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Review Article

Spermatogenesis: Why Some Treatments or Conditions Make Men Infertile?

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Abstract

Spermatogenesis is required to transform the 46 chromosome bearing spermatogonial cell to 23 chromosome bearing spermatozoa. During this process, the sperm attains unique properties to be able to fertilize an oocyte. Some diseases or their treatments, injuries and environmental conditions cause either temporary or permanent damage to spermatogenesis rendering male infertile. The most common are cancers, chemotherapy, radiotherapy, environmental toxins, heavy metals and conditions causing oxidative stress. With technological advancements, it is now possible to protect and preserve fertility in men at risk for damage to spermatogenesis. For adult men or individual capable of producing semen, sperm cryopreservation is the method of choice. For pre-pubertal boys, testicular tissue cryopreservation is an option. This mini review explains process of spermatogenesis, its endocrine control, diseases/conditions causing damage to spermatogenesis and strategies to preserve fertility in males.

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

Introduction

Spermatogenesis is the process of sperm formation. Sperm are the only cells in male human body that have 23 chromosomes. All other cells, except red blood cells, have 46 chromosomes. During the process of spermatogenesis, the precursor cells of sperm (spermatogonial cells), go through mitosis, meiosis and a series of structural modifications resulting in reduction in the chromosome number and attaining a shape, similar to a tadpole, which can swim in the seminal fluid (Figure 1). The process of sperm formation takes place in testicles. The hormones released from hypothalamus and pituitary initiates spermatogenesis.

In the female human body oocytes are the cells that have 23 chromosomes. The fusion of egg and sperm chromosomes, results in 46 chromosomes, from which a new normal individual is born with 46 chromosomes. Each sperm has 22 chromosomes and either X or Y chromosome. The oocyte has 22 chromosomes and only X chromosome. If X chromosome bearing sperm fuses with the egg chromosomes, the resulting individual is female and if Y chromosome bearing sperm fuses with oocyte chromosomes, the resulting individual is male.

Spermatogenesis is a very lengthy process. It takes about 74 days for transformation of round spermatogonial cells to sperm and its transport to the epididymis. Another 12 days are needed for sperm maturation in epididymis. Therefore, a complete cycle of spermatogenesis and sperm epididymal transit takes about 3 months [1].

For a man to be fertile, the process of spermatogenesis is needed. Any treatment or condition that hinders the process of spermatogenesis causes damage to the spermatogonial cells or any other component of spermatogenesis will adversely affect normal male fertility. The purpose of this mini review is to elaborate conditions or treatments that will make a man infertile.

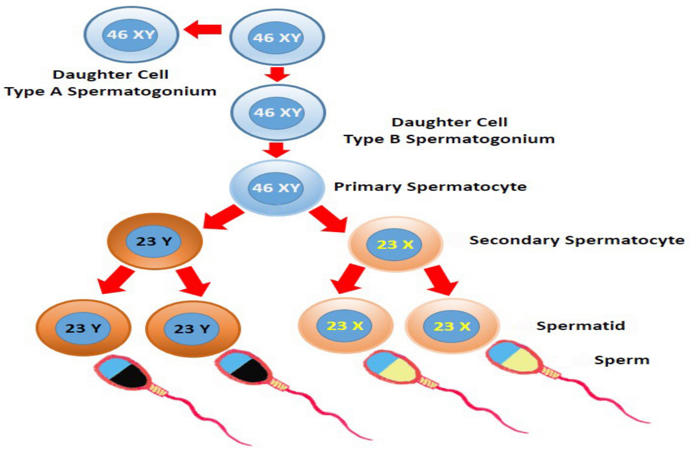

Figure 1: Diagrammatic presentation of spermatogenesis. One spermatogonial cell divides into 2 daughter cells; the daughter cell divides into 2 secondary spermatocytes, each secondary spermatocyte divides to 2 spermatids, each spermatid makes a sperm. Thus from one daughter cell 4 sperm are produced.

