INTRODUCTION

Sperms are derived from the primordial germ cells, which enter the gonads during development. The primordial germ cells may arise at some distance from the presumptive gonads, to which they migrate and become established. The formation of the germ line is dependent upon the presence of the germ-plasm, which is a cytoplasmic component that causes these cells to become distinct from the somatic cells. When the primordial germ cells become established in the gonad, they become stem cells that divide by mitosis to produce the supply of gametes that the organism requires for reproduction. When they enter the gonads, the germ cells may associate with specific somatic cells that support, nurture and protect them; these somatic cells are called Sertoli cells.

During the proliferative phase, the germ cells are called gonia (spermatogonia) and act as a stem cell population that will divide by mitosis to produce the lifetime supply of gametes that the organism requires for reproduction. When the organism reaches maturity, germ cells acquire the ability to differentiate into functional gametes and undergo meiosis to reduce the chromosome number from 2n to 1n. Sperms are produced through the process of spermatogenesis. Spermatogenesis is divided into four phases: (a) Extra-gonadal origin of primordial germ cells, (b) Proliferation of germ cells by mitosis, (c) Meiosis, (d) Structural and functional maturation of the spermatozoa.

HUMAN SEX DETERMINATION AND DIFFERENTIATION

Sex determination is a biological system that determines the development of sexual characteristics in an organism. In many cases, sex determination is genetic: males and females have different genes that specify their sexual morphology. The early stages of human sex differentiation appear to be quite similar to the same biological processes in other mammals. However, at early embryonic stage, both 46, XX and 46,XY fetuses have similar sex organs, specifically, the gonadal ridges and the internal ducts [1].

The gonadal ridges can be easily recognized by 4-5 weeks of gestation. At that time, they already include the undifferentiated germ (stem) cells which will later develop into either eggs or sperm under direct genetic and hormonal effect. The formation of gonadal ridges is similar in both sexes, and is a prerequisite step in the development of differentiated gonads. The organization of cells into a ridge requires the effects of several genes, such as SF-1, DAX-1, SOX-9, WT1, and others. If any of these genes is non-functional, then there is no formation of a gonadal ridge and therefore no formation of either testes or ovaries. By 6-7 weeks of fetal life, fetuses of both sexes have two sets of internal ducts, the Mullerian (female) ducts and the Wolffian (male) ducts [2].

Under typical circumstances, the sex of an individual will be determined and expressed through the following mechanisms:

Review Article

Review: Genetics of Spermatogenesis

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Abstract: Development of mammals is usually initiated by fertilization of an egg by a sperm. The sperm and the egg have distinct roles to play in launching development of a new generation. The sperm must seek out the egg, fuse with it and deliver its precious haploid nucleus. The egg, on the other hand, must make itself apparent to the sperm and be capable of responding appropriately to its contact. That response allowing a sperm of its own species to fuse with it, once fusion has occurred; the egg exaggerates its defenses to prevent the fusion of additional sperm. It also initiates a sequence of events that enable the sperm nucleus to fuse with the egg nucleus to form the zygote nucleus and begin the complicated process that produces an embryo that develops into an organism consisting of many different cell types that are organized into tissues and organs to enable the organism to function like its parents.

Keywords: Sperms, Sex determination, differentiation, Hormonal Effect, Spermatogenesis, Spermogenesis.
• Chromosomal Sex (genetic): Presence or absence of Y chromosome.
• Gonadal Sex (Primary Sex Determination): Controlled by presence or absence of testis determining factor (TDF).
• Phenotypic Sex (Secondary Sex Differentiation): Determined by the hormonal products produced by the gonads.

Sex determination at the chromosome/gene level

For the majority of individuals, sex determination is as simple as the presence or absence of a Y chromosome. Those individuals with a Y chromosome (including XY, XXY, XXXY, etc.) will develop into males, and those without one will become female. Y chromosome carries many genes that affect the male germ line development and also the process of spermatogenesis [3].

