MALE INFERTILITY

PATIENT GUIDE

MALE INFERTILITY

Provided by_____

INTRODUCTION

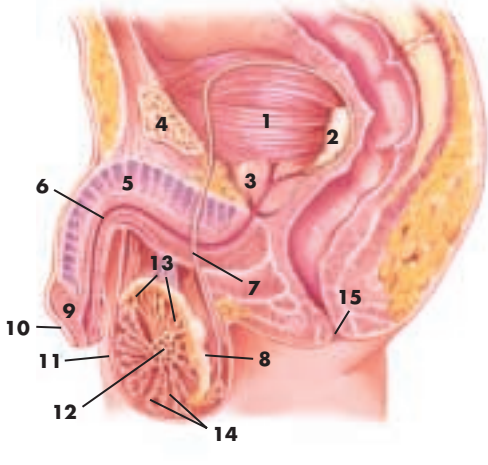
Approximately 15% of all couples have difficulty achieving a pregnancy during their reproductive years. In about 50% of these couples, a male factor is involved, either alone or with a coinciding female factor. The spectrum of causes of male infertility is quite variable, as are the possible treatments. Fortunately, significant progress has been made in the past decade in both the diagnosis and treatment of these infertile couples. These advances have allowed for the successful correction of problems and the ultimate ability to establish a pregnancy for men who just a few years ago had little chance of having a biologic child of their own.

NORMAL MALE REPRODUCTIVE ANATOMY

The testes are paired organs located within the scrotum, which is a multi-layered muscular structure that protects the testes and assists in temperature regulation (Fig. 1). The testes have two very important functions, and each of them is essential for normal male fertility:

1) Production of testosterone
2) Production of sperm

The testes are normally 4 to 5 cm long, and they are each encased by a firm, fibrous capsule called the tunica



1. Bladder
2. Seminal vesicle
3. Prostate
4. Pubic bone
5. Erectile tissue
6. Urethra
7. Vas deferens (spermatic duct)
8. Epididymis
9. Glans penis
10. Foreskin
11. Testis
12. Rete testis
13. Efferent ductules
14. Seminiferous tubules
15. Anus

Figure 1. The normal male reproductive tract.

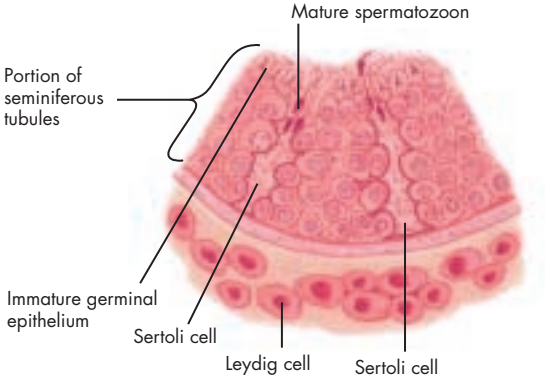


Figure 2.Transverse section of the seminiferous tubules and adjacent interstitial tissue (500x magnification)

albuginea. Within this capsule, the seminiferous tubules are found (Fig. 2). These tubules are very small structures containing Sertoli cells (support and nurturing cells for the sperm) and the germinal epithelium, the precursor cells that mature into spermatozoa. Along the course of normal seminiferous tubules, one finds sperm present at various stages of development, from the immature spermatogonium to the mature spermatozoon. Surrounding the seminiferous tubules are interstitial cells, which include the Leydig cells (Fig. 3). The primary role of the Leydig cells is to produce testosterone, which is essential for spermatogenesis.

