NON-OBSTRUCTIVE AZOOSPERMIA

Secretory Azoospermia, Noa

Complete absence of sperm in the ejaculate due to testicular failure.

Diagnosis  Male

Related Diagnoses:
- Varicocele
- Azoospermia
- Erectile dysfunction
- Undescended testes
- Ejaculatory disorders
- Klinefelter syndrome
- Kallmann syndrome
- XX male syndrome
- Hypogonadism
- Testicular cancer
- Hypospерmia
- Idiopathic male infertility
- Testicular failure
- Prader-Willi syndrome
- Laurence-Moon syndrome
- Hypergonadotropic hypogonadism

About Non-obstructive azoospermia

NOA represents a failure of spermatogenesis within the testis and, from a management standpoint, is due to either a lack of appropriate stimulation by gonadotropins or an intrinsic testicular impairment. The former category of patients has hypogonadotropic hypogonadism and benefits from specific hormonal therapy. These men show a remarkable recovery of spermatogenic function with exogenously administered gonadotropins or gonadotropin-releasing hormone. This category of patients also includes some individuals whose spermatogenic potential has been suppressed by excess androgens or steroids, and they also benefit from medical management. The other, larger category of non-obstructive azoospermia consists of men with an intrinsic testicular impairment where empirical medical therapy yields little benefit.

Non-obstructive azoospermia is generally considered a non-medically manageable cause of male infertility. These patients, who constitute up to 10% of all infertile men, have abnormal spermatogenesis as the cause of their azoospermia. The establishment of in vitro fertilization using intracytoplasmic sperm injection (ICSI) as a standard treatment modality has resulted in a number of these men successfully fathering a child through surgically retrieved sperm from the testis. The challenge, however, is to improve their spermatogenic function to enable the appearance of sperm in their ejaculate or to improve the chances of a successful retrieval from the testis for ICSI.

The initial evaluation of this condition aims at resolving the following issues:

1. confirming azoospermia,
2. differentiating obstructive from non-obstructive etiology,
3. assessing for the presence of reversible factors and
4. evaluating for the presence of genetic abnormalities.

An elevated follicle-stimulating hormone (FSH) level or an absence of normal spermatogenesis by testicular histology in the presence of azoospermia is generally considered sufficient evidence of a non-obstructive etiology.

The most common reversible factors that need to be ruled out include recent exogenous hormone administration, severe febrile illnesses, chemotherapy/radiation or prolonged antibiotic use.

Hormone analysis forms the cornerstone of the further evaluation and management of NOA and serves two important functions. The first function is to identify a distinct subset of men who have hypogonadotropism (low FSH), in which azoospermia results from an inadequate stimulation of the testis by gonadotropins. The inherent spermatogenic potential of the testis may be partially recoverable, and the management and prognosis of infertility in these men differ from all other subsets. The second function is to predict the success of medical therapy and of surgical sperm retrieval. Based on these initial hormone studies, the two broad categories are hypogonadotropic hypogonadism and hypergonadotropic hypogonadism or eugonadism (Tab. 1 in picture
There is considerable overlap in the hormone statuses of men who do not have hypogonadotropism, with similar etiologies producing a spectrum of hormonal changes. The American Urological Association recommends an estimation of serum FSH and testosterone as the initial hormonal assessment. However, endocrine abnormalities are a rare cause of male infertility and account for less than 3% of all cases. Additional hormone analysis, including luteinizing hormone (LH), estradiol and prolactin evaluations, is performed based on the likelihood of their abnormality and potential impact on management.

**Associated disease**
- hypogonadotropic hypogonadism
- hypergonadotropic hypogonadism
- Kallmann syndrome
- Prader-Willi syndrome
- Laurence-Moon syndrome
- pituitary tumor
- hyperprolactinemia
- congenital adrenal hyperplasia
- testicular adrenal rest tumors (TARTs)

**Complications**
- infertility

**Risk factors**
- recent exogenous hormone administration (steroids or androgens)
- severe febrile illnesses
- chemotherapy/radiation
- prolonged antibiotic use

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**Impact on fertility**

The main problem is that in ejaculate, there are no sperms which could fertilize an egg spontaneously. The only option is chirurgical extraction of sperm from testicles (MESA, TESE, micro TESE) with intracytoplasmatic sperm injection (ICSI). If the extraction methods fails to obtain any sperm, use of donor spermatozoa should be considered.

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**Prevention**

Non-obstructive azoospermia cannot be prevented, but clinicians should be attentive to the concomitant presence of infertility in the patient’s male relatives (as a result of chromosomal abnormalities, genetic conditions, etc.).

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**Symptoms**

In many cases, men with non-obstructive azoospermia typically have small-volume testes and elevated FSH. The finding of atrophic testes and elevated FSH levels indicates germ cell failure. Patients with normal sperm production typically have FSH values in the lower end of the normal range, and levels above this should raise suspicion of a defect in spermatogenesis. In addition, patients with unilateral testicular disease may have elevated FSH levels. A diagnostic testicular biopsy is not indicated in patients with elevated FSH levels. Instead, patients with non-obstructive azoospermia due to a primary testicular defect and not to a hormonal deficiency should be offered genetic testing, consisting of a karyotype and a Y-chromosome microdeletion analysis. If abnormalities are found, a couple should be offered genetic counseling prior to proceeding with assisted reproductive techniques.