Yes, that was generally accepted task about sex differentiation. However, some individuals, undergo what is referred to as primary sex reversal, relatively rare occurrence (approximately 1 in 20000 births) can lead to males with XX chromosomes. In such cases, patients might manifest normal primary and secondary sexual organs, or ambiguous genitalia. Thus, the presence of Y chromosome alone is not essential for the presence of maleness characters [4].

SEX DETERMINING GENE

Y chromosome carries genes or factors that determine the testes formation. It was believed that the testis determining factor (TDF) is situated within the SRY region at the proximal border of the pseudoautosomal region. And, SRY induces differentiation of cells derived from the genital ridges into testes, and acts as inhibitor of another gene/s involved in female development [5]. Recently, Blecher and Erickson [6] suggested that the testis-determining factor on the human Y chromosome is not directly related to SRY, but this gene is neither necessary nor sufficient for testis induction. However, the male determining factors could directly related to SRY when interact with other genes.

Fig. 1: Diagram showing the Y-chromosome and its genetic content that affect gonadal differentiation and spermatogenesis process.

On the other hand, The two cases reported by Maciel-Guerra et al. [4] with XX maleness syndrome showing absence of both Y chromosome and SRY region; i.e. no translocation has been occurred between the parental X and Y chromosomes. Therefore; other genes located on X chromosome can help in sex determination when working together in dose dependant manner. These genes include DAX-1, SF-1, SOX-9, WT-1, and others [5, 7].

Some sex determining genes are

• **DAX1**: is a nuclear receptor that regulates adrenal and gonadal development. Exerts its effects early on in development. DAX1 was considered as an 'anti-testis' gene [8].

• **SF-1 (steroidogenic factor 1)**: is a nuclear receptor with critical roles in steroidogenic tissues. SF-1 has emerged as an essential regulator of adrenal and gonadal functions and development [9]. SF-1 is expressed in both male and female genital ridge, throughout the critical window of sex determination. It is essential for the initiation of the testicular differentiation by SRY gene. Mutation and/or loss of SF-1 function can be associated with a wide variety of reproductive defects ranges from complete testicular dysgenesis with Mullerian structures, through individuals with mild clitoromegaly or genital ambiguity, to severe penoscrotal hypospadias or even anorchia [10].

• **WT-1**: Wilms tumor suppressor gene-1: the gene encoding steroidogenic factor 1 (SF1) that
implicated in the development of the indifferent gonad prior to sexual differentiation. The activity of WT1 is required for gonadogenesis, whereas gene deletion or inactivation produces severe impaired sexual development [11].

- **SOX-9: SRY box-related gene-9**: is expressed in the testis and in the ovary, but at different levels; i.e. it is a dosage sensitive gene. The SOX-9 gene is a key gene in human sex determination together with SRY and WT-1 [12].

**HORMONAL EFFECT**

- **Testosterone**: Fetal Leydig cells produce testosterone in high amounts, its presence is required for Wolffian duct development in the male [13].

- **Müllerian inhibiting substance (MIS)**: Fetal Sertoli cells produce the antimüllerian hormone (AMH, also named müllerian-inhibiting hormone). MIS blocks the development of Müllerian ducts, promoting their regression. Human gene for AMH, which is located on chromosome 19, has been cloned and sequenced. AMH has extra-müllerian effects, such as an inhibiting the development of ovarian and uterine tumoral cells [13].

Fig. 2: Diagram showing some genes as well as hormones that running the human sex differentiation

- **5-alpha dihydrotestosterone (DHT)**: Testosterone is converted to the more potent DHT by 5-alpha reductase. DHT is necessary to exert androgenic effects farther from the site of testosterone production, where the concentrations of testosterone are too low to have any potency. A 5-alpha reductase deficiency results in an androgen disorder characterized by female phenotype or severely undervirilized male phenotype with development of the epididymis, vas deferens, seminal vesicle, and ejaculatory duct, but also a pseudovagina [14].