The rete testes and efferent ductules are tubes that lead from the testis to the epididymis (Fig. 1). It is through these tubes that sperm pass from the seminiferous tubules to their next destination, the epididymis. The epididymis is a long, narrow duct, approximately 6 meters in length, which is coiled and

housed beneath a fibrous sheath. The epididymis sits on the back of the testis, and it is divided into head, body, and tail regions. Sperm undergo their final stages of maturation here and then proceed into the vas deferens (Fig. 4). The vas deferens is a long tubular structure that arises from the tail of the epididymis and proceeds superiorly in the scrotum with the spermatic cord. The vas travels up the inguinal canal within the spermatic cord, diverges from the cord behind the abdominal wall, where it then proceeds to the pelvis, to an area behind the prostate. Near the prostate the vas merges with a lateral pouch like structure called the seminal vesicle. There are two seminal vesicles, each seminal vesicle is about 4 cm in length and contributes fructose to the seminal fluid. The seminal vesicle and vas deferens fuse to

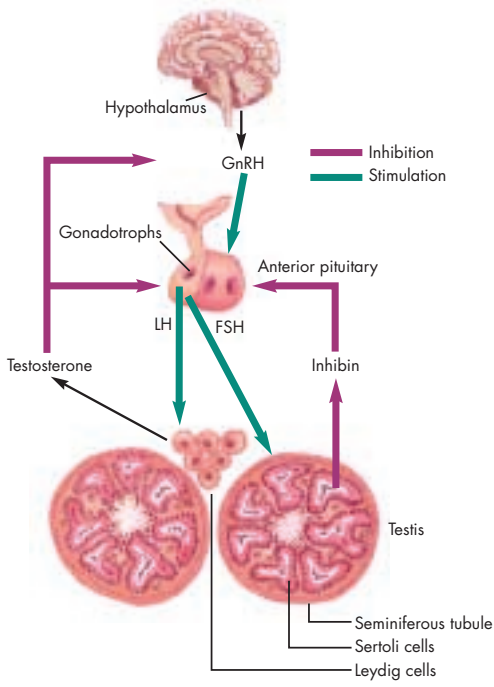


Figure 3.The hypothalamic-pituitary-gonadal (HPG) axis.

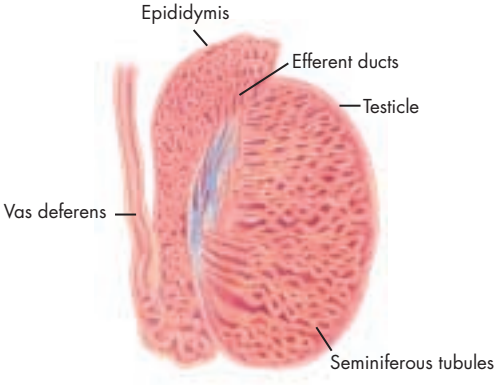


Figure 4. The testicle, epididymis, and vas deferens.

form the ejaculatory duct, which courses through the prostate to terminate in the urethra (Fig. 5). During ejaculation, the seminal fluid, a combination of sperm, prostatic secretions, and seminal vesicle secretions, is expelled out the urethra.

NORMAL MALE REPRODUCTIVE PHYSIOLOGY

The production of sperm that are capable of achieving of a pregnancy is a very complicated process. The purpose of sperm production is simple — to create a mechanism by which the male's chromosomal material may be combined with that of the female partner to proceed an embryo. This process of active spermatogenesis begins at puberty and lasts, in healthy males, until death.

Sperm production in the testicle is under hormonal control, which is regulated by the hypothalamus and the pituitary gland in the brain (Fig. 3). These hormonal actions are known as the hypothalamic-pituitary-gonadal (HPG) axis. The hypothalamus regulates the hormonal activity of the anterior pituitary gland by secreting gonadotropin-releasing hormone

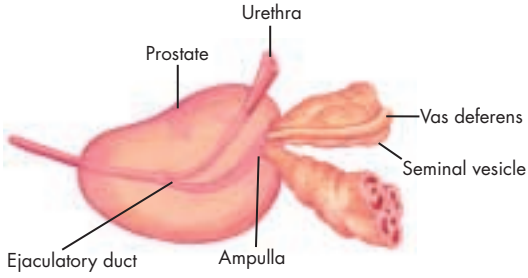


Figure 5. Sagittal view depicting prostate and ejaculatory duct anatomy.

