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**SPERMATOGENESIS**

**Spermatogenesis** is the process by which haploid spermatozoa develop from germ cells in the seminiferous tubules of the testis. This process starts with the mitotic division of the stem cells located close to the basement membrane of the tubules. These cells are called spermatogonial stem cells. There are **three phases**: (1) Spermatocytogenesis (Mitosis), (2) Meiosis, and (3) Spermiogenesis. Spermatocytogenesis (also called Mitosis): Stem cells (Type A **spermatogonia**; singular = spermatogonium) divide mitotically to replace themselves and to produce cells that begin differentiation (Type B **spermatogonia**). **Spermatogenesis**, the origin and development of the sperm cells within the male reproductive organs, the testes. The testes are composed of numerous thin, tightly coiled tubules known as the seminiferous tubules; the sperm cells are produced within the walls of the tubules. Within the walls of the tubules, also, are many randomly scattered cells, called Sertoli cells, that function to support and nourish the immature sperm cells by giving them nutrients and blood products. As the young germ cells grow, the Sertoli cells help to transport them from the outer surface of the seminiferous tubule to the central channel of the tubule.

**STAGES OF SPERMATOGENESIS**

**FIRST STAGE:** Spermatocytogenesis is the male form of gametocytogenesis and results in the formation of spermatocytes possessing half the normal complement of genetic material. In spermatocytogenesis, a diploid spermatogonium, which resides in the basal compartment of the seminiferous tubules, divides mitotically, producing two diploid intermediate cells called primary spermatocytes. Each primary spermatocyte then moves into the adluminal compartment of the seminiferous tubules and duplicates its DNA and subsequently undergoes *meiosis I* to produce two haploid secondary spermatocytes, which will later divide once more into haploid spermatids. This division implicates sources of genetic variation, such as random inclusion of either parental chromosomes, and chromosomal crossover that increases the genetic variability of the gamete. The DNA damage response (DDR) machinery plays an important role in spermatogenesis. The protein FMRP binds to meiotic chromosomes and regulates the dynamics of the DDR machinery during spermatogenesis. FMRP appears to be necessary for the repair of DNA damage. Each cell division from a spermatogonium to a spermatid is incomplete; the cells remain connected to one another by bridges of cytoplasm to allow synchronous development. Not all spermatogonia divide to produce spermatocytes; otherwise, the supply of spermatogonia would run out. Instead, spermatogonial stem cells divide mitotically to produce copies of themselves, ensuring a constant supply of spermatogonia to fuel spermatogenesis.

**SECOND STAGE:** Spermatidogenesis is the creation of spermatids from secondary spermatocytes. Secondary spermatocytes produced earlier rapidly enter meiosis II and divide to produce haploid spermatids. The brevity of this stage means that secondary spermatocytes are rarely seen in histological studies. The intermediate stage of spermatogenesis that is highlighted by the meiotic division of the spermatocytes, giving rise to haploid spermatids, each with a different genetic content.

**THIRD STAGE:** During spermiogenesis, the spermatids begin to form a tail by growing microtubules on one of the centrioles, which turns into basal body. These microtubules form an axoneme. Later the centriole is modified in the process of centrosome reduction. The anterior part of the tail (called midpiece) thickens because mitochondria are arranged around the axoneme to ensure energy supply. Spermatid DNA also undergoes packaging, becoming highly condensed. The DNA is packaged firstly with specific nuclear basic proteins, which are subsequently replaced with protamines during spermatid elongation. The resultant tightly packed chromatin is transcriptionally inactive. The Golgi apparatus surrounds the now condensed nucleus, becoming the acrosome. Maturation then takes place under the influence of testosterone, which removes the remaining unnecessary cytoplasm and organelles. The excess cytoplasm, known as *residual bodies*, is phagocytosed by surrounding Sertoli cells in the testes. The resulting spermatozoa are now mature but lack motility. The mature spermatozoa are released from the protective Sertoli cells into the lumen of the seminiferous tubule in a process called *spermiation*. The non-motile spermatozoa are transported to the epididymis in *testicular fluid* secreted by the Sertoli cells with the aid of peristaltic contraction. While in the epididymis the spermatozoa gain motility and become capable of fertilization. However, transport of the mature spermatozoa through the remainder of the male reproductive system is achieved via muscle contraction rather than the spermatozoon's recently acquired motility.

