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Processes, Regulation, and Environmental Impacts of Spermatogenesis: A Review

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Abstract

Male fertility depends on spermatogenesis, the intricate process by which sperm cells form in the testes. Current understanding of its physiological mechanisms, endocrine regulation, and susceptibility to environmental and lifestyle variables is summarised in this study. Meiosis (genetic recombination), spermatogonogenesis (mitotic proliferation of spermatogonia), and spermiogenesis (morphological maturation into spermatozoa) are the three main stages of the process. Sertoli cells (nutrition, phagocytosis) and Leydig cells (testosterone production) provide intrinsic support for these processes. Numerous hormonal, genetic, and environmental factors-including temperature-control this process. For proper spermatogenesis development from the earliest stages of spermatogonia proliferation to germ cell maturity, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone (T) are crucial for hormonal regulation. Other hormones, such as activin and inhibin, play a delicate role in regulating the spermatogenesis process. Importantly, this process is severely hampered by lifestyle and environmental factors. By interfering with testicular thermoregulation, scrotal hyperthermia (caused by sedentary employment or laptop use) lowers the number of sperm. Obesity (BMI >25) reduces sperm counts by 25% by increasing oestrogen and decreasing testosterone. Sertoli-germ cell connections are harmed by heavy metals (like cadmium) and occupational pollutants (such as glycol ethers and pesticides like DBCP). Up to 40% fewer sperm are produced by sons of pregnant mothers who smoke. It is concerning to note that 15-20% of young men in Europe have subfertile sperm quantities (<20 million/ml). Environmental endocrine disruptors (such as phthalates) and the combination of chemical exposures and obesity are examples of emerging hazards. The study urges more investigation into the foetal causes of spermatogenic disruption and emphasises the need for immediate public health measures to reduce these hazards.

Keywords: *Spermatogenesis; Testosterone; Sertoli Cells; Endocrine Disruptors; Male Infertility; Environmental Toxins*

Introduction

From puberty to old age, male germ cells grow in the seminiferous tubules of the testes from a self-renewing stem cell pool. Spermatogenesis is the term used to describe the entire process of germ cell development. Meiosis, spermiogenesis, spermiation, and spermatogoniogenesis are the subdivisions. The adult male gametes, or spermatozoa, are the result of spermatogenesis. The amount of spermatozoa, their morphology and motility patterns, and other cellular components can all be evaluated by light microscopy of the ejaculate. These all offer the first details regarding spermatogenesis success [1]. Infertility in men may be caused by a decreased number of spermatozoa, a preponderance of defective spermatozoa, or reduced and inefficient motility. However, in many instances, the conventional assessment of the ejaculate does not yield enough details regarding the spermatogenesis problems. A complete analysis of the ejaculate could reveal several abnormalities that stem from the various stages of spermatogenesis, as well as disrupted testicular functions or even early testis cancer. The intertubular microvasculature, Leydig cells, and other cellular components of the intertubular area, as well as intratesticular and extratesticular hormonal regulatory systems, are essential for spermatogenesis. The male gonad, the testis, is where spermatogenesis takes place. Thus, the process by which basic spermatogonia in the testis develop into highly specialized mature spermatozoa is referred to as spermatogenesis. Primordial germ cells (PGCs) are the source of spermatogonia, which mature into gonocytes once they reach the testis. Spermatozoa move from the testis into the epididymis following spermatogenesis, where they are ready to reach and fertilize eggs and pass on the paternal genetic information to the following generation. The germ cells are found in tubules in the testis, and the seminiferous epithelium covering their inner side contains somatic Sertoli cells that maintain and nourish the germ line cells. A gamete must mature through several stages before it may exit the testis. These include meiotic recombination of genetic material, testicular maturation of spermatozoa, and mitotic multiplication and propagation of spermatogonial stem cells (SSCs) [2]. The meiotic division, or haploidization of the genome, is the primary event among the various developmental stages of germ cells. Type A spermatogonia make up the majority of the germ line undifferentiated cells in the fully grown mammalian testis. The SSCs are part of this cell population as well. The acrosome, an organelle formed by the spermatids, is necessary for subsequent interaction with the egg membrane during fertilization. Additionally, the germ cells change from being comparatively spherical to being little spindle-shaped. Following spermatid elongation, the spermatozoa typically have a head with the nucleus, an acrosome, a midpiece that supplies mitochondria with metabolic energy, and a flagellum, which is necessary for the sperm to pass through the female tract [3]. The fundamental spermatogenesis pathways that produce mature male gametes are very consistent among mammals. Their high level of organization necessitates intricate endocrine and genomic regulation, which is supported and mediated by somatic cell types, including the Leydig cells in the testicular interstitium, the peritubular myoid cells, and the Sertoli cells in the tubules. Human fecundity is surprisingly low when compared to the majority of other animals. Couple infertility is incredibly widespread, affecting one in seven couples in various countries. The "male factor" is the most often cited cause. The prevalence of an abnormally low sperm count (less than 20 million sperm ml; the cut-off for normal based on WHO standards) in young men (18-25 years old) is actually as high as 15-20%, according to a number of prospective and well-standardized studies conducted throughout Europe over the past ten years [4]. Human spermatogenesis may be more vulnerable to outside disruptions because it is less flexible in maintaining the production of enough amounts of healthy sperm and, hence, fertility. The fact that human sperm counts may have decreased significantly over the last 50 years or more, though this is still up for debate, supports these worries [6]. Additionally, there is strong evidence of significant regional variation in sperm counts, which may reflect differences in environmental exposures and/or genetic/ethnic factors [5]. In healthy males, the process of spermatogenesis does not start until puberty and continues for the remainder of their lives. Therefore, it is only during this time that the spermatogenic process itself is directly susceptible to negative consequences brought on by the man lifestyle, exposure to toxins in the environment, or his line of work. However, since spermatogenesis foundations are established throughout fetal development, it is becoming more widely acknowledged that any disruptions during this phase may affect the quantity or caliber of spermatogenesis in adulthood.