Body Organs and Cells Involved in Spermatogenesis

The major body organs directly involved in spermatogenesis includes hypothalamus, pituitary and both testes. The hormonal signal for spermatogenesis is initiated from hypothalamus in the form of releasing hormones for Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH), also called gonadotropin releasing hormones. In response, pituitary gland secretes FSH and LH which are called gonadotropins (because their target organ is gonad). The FSH works on Sertoli cells and the LH on Leydig cells in the testes. The testosterone produced from Leydig cells initiate spermatogenesis. The Leydig cells, seminiferous epithelium and other male organs produce aromatase that converts androgens to estrogen which binds to many male tissues indicating estrogen's role in normal male physiology [2]. The estrogen regulates functions in reproductive and non-reproductive organs of male. The efferent ductules and epididymal functions are dependent on estrogen. The increased amount of testosterone exerts negative feed-back on anterior pituitary and hypothalamus. The inhibin produced by Sertoli cells exerts negative feed-back on anterior pituitary and hypothalamus (Figure 2).

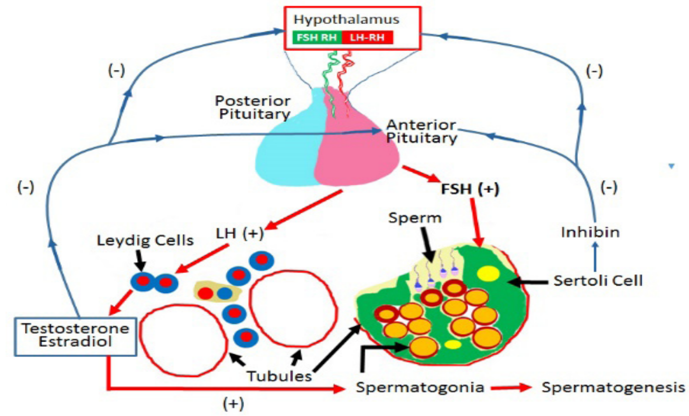

Figure 2: Body organs, cellular components and hormones involved in spermatogenesis.

Treatments and Condition Damaging Spermatogenesis

The spermatogenesis can be damaged by cancer, chemotherapeutic agents, radiation and environmental toxins by numerous ways. Also, damage to hypothalamus, pituitary or testicular cells will interrupt or permanently damage spermatogenesis. The degree of damage may vary from oligospermia to azoospermia. The chemotherapy damage and its reversal dependents on chemotherapeutic agent, the dose, age of patient and duration of treatment [3]. Following sections will elaborate the damage caused by various conditions.

Cancers

Testicular Germ Cell Tumor (TGCT) incidence is increasing and it is the most common cancer in young men. The TGCT or any malignancy affecting the hypothalamic-pituitary-gonadal axis will severely impair spermatogenesis. Either the malignancy itself or its chemical or radiotherapy may lead to oligospermia or azoospermia.

Chemotherapy or radiotherapy

The chemotherapy or radiotherapy in the treatment of TGCT exerts drastic deleterious effects on spermatogenesis with possible recovery 2 years after treatment in patients receiving more than 2 cycles of chemotherapy. For patients receiving chemotherapy or radiotherapy, the lowest values of sperm characteristics were noted 3 months after treatment and azoospermia increased from 0 to 16%. The decrease was more marked in patients receiving more than 2 cycles of chemotherapy or radiotherapy. The radiotherapy induced minor chromatin changes 6 months post treatment [1]. Chemotherapy or radiotherapy may damage Leydig cells, Sertoli cells and spermatogonia either directly or by activating numerous molecular pathways involved in apoptosis. There are many manifestations of toxic damage to spermatogenesis including defects in spermatogenesis, retained spermatids and sloughing of the seminiferous epithelium [4]. The rapidly dividing and differentiating spermatogonia are generally more sensitive to toxic effect than other slow dividing cells in the body. Most alkylating anticancer drugs are toxic to stem cells, therefore, produce prolonged azoospermia [5].

Many men receiving procarbazine for the treatment of lymphoma will become permanently infertile. Chemotherapy with doxorubicin hydrochloride, vinblastine, dacarbazine and bleomycin will cause temporary fertility decline but many men will regain normal fertility. Testicular cancer treatment with Cisplatin results in temporary azoospermia in most men, 50 % of which will recover in 2 years and 80 % in 5 years [3].

Prescription Medications

Some USA Food and Drug Administration (FDA) approved medicines affect spermatogenesis. The most common among those are hormone based medicines. The second most common are anti-cancer medicines. Several anti-inflammatory drugs may affect spermatogenesis. Other medications like antibacterial, antiviral and analgesic drugs may affect human spermatogenesis. About 65 prescription drugs have potential to impair human spermatogenesis and maturation. Other medications that can lead to significant but reversible suppression of spermatogenesis are; use of tricyclic antidepressants and Selective Serotonin Reuptake Inhibitors (SSRIs), e.g. clomipramine and paroxetine. Some medicines result in a substantial increase in prolactin level which suppresses the release of FSH and LH releasing hormones, thus stopping the signals for spermatogenesis. Most antipsychotic medicines block dopamine in the central nervous system leading to suppression of hypo-thalamic-pituitary-gonadal function [5].