**HORMONAL CONTROL**

Hormonal control of spermatogenesis varies among species. In humans the mechanism is not completely understood; however it is known that initiation of spermatogenesis occurs at puberty due to the interaction of the hypothalamus, pituitary gland and Leydig cells. If the pituitary gland is removed, spermatogenesis can still be initiated by follicle stimulating hormone (FSH) and testosterone. In contrast to FSH, luteinizing hormone (LH) appears to have little role in spermatogenesis outside of inducing gonadal testosterone production. FSH stimulates both the production of androgen binding protein (ABP) by Sertoli cells, and the formation of the blood-testis barrier. ABP is essential to concentrating testosterone in levels high enough to initiate and maintain spermatogenesis. Intratesticular testosterone levels are 20–100 or 50–200 times higher than the concentration found in blood, although there is variation over a 5- to 10-fold range amongst healthy men. FSH may initiate the sequestering of testosterone in the testes, but once developed only testosterone is required to maintain spermatogenesis. However, increasing the levels of FSH will increase the production of spermatozoa by preventing the apoptosis of *type A spermatogonia*. The hormone inhibin acts to decrease the levels of FSH. Studies from rodent models suggest that gonadotropins (both LH and FSH) support the process of spermatogenesis by suppressing the proapoptotic signals and therefore promote spermatogenic cell survival. The Sertoli cells themselves mediate parts of spermatogenesis through hormone production. They are capable of producing the hormones estradiol and inhibin. The Leydig cells are also capable of producing estradiol in addition to their main product testosterone. Estrogen has been found to be essential for spermatogenesis in animals. However, a man with estrogen insensitivity syndrome (a defective ERα) was found produce sperm with a normal sperm count, albeit abnormally low sperm viability; whether he was sterile or not is unclear. Levels of estrogen that are too high can be detrimental to spermatogenesis due to suppression of gonadotropin secretion and by extension intratesticular testosterone production. Prolactin also appears to be important for spermatogenesis.

**MALE INFERTILITY**

**Male infertility** refers to a male's inability to cause pregnancy in a fertile female. In humans it accounts for 40–50% of infertility. It affects approximately 7% of all men. Male infertility is commonly due to deficiencies in the semen, and semen quality is used as a surrogate measure of male fecundity.

**CAUSES**

**Immune infertility**

Antisperm antibodies (ASA) have been considered as infertility cause in around 10–30% of infertile couples. ASA production are directed against surface antigens on sperm, which can interfere with sperm motility and transport through the female reproductive tract, inhibiting capacitation and [acrosome reaction](https://en.wikipedia.org/wiki/Acrosome_reaction), impaired [fertilization](https://en.wikipedia.org/wiki/Fertilisation), influence on the implantation process, and impaired growth and development of the [embryo](https://en.wikipedia.org/wiki/Embryo). Risk factors for the formation of antisperm antibodies in men include the breakdown of the blood‑testis barrier, trauma and surgery, orchitis, [varicocele](https://en.wikipedia.org/wiki/Varicocele), infections, [prostatitis](https://en.wikipedia.org/wiki/Prostatitis), [testicular cancer](https://en.wikipedia.org/wiki/Testicular_cancer), failure of immunosuppression and unprotected receptive anal or oral sex with men.

**Genetics**:Chromosomal anomalies and genetic mutations account for nearly 10–15% of all male infertility cases.

**Klinefelter Syndrome**: One of the most commonly known causes of infertility is [Klinefelter Syndrome](https://en.wikipedia.org/wiki/Klinefelter_Syndrome), affecting 1 out of 500–1000 newborn males Klinefelter Syndrome is a chromosomal defect that occurs during gamete formation due to a non-disjunction error during cell division. Resulting in males having smaller testes, reducing the amount of testosterone and sperm production. Males with this syndrome carry an extra X chromosome (XXY), meaning they have 47 chromosomes compared to the normal 46 in each cell. This extra chromosome directly affects sexual development before birth and during puberty (links to learning disabilities and speech development have also been shown to be affected). There are varieties in Klinefelter Syndrome, where some cases may have the extra X chromosome in some cells but not others, referred to as Mosaic Klinefelter Syndrome, or where individuals have the extra X chromosome in all cells. The reduction of testosterone in the male body normally results in an overall decrease in the production of viable sperm for these individuals thereby forcing them to turn to fertility treatments to father children.

