IDIOPATHIC MALE INFERTILITY

A condition in which fertility impairment occurs spontaneously or due to an unknown cause.

 Diagnosis  Male

Related Diagnoses:
Varicocele  Azoospermia  Erectile dysfunction  Undescended testes  Anejaculation  Retrograde ejaculation  Non-obstructive azoospermia  XX male syndrome  Oligozoospermia  Sperm autoantibodies  Oligoasthenoteratozoospermia  Orchitis  Teratospermia  Globozoospermia  Epididymitis

About Idiopathic male infertility

Unexplained male infertility (UMI) is clinically defined as failure of a couple to conceive after one year of regular sexual intercourse. An estimated 4-17% of couples seek medical treatment in order to rectify their infertility, and it is reasonable to assume that there are many more cases of infertility that are unreported. It has been shown that the male factor is solely and partially implicated in 20-50% of the cases of infertility. However, despite advances in technologies and diagnostic methods in the field of andrology, there remains a significant subset of these subfertile men who are classified as having unexplained male infertility (UMI). Men are categorized as having UMI when they are infertile despite having normal semen analysis, normal history and physical examination and when female factor infertility has been ruled out. The average incidence of UMI is approximately 15%, although reports of UMI in study populations have ranged from 6% to 37%. Possible factors that might explain the difficulties to conceive in UMI include the presence of antisperm antibodies, sperm DNA damage, elevated levels of reactive oxygen species (ROS), and sperm dysfunction. A further possibility to consider is unexplained female factor infertility and coital factors such as inappropriate timing of intercourse (not within the female fertile window), erectile dysfunction or anejaculation. It is therefore important that both a thorough initial assessment is performed, including a detailed sexual history and gynecological examination, as well as advanced investigations that test for autoimmune infertility and sperm defects.

Infertility remains both prevalent and problematic among couples worldwide. Studies have shown that spontaneous conception occurs in the majority of couples with unexplained infertility in the next 1-2 years if they continue to have fertility-focused intercourse. One study reported that over 50% of such couples will have a live birth within 36 months after failing to achieve pregnancy in the first year. Female partner age greater than 35 or infertility duration of more than 3 years are associated with a significant decrease in spontaneous pregnancy rate. After more than 3 years of infertility, the chance of spontaneous pregnancy drops 2% every year after the age of 25.

Currently, routine semen analysis remains the backbone of the evaluation of the male factor infertility, besides detailed medical history and thorough physical examination. Such practice is based on the fact that the semen parameters such as sperm concentration, motility, and morphology have been shown to be significantly related to conception. In addition, being a cost-effective and non-invasive test has led to the widespread use of semen analysis in the initial evaluation of infertile men. Nonetheless, the criteria for normal semen parameters vary according to which edition of the WHO laboratory manual for the examination and processing of human semen is used.

Seminal fluid collected from the patient following 2-5 days of abstinence should be assessed with regard to volume, sperm concentration, motility, and morphology in comparison to WHO defined cutoff values for fertile men. At least two samples should be analyzed although the ideal interval between analyses has not been defined yet. Although fertilization potential decreases as semen parameters decrease in quality, it is difficult to designate patients as fertile or subfertile based on semen analysis alone. However, semen analysis in conjunction with previous evaluations in the initial workup may contribute to the diagnosis of infertility or
Normal semen analysis does not guarantee the fertilization potential of sperm, and studies have shown significant overlap in semen parameter values between fertile and infertile men. This overlap could be due in part to the marked biological variability in semen parameters characteristics, even those taken only a few days apart from the same individual. Furthermore, semen analysis does not provide information regarding defects in sperm function. Many key aspects of the fertilization process such as transport of the sperm to the oocyte, sperm interaction with the cervical mucus, and sperm interaction with the oocyte cannot be assessed by conventional semen analysis. For this reason, it has been suggested that sperm function tests should be included in the semen analysis of individuals seeking fertility evaluation. Lastly, the male evaluation regarding fertility must go far beyond counting spermatozoa and assessing motility and morphology. It has to be complemented with a proper clinical examination, a comprehensive history taking, and relevant endocrine, genetic, and/or other investigations.

The initial workup should first include an exhaustive recording of the patient’s medical history and physical examination. For men with normal semen analysis particular emphasis should be applied upon history of previous fertility, duration of infertility, history of frequent miscarriages, congenital abnormalities in the previous pregnancies and medications. Detailed coital history from both partners discloses several problems such as erectile dysfunction, anejaculation, inappropriate coital technique, infrequent intercourse and inappropriate timing of the intercourse.