(GnRH), which in turn, controls the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. Under the influence of LH, the Leydig cells within the testes make testosterone, an essential cofactor in spermatogenesis. Under the influence of FSH, Sertoli cells within the testes facilitate the production of sperm by secreting various growth factors. From beginning to end, sperm production takes about 72 days. The first 50 days are spent in the testis and the last 22–24 days in the epididymis. In the epididymis, sperm both mature and gain motility. During sexual activity, motile sperm are ejaculated into the female reproductive tract and thus begin their journey to the fallopian tubes, the site of fertilization.

SHOULD I BE EVALUATED?

In the past, couples were instructed to initiate an infertility workup only after at least one year of unsuccessful attempts. Often, the evaluation was limited to the female partner alone. This view has subsequently changed, and couples are now encouraged to proceed with an evaluation when they first suspect a problem with their reproductive function. Issues such as patient anxiety and advanced maternal age are among the factors that have led to this new approach.

For the male patient, the workup should generally begin when the female partner's evaluation is initiated. A male fertility specialist, usually a urologist who has a focus in his practice on male fertility problems as well as some postgraduate training in this area, should perform this workup. The important point, as mentioned earlier, is that a male factor is involved in as many as 50% of fertile couples. Thus a delay in evaluation and diagnosis may ultimately impair the couples chances for achieving pregnancy.

EVALUATION OF THE MALE PATIENT

HISTORY

The evaluation of the male patient begins with a thorough history. The physician will ask about a number of items, including duration of the problem, sexual habits, prior pregnancies and previous treatment, as well as the general health of the patient. A childhood or developmental history, including questions regarding a history of testicular torsion or

postpubertal mumps, is included. The patient's medical and surgical history should be discussed, including items such as a history of diabetes, prostate surgery, or hernia repairs. A discussion of exposure to possible toxic agents such as radiation, heavy metals, and organic solvents should be included.

PHYSICAL EXAMINATION

The physical examination should be thorough and complete. The physician will likely pay close attention to the penis and scrotal contents. Testicular size and consistency, as well as the presence or absence of the vas deferens and swelling or tenderness of the epididymides, are noted. For this portion of the examination, the physician may ask you to stand, take a deep breath, and "bear down" (the Valsalva maneuver) as he examines you for the presence of enlarged veins around the testicle (varicoceles). Additionally, a prostate examination is a key aspect of a thorough evaluation.

ROUTINE LABORATORY TESTING

SEMEN ANALYSIS

A central component of laboratory testing is the semen analysis. To perform this, a man is asked to produce sample generally through masturbation. Special containers are also available for home collection, but prompt return of the specimen to the laboratory (within one hour) is mandatory. Collection of the entire ejaculated fluid is important for

accurate diagnosis. A period of 48–72 hours of abstinence should precede the collection. Table 1 lists minimal standards for adequate semen parameters. It is important to note that these values are not absolute values needed to achieve a pregnancy. Rather they are statistical limits below which male infertility is more likely to be a problem. Furthermore, significant variation in one or several semen parameters from one specimen to another may occur. For these reasons, at least two semen specimens should be analyzed. Adherence to strict collection techniques and abstinence periods is therefore crucial to minimize variation.

Table 1: Semen Analysis: Minimal Standards of Adequacy

On at least two occasions:	
Ejaculate volume	1.5–5.0 cc
Sperm density	>20 million/cc
Motility	>60%
Forward progression	>2 (scale 1–4)
Morphology	>60% normal
And:	
No significant sperm agglutination	
No significant pyospermia	
No hyperviscosity	

(Adapted from Sigman, M., Lipshultz, L.I., and Howards, S.S.: Evaluation of the subfertile male. In: Infertility in the Male, 3rd Edition. Edited by L.I. Lipshultz and S.S. Howards. St. Louis: Mosby–Year Book, 1997, p. 177.)

SERUM HORMONE LEVELS

A routine part of the initial male evaluation is a determination of specific hormones in the blood, which usually include FSH, LH, testosterone, prolactin, and estradiol. The interrelationship of these five hormones is closely tied to normal sperm production. Abnormalities may be a sign of a primary hormone problem in the hypothalamus, pituitary, or testis.