Organization of the testis

The ellipsoid-shaped testes are 2.5 × 4 cm in breadth [9], 4.5-5.1 cm in length [7,8], and have a capacity of 15-25 mL [10]. They are the sole organs in humans that are external to the body and are encased in a robust capsule of connective tissues called tunica albuginea [9]. The ideal temperature range for spermatogenesis is 2-4° below the body average temperature [11]. The epididymis, which gives birth to the vas deferens at its lower pole, is loosely attached to the testis along its posterior border [9]. The production of male gametes, or spermatozoa, and hormones, especially testosterone, are the two primary roles of the testis.

Supporting cells: Leydig cells

The Leydig cells are amorphous cells with granular cytoplasm that can be seen in the connective tissue alone or, more frequently, in clusters. About 5-12% of the testicular volume is made up of them [13-15]. The primary source of the male sex hormone testosterone is Leydig cells [16-18]. LH stimulates the generation of testosterone by acting on Leydig cells. The pituitary receives negative "feedback" from this, which suppresses or modifies additional LH secretion [18]. The amount of testosterone in the blood is much lower than the amount in the intratesticular space. The following are some of testosterone primary roles, the hypophysial testicular axis is activated, the brain and sexual behaviors are mated, spermatogenesis is started and maintained, the male genital organs differentiate, and secondary sex traits are acquired.

Seminiferous tubules and sertoli cells

Seminiferous tubules, which are enclosed by fibrous septa and packed in connective tissue, make up the majority of the testis volume. The seminiferous tubules and the intertubular tissue make up the roughly 370 lobules or fibrous septae that make up the testis incomplete division. The testes include a network of twisted tubules called seminiferous tubules. These tubules, which are dispersed among numerous proliferating and growing pockets, are where spermatogenesis occurs (Figure 1). Groups of Leydig cells, blood arteries, lymphatics, and nerves divide the looped or blind-ended seminiferous tubules. The diameter of each seminiferous tubule is approximately 180 mm. The peritubular tissue is approximately 8 mm thick, and the germinal epithelium is 80 mm tall [19]. Three layers of peritubular tissue make up seminiferous tubules: (1) the outer adventitial layer of fibrocytes, which is derived from a crude diagrammatic representation of a fully developed spermatozoon connective tissue from the interstitium; (2) the middle layer, which is made up of myoid cells dispersed adjacent to the connective tissue lamellae; and (3) the peritubular layer, a thick inner lamella primarily composed of collagen. Strong intercellular junctional complexes known as "tight junctions" separate the basal (basement membrane) and adluminal (lumen) compartments of the seminiferous tubule space. Highly specialized Sertoli cells, which lie on the tubular basement membrane and extend into the lumen with a complicated cytoplasmic ramification, line the seminiferous tubules. Throughout the gestational period, they promote the growth and proliferation of Sertoli cells. Both ends of the seminiferous tubules open into the spaces of the rete testis [20]. The excurrent ductal system of the epididymis receives the fluid released by the seminiferous tubules after it has been collected in the rete testis. Sertoli cells make up about 40% of the seminiferous tubules, while elongated spermatids occupy around 40% of the Sertoli cells [21,22]. The nuclei of Sertoli cells are bigger than those of most other cells, measuring between 250 and 850 cm^3 [21]. At different phases of growth and differentiation, each Sertoli cell contacts five additional Sertoli cells as well as roughly 40-50 germ cells. Germ cells are supported structurally, functionally, and metabolically by the Sertoli cells. For the best spermatogenesis, Sertoli cells must be both functionally and endocrinologically competent. The more developed germinal cells travel toward the lumen of the seminiferous tubules to exit the seminiferous tubule system and proceed with the final stages of spermatogenesis, while the earlier germinal cells rest toward the epithelium region of the seminiferous tubules to develop and mature. Sertoli cells support germ cells during their development and take part in germ cell phagocytosis, acting as "nurse" cells for spermatogenesis. For the maintenance of spermatogenesis in a suitable hormonal environment, Sertoli cells and developing germ cells have multiple communication points. FSH signals the release of androgen-binding protein (ABP) by attaching to the high-affinity FSH

receptors on Sertoli cells. To start and/or continue the process of spermatogenesis, androgens like testosterone and dihydrotestosterone can bind to ABP and raise their concentrations. Additionally, Sertoli cells release anti-Müllerian hormone, which inhibits the formation of the Müllerian ducts and permits the male embryo to develop [23,24]. Inhibin is another important macromolecule secreted by Sertoli cells that plays a role in the control of pituitary FSH. The immune system that develops during the first year of life does not identify spermatozoa, which are created after puberty. Spermatogenesis can take place in an immunologically favorable location thanks to the blood testis barrier. The two parts of the blood testis barrier are the adluminal region, which is situated toward the lumen region of the seminiferous tubules, and the basal region, which is situated close to the seminiferous epithelium. The formation of spermatogonial and primary spermatocytes occurs in the basal region, whereas the development of secondary spermatocytes and spermatids occurs in the adluminal region. There are three levels to the blood-testis barrier: (1) Sertoli cell-to-cell tight connections, which aid in separating premeiotic spermatogonia from the remaining germ cells, (2) epithelial cells in the capillaries and (3) Peritubular myoid cells.