Part of the assessment should be the evaluation of psychological stress. Stress might increase the risk for variety of illnesses; including fertility. Sperm quality can be reduced in stressed men compared to those who are not having any significant stressors in their life. Prolonged stress might also increase the likelihood of depression, anxiety, or cardiovascular diseases. Increased alcohol usage, smoking and unhealthy diet has been also found to be related to stress. The relationships between stress and mental and physical health is not clear. Stress may trigger an existing mental or physical problem that could have been successfully managed. For people with an existing problem, including infertility, it may worsen their situation. When it gets to the point when it triggers maladaptive behaviours (e.g. smoking, drinking), anxiety, create conflicts within a couple, thus affecting sexual life, it becomes difficult to separate precipitating factors from the outcomes. Moreover, men are less likely to disclose their problems due to several reasons (e.g. culture, stigma, personality characteristics) and less attention is devoted to them when comes to infertility. Therefore, evaluation of stress and stress management techniques, and providing emotional support not only for women but also men is recommended.

Next, a physical examination of the patient should be performed to rule out other potential sources of infertility. Again for infertile men with normal semen analyses, attention should be paid towards penile abnormalities such as a hypospadias urethral meatus or severe chordee which may lead to deposition of sperm into the vaginal cavity at an insufficient proximity to the cervix. The testes and epididymis and spermatic cord should be carefully palpated in order to rule out the presence of potential sources of oxidative stress culminating in sperm dysfunction such as epididymitis, epididymo-orchitis, and varicocele. Genetic damage in sperm can occur at several levels, all of which have the potential to cause infertility in men. Sperm chromosomal abnormalities are most often seen in men with decreased sperm cell count (oligozoospermia), decreased motility (asthenozoospermia), or high percentage of morphologically abnormal sperm (teratozoospermia). The likelihood of sex chromosomal abnormalities are 15 times greater in infertile men than in the general population, while autosomal abnormalities occur with six times greater frequency.

Spermatogenesis does not occur until the onset of puberty and sperm are kept separated from the immune system by the blood-testis barrier. When the blood-testis barrier is breached for any reason and sperm antigens come into contact with the immune system they will be treated as foreign agents resulting in antisperm antibody (ASA) formation. Antisperm antibody formation has been reported in 42% of men with unexplained infertility.

**Associated disease**

- antisperm antibodies
- sperm DNA damage
- epididymitis
- epididymo-orchitis
- varicocele
- hypospadias
- all possible infertility-related diagnosis, which were not be revealed

**Complications**

- profound psychological effects - partners may become more anxious to conceive, increasing sexual
Dysfunction

Risk factors

- advanced paternal age
- duration of infertility/subfertility
- decreased maternal immune tolerance
- genetic defects
- autoimmune diseases
- chronic inflammatory diseases
- stress

Impact on fertility

The main cause of idiopathic male infertility is low semen quality potentially linked with antisperm antibodies, sperm DNA damage, elevated levels of reactive oxygen species (ROS), and sperm dysfunction. Another possible cause is a low sperm count. In some cases, both the man and woman may be infertile or sub-fertile, and the couple's infertility arises from the combination of these conditions. In other cases, the cause is suspected to be immunological or genetic; it may be that each partner is independently fertile but the couple cannot conceive together without assistance.

Prevention

Maintain healthy lifestyle, do not smoke and drink alcohol and do some sport activity at least twice a week for an hour.

Symptoms

Infertility (infertility that is idiopathic in the sense that its cause remains unknown even after an infertility work-up, usually including semen analysis in the man and assessment of ovulation and fallopian tubes in the woman).

Therapies

Self therapy

Reactive oxygen species (ROS) play an important role in male infertility and are proved to be higher in infertile men; antioxidants could oppose their effect. The majority of studies confirmed beneficial effect of different antioxidants on at least one of the semen parameters and the biggest effect was determined on sperm motility. In many of these trials combinations of more antioxidants were assessed. The optimal dosages of one or more antioxidants were not defined. Most commonly antioxidants studied were vitamin E, vitamin C, selenium, CoQ10, N-acetyl-cysteine, L-carnitine, and zinc and their favorable effect was confirmed.