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**Therapies**
Self therapy

Does not exist.

Conventional medicine

Pharmacotherapy

Among men with NOA, gonadotropin therapy for hypogonadotropic hypogonadism is the only specific indication that has universally shown an improvement in semen analysis and pregnancy rates. Gonadotropins (hCG and rFSH) in combination constitute a standard therapy, with GnRH therapy reserved for non-responders. The medical management of other forms of NOA remains empirical. Drug therapy with aromatase inhibitors and gonadotropins shows potential promise in improving outcomes in men requiring surgical sperm retrieval, but there is lack of level I clinical evidence for this indication.

Surgical therapy

There is no surgical therapy for this condition.

Assisted reproduction

Assisted reproduction offers men to undergo surgical sperm extraction. For sperm extraction, these four techniques are used: testicular sperm aspiration, testicular sperm extraction, fine needle aspiration mapping and microdissection testicular sperm extraction. The establishment of in vitro fertilization using intracytoplasmic sperm injection (ICSI) as a standard treatment modality has resulted in a number of these men successfully fathering a child through surgically retrieved sperm from the testis. However, in case of genetically determined NOA, PGD/PGS of early embryos is recommended.

Even with surgery, there is still the possibility that no sperm may be obtained. Then, the fertilization with donated sperm should be considered.

Find more about related issues

- **Varicocele**
  An abnormal enlargement of the pampiniform venous plexus in the scrotum.
  Learn more at: www.fertilitypedia.org/therapy/diag/varicocele

- **Azoospermia**
  Complete absence of sperm in the ejaculate of a man.
  Learn more at: www.fertilitypedia.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.fertilitypedia.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
Ejaculatory disorders
A class of sexual disorders defined as the subjective lack of normal ejaculation.
Learn more at: www.fertilitypedia.org/therapy/diag/ejaculatory-disorders

Klinefelter syndrome
The set of symptoms that result from two or more X chromosome in males.
Learn more at: www.fertilitypedia.org/therapy/diag/klinefelter-syndrome

Kallmann syndrome
A genetic condition where the primary symptom is a failure to start puberty or a failure to fully complete puberty.
Learn more at: www.fertilitypedia.org/therapy/diag/kallmann-syndrome

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

Hypogonadism
A medical term which describes a diminished functional activity of the gonads – the testes and ovaries.
Learn more at: www.fertilitypedia.org/therapy/diag/hypogonadism

Testicular cancer
Cancer that develops in the testicles.
Learn more at: www.fertilitypedia.org/therapy/diag/testicular-cancer

Hypospermia
A condition in which a man has an unusually low ejaculate (or semen) volume.
Learn more at: www.fertilitypedia.org/therapy/diag/hypospermia

Idiopathic male infertility
A condition in which fertility impairment occurs spontaneously or due to an unknown cause.
Learn more at: www.fertilitypedia.org/therapy/diag/idiopathic-male-infertility

Testicular failure
The inability of the testicles to produce sperm or testosterone.
Learn more at: www.fertilitypedia.org/therapy/diag/testicular-failure

Prader-Willi syndrome
A genetic disorder due to loss of function of specific genes on chromosome 15.
Learn more at: www.fertilitypedia.org/therapy/diag/prader-willi-syndrome

Laurence-Moon syndrome
Laurence-Moon syndrome (LMS) is a genetically predisposed disorder affecting both genders.
Learn more at: www.fertilitypedia.org/therapy/diag/laurence-moon-syndrome

Hypergonadotrophic hypogonadism
Decreased functional activity of the gonads, with retardation sexual development, associated with high levels of hormones that stimulate the gonads.
Learn more at: www.fertilitypedia.org/therapy/diag/hypergonadotrophic-hypogonadism

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Hypothalamus
A region of the forebrain that regulates body temperature, some metabolic processes and governs the autonomic nervous system.
Learn more at: www.fertilitypedia.org/edu/organs/hypothalamus

Pituitary gland
An endocrine gland, about the size of a pea, whose secretions control the other endocrine glands and influence growth, metabolism, and maturation.
Learn more at: www.fertilitypedia.org/edu/organs/pituitary-gland

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

Reproductive cells

Spermatogonium
An undifferentiated male germ cell with self-renewing capacity representing the first stage of spermatogenesis.
Learn more at: www.fertilitypedia.org/edu/reproductive-cells/spermatogonium

Biological control

Estradiol
A steroid and estrogen sex hormone produced in the ovaries of females.
Learn more at: www.fertilitypedia.org/edu/biological-control/estradiol

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

Gonadotropin-releasing hormone
A releasing hormone responsible for the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary.
Learn more at: www.fertilitypedia.org/edu/biological-control/gonadotropin-releasing-hormone