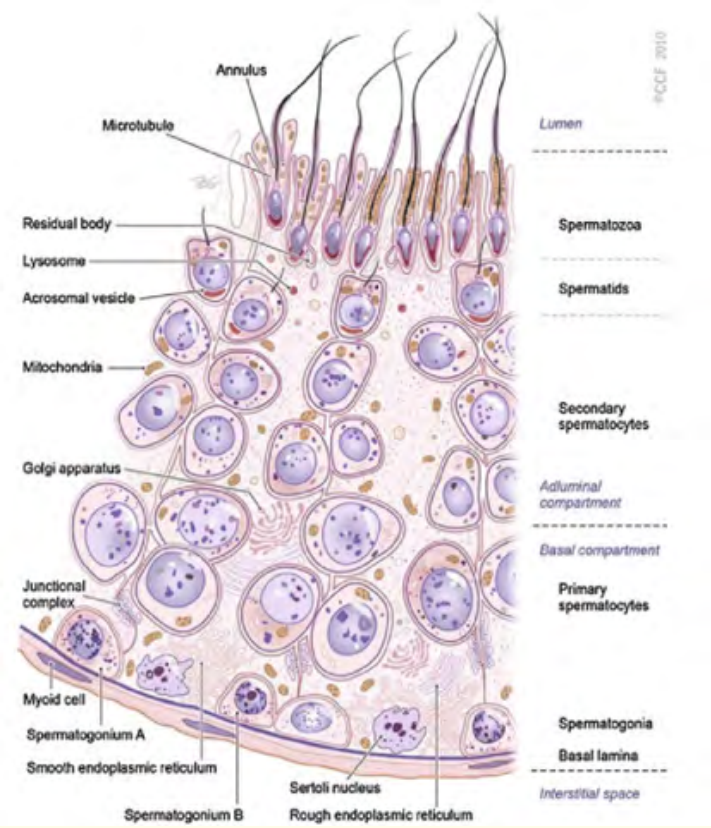

Figure 1: *A segment of the seminiferous tubules germinal epithelium. Through the Sertoli cell, the germinal epithelium is divided into a basal and an adluminal compartment.*

The following are a few of the Sertoli cells primary roles:

1. Preservation of seminiferous epithelium integrity.
2. Seminiferous epithelium compartmentalization.

3. Fluid secretion to create a tubular channel for sperm transportation into the duct.
4. Spermiation participation.
5. Cytoplasmic phagocytosis and removal.
6. Nutrient delivery to germ cells.
7. The production and metabolism of steroids.
8. Cell migration within the epithelium.
9. Inhibin and ABP secretion.
10. Spermatogenic cycle regulation.
11. Give the Sertoli cells LH, FSH, and testosterone receptors a target.

Spermatogenesis

Spermatogenesis is the process by which a basic diploid spermatogonium differentiates into a spermatid [20]. Primitive totipotent stem cells reproduce in a complicated, time-varying process that either renews them or creates daughter cells that develop into specialized testicular spermatozoa. It entails significant cellular remodeling as well as meiotic and mitotic divisions. Three stages comprise spermatogenesis: (1) spermatogonia growth and differentiation, (2) meiosis, and (3) spermiogenesis. After meiosis, a complicated process turns spherical spermatids into the intricate structure known as the spermatozoon. The spermatogenesis process in humans begins during adolescence and lasts the duration of the person life. Very early in embryonic development, a vigorous phase of mitotic replication starts once the gonocytes have differentiated into fetal spermatogonia. From the basement membrane to the lumen, germ cells are arranged in a highly orderly sequence inside the seminiferous tubule. Primary spermatocytes, secondary spermatocytes, and spermatids move into the tubule lumen after spermatogonia, which are directly on the basement membrane. All successive germ cells in the adluminal compartment and spermatogonia and early spermatocytes in the basal compartment are supported by the tight junction barrier.

Types of spermatogonia

Fetal spermatogonia becomes transitional spermatogonia and later spermatogonia type Ad (dark). Spermatogonial stem cells undergo proliferative events and produce a population of cells that have a distinct nuclear appearance that can be seen with hematoxylin and eosin staining. Spermatogonia can be categorized into three types: (1) Dark Type A, (2) Pale type A, and (3) Type B spermatogonia.

The stem cells of seminiferous tubules, known as dark type A spermatogonia, have a dark, ovoid nucleus that is highly pigmented and contains fine, granular chromatin. Dark Type A and Pale Type A spermatogonia are produced when these cells divide through mitosis. Pale staining and fine granular chromatin in the ovoid nucleus are characteristics of pale Type A spermatogonia. Other proliferative spermatogonia are Apaired (Apr), which is produced when Aisolated divides and then Aaligned (Aal) is produced. The cellular division of the preceding type produces Type A1, A2, A3, A4, Intermediate, and Type B spermatogonia, which are further differentiated, Adark, Apale, and Type B are the four spermatogonial cell types with chromosomal content that have been found in humans [25-27].

