Of these routine semen parameters, concentration and motility appear to correlate best with fertility. Typically two well performed semen analyses are required.

Table 1 World Health Organization Semen Analysis-Minimal Standards of Adequacy

Ejaculate volume 1.5-5.5cc
Sperm concentration >20 x 106 sperm/cc
Motility >50%
Forward progression 2 (scale 1-4)
Morphology >30% WHO
(>14% Kruger Strict Morphology)
Also: No agglutination (clumping), white cells, or increased viscosity

The evaluation of the various shapes of sperm is termed morphologic assessment. Several descriptive systems exist to evaluate morphology, and within each classification system, sperm are designated normal or abnormal based on a list of criteria. It is believed that sperm morphology may correlate with a man's fertility potential. In general, sperm morphology is a sensitive indicator of testicular health because morphologic characteristics are largely determined during spermatogenesis. The main role of sperm morphology in the male infertility evaluation is to complement the information obtained from the semen analysis to better estimate the chances of fertility.

One of the most important aspects of semen analysis accuracy is the adequacy of collection. Here are some tips: 1. Abstain from ejaculation for 2-3 days prior to collection. Longer periods of abstinence may result in higher sperm density and lower motility.

2. Clean or sterile containers should be used for semen collection. The entire specimen must be collected. Regular condoms and lubricants should be avoided.

3. The specimen should be kept at body temperature during transport (shirt pocket); it should be delivered within one hour of collection.

4. HORMONE ASSESSMENT

An evaluation of the pituitary-gonadal axis can provide valuable information on the state of sperm production. In turn, there are abnormalities of the pituitary axis which can cause states of infertility (hyperprolactinemia, gonadotropin deficieny, congenital adrenal hyperplasia). This evaluation should include a measure of serum FSH, testosterone, LH, and prolactin.

5. FURTHER TESTING

1. **Seminal Fructose and Post Ejaculate Urinalysis (Retrograde Semen Analysis)** Fructose is normally present in the ejaculate. If absent, seminal vesicle agenesis or obstruction may exist. A post ejaculate urinalysis (PEU) is a microscopic inspection of the first voided urine after ejaculation for sperm. Retrograde ejaculation is diagnosed is this manner.

2. **Semen Leukocyte Analysis** On a routine light microscopic semen analysis, "round" cells are often found in addition to sperm. These are either immature sperm forms (spermatocytes) or white blood cells (leukocytes). It is important to distinguish between these two cell types because the treatments differ. Specific assays are used to stain the ejaculate for leukocytes (CD45 monoclonal antibody).

3. **Anti-Sperm Antibody Test** The presence of IgA and IgG antibodies on sperm have been implicated as a cause of infertility in 5-10 % of men. Certain risk factors may predispose to the presence of sperm antibodies and include obstruction (vasectomy), trauma or torsion, infection (prostatitis) and chronic heat exposure.

4. **Sperm Penetration Assay (SPA)** A test of sperm function, the SPA measures the ability of human sperm to penetrate a specially prepared hamster egg in the laboratory setting. For a positive penetration result, sperm capacitation and acrosome reactivity must occur.

5. **Scrotal Doppler Ultrasound** High frequency (7.5 to 10mHz) ultrasound of the scrotum has become a mainstay in the evaluation testicular and scrotal lesions.

6. **Transrectal Ultrasound (TRUS)** High frequency (5-7mHz) transrectal ultrasound offers great imaging of the prostate, seminal vesicles and ejaculatory ducts. Transrectal ultrasound has virtually replaced the more invasive vasography in diagnosing obstructive lesions.

7. **CT Scan/MRI Pelvis** Since the advent of TRUS, these studies are only rarely indicated. One indication is the evaluation of the retroperitoneum in a patient with a solitary right varicocele in order to rule out significant retroperitoneal pathology such as a right renal tumor with vena cava extension.

8. **Karyotyping** Chromosomal analysis may be performed in men with testis failure whose physical habitus is suggestive of Klinefelter's syndrome, although it should be performed in patients with azoospermia and/or severe oligospermia.