**Y chromosome deletions**: Y chromosomal infertility is a direct cause of male infertility due to its effects on sperm production, occurring in 1 out of every 2000 males. Usually affected men show no sign of symptoms other than at times can exhibit smaller teste size. Men with this condition can exhibit [azoospermia](https://en.wikipedia.org/wiki/Azoospermia) (no sperm production), [oligozoospermia](https://en.wikipedia.org/wiki/Oligozoospermia) (small number of sperm production), or they will produce abnormally shaped sperm (teratozoospermia). This case of infertility occurs during the development of gametes in the male, where a normal healthy male will produce both X and a Y chromosome, affected males have genetic deletions in the Y chromosome. These deletions affect protein production that is vital for [spermatogenesis](https://en.wikipedia.org/wiki/Spermatogenesis). Studies have shown that this is an inherited trait; if a male is fathered by a man who also exhibited y chromosome deletions then this trait will be passed down. These individuals are thereby “Y-linked”, although daughters are not affected due to the lack of the Y chromosome.

**Other**

* Age (*see also:* [*Paternal age effect*](https://en.wikipedia.org/wiki/Paternal_age_effect))
* Abnormal set of chromosomes
* Centriole.
* [Neoplasm](https://en.wikipedia.org/wiki/Neoplasm), e.g. [seminoma](https://en.wikipedia.org/wiki/Seminoma)
* [Idiopathic](https://en.wikipedia.org/wiki/Idiopathic) failure
* [Cryptorchidism](https://en.wikipedia.org/wiki/Cryptorchidism)
* [Trauma](https://en.wikipedia.org/wiki/Physical_trauma)
* [Hydrocele](https://en.wikipedia.org/wiki/Hydrocele)
* [Hypopituitarism](https://en.wikipedia.org/wiki/Hypopituitarism) in adults, and hypopituitarism untreated in children (resulting in growth hormone deficiency and proportionate dwarfism.)
* [Mumps](https://en.wikipedia.org/wiki/Mumps)
* [Malaria](https://en.wikipedia.org/wiki/Malaria)
* [Testicular cancer](https://en.wikipedia.org/wiki/Testicular_cancer)
* Defects in [USP26](https://en.wikipedia.org/wiki/USP26) in some cases
* [Acrosomal](https://en.wikipedia.org/wiki/Acrosomal) defects affecting egg penetration
* [Idiopathic oligospermia](https://en.wikipedia.org/wiki/Oligospermia) - unexplained sperm deficiencies account for 30% of male infertility.

**Pre-testicular causes**

Pre-testicular factors refer to conditions that impede adequate support of the testes and include situations of poor hormonal support and poor general health including:

**Varicocele:** [Varicocele](https://en.wikipedia.org/wiki/Varicocele), is a condition of swollen testicle veins. It is present in 15% of normal men and in about 40% of infertile men. It is present in up to 35% of cases of primary infertility and 69–81% of secondary infertility.

