

Developments in Reproductive Health and Reproductive Sciences Infertility

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Abstract

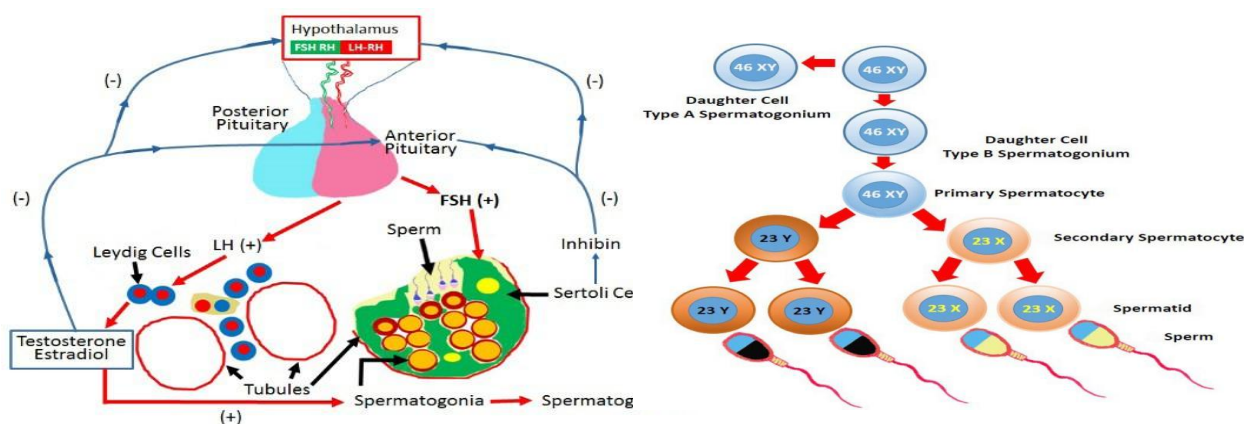
To change a spermatogonial cell with 46 chromosomes into spermatozoa with 23 chromosomes, spermatogenesis is necessary. The sperm acquires special qualities throughout this phase that enable it to fertilise an egg. Male infertility may result from temporary or permanent impairment to spermatogenesis caused by certain illnesses, their treatments, trauma, and environmental factors. Cancers, chemotherapy, radiation, environmental pollutants, heavy metals, and oxidative stress-causing diseases are the most prevalent. Men who are at danger of spermatogenesis damage may now have their fertility protected and preserved thanks to technological breakthroughs. Sperm cryopreservation is the preferred technique for mature males or anybody who can produce semen. Testicular tissue cryopreservation is an alternative for males who are not yet pubertal. This brief overview describes the process of spermatogenesis, its endocrine regulation, illnesses and disorders that impair spermatogenesis, and methods for maintaining male fertility.

Keywords: Cancer; Chemotherapy; Infertility; Radiotherapy; Spermatogenesis; Testosterone

Introduction

The process of sperm production is called spermatogenesis. The only cells in a male human body with 23 chromosomes are sperm. With the exception of red blood cells, every other cell has 46 chromosomes. The precursor cells of sperm (spermatogonial cells) undergo mitosis, meiosis, and a number of structural changes during spermatogenesis, which reduces the number of chromosomes and gives them a tadpole-like shape that allows them to swim in seminal fluid (Figure 1). The testicles are where sperm production occurs. Spermatogenesis is started by hormones secreted by the pituitary and brain. Oocytes are cells with 23 chromosomes found in the female human body. A new, healthy human is born with 46 chromosomes as a consequence of the fusion of egg and sperm chromosomes. In addition to the X or Y chromosome, each sperm carries 22 chromosomes. Only the X chromosome is present among the oocyte's 22 chromosomes. A female is produced when X chromosome-bearing sperm fuses with egg chromosomes, while a man is produced when Y chromosome-bearing sperm fuses with oocyte chromosomes.

The process of spermatogenesis takes a very long time. The process of transforming round spermatogonial cells into sperm and transporting them to the epididymis takes around 74 days. Sperm maturation in the epididymis requires an additional 12 days. As a result, spermatogenesis and sperm epididymal transit take around three months to complete [1]. The process of spermatogenesis is necessary for a guy to be fertile. Normal male fertility will be negatively impacted by any disease or therapy that interferes with spermatogenesis, damages spermatogonial cells, or affects any other aspect of spermatogenesis. This brief study aims to describe the circumstances or therapies that will render a guy infertile.