Conventional medicine

Psychotherapy

There are several psychological (e.g. stress, anxiety) as well as sexual problems (e.g. erectile dysfunction) that can affect male fertility. These problems might be psychological as well as physical in nature; it is hard to separate the physical and psychological aspects. Therefore, individual and/or couple’s counselling is recommended to determine whether there is an underlying cause of male idiopathic infertility.

Majority of studies have focused on impact of infertility on a female and ignored the emotional reaction...
of a male. Working with a couple, establishing an open communication within a couple and decreasing level of stress through the stress management therapy, may improve couples' relationship and increase the probability of conception.

**Pharmacotherapy**

There is no significant scientific evidence for empirical drug treatment of idiopathic male infertility. A variety of drug are used, but there is still no proven evidence for their benefit. Clomiphene citrate and tamoxifen showed some improvement in sperm quality and spontaneous pregnancy rate in a recent meta-analysis.

**Surgical therapy**

There is no surgical therapy for idiopathic male infertility.

**Assisted reproduction**

ICSI may help solve the problem of unexplained male infertility and bypass all the natural barriers that a dysfunctional sperm must overcome to induce fertilization. However, such therapy is not without risks and complications. The successful pregnancy achieved by using a dysfunctional sperm carries a risk of transmission of the same infertility traits to the male offspring. Furthermore, the paternal part of the embryonic genome is actively expressed at the four- to eight-cell stage in human embryos. Therefore, sperm DNA strand breaks that can not be repaired by the oocyte DNA repair system may adversely affect the later stages of embryonic development. Aitken and Krausz recognized that sperm DNA damage is promutagenic and can give rise to mutations after fertilization. Mutations sustained at the very early stage of embryonic development will be fixed in the germline and may give rise to the induction of infertility, childhood cancer and higher risk of imprinting diseases in the offspring.

Taking this risk into account mandates frequent conduction of sperm function testing to elucidate the basic sperm molecular defects which should be rectified by utilizing molecular targeted therapies before using of the dysfunctional sperm in ICSI. Although these types of therapies are still under investigations, exploring the presence and frequency of metabolic targets may help specifically direct the therapeutic research plans on correcting these metabolic alterations. In addition, identifying certain abnormalities in these tests e.g. sperm DNA integrity defects may help in pre-ICSI counseling of the couples about the advantages as well as the possible failures and complications of ART procedure.

If assisted reproduction with own gametes provide inadequate outcome, it is possible to use donated oocytes/ donated sperm or eventually donated embryos (based on the recommendations of IVF specialists taking into account the individual medical condition of the partners). A surrogacy may be another option which may be used if all previous attempts have failed.

**Find more about related issues**

**Diagnoses**

**Varicocele**
An abnormal enlargement of the pampiniform venous plexus in the scrotum.
Learn more at: [www.fertilypedia.org/therapy/diag/varicocele](http://www.fertilypedia.org/therapy/diag/varicocele)

**Azoospermia**
Complete absence of sperm in the ejaculate of a man.
Learn more at: [www.fertilypedia.org/therapy/diag/azoospermia](http://www.fertilypedia.org/therapy/diag/azoospermia)

**Erectile dysfunction**
The inability (that lasts more than 6 months) to develop or maintain an erection of the penis during sexual activity.
Learn more at: [www.fertilypedia.org/therapy/diag/erectile-dysfunction](http://www.fertilypedia.org/therapy/diag/erectile-dysfunction)
Undescended testes
In the case of cryptorchidism one or both testes are absent from the scrotum. It is the most common etiologic factor of azoospermy in the adult.
Learn more at: www.fertilitypedia.org/therapy/diag/undescended-testes

Anejaculation
The pathological inability to ejaculate in males, with (orgasmic) or without (anorgasmic) orgasm.
Learn more at: www.fertilitypedia.org/therapy/diag/anejaculation

Retrograde ejaculation
The semen, which would normally be ejaculated via the urethra, is redirected to the urinary bladder.
Learn more at: www.fertilitypedia.org/therapy/diag/retrograde-ejaculation

Non-obstructive azoospermia
Complete absence of sperm in the ejaculate due to testicular failure.
Learn more at: www.fertilitypedia.org/therapy/diag/non-obstructive-azoospermia