While it is unknown which Type A spermatogonia in humans is the stem cell, Type A isolated (Ais) is thought to be the stem cell in rats [28,29]. Large clusters of condensed chromatin beneath the nuclear membrane of an ovoid nucleus are characteristic of type B spermatogonia. Primary spermatocytes (preleptotene, leptotene, zygotene, and pachytene), secondary spermatocytes, and spermatids (Sa, Sb, Sc, Sd1, and Sd2) are produced by the mitotic division of type B spermatogonia [25]. Intercellular bridges hold spermatogonia together during all phases of spermatogenesis, preventing them from fully separating after meiosis. This synchronizes the maturation of germ cells and promotes biochemical connections [30].

Spermatocytogenesis

The meiotic phase, during which primary spermatocytes go through meiosis I and meiosis II to produce haploid spermatids, is known as spermatocytogenesis. The basal compartment is where this occurs. To create secondary spermatocytes, primary spermatocytes undergo the first meiotic division. The first meiotic division has a relatively lengthy prophase. The longest-lived spermatocytes are the primary ones. To create spermatids, secondary spermatocytes go through the second meiotic division. The lifespan of secondary spermatocytes is brief (1.1-1.7 days).

Mitosis

Spermatogonia are maintained and proliferate throughout mitosis. It is an exact, carefully planned series of events where the chromosomes, the genetic material, are duplicated, the nuclear membrane breaks down, and the cytoplasm and chromosomes divide equally to form two daughter cells [31]. Certain regulatory proteins interact with the loop domains that make up DNA [32-36]. Primary spermatocytes (spermatocytes I) and spermatogonia (types A and B) are involved in the mitotic phase. Through a series of mitotic divisions, developing germ cells joined by intracellular bridges form primary spermatocytes. Following puberty, the mitotic component provides precursor cells and starts the process of differentiation and maturation once the baseline number of spermatogonia is determined.

Meiosis

During the meiotic phase, which lasts from primary spermatocytes to spermatid formation, chromosome pairing, crossover, and genetic exchange occur until a new genome is identified. One diploid original spermatocyte undergoes two consecutive divisions during meiosis to produce four haploid spermatids. Each daughter cell, known as a secondary spermatocyte (2n), carries one partner of the homologous chromosomal pair following the first meiotic division (reduced division). The phases of meiosis are telophase, anaphase, metaphase, and prophase. The process begins when type B spermatogonia become preleptotene primary spermatocytes and lose contact with the basement membrane. The prophase leptotene stage is when the chromosomes are organized into long filaments. The homologous chromosomes, known as tetrads, form synaptonemal complexes during the zygotene stage when they are aligned linearly by a process termed synapsis. The chromosomes shorten in the pachytene stage, and crossing over occurs during this phase. During diakinesis, the homologous chromosomes condense and split apart from the crossing-over locations. To preserve genetic variation in sperm, this random sorting is crucial. The nuclear envelope disintegrates at the conclusion of prophase, and chromosomes are positioned in the equatorial plate during metaphase. Each chromosome has two chromatids that migrate to opposing poles during anaphase. Cell division during telophase results in the production of secondary spermatocytes with half as many chromosomes. Theoretically, each primary spermatocyte can produce four spermatids, but in practice, fewer are produced since meiosis is complicated and involves the death of some germ cells. The biggest germ cells in the germinal epithelium are the primary spermatocytes. The DNA content is cut in half during the brief prophase of the second meiotic division, which occurs when each chromosome two chromatids split apart and go to opposing poles. The spermatids remain joined by tiny bridges enabling synchronous development at the end of telophase rather than fully separating. These haploid spermatids have either the (22, X) or (22, Y) chromosome and go through a process called spermiogenesis, which is full differentiation and morphogenesis.

Spermiogenesis

The process by which spermatids differentiate into spermatozoa with fully compacted chromatin is known as spermiogenesis. After meiosis is finished, morphological changes take place during this process. Sa-1 and Sa-2, Sb-1 and Sb-2, and Sc-1 and Sc-2 are the names of the six distinct phases of spermatid maturation that have been identified in humans. Morphological traits can be used to identify each level. The Golgi complex and mitochondria are both fully formed and differentiated during the Sa-1 stage. Furthermore, the acrosomal vesicle emerges, the axial filament and proximal centriole appear, and the chromatoid body forms in the cell pole opposite the acrosomal vesicle. The intermediate piece is created, the tail develops, and the acrosome is finished during the Sb-1 and Sb-2 stages. The Sc stages are when

this procedure is finished. In the postmeiotic phase, the genome becomes inactive and the nucleus gradually condenses. Transitional proteins are created from the histones, and protamines are ultimately transformed into fully formed disulfide linkages.