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Figure 1: Diagrammatic presentation of spermatogenesis. One spermatogonial cell divides into 2 daughter cells; the daughter cell divides into 2 secondary spermatocytes, each secondary spermatocyte divides to 2 spermatids, each spermatid makes a sperm. Thus from one daughter cell 4 sperm are produced.

Body Organs and Cells Involved in Spermatogenesis

The hypothalamus, pituitary, and both testes are the main bodily organs directly involved in spermatogenesis. Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH), often known as gonadotropin releasing hormones, are released by the brain to commence the hormonal signal for spermatogenesis. The pituitary gland responds by secreting FSH and LH, which are known as gonadotropins since the gonad is their target organ. In the testes, Leydig cells are affected by LH and Sertoli cells by FSH. Spermatogenesis is started by the testosterone that Leydig cells generate. Aromatase, which is produced by the seminiferous epithelium, Leydig cells, and other male organs, transforms androgens into oestrogen, which binds to several male tissues and demonstrates the function of oestrogen in normal male physiology [2]. Male reproductive and non-reproductive organ functioning are regulated by oestrogen. Oestrogen is necessary for the epididymal and efferent ductules to operate. The anterior pituitary and hypothalamus are negatively impacted by the elevated testosterone levels. The anterior pituitary and hypothalamus are negatively impacted by the inhibin that Sertoli cells release (Figure 2).

Figure 2: Spermatogenesis-related body organs, cellular components, and hormones.

Treatments and Condition Damaging Spermatogenesis

Chemotherapy drugs, radiation, cancer, and environmental pollutants may all harm spermatogenesis in different ways. Additionally, spermatogenesis will be disrupted or irreversibly harmed by injury to the brain, pituitary, or testicular cells. Damage might range from oligospermia to azoospermia. Chemotherapeutic agent, dosage, patient age, and length of treatment all affect chemotherapy damage and its reversal [3]. The harm produced by different situations will be explained in more detail in the sections that follow.

Cancers

The most prevalent malignancy among young men is testicular germ cell tumour (TGCT), whose frequency is rising. Spermatogenesis will be seriously hampered by the TGCT or any cancer impacting the hypothalamic-pituitary-gonadal axis. Oligospermia or azoospermia may result from the cancer itself, its chemicals, or radiation treatment.

Chemotherapy or radiotherapy

When TGCT is treated with chemotherapy or radiation, spermatogenesis is severely harmed; individuals who have more than two rounds of chemotherapy may be able to recover two years following treatment. Three months following treatment, individuals undergoing chemotherapy or radiation had the lowest values of sperm characteristics, and azoospermia rose from 0 to 16%. Patients who had more than two rounds of chemotherapy or radiation showed a more pronounced decline. Six months after treatment, the radiation caused slight chromatin alterations [1]. Leydig cells, Sertoli cells, and spermatogonia may be directly harmed by chemotherapy or radiation treatment, or they may be indirectly harmed by the activation of several apoptotic molecular pathways. Defects in spermatogenesis, retained spermatids, and sloughing of the seminiferous epithelium are only a few of the many signs of toxic damage to spermatogenesis [4]. Compared to other slow-dividing cells in the body, quickly developing and differentiating spermatogonia are often more vulnerable to toxic effects. The majority of alkylating anticancer medications cause extended azoospermia because they are harmful to stem cells [5]. Procarbazine therapy for lymphoma causes irreversible infertility in many males. Many men will restore normal fertility after receiving chemotherapy with doxorubicin hydrochloride, vinblastine, dacarbazine, and bleomycin. Most men who get cisplatin therapy for testicular cancer have transitory azoospermia; 50% of them recover in two years, and 80% in five [3].

Prescription Medications

Spermatogenesis is impacted by certain FDA-approved medications in the United States. Hormone-based medications are the most prevalent of those. Anti-cancer medications are the second most popular. Spermatogenesis may be impacted by a number of anti-inflammatory medications. Human spermatogenesis may be impacted by other pharmaceuticals such as antibacterial, antiviral, and analgesic drugs. Human spermatogenesis and maturation may be hampered by around 65 prescription medications. Additional drugs that may significantly but reversibly reduce spermatogenesis include tricyclic

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antidepressants and selective serotonin reuptake inhibitors (SSRIs), such as paroxetine and clomipramine. Certain medications cause a significant rise in prolactin levels, which inhibits the production of hormones that produce FSH and LH, therefore halting the signals for spermatogenesis. The majority of antipsychotic medications decrease hypothalamic-pituitary-gonadal activity by blocking dopamine in the central nervous system [5].