ADDITIONAL LABORATORY TESTING

Semen Leukocytes: Increased numbers of white blood cells (WBC) in the semen have been associated with deficiencies in sperm function and motility. Recently, the development of specialized staining techniques for WBC has allowed their definitive identification within the semen. Semen WBC have been associated with genitourinary infections and/or inflammation. WBC have also been implicated in the release of harmful substances called reactive oxygen species (ROS). ROS will be discussed at length below. Evidence of elevated levels of WBC in the semen should lead to a semen culture, which is used to identify the presence or absence of infection.

Antisperm Antibody Testing: Antisperm antibodies (ASA) in the semen are associated with lower pregnancy rates. Conditions associated with the presence of seminal ASA include genitourinary infections, testicular trauma, thermal injury, and genital tract obstruction. The most accurate means of detecting ASA is through the use of the Immunobead® test. Microscopic beads are used to detect the presence or

absence of sperm-bound antibodies. Greater than 20% of sperm with ASA binding is usually clinically significant and possibly associated with functional sperm deficits.

Under the microscope, the semen of a man with positive ASA may frequently be noted to have excessive clumping and decreased sperm motility.

Reactive Oxygen Species (ROS): ROS are molecules with an extra electron that can be easily passed on to another molecule. When present in excessively high levels, ROS can cause injury to sperm and other genital tract cells. Specifically, this damage can involve the sperm membrane and DNA and may lead to overall impaired sperm function.

Morphology: Morphology assays are descriptive analyses of sperm shape. Several studies have suggested a correlation between sperm morphology and function. Two types of morphology tests used include the "standard" morphology assay and Kruger's strict morphology assay. In the latter, sperm are actually measured in multiple areas to identify "perfect sperm shape." This perfect shape should be present in greater than 4% of the cells examined.

Sperm Penetration Assay (SPA): This is a functional test which evaluates the sperm's ability to penetrate hamster ova. The result of a normal SPA is correlated with a greater incidence of positive in vitro fertilization (IVF) outcomes. Abnormal results may steer a couple towards assisted reproductive techniques using specific sperm separation procedures prior to intrauterine insemination (IUI) or even to intracytoplasmic sperm injection (ICSI) with IVF.

DNA Damage: DNA fragmentation is the percentage of breakage or damage to the DNA ladder structure within sperm. Elevated levels of DNA damage can result in inaccurate transmission of genetic information required for fertilization with resultant embryos that do not grow normally, resulting in embryo loss. Two prime causes of DNA damage are smoking and exposure to environmental toxins. These gonadotoxins should be minimized to maintain sperm DNA integrity.

GENETIC TESTING

Karyotyping: This is a staining technique of peripheral white blood cells which are treated in the laboratory in order to allow characterization of chromosomal number and structure. This test provides information about whether extra chromosomes are present, whether a chromosome has been lost, whether the information on the chromosomes has been rearranged, or whether large deletions of DNA are present. Abnormalities in the number of chromosomes or the arrangements of genes on the chromosomes can influence male fertility as well as the health of the embryo. Identification of these abnormalities may provide a diagnosis and provide implications for treatment.

Y microdeletions: The Y chromosome contains genetic information required for the formation and function of the testes. Approximately 10-20% of men presenting without sperm and 5% of men with very reduced sperm counts in their ejaculate may be missing small parts of the Y chromosome

(microdeletions of Y chromosomal DNA). The identification of such deletions provides a diagnosis for these patients. Furthermore, patients carrying these deletions who are considering assisted reproductive techniques should be counseled as to the risk of infertility in their male offspring.

Cystic Fibrosis (CF) Testing: CF is the most common life-threatening autosomal-recessive inherited disease in the Caucasian population, with a 4% carrier frequency and affecting approximately 1 in 2000 live births. Mutations of the CF gene are associated with some male reproductive tract abnormalities, such as absence of the vas deferens or unexplained obstruction of the epididymis. Often patients with these conditions have no associated medical problems and present only because of their infertility. Identification of these findings will help determine choices for treatment, as well as estimating the risk of transmitting CF to offspring.