Spermiation

In a process known as spermiation, a mature spermatid separates from the Sertoli cell and enters the tubule lumen as a spermatozoon. Bridges keep spermatids from the same spermatogonia together so that cytoplasmic products can be transported more easily. Spermiation, which may also include the actual movement of the cells as the spermatids travel toward the lumen of the seminiferous tubules, is an active process in which Sertoli cells take part [21]. The mature spermatids become free cells known as spermatozoa after closing their intracellular bridges and severing their connection to the germinal epithelium. During spermiation, parts of the cytoplasm of the Sertoli cell called the cytoplasmic droplet, are either totally removed or occasionally kept in the immature spermatozoon [37].

Hormonal regulation of spermatogenesis

Mammals spermatogenesis depends on a complex web of peptide and steroid hormones, all of which are essential for the seminiferous epithelium proper operation (Figure 2). In addition to controlling the development of male germ cells, these hormone messengers are essential for the growth and operation of the somatic cell types needed for healthy testicular development [38,39].

These include the myoid cells that surround the seminiferous tubules and give them physical support and contractile motion, the interstitial steroidogenic Leydig cells, whose main function seems to be the production of testosterone, and the Sertoli cells, which are crucial for providing spermatogenesis with both nutritional and physical support because of their direct contact with proliferating and differentiating germ cells within the seminiferous tubules. One or more of the hormones whose actions are necessary for unimpaired male fertility directly target each of these cell types. The anterior pituitary secretes the glycoprotein hormones luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which directly affect the testis and promote somatic cell activity to aid in spermatogenesis. A common a-subunit unites these hormones, which belong to the transforming growth factor (TGF) b superfamily of secreted growth factors, while their hormone-specific b-subunit sets them apart. While LH receptors (LH-R) are mostly located in the Leydig cells, while receptor labeling is also seen in spermatogenic cells, FSH receptor expression (FSH-R) is exclusive to the testicular Sertoli cells in men [40]. The main function of FSH in spermatogenesis, according to genetic and pharmacological research in rodents, is to promote Sertoli cell proliferation throughout prepubertal development. The number of germ cells is mostly determined by the amount of Sertoli cells [38]. Although males are fertile in both situations, targeted mutations in the mouse FSH-R and FSHb subunit genes result in significantly decreased testis weights and epididymal sperm counts. Although FSH can also restore spermatogenesis in gonadotrophin-suppressed men without the help of T, these findings are in line with hormone depletion-replacement investigations in male humans, as opposed to rodents. However according to the study authors, this impact results from Sertoli cells heightened sensitivity to residual T synthesis in the testis due to FSH. The only essential role of LH in the adult testis appears to be the regulation of testosterone (T) production. In the lack of LH-R activity, spermatogenesis can be entirely restored in LH-R knockout mice treated with exogenous T [40]. In hpg mice, who are deficient in both FSH and LH due to an inactivating mutation at the GnRH locus, testosterone administration also results in a qualitative recovery of spermatogenesis. In hpg males, spermatogenesis is stopped during meiosis if T replacement is not present. Since T by itself fully restores spermatogenesis in rats given the Leydig cell-specific cytotoxin ethane dimethane sulphonate (EDS), it is also evident that this impact of T replacement is independent of the activation of other Leydig cell products by T or LH.

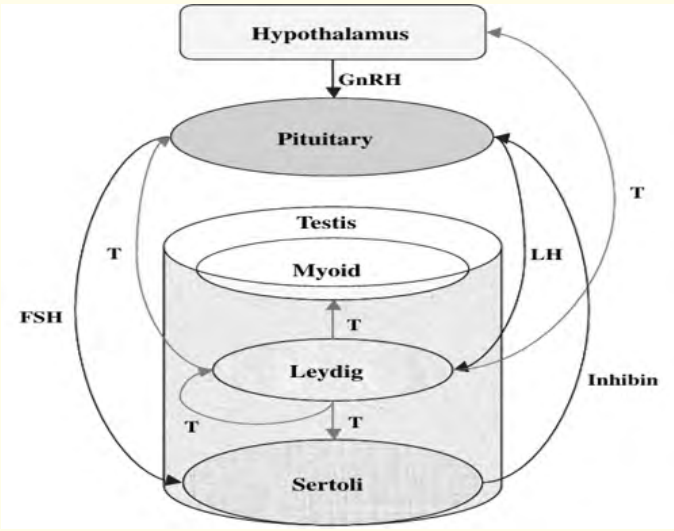

Figure 2: *The control of spermatogenesis by hormones the majority of hormones can have both beneficial and detrimental effects, either by activating and repressing downstream targets or by activating and desensitizing receptors. Follicle-stimulating hormone (FSH), luteinizing hormone (LH), gonadotropin-releasing hormone (GnRH), and testosterone (T).*