Luteinizing hormone
A hormone, that stimulates ovulation and the development of the corpus luteum in females, and the production of androgens in males.
Learn more at: www.fertilitypedia.org/edu/biological-control/luteinizing-hormone

Progesterone
Steroid hormone, secreted by the ovaries, whose function is to prepare the uterus for the implantation of a fertilized ovum and to maintain pregnancy.
Learn more at: www.fertilitypedia.org/edu/biological-control/progesterone

Reproductive functions

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

Chemotherapy
A category of cancer treatment that uses one or more anti-cancer drugs.
Learn more at: www.fertilitypedia.org/therapy/rf/chemotherapy

High level of FSH
FSH levels above what an expected levels for one's age and is indicator of proper ovarian function.
Learn more at: www.fertilitypedia.org/therapy/rf/high-level-of-fsh

High level of prolactin
The presence of abnormally high levels of prolactin in the blood.
Learn more at: www.fertilitypedia.org/therapy/rf/high-level-of-prolactin

Low level of FSH
A condition with low serum follicle-stimulating hormone (FSH) concentration.
Learn more at: www.fertilitypedia.org/therapy/rf/low-level-of-fsh

Radiation exposure
A damage to body caused by a large dose of radiation.
Learn more at: www.fertilitypedia.org/therapy/rf/radiation-exposure

Testicular adrenal rest tumors
A benign testicular tumor associated particularly with congenital adrenal hyperplasia.
Learn more at: www.fertilitypedia.org/therapy/rf/testicular-adrenal-rest-tumors

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

Atrophy of the testicles
A not-temporary condition in which the testes diminish in size and may be accompanied by loss of function.
Learn more at: www.fertilitypedia.org/edu/symptoms/atrophy-of-the-testicles

Infertility
The failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.
Learn more at: www.fertilitypedia.org/edu/symptoms/infertility

Small testes
Abnormally small testicular volume.
Learn more at: www.fertilitypedia.org/edu/symptoms/small-testes

Therapies

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

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
Laser-assisted immotile sperm selection
Method, which uses a laser to identify viable sperm cell, recommended in MESA/TESA IVF cycles or in patients diagnosed with sperm immotility.
Learn more at: www.fertilitypedia.org/edu/therapies/laser-assisted-immotile-sperm-selection-1

MESA
A microsurgical procedure to harvest sperm from the single epididymal tubule (epididymis), used in the case of obstructive azoospermia.
Learn more at: www.fertilitypedia.org/edu/therapies/mesa

Micro TESE
Microsurgical method used to identify areas of sperm production within the testes with the aid of optical magnification.
Learn more at: www.fertilitypedia.org/edu/therapies/micro-tese

PESA
Sperm aspiration procedure in which a needle is inserted into the epididymis in order to retrieve sperm.
Learn more at: www.fertilitypedia.org/edu/therapies/pesa

Preimplantation genetic diagnosis
Technology that allows couples with a family history of monogenic disorders, x-linked diseases and chromosomal abnormality have a healthy baby.
Learn more at: www.fertilitypedia.org/edu/therapies/preimplantation-genetic-diagnosis

Preimplantation genetic screening
The term PGS is used to denote procedures that do not look for a specific disease but to identify embryos at risk of de-novo occurring aneuploidies
Learn more at: www.fertilitypedia.org/edu/therapies/preimplantation-genetic-screening-1

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

TESE
Removal of a small portion of testicular tissue in order to extract a few viable sperm.
Learn more at: www.fertilitypedia.org/edu/therapies/tese

Gallery

Table 1 - Non-obstructive azoospermia classification

<table>
<thead>
<tr>
<th>Hypogonadotropic hypogonadism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low FSH, Low LH, Low testosterone</td>
</tr>
<tr>
<td>Congenital: Kallmann syndrome (hypothalamic GnRH deficiency)</td>
</tr>
<tr>
<td>Acquired: Pituitary tumors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypergonadotropic hypogonadism/eugonadism</th>
</tr>
</thead>
<tbody>
<tr>
<td>High/normal FSH, Normal/high LH, Normal/low testosterone</td>
</tr>
<tr>
<td>Congenital: Genetic abnormalities (Chromosomal)</td>
</tr>
<tr>
<td>Acquired:</td>
</tr>
<tr>
<td>Varicocele</td>
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<tr>
<td>Orchitis</td>
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<tr>
<td>Gonadotoxins (chemotherapy/radiation)</td>
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<tr>
<td>Trauma/ torsion</td>
</tr>
<tr>
<td>Idiopathic</td>
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</tbody>
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Sources

"Medical management of non-obstructive azoospermia [http://www.scielo.br/pdf/clin/v68s1/a08v68s1.pdf]" — by Kumar licensed under CC BY-NC 3.0

"Focus Issue on Male Infertility [http://www.hindawi.com/journals/au/2012/823582/]" — by Kobayashi et al. licensed under CC BY 3.0

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