Environmental Toxins

Notably vulnerable to environmental contamination is the male reproductive system, notably spermatogenesis. Spermatogenesis fails due to genetic and epigenetic alterations [6]. Men's spermatogenesis may be significantly impacted by radiation, pesticides, insecticides, and herbicides [5, 7]. Spermatogenesis may also be hampered by other environmental factors as elevated testicular temperature, psychological stress, air pollution, and welding fumes [8]. In addition to being an environmental endocrine disruptor, bisphenol A increases the damage to sperm DNA. Endocrine disruptors may interfere with the endocrine system by acting like naturally occurring hormones (androgens and oestrogens) [9]. Epoxy resins and polycarbonate plastics are made using bisphenol A [7]. It has estrogen-like and anti-androgen properties. Bisphenol A-containing items may have a negative impact on spermatogenesis.

Heavy Metals

By affecting enzyme function and producing free radicals, some metals, such as lead, aluminium, and cadmium, cause toxicity to living things. One of the most common and oldest recognised risks is inorganic lead poisoning. It may enter the body via skin absorption, ingestion, or inhalation. The main location of lead's neurotoxic effects is the hypothalamus [10]. Semen from infertile males had greater amounts of malondialdehyde, Fe²⁺, and Cd²⁺ than semen from the control group [11]. The drop in sperm concentration was strongly correlated with the rise. The content of cadmium is greatly increased by tobacco use. Sperm motility, morphology, and count are all negatively impacted by cadmium, even at low concentrations. Natural antioxidants called flavonoids bind metal ions and counteract the harmful effects of metals on sperm [12,13]. Rats' testicular toxicity caused by cadmium is effectively prevented by the proanthocyanidin extract from grape seeds [14]. Redox active heavy metals increase the amount of reactive oxygen species, which causes oxidative stress, sperm DNA damage, spermatozoa death, and blood-testes barrier disruption [9].

Defects in DNA Repair Mechanisms

The sperm's genomic integrity and stability are preserved by DNA repair processes such as nucleotide excision repair, base excision repair, DNA mismatch repair, double strand break repair, and post-replication repair. Male infertility is ultimately caused by aberrant recombination and spermatogenesis arrest brought on by flaws in repair systems [15].

Life Style Factors and Profession

Spermatogenesis may be greatly impacted by lifestyle choices. Spermatogenesis may be negatively impacted by a number of conditions, including excessive drinking, smoking, and using saunas with high temperatures [5]. In a similar vein, some occupations that include extended sitting, such as long-distance truck drivers, taxi drivers, IT specialists, bank managers, and office managers, may have compromised spermatogenesis, most likely as a result of elevated scrotal temperature [8]. Testicular inflammation, increased DNA fragmentation, decreased mitochondrial activity, telomere shortening, an increase in paediatric cancer, and leukocytospermia are just a few of the many ways that smoking impacts spermatogenesis. Increased sperm DNA fragmentation, decreased sperm motility, and hormonal disruptions are associated with excessive usage of mobile phones (>4 hours per day), storing them in trouser pockets, and using computers on closed legs [7].

Oxidative Stress

An imbalance between the cell's antioxidant defence system and the generation of reactive oxygen species (ROS) is known as oxidative stress. ROS damage sperm membranes and cellular components, induce DNA breakage in the mitochondrial genome or sperm nucleus, deactivate vital metabolic enzymes, and obstruct signal transmission pathways. Oxidative stress may be lessened or eliminated with antioxidant treatment and a straightforward, healthy lifestyle.

Varicocele and Heat Damage

The testes should be 2-4 °C colder than the body's core temperature for proper spermatogenesis. Even a brief rise in scrotal temperature of 1-1.5 °C may cause germ cell death and testicular shrinkage, which results in reduced sperm production and aberrant sperm morphology. Testicular hypoxia and hyperthermia caused by the varicocele result in ischaemia and thermal damage [16]. Testicular germ cells and epididymal sperm are heat-sensitive. Sperm exposed to high temperatures have more DNA damage and are less able to fertilise. The severity, frequency, and length of heat exposure determine the extent of heat stress damage. Tight, unbreathable multilayer clothing, body posture, hot tubs,

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saunas, laptop usage on the legs, cycling in tight spandex clothing, obesity, ambient heat, certain jobs, radiant heat, cryptorchidism, and fever episodes are other reasons of elevated scrotal heat [17].