Lifestyle effects on spermatogenesis

Scrotal heating and sedentary position

Males typically have testicular descent into the scrotum from birth; if this does not happen, particularly as they enter adolescence and maturity, spermatogenesis is absent. Because spermatogenesis cannot occur at normal body temperature, the testes descend into the scrotum to maintain a temperature of 3-48°C below core body temperature [41]. Additionally, it is presumably crucial that the testes are lowered into the scrotum rather than at the top, where their proximity to the body surface could hinder testicular cooling. This is stated because it is believed that a type of cryptorchidism should likely be applied when the testes fail to descend into the bottom of the scrotum. The presence of a vascular-rich corrugated scrotal surface, which allows for heat loss, and an arterio-venous plexus (the pampiniform plexus) in the spermatic cord, which acts as a heat exchanger to cool incoming blood to the testis by exchanging heat with the cooler venous blood leaving the testis, are the two other essential components in guaranteeing cooling of the testis in addition to testis position. Maintaining testicular coolness depends on this plexus' normal functioning, which can be disrupted by chemicals, vasoactive medications, or conditions like varicocele, which causes the plexus veins to varicose [43]. Even when the pampiniform plexus is operating normally, the entering arterial blood cannot be cooled until the blood exiting the testis is already cool. This necessitates heat loss through the scrotal surface and its transfer to the testes underneath. As a result, anything that hinders the loss of heat from the scrotum will impact testicular temperature, and any increase in testicular temperature will negatively impact spermatogenesis. Generally speaking, the longer the testicular temperature rises, the more harmful the effect on spermatogenesis will be [41,42]. The most evident factors that can impact scrotal heat loss include exposure to an external heat source, such as those encountered in the workplace (e.g. bakers, welders, foundry workers), a hot bath, or a feverish disease like influenza [41].

The lifestyle and occupational factors that lead to males spending a lot of time in a sedentary position are perhaps more concerning because this is a regular occurrence for many men working in Western countries today (Figure 3). There is less effective cooling when

seated because air cannot move about the scrotum as easily. This effect is probably worsened by wearing tight pants or underwear. Lower sperm counts were linked to scrotal temperature increasing gradually with sedimentation length in investigations of males where scrotal temperature was continually recorded to posture and activity [44-46]. The effect of laptop computer use on scrotal temperature has been the most recently studied situation [47]. It is possible that scrotal heating will only have a major influence on fertility if it exacerbates the negative effects of other environmental or lifestyle factors or combines with them [48]. Scrotal heating has been studied and proven to be an effective form of male contraception [49]. However, as previously mentioned, other research that attempted to connect milder increases in scrotal temperature (such as those brought on by a sedentary lifestyle) to infertility failed to find significant or reliable correlations. It is prudent to advise all men who are trying to father a child, especially if they are known to have low sperm counts or low sperm motility, to take steps to minimize scrotal heating by any of the pathways mentioned above. This is because it is common sense that any factor that interferes with normal cooling of the scrotum/testes can only hurt spermatogenesis. Where this has been done in a controlled way, the results have been [50]. Spermatogenesis can only benefit from such minor lifestyle adjustments.

Obesity

Obesity is a significant lifestyle-dependent factor that negatively impacts spermatogenesis (Figure 3). Given that 1030% of adult males in Western nations are currently obese, male fertility is probably going to be affected more and more by this. Obesity is up to three times more common in infertile people than in people with normal semen quality, according to several studies [52]. Sperm motility and count are reduced by an average of 25% when a person's BMI exceeds 25. Numerous theories have been proposed to explain this correlation. The most compelling data suggests that variations in hormones are the primary cause of the changes in sperm production. Blood testosterone levels are lowered in males who are obese, and this decrease increases with the severity of the obesity. A change in the ratio of testosterone to oestradiol may also result from elevated levels of circulating oestradiol [51,52]. One explanation is that there is less intratesticular testosterone and, consequently, less androgen drive to spermatogenesis because these patients frequently exhibit lower blood levels of LH (and FSH), whereas an increase may be anticipated in the face of lower testosterone levels. The strongest evidence for this perspective comes from the fact that aromatase inhibitors used to lower oestradiol levels in obese men normalize the testosterone: oestradiol ratio and enhance the quality of semen. On the other hand, it might suggest that fat (young) males have fewer Sertoli cells. As was previously said, the latter is a much more dangerous issue because it is unknown how or when obesity would result in a decrease in the Sertoli cell population, which would permanently diminish sperm counts. Deposition of fat around the scrotal blood vessels may also contribute to decreased spermatogenesis in obese men by impairing blood cooling and raising the testicular temperature; obese men's more sedentary lifestyles are likely to make any temperature rise worse. The accumulation of toxicants in adipose tissue due to the lipophilicity of many persistent ECs is another possible explanation for the lower sperm counts in obese males [52]. However, given the high rates of obesity and low sperm counts among young men today, it is plausible that the obesity epidemic is affecting young men spermatogenesis and making them more vulnerable to negative effects from other environmental or lifestyle exposures. Over the ensuing decades, obesity is undoubtedly expected to have a significant impact on the hormonal and reproductive profile of Western men [53].

Smoking, alcohol, and drugs

Smoking and alcohol use are typically at the top of the list of Western lifestyle habits that are thought to hurt health. Although meta-analysis supports the idea that smoking has a minor detrimental effect on spermatogenesis, there is little evidence that either of these has a significant effect (Figure 3). Because of its vascular supply, which includes arterio-venous anastomoses in the spermatic cord that siphon off about 50% of incoming arterial blood, as well as its high metabolic needs due to spermatogenesis, the testis is physiologically thought to be on the verge of hypoxia [43].

Therefore, it would be assumed that variables that impair the transport of oxygen to the testis would have a negative impact. This reasoning is thus supported by the fact that smoking lowers a man sperm count. However, the drop (10-17%) in sperm counts in adult males who smoke heavily is moderate compared to the very dramatic (up to 40%) decline in sperm counts that is caused in sons by

maternal smoking during pregnancy, and no significant effects were reported in many individual investigations. Smoking may decrease spermatogenesis through a variety of methods, including activation of the Ah receptor, which is believed to happen when a mother smokes during pregnancy, and exposure to cadmium. One obvious cause is interference with the oxygen supply.