XX male syndrome
The male sex chromosomal disorder characterized by a spectrum of clinical presentations, ranging from ambiguous to normal male genitalia.
Learn more at: www.fertilitypedia.org/therapy/diag/xx-male-syndrome

Oligozoospermia
Semen with a low concentration of sperm and is a common finding in male infertility.
Learn more at: www.fertilitypedia.org/therapy/diag/oligozoospermia

Sperm autoantibodies
Antibodies that bind to sperm, inhibiting their movement, stopping recognition and entry into the egg.
Learn more at: www.fertilitypedia.org/therapy/diag/sperm-autoantibodies

Oligoasthenoteratozoospermia
Male fertility diagnosis defined as a combination of low sperm concentration, reduced motility and abnormal sperm morphology in the ejaculate.
Learn more at: www.fertilitypedia.org/therapy/diag/oligoasthenoteratozoospermia

Orchitis
An inflammation of the testes, involving swelling and heavy pains.
Learn more at: www.fertilitypedia.org/therapy/diag/orchitis

Teratospermia
Teratospermia is a condition characterized by the presence of sperm with abnormal morphology that affects fertility in males.
Learn more at: www.fertilitypedia.org/therapy/diag/teratospermia

Globozoospermia
A rare abnormality of sperm morphology, with the majority of sperm cells being round-headed, which leads to male infertility.
Learn more at: www.fertilitypedia.org/therapy/diag/globozoospermia

Epididymitis
An inflammation of epididymis.
Learn more at: www.fertilitypedia.org/therapy/diag/epididymitis

Organs
Penis
External male sex organ that additionally serves as the urinal duct.
Learn more at: www.fertilitypedia.org/edu/organs/penis

Testes
Male gonads which produce both sperm and androgens, such as testosterone, and are active throughout the reproductive lifespan of the male.
Learn more at: www.fertilitypedia.org/edu/organs/testes

Vas deferens
The duct in the testicle that carries semen from the epididymis to the ejaculatory duct.
Learn more at: www.fertilitypedia.org/edu/organs/vas-deferens

 Biological control

Follicle-stimulating hormone
FSH is a hormone secreted by the anterior pituitary gland. It regulates the development, growth, pubertal matur and reproductive functions of the body.
Learn more at: www.fertilitypedia.org/edu/biological-control/follicle-stimulating-hormone

Testosterone
Steroid hormone produced primarily in the testes of the male; responsible for the development of secondary sex characteristics in the male.
Learn more at: www.fertilitypedia.org/edu/biological-control/testosterone

 Reproductive functions

Ejaculation
Discharge of the semen (usually containing sperm) from the male reprodutory tract, normally accompanied by orgasm.
Learn more at: www.fertilitypedia.org/edu/reproductive-functions/ejaculation

Erection
The physiological process by which a penis becomes erect by being engorged with blood.
Learn more at: www.fertilitypedia.org/edu/reproductive-functions/erection

Fertilization
The fusion of an ovum with a sperm to initiate the development of a new individual organism.
Learn more at: www.fertilitypedia.org/edu/reproductive-functions/fertilization

Spermatogenesis
Process in which spermatozoa are produced from male primordial germ cells in testicles by way of mitosis and meiosis.
Learn more at: www.fertilitypedia.org/edu/reproductive-functions/spermatogenesis

 Risk factors

Advanced paternal age
Age that may lead to the accumulation of de novo mutations, male infertility and increased genetic risks on the offspring.
Learn more at: www.fertilitypedia.org/therapy/af/advanced-paternal-age

Alcohol drinking
A pattern of drinking that results in harm to one's health, interpersonal relationships, or ability to work.
Learn more at: www.fertilitypedia.org/therapy/af/alcohol-drinking
Drug use
A patterned use of a drug in which the user consumes the substance in amounts or with methods which are harmful to themselves or others.
Learn more at: www.fertilitypedia.org/therapy/lf/drug-use-1

Emotional stress
Learn more at: www.fertilitypedia.org/therapy/lf/emotional-stress

Obesity
A medical condition of excess body fat that can have a negative effect on health, leading to reduced life expectancy and other health problems.
Learn more at: www.fertilitypedia.org/therapy/lf/obesity

Poor dietary habits
Eating habits are one of the few factors within our control that impact not only our chances of falling pregnant.
Learn more at: www.fertilitypedia.org/therapy/lf/poor-dietary-habits