9. **Y Chromosome Analysis** It has become apparent that up to 7% of men with low sperm counts and 15% of men with non-obstructive azoospermia may have an underlying microdeletions on the Y chromosome.

Azoospermia

Azoospermia is the complete lack of sperm in the ejaculate. It occurs in approximately 5-10% of infertile men who are evaluated. The first step in figuring out the problem is to make sure that the male being investigated truly has no sperm in the ejaculate. In all men with azoospermia, the entire volume of the ejaculate should be spun down (centrifuged) and the pellet of material at the container bottom inspected for any sperm. If he is truly zero by this measure, then either (or both) of two conditions are present: a) there is a problem with **sperm production** b) there is a **blockage (obstruction)** such that normally made sperm cannot reach the ejaculate. The minimal essential elements in the evaluation of the azoospermic man include:

1. A complete and thorough review of medical problems, past surgeries, family history, medications, toxin, chemical and heat exposure.
2. A complete physical examination, including a detailed exam of the genitals.
3. Basic hormone profile that typically includes, but not restricted to a testosterone and FSH levels
4. A reliable semen analysis with a spun sample to look for sperm in the sediment.

If, based on the above evaluation, it is not entirely clear as to whether there is a problem with sperm production or one of a blockage in the ducts of the reproductive tract, then the next step is to have a testis biopsy performed. A biopsy allows the urologist along with pathologist to directly inspect a small piece of testis tissue and determine whether there is a problem with sperm production.

Testicular tissue contains:
(a) sperm-producing cells that are found in tubules called seminiferous tubules, and (b) cells between the tubules that are called interstitial or Leydig cells. The Leydig cells are the major hormone-producing cells.

Some of the patterns that can be found on examination of a biopsy specimen include:

1) **Normal**. The testis architecture and sperm production look entirely normal. This means that an absence of sperm in the ejaculate is due to an obstruction or absence of the ducts leading from the testicle to the penis.

2) **Maturation Arrest.** Sperm are derived from immature germ cells that develop within the testicle. The process of sperm maturation can be interrupted at several levels and can result in a variety of "arrest" patterns. If the halt in development occurs early in the process of sperm maturation, the worse the prognosis.

3) **Hypospermatogenesis.** In this pattern, all of the elements of sperm production are present, but there are fewer of them than normal. This will generally result in lower numbers of sperm in the ejaculate.

4) **Germ Cell Absence or Aplasia (Sertoli Cell Only).** This pattern is characterized by a complete absence of germ cells in the testis, and so there is no sperm production.

5) **Other.** Other abnormalities can be detected by examining a testis biopsy, including evidence of previous infection within the testis and abnormalities of the Leydig or interstitial cells. Occasionally, a malignancy of the testis can be detected, but is usually an unexpected finding.

Treatment Options:

A) For Obstructive Azoospermia: Typically, in an obstructed man without an obvious reason for the problem, a blockage can be found in the epididymis 65% of the time, in the vas deferens 30% of the time and in the ejaculatory duct 5% of the time. The actual location of the blockage can be pinpointed with scrotal microsurgery and involves opening the vas deferens and inspecting the entire length of the tube with an X-ray (vasogram or vasography). Operations can be performed at most of these sites to repair the blockage have a reasonable chance of returning sperm into the ejaculate. In experienced hands, epididymovasostomy can result in an ejaculate with sperm in 60% of attempts. Vasal repair, termed vasovasostomy can result in sperm back in the ejaculate in 70-90% of attempts and in case of obstructed ejaculatory ducts, the procedure designed to unblock this particular ducts and termed transurethral resection of ejaculatory ducts (TURED) has positive results in approximately 70% of attempts. Pregnancy rates are lower than these "patency" rates, partly because pregancy depends on more factors than simply surgical success (i.e. partner's fertility potential).