TREATMENT OPTIONS

After a thorough history, physical examination, and diagnostic testing, your physician should be able to recommend treatment options. These have generally been organized into medical and surgical approaches. It should be emphasized that the effects of nearly all treatments, both medical and surgical, takes at least three months to see an effect. This time period corresponds to one full cycle of sperm production. Often two to three sperm cycles are necessary to see the maximal benefit of therapy. For this reason, patients and treating physicians alike must keep reasonable time tables and expectations for successful following all types of treatment.

MEDICAL THERAPY

1. Human Chorionic Gonadotropin (hCG), Menotropins (hMG), and GnRH Treatments: These agents are generally used for patients with hypogonadotropic hypogonadism, a condition which results in impaired sperm production due to a deficit in essential hormonal levels, specifically LH and FSH. Human chorionic gonadotropin (hCG) behaves much like LH, and stimulates the testicular Leydig cells to produce testosterone. Human menopausal gonadotropin (hMG) activity is similar to both LH and FSH stimulation and has therapeutic effects similar to hCG. GnRH therapy may also be used in men with hypogonadotropic hypogonadism. Its role is to increase production of LH and FSH in the brain, thus correcting their low levels in the circulation. Use of these agents outside of the setting of hypogonadotropic hypogonadism rarely improves semen quality.

2. Aromatase Inhibitors: These medications reduce the conversion of testosterone and androstenedione to estradiol and estrone, thereby increasing serum testosterone levels. With this treatment, improvements in semen concentration and motility have been demonstrated in men with low sperm counts. Elevated estrogen levels are more frequently seen in obese men.

3. Antioxidants: (Vitamin E and Vitamin C): These medications are used primarily to treat high levels of oxidants also known as reactive oxygen species (ROS). ROS are normally present in semen, and at normal concentrations they serve a physiologic function. As previously discussed, they possess an extra electron which is very easily passed onto other molecules. When ROS are present at excessively high levels, their cumulative effects can result in significant damage to the sperm DNA and sperm

membrane, as well as other genital tract cells. Antioxidants help neutralize ROS to minimize their harmful effects.

SURGICAL THERAPY

1. Varicocele Ligation: The group of blood vessels which collectively provide the primary venous drainage from the testis is called the pampiniform plexus. Varicoceles are dilated veins in the scrotum surrounding the testis, in other words, dilated pampiniform plexus veins (Figs. 6-A & 6-B). Two separate groups of veins also effectively drain blood away from the testis.

Approximately 15% of all men have varicoceles, and for most men they do not seem to impair testicular function. However, about 40% of all men presenting with fertility problems do have varicoceles. It is generally believed that a varicole's presence, either directly or indirectly, impairs sperm production. Although the precise pathophysiologic

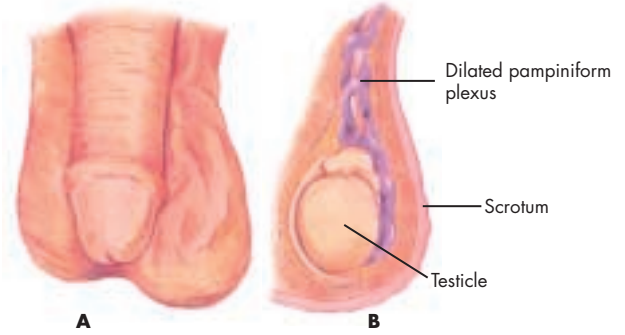


Figure 6. A, Appearance of a visibly evident varicocele. B, Dilated veins of the pampiniform plexus traveling within the spermatic cord.

mechanism of the varicocele effect has not been delineated, many investigators believe that a secondary increase in testicular temperature causes impaired spermatogenesis.

Whatever the cause, many studies have demonstrated that 40%–70% of men undergoing varicocele repair will have an improvement in semen quality, and about 40% will subsequently initiate a pregnancy.

Many urologists prefer an operative approach that employs the use of an operating microscope. The use of this higher magnification ensures better preservation of important spermatic cord structures (e.g., artery and lymphatics) with effective ligation of those veins contributing to the varicocele.