In other words, gonad development is a result of the presence or absence of the sex determination genes on the Y and X chromosome, and sex differentiation is induced by the hormones produced by the gonads. Additionally, two products of the developing testes are needed for normal male development; (a) MIS (Müllerian inhibiting substance) must be secreted to inhibit female duct growth and (b) androgens must be secreted to enhance male duct growth. In contrast, a female fetus with no developing testes will produce neither MIS nor androgens, and hence female ducts will develop [12].

**Outcome of abnormal sex determination and differentiation**

The following disorders are caused by a malfunction in the sex determination and differentiation process:

- **Congenital Adrenal Hyperplasia**: Excess adrenal androgens are produced as an indirect result of a cortisol biosynthetic defect. So, inability of adrenal to produce sufficient cortisol, leading to increased production of testosterone resulting in severe masculinization of 46 XX females [1].

- **Androgen insensitivity syndrome (46 XY female)**: All patients had normal female appearance and psychosexuality, well-developed breasts, sparse pubic and auxiliary hair, normal female external genitalia and short blind-ending vagina [1].

- **The XX maleness syndrome**: or true hermaphroditism now called ovotesticular disorder of sex development (OT-DSD). XX males usually have genital ambiguity combined with both ovarian and testicular tissue, but sometimes affected males have normal male genitalia, small azoospermic testes, and hypogonadism [15].

- **Persistent Müllerian Duct Syndrome**: A rare type of pseudohermaphroditism that occurs in 46 XY males, caused by either a mutation in the Müllerian inhibiting substance (MIS) gene, on 19p13; or its type II receptor, on chromosome 12q13. Results in a retention of Müllerian ducts and unilateral or bilateral undescended testes [1].
• Male Pseudohermaphroditism: Failure of androgen production or inadequate androgen response, which can cause incomplete masculinization in XY males. Varies from mild failure of masculinization with undescended testes to complete sex reversal and female phenotype [16].

• Klinefelter Syndrome: Klinefelter Syndrome is the term given to individuals with a 47, XXY karyotype. At puberty Klinefelter men can experience female breast growth, low androgen production, small testes and penis, and commonly azospermia. Whereas, mosaic XXY/XY patients could produce spermatozoa in variable numbers [17].

• 45, XO/46,XY Mosaicism: Individuals born with 45, XO/46,XY Mosaicism can appear male, female, or ambiguous at birth. Males experience normal male sex differentiation and females are essentially identical to girls born with Turner Syndrome. Because the Y chromosome is affected, abnormal sex differentiation can result from this condition. Patients show partial testes determination, variable amount of androgen produced, some Wolffian Duct development, some Mullerian Duct development, ambiguous external genitalia, feminizing puberty with estrogen therapy; or masculinizing puberty with testosterone therapy [1].

STRUCTURE OF THE TESTES AND SPERMATOGENESIS

Fig. 3: Seminiferous epithelium which is formed by two cell populations (the spermatogenic cells and the Sertoli cells) and the surrounding tissue

Sperm are among the most highly specialized cell types ever described. Such specialization is designed to get the sperm to the egg and to fuse with it. The testes are very efficient "sperm factories," which produce vast numbers of these elaborate cells. The testes are bilateral gonads lying within a common musculo-cutaneous sac, the scrotum. Septa extending internally from the capsule incompletely divide the parenchyma (seminiferous tubules) into about 250 lobules. Each lobe contains 1–4 seminiferous tubules that are separated from one another by a connective tissue stroma (tunica propria) within which are found the hormone producing interstitial (Leydig) cells. The seminiferous tubules are formed by the seminiferous epithelium, a complexly stratified epithelium resting upon a basal lamina and containing 2 cell populations: Sertoli cells and germ (spermatogenic) cells.