Studies on animals have shown that cannabinoids, like marijuana, have negative effects on sperm generation, maturation and motility, and testicular steroidogenesis. Endogenous cannabinoid-type receptors (CB1, CB2), which are expressed in people as well as in sperm, are how these effects function. Nevertheless, there isn't any solid proof that cannabis use has a significant impact on human spermatogenesis, despite some research suggesting that it negatively affects testosterone levels and sperm motility. Similarly, long-term cocaine usage may be linked to decreased sperm counts, although there isn't enough specific data to support the consequences and causes.

Due to the reduction of LH release from the pituitary gland and consequent lowering of intratesticular testosterone levels, the administration of androgenic steroids to men reduces spermatogenesis; this method of male contraception has been extensively studied. Therefore, it is not surprising that anabolic steroid usage by bodybuilders, weightlifters, and athletes might have similar negative effects; stopping anabolic steroid use causes spermatogenesis to recover, just like with male contraception. Normal males use a variety of prescription drugs, and while their effects on spermatogenesis cannot be categorized as lifestyle or environmental, they may be suspected of having an environmental cause if they negatively affect spermatogenesis, particularly if the drug is taken over an extended period. For instance, sulfasalazine, which has been used extensively to treat irritable bowel diseases over the long term, might cause infertility in rats and men through effects that are likely to occur late in spermatogenesis. In a similar vein, several chemotherapy drugs (anti-mitotic like cyclophosphamide) used to treat cancer or certain kidney disorders have known negative effects on spermatogenesis and/or fertility. In the men's treatment-continuing control group. According to other research, men with epilepsy had lower fertility rates. One explanation for this is that the medications used to treat the condition (valproate, carbamazepine, and oxcarbazepine) have negative effects on sperm motility, morphology, and number. There is evidence that valproate, at least, has negative effects on spermatogenesis in rats; however, these effects are only noticeable at supra-therapeutic dose levels. At therapeutic dose levels, however, only impacts on reproductive hormone levels (lower levels of LH and oestradiol) are observed. Since some medications (such as cimetidine, an H2-receptor antagonist) modify androgen activity to influence spermatogenesis, alternative molecules without this adverse effect have been developed.

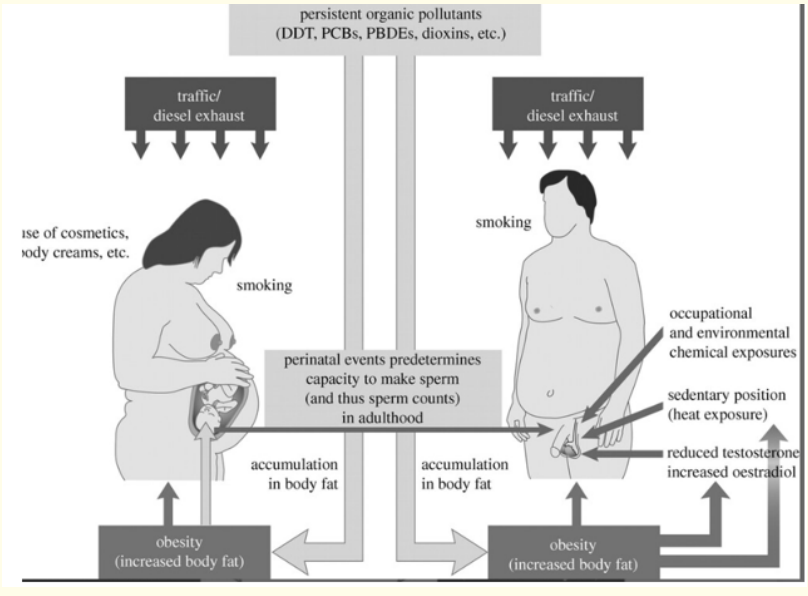

Figure 3: *Diagrammatic representation of the primary environmental and lifestyle factors known to adversely affect spermatogenesis and sperm counts in male humans, either directly on the testis during maturity or through the mother during fetal testis development. Keep in mind that a number of things have detrimental consequences at both phases of life.*

Effects of environmental chemicals on spermatogenesis

There are three different types of EC exposures: those that happen at work, those that happen in the house or general environment (such as pollution), and those that happen as a result of our lifestyle choices (like using deodorants, skin creams, etc.). It is well-accepted that exposure to ECs through one or more of these pathways can affect adult male spermatogenesis and result in lower sperm counts. Concerns over "falling sperm count" in men [54] and the great frequency of ECs in the contemporary environment [55] have likely coincided to give rise to this idea. Nevertheless, there is a startling lack of empirical data to back up this notion.