B) For Non-Obstructive Azoospermia. If the testis biopsy is abnormal, then it is generally assumed that obstruction does not exist. Some of the reasons or conditions that may lead to this situation are listed in Table 1. In most of these instances, the only hope for achieving a biological child is to use extracted testis sperm with the available IVF and ICSI technology. However, a few, rare diagnoses that are very medically treatable (Kallman's syndrome, hyperprolactinemia).

Table 1. Conditions that can produce azoospermia.

Germ cell late maturation arrest
Germ cell hypospermatogenesis
Primary testicular failure
Klinefelter's syndrome
Secondary testicular failure
Kallman’s Syndrome
Idiopathic gonadotropin deficiency
Hypothalamic/Pituitary Tumor
Hyperprolactinemia
Chemotherapy/Radiotherapy treatment
Varicoceles
Gonadotropin suppression
Drug induced (anabolic steroids, alcohol, glucocorticoids)
Congenital adrenal hyperplasia
Severe systemic illness (cancer, renal failure)

Sperm autoimmunity
Pesticide/Toxin exposure
Cryptorchidism (Undescended testis)

GENETIC CONDITIONS ASSOCIATED WITH AZOOSPERMIA

A) Obstructive Azoospemia

Recently, it has become apparent that certain blockages with the ducts of the male genital tract are associated with specific diseases. Since some of these diseases not only affect the man with the problem but can be genetically passed on to offspring and therefore important to diagnose.

They are, as follows:

Congenital Absence of the Vas Deferens (CAVD): Diagnosed when no vas deferens can be found on examination of the scrotum. Men with this problem are sterile and most (65%) are also carriers of the cystic fibrosis gene.

Young's Syndrome is a condition in which sinusitis, peumonias and reproductive tract obstruction are present.

Epididymal Obstruction: About 37% of men with will also be carriers for cystic fibrosis.

Adult Polycystic Kidney Disease is an autossomic dominant kidney problem (at least one family member is affected) associated with renal failure and with cysts within the reproductive tract that can block the flow of sperm through the ducts.

B) Non-Obstructive Azoospermia
Several reports describing deletions or mutations in very specific areas of the **Y chromosome** (the male chromosome) known as DAZ region and AZF a, b or c region. Different areas offer different prognosis. Genetic counseling is of extreme importance for couples where a Y chromosome deletion is involved, as this condition will be passed on to the male offspring.

Varicocele –

General Concepts

Varicoceles are found in approximately 15% of the general population, including adolescents and adults, in 35% of men with primary infertility (reported range: 19%-41%), and in 80% of men with secondary infertility. Improvements in seminal variables, testicular size, and testicular histology have been observed after varicocelectomy. Varicocele repair has been reported to improve spermatogenesis in 50%-80% of patients, and 30%-40% will initiate a pregnancy after the procedure.

Clinically, varicoceles occur more commonly as isolated left-sided lesions (60%-90%). Although the incidence of bilateral varicoceles historically has been reported to be approximately 10%, more recent studies have shown bilaterality in 30%-50% of cases. The isolated right-sided varicocele is uncommon and causes concern regarding the possibility of an underlying retroperitoneal abnormality, such as renal tumor with venous invasion.

The left internal spermatic vein drains perpendicularly into the left renal vein, taking a course that is approximately 8-10 cm longer than that of the right internal spermatic vein, which enters the inferior vena cava at an oblique angle. This unique venous insertion on the left can result in increased hydrostatic pressure, overcoming valvular mechanisms and resulting in venous backflow, venous dilatation, and ultimate varicocele formation.

Increased hydrostatic pressure within the left internal spermatic vein may also result from compression of the left renal vein between the superior mesenteric artery and the aorta, the so-called "nutcracker" effect.

Absence or incompetence of valves appears to play a role in the etiology of the varicocele. Most varicoceles are thought to be due to abnormalities of the internal spermatic venous system. Nonetheless, dilatation of the external spermatic (cremasteric) system may be clinically significant, and it has been suggested that any vein greater than 4 mm in diameter should be ligated.

(c) Pathophysiology

There are several hypotheses to explain the mechanisms by which a unilateral varicocele may exert a bilaterally deleterious effect on spermatogenesis and fertility. These include renal and adrenal reflux, hypoxia, hormonal dysfunction, and hyperthermia.