• Sertoli cells (sustenacular cells) are columnar, non-replicating (post-mitotic) support cells that extend from the basal lamina to the lumen; they have extensive apical and lateral projections that envelop the adjacent germ cells and make contact with adjacent Sertoli cells. At these contacts, highly modified zonula occludens create 2 epithelial compartments: basal and luminal. The basal compartment lies below the occluding junctions and houses the spermatagonia (stem cells) and early primary spermatocytes. The luminal compartment houses the later stage spermatocytes and spermatids. The occluding junctions of the Sertoli cells also establish the blood-testis barrier. This barrier is both physiological and immunological in function; the barrier permits the luminal fluid to differ from that of the interstitium creating a more nutritive environment for the gametes and prevents an immunological response to the antigenic haploid spermatids.

Functionally, the Sertoli cells serve as nurse cells to the spermatogenic cells, exchanging metabolic and waste substances with them. They also phagocytose the residual bodies produced in the last stage of spermatogenesis. Finally, they secrete androgen-binding protein (ABP) into the luminal compartment to elevate the concentration of testosterone [18].

• The germ cells are stacked in four to eight layers; their function is to produce spermatozoa. The germ cells are comprised of spermatagonia, spermatocytes, spermatids and spermatozoa. The spermatagonia divide by mitosis to create stem cells and primary spermatocytes; the latter undergo further differentiation as they move apically through the seminiferous epithelium to form secondary spermatocytes, then spermatids and finally spermatozoa [19]. The production of spermatozoa is called spermatogenesis, a process that includes cell division through mitosis and meiosis and the final differentiation of spermatozoids, which is called spermiogenesis.
Spermatogenesis is the process by which spermatozooids are formed. It begins with a primitive germ cell, the spermatogonium, which is a relatively small cell, about 12 μm in diameter, situated next to the basal lamina of the epithelium. At sexual maturity, spermatogonia begin dividing by mitosis, producing successive generations of cells.

**Spermatogenesis could be divided into 3 phases [20]**

- **Spermatogonial phase:** Spermatogonia divide by mitosis to create stem cells and primary spermatocytes. During the spermatogonial phase the type Ap spermatogonia (daughter cells of type Ad) undergo repeated mitotic division to produce multiple clones; cytokinesis during these divisions is incomplete and the daughter cells are all linked by a cytoplasmic bridge forming a plasmodium. This cytoplasmic continuity is responsible for the synchronous development of the linked “cells”. At the end of this phase the linked type Ap spermatogonia differentiate into type B spermatagonia.

- **Spermatocyte phase:** primary spermatocytes undergo two meiotic divisions to produce haploid spermatids. During the spermatocyte phase mitotic division of each type B spermatagonia produces 2 daughter primary spermatocytes that migrate into the lumenal compartment of the seminiferous tubule. Prior to undergoing meiosis I, these cells replicate their DNA so that the chromatids are doubled (4N) as is the amount of DNA (2d). As meiosis I begins crossing over can occur and that during metaphase the maternal and paternal chromosome are randomly segregated. At the end of meiosis I, two secondary spermatocytes (2N, 1d) are formed. The secondary spermatocytes move rapidly into meiosis II without DNA synthesis (S phase) resulting in the formation of spermatids (1N, 0.5d).

- **Spermatid phase:** Spermatids differentiate into mature sperm cells (spermatozoa). During the spermatid phase (spermiogenesis) the spermatids (immature gametes) develop into spermatozoa (mature gametes) while remaining physically attached to the Sertoli cells.

**SPERMIOGENESIS**

Spermiogenesis is the final stage of production of spermatozooids. During spermiogenesis the spermatids are transformed into spermatozoa, cells that are highly specialized to deliver male DNA to the ovum. No cell division occurs during this process. Spermiogenesis is a complex process that includes formation of the acrosome, condensation and elongation of the nucleus, development of the flagellum, and loss of much of the cytoplasm. The end result is the mature spermatozoon, which is then released into the lumen of the seminiferous tubule.

**This occurs in 4 stages:** Golgi, cap, acrosome and maturation phases [21].

**Golgi phase**

The polarity of the spermatids is established. Proacrosomal vesicles, derived from the trans-Golgi network, fuse to form a single large acrosomal vacuole that contains the acrosomal granules, which is closely associated with the nuclear envelope at the center and with the proximal part of the perinuclear theca at the periphery. Following this, the centrioles migrate to the opposite end to establish the posterior pole and initiate flagellum formation.