* [Hypogonadotropic hypogonadism](https://en.wikipedia.org/wiki/Hypogonadotropic_hypogonadism) due to various causes
* [Obesity](https://en.wikipedia.org/wiki/Obesity) increases the risk of hypogonadotropic hypogonadism. Animal models indicate that obesity causes leptin insensitivity in the [hypothalamus](https://en.wikipedia.org/wiki/Hypothalamus), leading to decreased [Kiss1](https://en.wikipedia.org/wiki/Kiss1) expression, which, in turn, alters the release of [gonadotropin-releasing hormone](https://en.wikipedia.org/wiki/Gonadotropin-releasing_hormone) (GnRH).
* Undiagnosed and untreated [coeliac disease](https://en.wikipedia.org/wiki/Coeliac_disease) (CD). Coeliac men may have reversible infertility. Nevertheless, CD can present with several non-gastrointestinal symptoms that can involve nearly any organ system, even in the absence of gastrointestinal symptoms. Thus, the diagnosis may be missed, leading to a risk of long-term complications In men, CD can reduce [semen](https://en.wikipedia.org/wiki/Semen) quality and cause immature [secondary sex characteristics](https://en.wikipedia.org/wiki/Secondary_sex_characteristic), [hypogonadism](https://en.wikipedia.org/wiki/Hypogonadism) and [hyperprolactinaemia](https://en.wikipedia.org/wiki/Hyperprolactinaemia), which causes [impotence](https://en.wikipedia.org/wiki/Erectile_dysfunction) and loss of [libido](https://en.wikipedia.org/wiki/Libido). The giving of gluten free diet and correction of deficient dietary elements can lead to a return of fertility. It is likely that an effective evaluation for infertility would best include assessment for underlying celiac disease, both in men and women
* [Drugs](https://en.wikipedia.org/wiki/Drugs), [alcohol](https://en.wikipedia.org/wiki/Alcohol_%28drug%29)
* Strenuous riding ([bicycle riding](https://en.wikipedia.org/wiki/Bicycle_riding), [horseback riding](https://en.wikipedia.org/wiki/Horseback_riding))
* Medications, including those that affect spermatogenesis such as [chemotherapy](https://en.wikipedia.org/wiki/Chemotherapy), [anabolic steroids](https://en.wikipedia.org/wiki/Anabolic_steroids), [cimetidine](https://en.wikipedia.org/wiki/Cimetidine), [spironolactone](https://en.wikipedia.org/wiki/Spironolactone); those that decrease FSH levels such as [phenytoin](https://en.wikipedia.org/wiki/Phenytoin); those that decrease sperm motility such as [sulfasalazine](https://en.wikipedia.org/wiki/Sulfasalazine) and [nitrofurantoin](https://en.wikipedia.org/wiki/Nitrofurantoin)
* Genetic abnormalities such as a [Robertsonian translocation](https://en.wikipedia.org/wiki/Robertsonian_translocation)

**Tobacco smoking**

See also: Smoking and pregnancy

There is increasing evidence that the harmful products of tobacco smoking may damage the testicles and kill sperm,but their effect on male fertility is not clear. Some governments require manufacturers to put warnings on packets. Smoking tobacco increases intake of cadmium, because the tobacco plant absorbs the metal. Cadmium, being chemically similar to zinc, may replace zinc in the DNA polymerase, which plays a critical role in sperm production. Zinc replaced by cadmium in DNA polymerase can be particularly damaging to the testes.

**DNA damage**

Common inherited variants in genes that encode enzymes employed in DNA mismatch repair are associated with increased risk of sperm DNA damage and male infertility. As men age there is a consistent decline in semen quality, and this decline appears to be due to DNA damage. The damage manifests by [DNA fragmentation](https://en.wikipedia.org/wiki/DNA_fragmentation) and by the increased susceptibility to denaturation upon exposure to heat or acid, the features characteristic of [apoptosis](https://en.wikipedia.org/wiki/Apoptosis) of somatic cells These findings suggest that DNA damage is an important factor in male infertility.

**Epigenetic**

See also: [DNA methylation](https://en.wikipedia.org/wiki/DNA_methylation)

An increasing amount of recent evidence has been recorded documenting abnormal sperm [DNA methylation](https://en.wikipedia.org/wiki/DNA_methylation) in association with abnormal semen parameters and male infertility. Until recently, scientists have thought that epigenetic markers only affect the individual and are not passed down due to not changing the DNA. New studies suggest that environmental factors that changed an individual's epigenetic markers can be seen in their grandchildren, one such study demonstrating this through rats and fertility disruptors. Another study bred rats exposed to an [endocrine disruptor](https://en.wikipedia.org/wiki/Endocrine_disruptor), observing effects up to generation F5 including decreased sperm motility and decreased sperm count These studies suggest that environmental factors that influence fertility can be felt for generations even without changing the DNA.