Diabetes Mellitus

The endocrine regulation of spermatogenesis, sperm maturation, penile erection, and ejaculation are all impacted by diabetes mellitus (DM), which has an impact on male fertility. Sperm mitochondrial and nuclear DNA defects are more common in diabetic males, which is a sign of ROS-induced damage [18]. In addition to altering the shape of the seminiferous epithelium, it results in decreased testicular weight, sperm count, and motility. It disrupts spermatogenesis and promotes germ cell death. Seafood contains carotenoids and omega-3 fatty acids, which have anti-inflammatory, anti-apoptotic, and antioxidant properties [19].

Spinal Cord Injury

Ejaculatory dysfunction, vas deference obstruction from infection, and poor spermatogenesis leading to sterility are common outcomes of spinal cord injuries. Anti-sperm antibodies, repeated urogenital infections, and elevated testicular temperature (caused by orchitis or epididymitis) may all contribute to impaired spermatogenesis [20].

Infections (Orchitis, Epididymitis, Autoimmune Orchitis)

Viral or bacterial infections of the testes and urogenital tract can interfere with spermatogenesis. Regulatory T cell defects may lead to aberrant immune responses to autologous components causing autoimmune diseases [21].

Strategies to Preserve Fertility

Sperm and Testicular Tissue Cryopreservation

Prior to chemotherapy and radiation treatment, all patients should have access to fertility cryopreservation. Semencryopreservation is the preferred technique for adults. After 24 to 48 hours of abstinence, semen samples may be taken until sufficient sperm are gathered for later use. An efficient, simple, and affordable method for preserving fertility is to store sperm in liquid nitrogen [22]. Without sacrificing quality, the sperm may be kept in liquid nitrogen for almost an infinite amount of time. While quality is unaltered during storage, harm occurs during cryopreservation and thawing.

For males who are not yet pubertal, testicular tissue cryopreservation (tissue containing spermatogonial cells) is an alternative. This service is provided by several places worldwide. Vitrification and gradual freezing are both effective [22]. In vitro sperm maturation is necessary to reduce the chance of cancer reintroduction. This method is currently in the experimental stage [23].

Shielding the Gonads from Radiotherapy

Because spermatogenesis constantly produces new germ cells, it is very vulnerable to radiation. Spermatogenesis is hampered by even moderate radiation doses (0.1–1.2 Gy), and doses greater than 4 Gy may cause irreversible harm. Applying an 8-cm thick lead block from both AP and PA fields to patients undergoing 2 and 3 Gy single fraction whole body irradiation may effectively reduce testicular dose exposure to less than 1 Gy [24].

Administration of Androgens before Chemotherapy

At 8 and 11 weeks after treatment, rats given four weekly doses of procarbazine hydrochloride (150 mg/kg for the first dosage and 100 mg/kg for the next three) developed full germinal aplasia. On the other hand, spermatogenesis was significantly protected when rats were pretreated for six weeks and then continued to receive procarbazine therapy with 240 micrograms of testosterone enanthate per 100 grams of body weight [25]. In rats, resveratrol protects against testicular injury caused by azoxymethane [26].

Use of Mesenchymal Stromal Cells

Mesenchymal stromal cells (MSCs) exhibit anti-inflammatory, trophic, and regenerative properties. However, there is debate in the research on whether they have an anti-cancer or cancer-promoting effect. It is hypothesised that their function varies according to the tumor's nature and origin. For instance, umbilical cord-derived MSCs have anti-cancer properties. As a result, it's critical to understand the kind of tumour, the source of MSCs, the duration of therapy, and the physiological and pathological conditions. The use of MSCs in male infertility is still in its early stages, but it may provide a different course of treatment for individuals who develop azoospermia after cancer treatment [27].

Improving Lifestyle

The majority of lifestyle problems cause DNA fragmentation, which may be reduced by more exercise, yoga, meditation, a healthy diet, quitting smoking, better sleep, and minimising heat exposure to the scrotum. Toxin exposure in the environment should be avoided [7, 8].

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Conclusion

Numerous diseases and environmental factors might hinder spermatogenesis. Some illnesses may have short-term effects, while others may result in long-term harm. It is very advised to preserve fertility before beginning any treatment or dealing with any illness that might negatively impact spermatogenesis. For mature males, sperm cryopreservation is the preferred technique. For males who are not yet pubertal, testicular tissue cryopreservation is a possibility. Despite advancements, there is still a critical requirement to comprehend and accomplish in vitro spermatogonial culture and in vitro sperm generation.

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