**Cap phase**

As spermatids develop, the acrosomal vesicle (cap) gradually becomes flattened and spreads over the nucleus, while the Golgi apparatus simultaneously migrates distally toward the growing neck region. At this stage, round spermatids express more than 200 specific transcripts (genes). However, the critical checkpoints in acrosome biogenesis is the transition from the cap phase to the elongation phase. Therefore, spermiogenesis is easily disrupted by gene deletion (such as; Herb and GOPC genes) at this stage. In these mutants, the Golgi-derived vesicles fail to fuse, and the acrosomal granules are completely detached from the nuclei as the spermatids grow.

**Acrosomal phase**

The spermatid re-orient the cytoplasm into the lumen and the acrosome spreads over the nucleus. The nucleus flattens and elongates and the cytoplasm moves posteriorly to concentrate the mitochondria around the flagellum. The centrioles migrate back to the nucleus and form the connecting piece (neck). The spermatid cytoplasm becomes thin, the acrosome is gradually oriented to face the underlying plasma membrane, and manchettes begin to develop from the nuclear ring region in the elongating spermatids. The acrosomic contents gradually condense into an electron-dense matrix while the acrosomal cap elongates. The next checkpoint is the period of transition from the elongation (acrosome) phase to the maturation phase. Deletion of the gene encoding the IgSF protein RA175 causes the disruption of spermiogenesis at approximately the stage of early elongating spermatids, resulting in oligoterozoospermia.

**Maturation phase**

The dense material (acrosomal granule) in the acrosomal vesicles spreads over the entire acrosomal
membrane, eventually differentiating the acrosome into the anterior acrosome and the posterior acrosome. During this period, fundamental molecules appear to be translocated and organized into the anterior acrosome and the posterior acrosome. Post-translational modifications of acrosomal matrix proteins can be observed in late spermatids; in fact, the expression of the acrosomal antigen MC41 suddenly becomes visible in late spermatids. Immediately prior to spermiation, most of the cytoplasm and organelles of the spermatids are discarded in the cytoplasmic droplet and the spermatids are released into the lumen as spermatozoa or sperm. The residual bodies that are released from spermatids are eventually engulfed by the Sertoli cells.

SPERMATOZOA

The function of mammalian spermatozoa is not only to carry the paternal genome to the oocyte, but also to activate the oocyte arrested at the metaphase of the second meiosis (MII). A mature spermatozoon is a highly differentiated haploid cell with a paddle-shaped head and a flagellum (tail). The sperm head comprises a nucleus, an acrosome, and a small volume of cytoplasm in the form of cytoplasmic layers. The nucleus contains the paternal genome along with the nuclear proteins, protamines. The mature sperm acrosome is a cap-like saccule that covers the proximal region of the head; it is entirely covered by an acrosomal membrane that encloses hydrolizing enzymes and matrix proteins. The cytoplasm between the nucleus and overlying plasma membrane becomes thin with narrow layers (spaces) toward the plasma membrane [21].

Mammalian sperm heads are divided into two major regions: the acrosomal region and the postacrosomal region (PAR). The acrosome region contains two subdomains: the anterior acrosome and the posterior acrosome. The anterior acrosome is involved in the acrosomal reaction. The posterior acrosome appears to be involved in gamete membrane fusion. The PAR extends from the end of the posterior acrosome and the posterior ring located at the distal-most end of the head, and it forms the neck region (connecting piece). The posterior ring exhibits a belt-like constricted zone of plasma membrane. It fuses with the underlying nuclear envelope. The proximal part of the PAR is also presumed to be involved in egg activation [21].