Smoking
Long-lasting inhalation of the smoke of burning tobacco.
Learn more at: www.fertilitypedia.org/therapy/lf/smoking-1

 Symptoms

Absence of sperm in ejaculate
The medical condition of a man whose semen contains no sperm.
Learn more at: www.fertilitypedia.org/edu/symptoms/absence-of-sperm-in-ejaculate

Anejaculation
The pathological inability to ejaculate in males, with (orgasmic) or without (anorgasmic) orgasm.
Learn more at: www.fertilitypedia.org/edu/symptoms/anejaculation

Anxiety
The emotional state characterized by unpleasant feelings such as uneasiness, worry, apprehension and dread.
Learn more at: www.fertilitypedia.org/edu/symptoms/anxiety

Delayed ejaculation
A man’s inability for or persistent difficulty in achieving orgasm, despite typical sexual desire and sexual stimulation.
Learn more at: www.fertilitypedia.org/edu/symptoms/delayed-ejaculation

Inability to have or maintain an erection
The inability to develop or maintain an erection of the penis during sexual activity in humans.
Learn more at: www.fertilitypedia.org/edu/symptoms/inability-to-have-or-maintain-an-erection

Lack of semen with ejaculation
Aspermia is the complete lack of semen with ejaculation.
Learn more at: www.fertilitypedia.org/edu/symptoms/lack-of-semen-with-ejaculation

Low self-esteem
A feeling of insignificance or a lack of importance.
Learn more at: www.fertilitypedia.org/edu/symptoms/low-self-esteem

Low semen volume
A condition in which a man has an unusually low ejaculate (or semen) volume, less than 1.5 ml.
Learn more at: www.fertilitypedia.org/edu/symptoms/low-semen-volume
Lowered libido
The absence of sexual appetite.
Learn more at: www.fertilitypedia.org/edu/symptoms/lowered-libido

Premature ejaculation
An uncontrolled ejaculation either before or shortly after sexual penetration.
Learn more at: www.fertilitypedia.org/edu/symptoms/premature-ejaculation

Therapies

Antioxidants
A molecules that inhibits the oxidation of other molecules.
Learn more at: www.fertilitypedia.org/edu/therapies/antioxidants

Avoid or decrease alcohol consumption
A process of discontinuing or lowering of alcohol drinking.
Learn more at: www.fertilitypedia.org/edu/therapies/avoid-or-decrease-alcohol-consumption

Egg donation
Process by which a woman donates eggs for purposes of assisted reproduction or biomedical research.
Learn more at: www.fertilitypedia.org/edu/therapies/egg-donation

Frequency and proper time of sexual intercourse
Best timing and regularity to get pregnant.
Learn more at: www.fertilitypedia.org/edu/therapies/frequency-and-proper-time-of-sexual-intercourse

ICSI
A micromanipulative fertilization technique in which a single sperm is injected directly into an egg.
Learn more at: www.fertilitypedia.org/edu/therapies/icsi

Psychotherapy of erectile dysfunction
Cognitive behavioural therapy or sex therapy is helpful in treatment of psychological problems which could be contributing to erectile dysfunction.
Learn more at: www.fertilitypedia.org/edu/therapies/psychotherapy-of-erectile-dysfunction

Sperm donation
The procedure in which a man (sperm donor) provides his sperm for fertility treatment.
Learn more at: www.fertilitypedia.org/edu/therapies/sperm-donation

Standard IVF
A process in which an egg is fertilised by sperm outside the body: in vitro. Own or donated gametes may be used.
Learn more at: www.fertilitypedia.org/edu/therapies/standard-ivf

Stop smoking
A process of discontinuing tobacco smoking.
Learn more at: www.fertilitypedia.org/edu/therapies/stop-smoking

Gallery
Algorithm for management of male's unexplained infertility
A proposed algorithm for the clinical management of men with unexplained male infertility.

Sources

“Unexplained infertility” —sourced from Wikipedia licensed under CC BY-SA 3.0

“Unexplained Male infertility: diagnosis and Management” —by Hamada et al. licensed under CC BY-NC 4.0

“Infertility, in both males and females, refers to the inability to contribute to conception.” —sourced from Boundless licensed under CC BY-SA 4.0

“Review of Clinical Trials on Effects of Oral Antioxidants on Basic Semen and Other Parameters in Idiopathic Oligoasthenoteratozoospermia” —by Kumalić and Pinter licensed under CC BY 3.0