**Post-testicular causes**

Post-testicular factors decrease male fertility due to conditions that affect the male genital system after testicular sperm production and include defects of the genital tract as well as problems in [ejaculation](https://en.wikipedia.org/wiki/Ejaculation):

* [Vas deferens](https://en.wikipedia.org/wiki/Vas_deferens) obstruction
* Lack of [Vas deferens](https://en.wikipedia.org/wiki/Vas_deferens), often related to genetic markers for [cystic fibrosis](https://en.wikipedia.org/wiki/Cystic_fibrosis)
* [Infection](https://en.wikipedia.org/wiki/Infection), e.g. [prostatitis](https://en.wikipedia.org/wiki/Prostatitis)
* [Retrograde ejaculation](https://en.wikipedia.org/wiki/Retrograde_ejaculation)
* [Ejaculatory duct obstruction](https://en.wikipedia.org/wiki/Ejaculatory_duct_obstruction)
* [Hypospadias](https://en.wikipedia.org/wiki/Hypospadias)
* Impotence

## TREATMENT

Treatments vary according to the underlying disease and the degree of the impairment of the male's fertility. Further, in an infertility situation, the fertility of the female needs to be considered. Pre-testicular conditions can often be addressed by medical means or interventions. Testicular-based male infertility tends to be resistant to medication. Usual approaches include using the sperm for intrauterine insemination (IUI), in vitro fertilization (IVF), or IVF with intracytoplasmatic sperm injection (ICSI). With IVF-ICSI even with a few sperm pregnancies can be achieved. Obstructive causes of post-testicular infertility can be overcome with either surgery or IVF-ICSI. Ejaculatory factors may be treatable by medication, or by IUI therapy or IVF. Vitamin E helps counter oxidative stress, which is associated with sperm DNA damage and reduced sperm motility. A hormone-antioxidant combination may improve sperm count and motility. Giving oral antioxidants to men in couples undergoing in vitro fertilisation for male factor or unexplained subfertility may lead to an increase in the live birth rate but overall the risk of adverse effects is unclear.

### Hormonal therapy

See also: Spermatogenesis § Hormonal control

Administration of luteinizing hormone (LH) (or human chorionic gonadotropin) and follicle-stimulating hormone (FSH) is very effective in the treatment of male infertility due to hypogonadotropic hypogonadism. Although controversial, off-label clomiphene citrate, an antiestrogen, may also be effective by elevating gonadotropin levels.Though androgens are absolutely essential for spermatogenesis and therefore male fertility, exogenous testosterone therapy has been found to be ineffective in benefiting men with low sperm count. This is thought to be because very high local levels of testosterone in the testes (concentrations in the seminiferous tubules are 20- to 100-fold greater than circulating levels) are required to mediate spermatogenesis, and exogenous testosterone therapy (which is administered systemically) cannot achieve these required high local concentrations (at least not without extremely supraphysiological dosages). Moreover, exogenous androgen therapy can actually impair or abolish male fertility by suppressing gonadotropin secretion from the pituitary gland, as seen in users of androgens/anabolic steroids (who often have partially or completely suppressed sperm production). This is because suppression of gonadotropin levels results in decreased testicular androgen production (causing diminished local concentrations in the testes) and because FSH is independently critical for spermatogenesis. In contrast to FSH, LH has little role in male fertility outside of inducing gonadal testosterone production. Estrogen, at some concentration, has been found to be essential for male fertility/spermatogenesis. However, estrogen levels that are too high can impair male fertility by suppressing gonadotropin secretion and thereby diminishing intratesticular androgen levels. As such, clomiphene citrate (an antiestrogen) and aromatase inhibitors such as testolactone or anastrozole have shown effectiveness in benefiting spermatogenesis. Low-dose estrogen and testosterone combination therapy may improve sperm count and motility in some men, including in men with severe oligospermia.

## FUTURE POTENTIAL TREATMENTS

Researchers at Münster University developed in vitro culture conditions using a three-dimensional agar culture system which induces mouse testicular germ cells to reach the final stages of spermatogenesis, including spermatozoa generation. If reproduced in humans, this could potentially enable infertile men to father children with their own sperm. Researchers from Montana State University developed precursors of sperm from skin cells of infertile men. Sharpe *et al.* comment on the success of intracytoplasmic sperm injection (ICSI) in women saying, "[t]hus, the woman carries the treatment burden for male infertility, a fairly unique scenario in medical practice. Ironically, ICSI's success has effectively diverted attention from identifying what causes male infertility and focused research onto the female, to optimize the provision of eggs and a receptive endometrium, on which ICSI's success depends.