The tail contains motility-related apparatus, mitochondria, an axoneme, and cytoskeletal structures such as outer dense fibers (ODFs) and fibrous sheaths (FSs). Structurally, the tail is divided into four major regions; the neck, middle piece (midpiece), principal piece, and end piece. The neck region is structurally complex. Its major components are the basal plate, a redundant nuclear envelope, mitochondria (neck mitochondria), and a connecting piece (comprising the capitulum, centrosome, and segmented columns connected to the ODFs). Centriosomes contain the proximal centriole and various pericentriolar matrix proteins. They are involved in microtubule formation when the sperm reaches the oocyte, and they morphologically develop into the sperm aster during fertilization. The distal centriole is transformed into the proximal part of the axoneme [21].

During the last stage of spermiogenesis, the nucleus flattens and condenses, as nonhistone basic proteins such as protamines displace the typical histones that associate with nuclear DNA, transcriptional activity in the spermatid is silenced, and nucleosomal structure is lost [22]. At the same time, the remaining cytoplasm is diminished as a cytoplasmic droplet. The testicular spermatozoa that are released from the Sertoli cells are mature at the genomic and morphologic level. The spermatozoa that enter the caput epididymidis are functionally immature; they do not possess the properties of forward motility and zona pellucida recognition. When sperm are released into the lumen of the tubule, their ribosomes are nearly absent, and their endoplasmic reticulum (ER) has been lost from the cytoplasm. Because they have no machinery to produce proteins, all of the factors that sperm will require for ascending the female reproductive tract must be provided from the outside; for example, by the cells of the cauda epididymis. Semen has an alkaline nature, and sperm do not reach full motility (hypermotility) until they reach the vagina where the alkaline pH is neutralized by acidic vaginal fluids. This gradual process takes 20–30 minutes. In this time, fibrinogen from the seminal vesicles forms a clot, securing and protecting the sperm. Just as they become hypermotile, fibrinolysin from the prostate dissolves the clot, allowing the sperm to progress optimally [23]. The production of mature sperm from a spermatogonium takes about 75 days [24].

FACTORS AFFECT EPIDIDYMAL SPERM MATURATION

- As spermatozoa move through the human epididymis they encounter a varied environment with respect to the proteins with which they come into contact. In the proximal epididymis sperm are subjected to the action of enzymes and exposure to proteins involved in membrane modification. In the middle region another set of proteins and enzymes predominates could modify the sperm membrane to permit the uptake of GPI-anchored zona binding proteins P34H and CD52. More distally sperm encounter increasing activities of lytic enzymes, proteins involved in both zona binding and oocyte fusion, the major maturation antigen CD52, antimicrobial activity and decapacitation factors, that help them to survive before ejaculation [25].

- Epididymosomes: There is evidence that proteins without any signal peptide are acquired by sperm cells during their epididymal transit, implying an unusual secretion pathway. In fact, a family of epididymis-specific proteins was characterized in
man and named P34H. This protein is located on the sperm surface, is attached via a glycosyl-phosphatidylinositol (GPI) anchor, and is involved in the zona pellucida recognition. The epididymal membranous particles present in the lumen, “prostasome-like particles” or epididymosomes, are responsible for anchoring the P34h to the sperm surface. Epididymosomes are directly involved in the epididymal maturation process of the sperm cells [26].

**Prostasomes and Post-ejaculatory Sperm Modifications:** The “prostasomes” are secreted by the prostate and mixed in the semen at the moment of ejaculation. Many different proteins have been shown to be present on prostasomes, some of which possess enzymatic properties. The effects of prostasomes on the post-testicular maturation of spermatozoa include an immunosuppressive activity, an enhancement of sperm motility, and an influence on the sperm capacitation process [26]. The immunosuppressive activity of prostasomes arises from the presence of several complement inhibitory molecules (eg, CD55, CD46 and from the presence of CD59 (protectin), which inhibits the formation of the membrane attack complex. The possible role of these molecules would be to protect spermatozoal phagocytosis in the female genital tract by white blood cells. Prostasomes also have an influence on sperm motility. They enhance the progressive motility of spermatozoa due to the modifications of the sperm microenvironment, since these vesicles contain a calcium-dependent ATPase [26].