2. Transurethral Resection of the Ejaculatory Duct: As described previously, the ejaculatory duct is a structure formed after the union of the vas deferens and seminal vesicle. It is a tubular structure that travels through the prostate on both the right and the left to the respective prostatic portion of the urethra. It is responsible for sperm and

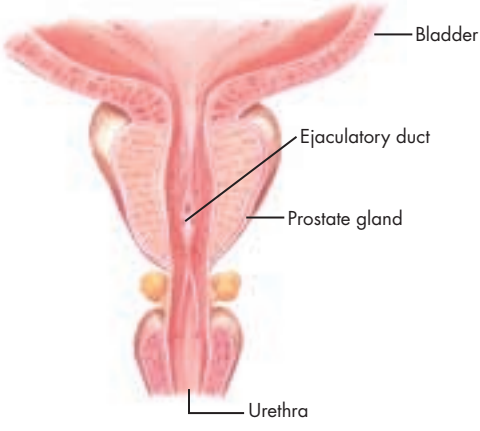


Figure 7. Location of resection in transurethral resection of the ejaculatory ducts.

seminal vesicle fluid transport into the prostatic urethra, which is the final destination of sperm prior to ejaculation.

A number of factors can cause obstruction of the ejaculatory duct, and thus block the flow of sperm. These include intrinsic problems such as congenital narrowing or scarring due to infection, and extrinsic problems such as compression due to a prostatic cyst or tumor.

Obstructed ejaculatory ducts are usually diagnosed by transrectal ultrasound imaging or by special radiographic tests called vasograms. Obstructed ducts are treated by a simple transurethral procedure whereby the obstructed part of the duct is removed, leaving normal, unobstructed ductal tissue behind (Fig. 7).

2. Microsurgical Reversal of Vasal or Epididymal Obstruction: Obstruction of the vas deferens is usually the result of a prior elective vasectomy procedure. Over time, this obstruction may lead to significant "backpressure" within the fragile epididymal tubules and can cause a secondary epididymal obstruction, often referred to as a "blowout." Vasal obstruction and even secondary epididymal obstruction can usually be corrected operatively using special microsurgical techniques to bypass the obstruction (Figs. 8-A & 8-B). These microscopic procedures are among the most technically demanding ones performed by urologists, and they are best accomplished by individuals with special training in this area.

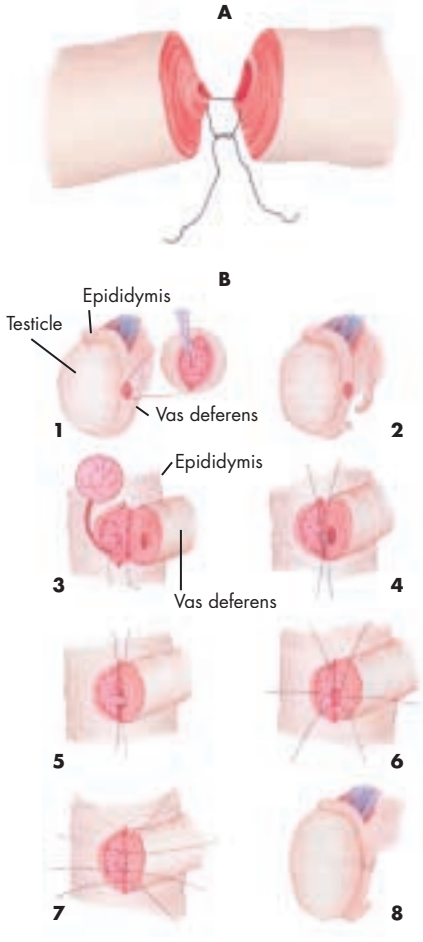


Figure 8. Technique for vasovasostomy (A) and epididymovasostomy (B), respectively.