Renal and Adrenal Reflux: The reflux of metabolic products or by-products of the adrenal glands and kidneys has been hypothesized to have a toxic effect on testicular function. The pathophysiology of the varicocele remains to be clearly defined. The role of renal metabolites has not been adequately investigated.

Hypoxia: It has been hypothesized that varicoceles cause hypoxia because of the stagnation of less oxygenated blood pooling around the testes. Hypoxia, indeed, may have a detrimental effect on spermatogenesis, but there is no evidence that varicoceles induce hypoxia.

Hormonal Dysfunction: Decreased levels of plasma testosterone were found in patients with varicocele; this hypoandrogenic state may play a part in the effects of varicocele on spermatogenesis.39 Other authors have shown that testosterone levels in venous or internal spermatic vein blood of patients with varicocele do not differ from those of normal men.
Also, a subtle alteration in the hypothalamic-pituitary-gonadal (HPG) axis can be found in some varicocele patients. Whether this is the mechanism of the effect of the varicocele or the result of the primary pathophysiologic effect of the varicocele is unclear.

Hyperthermia: Elevation of scrotal temperature is the factor most widely believed to explain the observed effects of the varicocele on spermatogenesis. In normal patients, intrascrotal temperatures are 0.6o-0.8oC lower than the intrascrotal temperatures of patients with varicoceles. In patients with preoperative sperm concentrations of less than 50 million/mL and postoperative counts of greater than 50 million/mL, a decrease in scrotal temperatures of 0.5oC was found after varicocelectomy.

(d) Indications for Repair

Infertility: Impaired fertility is the most common indication for varicocele repair. However, one must be certain that there are not other causes for the patient's infertility as well. Moreover, the mere presence of a varicocele in a subfertile male is not alone an indication for varicocele repair. The varicocele repair can improve parameters measured by the semen analysis and morphology measured by strict criteria.

Symptoms: Testicular or scrotal pain is not commonly experienced by patients with varicoceles; if pain is persistent, after other causes of pain are ruled out, a varicocele repair may be beneficial. Peterson et al. showed an 86% incidence of complete resolution of pain after varicocele ligation. However, conservative measures, such as scrotal support and analgesics, should be offered first.

Pediatric and Adolescent Varicocele: There are several reports in the literature indicating that the childhood varicocele may become apparent peripubertally and that early corrective therapy could prevent future damage to the individual's fertility status; however, this remains a controversial subject. As we noted previously, the presence of a varicocele is associated with loss of testicular mass that appears to be progressive with age. After a pediatric or adolescent varicocele is corrected, a significant increase in testicular volume can be observed- a phenomenon called "catch-up" growth of the affected testis.

Many authors have adopted the position that a pediatric varicocele should be left untreated unless there is significant testicular asymmetry or impaired testicular growth (>20% volume disparity)

Secondary Infertility: The role of varicoceles in infertility in males with secondary infertility is generally agreed upon. Witt and Lipshultz, in 1993, determined that the varicocele is a progressive lesion that can result in loss of previously established fertility.

(e) Surgical Treatment

Surgical varicocele repair is the mainstay of varicocele therapy. The goal of intervention is the complete disruption of the internal spermatic venous drainage of the testicle without damaging the internal spermatic artery, vas deferens with its blood supply, and spermatic cord lymphatics.

Several surgical approaches have been used. These include the scrotal approach, the inguinal approach (modified Ivanissevich), the retroperitoneal approach (modified Palomo), and the laparoscopic approach.

The scrotal approach is rarely used. Because of the complexity of the anatomy of the scrotal pampiniform plexus it is possible to damage all three major sources of blood to the testis and epididymis: the spermatic, the deferential, and the cremasteric arteries.

The popularity of laparoscopy in general has led in recent years to its use for the ligation of the internal spermatic veins. As a retroperitoneal approach, its advantages and disadvantages are similar to those of the open retroperitoneal approach.

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