Environmental Toxins

The male reproductive system especially spermatogenesis is particularly sensitive to environmental pollution. Genetic and epigenetic changes are involved in the failure of spermatogenesis [6]. Exposure of men to pesticides, insecticides, herbicides or radiation may severely impact spermatogenesis [5,7]. Other environmental conditions like increased testicular temperature, mental stress, air pollution and welding fumes can also impair spermatogenesis [8]. Bisphenol A is an environmental endocrine disruptor and also cause increased sperm DNA damage. The endocrine disruptor act like naturally occurring hormones (estrogens and androgens) which can in turn interfere with the endocrine system [9]. Bisphenol A is used in the production of polycarbonate plastics and epoxy resins [7]. It has anti-androgen and estrogen like activity. Use of products containing bisphenol A may adversely affect spermatogenesis.

Heavy Metals

Some metals like lead, aluminum and cadmium induce toxicity to living organisms by impacting enzyme activity and generation of free radicles. Inorganic lead poisoning is the oldest known and among the most ubiquitous hazards. It may enter the body through ingestion, inhalation or skin absorption. The hypothalamus is the primary site of the neurotoxic effect of the lead [10]. The levels of malondialdehyde, $Fe2+$ and $Cd2+$ were found higher in semen from infertile men as compared to those in semen from control group [11]. The increase was highly associated with decrease in sperm concentration.

Tobacco smoking significantly increases cadmium concentration. Cadmium even at low levels adversely affects sperm count, motility and morphology. Flavonoids are natural antioxidants that chelate metal ions and neutralize toxic effects of metals on sperm [12,13]. The grape seed proanthocyanidin extract acts as a potent protective agent against cadmium induced testicular toxicity in rats [14]. Redox active heavy metals increase level of reactive oxygen species leading to oxidative stress, increase sperm DNA damage, apoptosis of spermatozoa and disruption of blood-testes barrier [9].

Defects in DNA Repair Mechanisms

The DNA repair mechanisms including nucleotide excision repair, base excision repair, DNA mismatch repair, double strand break repair and post-replication repair maintain genomic integrity and stability of the sperm. Arrest of spermatogenesis and abnormal recombination due to defects in repair mechanisms, ultimately cause male infertility [15].

Life Style Factors and Profession

Lifestyle can significantly impact spermatogenesis. Some factors like smoking, heavy drinking and use of high temperature saunas can have negative impact on spermatogenesis [5]. Similarly, some professions that require prolonged sitting, for example long distance truck drivers, taxi drivers, IT professionals, bank managers and office managers may have impaired spermatogenesis, most likely due to increased temperature in scrotum [8]. Smoking affects spermatogenesis in many different ways including testicular inflammation, increase in DNA fragmentation, decrease in mitochondrial activity, shortening of telomere, increase in childhood cancer and leukocytospermia. Excessive use of mobile phones (>4 hours per day) and their storage in trouser pocket and use of laptops on closed legs are linked with increased sperm DNA fragmentation, reduced sperm motility and hormonal disturbances [7].

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Oxidative Stress

Oxidative stress is an imbalance in the production of reactive oxygen species (ROS) and antioxidant defense mechanism of the cell. ROS cause damage to cellular components and sperm membrane, increase DNA fragmentation in sperm nucleus or mitochondrial genome, inactivate essential metabolic enzymes and interfere with signal transduction pathways. Anti-oxidant therapy and adoption of simple healthy lifestyle can reduce or eliminate oxidative stress.

Varicocele and Heat Damage

For normal spermatogenesis, the temperature of the testes should be 2-4 ˚C lower than the core body temperature. A prolonged increase in scrotal temperature of only 1-1.5 ˚C is able to induce germ cell apoptosis and reduction in testes size leading to lower sperm production and abnormal sperm morphology. The varicocele induces testicular hypoxia and hyperthermia leading to ischemic and heating damage [16]. The epididymal sperm and testicular germ cells are sensitive to heat. The sperm exposed to hyperthermia have increased DNA damage and reduced fertilizing ability. The degree of heat stress damage depends on intensity, frequency and duration of heat exposure. Other causes of increased scrotal heat are; tight unbreathable multiple layer clothes, body posture, hot tubs, sauna, laptop use on legs, cycling in tight spandex outfit, obesity, ambient heat, certain occupations, radiant heat, cryptorchidism and febrile episodes [17].