Occupational exposures

Dibromochloropropane (DBCP), a nematocide used on crops like bananas and pineapple, is the most well-known example of occupationally caused infertility brought on by EC exposure. There are one or two other well-documented cases as well. Men who were exposed to DBCP during production or application experienced significant spermatogenesis damage, which led to infertility in a significant percentage of cases. Recovery from exposure did not always happen after cessation. Exposure to glycol ethers, such as ethylene glycol monomethyl ether, which are extremely volatile substances utilized as solvents in a variety of operations, is a less dramatic example. Numerous investigations conducted in infertility clinics have suggested that occupational exposure to glycol ethers may be the cause. Similar detrimental effects of glycol ethers on spermatogenesis have been shown in numerous investigations conducted on laboratory animals (such as rats and rabbits) [56]. Glycol ether types have changed as a result, and new data indicates that the replacement chemicals could not have an impact on male spermatogenesis and/or fertility [56]. Numerous studies have examined whether occupational exposure to pesticides in general (such as that of crop sprayers and greenhouse workers) can impact male spermatogenesis or fertility in light of DBCP experience; however, the majority of these studies involve individuals who have been exposed to multiple pesticides rather than just one, which complicates interpretation. Despite the fact that numerous research has demonstrated evidence of negative consequences [57-59]. In addition, the metal welding fumes, carbon disulfide, inorganic lead, and other heavy metals (cadmium, mercury) have a detrimental effect on men spermatogenesis and/or sperm counts. Heavy metal exposure is arguably the most intriguing of these for two reasons. First, new research has revealed that infertile men have much higher blood and seminal plasma cadmium levels than either fertile men or males from the general population. Additionally, sperm concentration and motility were negatively correlated with cadmium levels in infertile men. Adult rats can also be used in experiments to replicate this connection. Second, before lead was removed from paints and gasoline, the whole public was exposed to lead through these goods. This exposure continues through the intake of some fish, such as tuna, which may contain these metals. For instance, tollgate employees who are exposed to vehicle emissions have been linked to lower sperm counts and quality, which are correlated with elevated amounts of lead and hemoglobin in their blood. This pathway or other work environments may also expose people to hexanedione, a component in gasoline, which has been demonstrated in lab animal experiments to interfere with spermatogenesis by disrupting Sertoli-germ cell junctions and/or adhesion.

Similar to this, recent research in rats has demonstrated that cadmium, at relatively low concentrations (albeit still beyond environmental values), can particularly damage tight connections between serotonin cells, which in turn can affect spermatogenesis [60]. It is uncertain if additional heavy metals can affect the same testicular cellular functions as cadmium.

Environmental exposure to pollutants

In a large population of sperm donors, exposure to ozone due to general air pollution has been negatively correlated with sperm counts; these effects may amplify the effects of traffic pollution as previously mentioned. Since ozone does not seem to affect erythrocytes' ability to transport oxygen in the same manner as carbon monoxide, it is unclear exactly how such effects take place. Many people think that exposure to environmental pesticides through fruits, vegetables, or the environment in general can negatively impact spermatogenesis in men in general.

Based on studies of men who are exposed to these agents on the job, this appears to be essentially implausible, but it is logical to predict that the general population will be less highly exposed than these workers. Exposure to organochlorine pesticides (like DDT), which are prohibited in Western nations, may be an exception to this rule because occupational exposure to these compounds will no longer occur, but the general public will still be exposed due to their persistence in the environment and food chain. Though some research suggests that exposure to DDT may have an impact on semen parameters, most of these studies are from underdeveloped nations where DDT is still in use, and the effects are often negligible. However, research conducted in North America and Europe, particularly among the heavily exposed Inuit population, has not found any indication of significant impacts on fertility or semen characteristics. Although some studies show trends toward lower sperm quality with high PCB exposure or following exposure to perfluorinated compounds, this finding also holds for other persistent environmental toxins like PCBs. Based on these and other findings, the general conclusion is that persistent pollutants have little influence on fertility, although maybe have some slight effects on spermatogenesis [61]. One study of US men, however, found a highly significant correlation between the prevalence of poor sperm counts in male partners of pregnant women and the urinary metabolite levels of three currently used pesticides (alachlor, atrazine, and diazinon). Although more research on these substances is necessary, it is clear that any spermatogenesis-related effects in these guys were insufficient to impact fertility. It is interesting to note that exposure to non-persistent, pyrethroid pesticides has also been linked to changes in adult male reproductive hormones as well as decreases in sperm concentration, motility, and DNA integrity [62]. Because of restrictions on the use of some other pesticides, the use of these pesticides is probably going to rise.

Environmental chemical exposure

As a result of lifestyle decisions, even though men are thought to be far less exposed to chemicals through cosmetics and/or body creams than women, young men in Western nations are using these items more frequently, and suncream and basic toiletries will be used more widely. Among the many chemicals found in these products, at least two (different kinds of parabens or phthalates) have been linked in animal studies to possibly having negative effects on testosterone and/or sperm production; however, for phthalates, these effects have only been discovered after exposure to extremely high levels (500-1500 mg kg21 d21). Although there is no information linking male sperm counts to paraben exposure, current comprehensive safety evaluations (based on animal research) found that impacts are improbable [63].

Conclusion

Numerous processes, including hormonal influence, appropriate genetic and epigenetic regulation, and the optimal balance between cellular proliferation and differentiation, are necessary for the complicated process of spermatogenesis to function properly. The right temperature and ambient conditions are necessary for all of these processes to take place. This sensitive process is threatened by environmental contaminants, lifestyle choices, and climate change. The development of cell culture techniques has made *in vitro* spermatogenesis a potentially useful tool for studying and comprehending this intricate process. A appropriate microenvironment that replicates the testis' *in vivo* settings and promotes the survival and growth of all spermatogenesis-related cell types is required to do this, leading to full and functional spermatogenesis.

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