3. Sperm Procurement Techniques: Some couples, either as a result of male or female fertility issues, will need to proceed to assisted reproductive techniques such as in vitro fertilization (IVF). In some male patients, sufficient sperm are not available in the ejaculate. This deficiency may be due to problems with sperm production, obstruction of the male reproductive tract, or disorders of ejaculation. Therefore, sperm retrieval techniques must be employed to obtain sperm for use in IVF. The type of procurement technique used depends largely on the nature of the patient's problem. If obstruction or ejaculatory disturbance is the primary issue, then epididymal sperm retrieval is the preferred method. This will typically yield motile, mature sperm. If the problem is one of abnormal sperm production, then removal of a small amount of testicular tissue with sperm extraction is usually performed. Sperm obtained by these techniques may be injected directly into the egg, a process known as intracytoplasmic sperm injection (ICSI). Only one live sperm is needed for each egg. Sperm obtained via procurement techniques can be used fresh or also cryopreserved at a later date.

A BRIEF WORD ABOUT ASSISTED REPRODUCTIVE TECHNIQUES

Assisted reproductive techniques (ART) describe several special methods used to help couples achieve a pregnancy. The first of these is called intrauterine insemination (IUI). IUI involves the collection of the male's ejaculate and subsequent processing or "washing." The ejaculate is then inserted into the female's cervix or uterus using a special injection catheter. Among ART, this is generally considered to be the least invasive, but its effectiveness is limited for those patients with severe fertility problems.

IVF occurs by incubating the male's sperm with the female's eggs in the laboratory. The development of the eggs are regulated with hormones, and the conditions in the laboratory dish are meticulously controlled to optimize the chances for fertilization. Those eggs which are fertilized (i.e., "embryos") are then assessed on the basis of their appearance. The best embroyals are selected and planted back into the woman. These embryos have been shown to be the ones with the highest likelihood of resulting in a successful pregnancy. Embryos not used can be frozen (cryopreserved) for later use.

A modification of the IVF procedure is the ICSI procedure (Fig. 9). ICSI utilizes the same methods as standard IVF, except instead of simply incubating the sperm and egg together in a Petri dish, the egg is stabilized under a special microscope using a micro-suction instrument while a very fine pipette is used to inject a selected sperm into the egg. This sperm injection technique allows couples to overcome many barriers in sperm count, motility, morphology, and degree of sperm maturity. ICSI has made it possible for couples, who in the past would have been unable to achieve pregnancies, to bear their own biologic children.

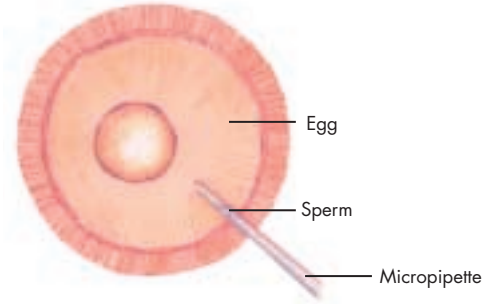


Figure 9. Intracytoplasmic sperm injection (ICSI).

COMMON CONCERNS

What should I expect at the first visit to the doctor?

You should anticipate a thorough history and physical examination. It is beneficial to have both partners present at this first visit to facilitate data gathering by the physician. This will also allow your partner to have her questions adequately answered in person.

What testing is usually ordered?

Testing will often be initiated at the time of the first visit, and this generally includes measurement of blood hormone levels (FSH, LH, testosterone, prolactin, and estradiol) to ensure an intact HPG axis. Additionally, you should ask ahead of time if you would be expected to collect a semen sample for semen analysis at that visit. It is usually recommended that men observe two to three days of abstinence prior to undergoing a semen analysis. Most doctors will allow collection of the semen sample at your home, as long as it arrives in the laboratory within one hour.

Other specialized semen and genetic testing may be ordered as well. Clinical history as well as the availability of the specific tests usually determine which tests will be ordered.

I am concerned about my job. How much time should I expect to miss if I have one of the surgical procedures described above?

The majority of the procedures discussed in this booklet can be performed on an outpatient basis. The timing of return to work is variable, depending on the nature of the patient's work

duties. Generally, even with the more invasive procedures described above, patients are able to return to work within several days. There may be some activity restrictions for a few weeks, and these should be discussed on an individual basis with your physician.