Diabetes Mellitus

Diabetes Mellitus (DM) affects male fertility by affecting the endocrine control of spermatogenesis, sperm maturation, impairment in penile erection and ejaculation. Diabetic men show increased defect in sperm mitochondrial and nuclear DNA, indicative of ROS induced damage [18]. It causes reduction in testicular weight, sperm count and motility as well as changes in the seminiferous epithelium morphology. It increases apoptosis in germ cells and interruption in spermatogenesis. The omega-3 fatty acids and carotenoids present in sea food play an antioxidant, anti-inflammatory and anti-apoptotic role [19].

Spinal Cord Injury

Spinal cord injury usually results in ejaculatory dysfunction, vas deference blockage due to infection and impaired spermatogenesis leading to sterility. Impaired spermatogenesis may be due to elevation of testicular temperature (Due to orchitis or epididymitis), anti-sperm antibodies and recurrent urogenital infections [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

Fertility cryopreservation should be offered to all patients before chemo or radiotherapy. For adult men, semen cryopreservation is the method of choice. Semen samples can be collected after 24-48 hour abstinence until enough sperm are collected for future use. The storage of sperm in liquid nitrogen is an effective, easy and low-cost strategy for fertility preservation [22]. The sperm can be stored in liquid nitrogen almost indefinitely without compromising quality. The damage happens at cryopreservation and thawing but during storage quality remains unaffected.

Testicular tissue cryopreservation (tissue containing spermatogonial cells) is an option for pre-pubertal boys. There are many centers around the world offering this service. Both slow freezing and vitrification are successful [22]. To avoid the risk of re-introduction of cancer in-vitro sperm maturation is needed. This approach is still experimental [23].

1. **Shielding the Gonads from Radiotherapy**

Spermatogenesis is highly sensitive to radiation due to its constant turnover of germ cells. Even low dose of radiation (0.1-1.2 Gy) impairs spermatogenesis and doses of >4 Gy may result in permanent damage to spermatogenesis. An effective reduction in testicular dose exposure to <1 Gy can be achieved by applying 8-cm thick lead block used from both AP and PA fields in patient, receiving 2 and 3 Gy single fraction total body irradiation [24].

2. **Administration of Androgens before Chemotherapy**

Administration of 4 doses of procarbazine hydrochloride at weekly intervals (150 mg/kg, first dose; 100 mg/Kg 3 subsequent doses) caused complete germinal aplasia in rat at 8 and 11 weeks post treatment. However, pretreatment of rats for 6 weeks plus continued treatment during procarbazine therapy with testosterone enanthate, 240 microgram/100 g body weight, resulted in a marked protection of spermatogenesis [25]. Resveratrol protects against azoxymethane induced testicular damage in rat [26].

3. **Use of Mesenchymal Stromal Cells**

Mesenchymal Stromal Cells (MSCs) have regenerative, trophic and anti-inflammatory effects. However, there is controversy in literature regarding their anti-cancer or cancer promoting role. It is suggested that their role depends on the source of origin and the type of tumor. For example, MSCs derived from umbilical cord has anti-cancer effects. Therefore, it is important to know the source of MSCs, type of tumor, time of treatment and physiological and pathological condition. Use of MSCs in male infertility is at initial stages and it may offer an alternative treatment for patients becoming azoospermic after cancer therapy [27].

4. Improving Lifestyle

Majority of the lifestyle issues increase DNA fragmentation which can be improved by increased physical activity, performing yoga, meditation, balanced nutrition, quit smoking, improve sleep and avoiding heat to the scrotum. Exposure to environmental toxins should be avoided [7,8].

Conclusion

Spermatogenesis can be impaired by a number of pathologies and environmental conditions. Effects of some may be temporary but other conditions may cause permanent damage. Fertility preservation before initiating any therapy or facing any condition with potential to adversely affect spermatogenesis is highly recommended. Sperm cryopreservation is a method of choice for adult men. Testicular tissue cryopreservation is an option for pre-pubertal boys. Although progress has been made but still there is dire need to understand and achieve in vitro spermatogonial culture and in vitro sperm production.

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