I feel healthy and take care of myself. Could I have done something differently to prevent this from happening?

Most patients with male factor fertility problems are, overall, quite healthy. Although some individuals do develop problems after "preventable events" (exposure to environmental toxins, radiation, trauma, etc.), most causes of male infertility are likely present from birth and thus unavoidable. Unavoidable does not mean untreatable, and under the care of a properly trained physician, the chances of a successful pregnancy with subsequent childbirth are optimized.

WHERE TO TURN FOR HELP

There are a number of established resources in place to help patients with male factor fertility problems. The first goal should be to find a urologist with special training in male reproductive medicine and surgery. A number of organizations can assist you in identifying such physicians near your community. These include:

American Society for Reproductive Medicine (ASRM)
1209 Montgomery Highway
Birmingham, Alabama 35216-2809
Phone: (205) 978-5000
Fax: (205) 978-5005
www.asrm.org

The American Society for Reproductive Medicine is interested in all aspects of the reproductive life cycle and is committed to providing patient information on a wide range of topics. ASRM provides information on infertility, menopause, contraception, reproductive surgery, endometriosis, and other reproductive disorders. ASRM encourages you to review all information on their Web site - www.asrm.org - and consult your health care professional if you still have questions.

Patient features available at www.asrm.org include:
- Find a Doctor
- Patient Booklets
- Patient Fact Sheets
- Frequently Asked Questions
- Topic Index
- Links to Professional Organizations
- Link to Newest Journal, "Sexuality, Reproduction & Menopause"

American Urological Association (AUA)
1000 Corporate Boulevard
Linthicum, MD 21090
Phone: (866) RING AUA (1-866-746-4282) or (410) 689-3700
Fax: 410-689-3800
www.auanet.org

The American Urological Association (AUA) offers an online patient information resource, which was written and reviewed by urology experts in partnership with the American Foundation for Urologic Disease. You can access this online patient information source at www.urologyhealth.org.

A number of patient organizations also exist to help individuals facing reproductive heath issues and provide resources and support groups:

American Fertility Association (AFA)
666 Fifth Avenue
Suite 278
New York, NY 10103
Phone: (888) 917-3777
www.theAFA.org

The American Fertility Association (AFA) is a national organization dedicated to supporting women, men and families facing infertility and decisions related to family building and reproductive health – from prevention and treatment to social, psychological and financial concerns. Through educational symposia and forums, free publications, interactive media and advocacy for research funding and policy, The American Fertility Association serves as a lifetime resource for men, women and families needing reproductive information and support and to forward the causes of adoption and reproductive health.

As a part of membership, AFA provides free access to all of their educational material via No Barriers membership:

· Monthly newsletter
· in*focus*, quarterly special interest magazine

- National Infertility and Adoption Resource Directory
- Fact sheets and brochures
- Referral network database
- Online discussions and message boards, moderated by physicians, therapists and adoption professionals

To become an AFA member, visit AFA's website or call the toll-free number listed above.

RESOLVE: The National Infertility Association

7910 Woodmont Avenue
Suite 1350
Bethesda, MD 20814
Phone: (888) 623-0744 (National Helpline)
Phone: (301) 652-8585 (National Office)
Fax: (301) 652-9375
Email: info@resolve.org
www.resolve.org

The mission of RESOLVE: The National Infertility Association is to provide timely, compassionate support and information to people who are experiencing infertility and to increase awareness of infertility issues through public education and advocacy.

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Organon USA Inc. would like to thank
R.E. Brannigan, M.D., L.I. Lipshultz, M.D.,
and D. Shin, M.D. for their assistance
in the development of this booklet.

While this booklet provides important information about the medical approaches to assisted reproductive technologies, it does not contain all the possible precautions, side effects, warnings, contraindications, and interactions which may be associated with your drug treatments. Your physician should discuss your treatment and possible side effects. Be sure to discuss any questions that you may have with your physician before beginning treatment.

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 Printed in the USA January 2006 FER-3024