**Acrosomal reaction and capacitation**

The acrosome, a cap-like structure covering the anterior portion of the sperm nucleus, contains multiple hydrolytic enzymes (such as hyaluronidase, neuraminidase, acid phosphatase, and a protease that has trypsin-like activity) that are released by exocytosis prior to fertilization. These enzymes are known to dissociate cells of the corona radiata and to digest the zona pellucida. Simultaneously, extensive changes occur in all sperm compartments (head and flagellum, membrane, cytosol, and cytoskeleton). Factors originating from epididymal fluid and seminal plasma are lost or redistributed, membrane lipids and proteins are reorganized, and complex signal transduction mechanisms are initiated. When spermatozoa encounter an oocyte, the outer membrane of the acrosome fuses with the plasma membrane of oocyte at several sites, liberating the acrosomal enzymes to the extracellular space. This process, the acrosomal reaction, is a vital steps in fertilization [27].

In mammals, sperm–egg interaction and mutual activation are mediated by the zona pellucida (ZP), the glycoprotein coat of the egg. The spermatozoon binds to the ZP with its plasma membrane intact, via specific receptors that are localized over the anterior acrosomal region. The binding of the sperm to the ZP stimulates it to undergo an acrosome reaction, which enables the sperm to penetrate and fertilize the egg. The binding of the sperm to the egg and the occurrence of the acrosome reaction will take place only if the sperm has previously undergone a poorly defined maturation process in the female reproductive tract, known as capacitation [28, 39, 40].

**Capacitation**

Binding to the egg’s zona pellucida stimulates the spermatozoon to undergo acrosome reaction, which enables the sperm to penetrate the egg. Before binding the spermatozoon undergoes a series of biochemical transformations, in the female reproductive tract, collectively called capacitation. The first event is cholesterol efflux leading to the elevation of intracellular calcium and bicarbonate to activate adenyl cyclase (AC). It produces cyclic-AMP, which activates protein kinase A (PKA) that indirectly phosphorylates certain proteins on tyrosine. There is also an increase in protein tyrosine phosphorylation dependent actin polymerization and in the membrane-bound phospholipase C. Sperm binding to zona-pellucida activates cAMP/PKA and protein kinase C (PKC), respectively. PKC opens a calcium channel in the plasma membrane. PKA together with inositol-trisphosphate activate calcium channels in the outer acrosomal membrane, which leads to an increase in cytosolic calcium [28]. The increased cytosolic calcium result in F-actin depolymerization and dispersion which enable the outer acrosomal and the plasma membrane to come into contact and fuse, completing the acrosomal reaction [41].

The acrosomal matrix interacts with the outer acrosomal membrane, forming matrix–membrane complexes, and these complexes in turn interact with substances in the zona pellucida. During these interactions, soluble hydrolytic enzymes are rapidly released. Upon penetration, the oocyte becomes activated. It undergoes its secondary meiotic division, and the two haploid nuclei (paternal and maternal) fuse to form a zygote. In order to prevent polyspermy and to minimise the possibility of producing a triploid zygote, several changes occurs to the egg’s cell membranes, that renders them impenetrable shortly after the first sperm enters the egg [29].

**FACTORS AFFECTING SPERMATOGENESIS**

**Genetics factors**

- The function of Y chromosome is the propagation of species through sex determination and control of spermatogenesis. The distal end of the long arm of the Y chromosome includes the azoospermia factor (AZF) locus, which contains gene/s required for spermatogenesis. The AZF locus has been mapped to a region in band q11.23 of the Y
chromosome [30]. There are three sub-regions designated as "azoospermia factor" AZFa, AZFb, and AZFc. Each of these regions may be associated with a particular testicular histology. However, spontaneous mutation, or loss of one of these loci in the paternal germ line leads to severely disturbed fertility. The deleted regions are usually submicroscopic and are known as Y-chromosome microdeletions [30]. Microdeletions in the Y-chromosome were found in 7% of unselected group of infertile men which suggests that Y-chromosome microdeletions constitute the second most common specific cause of male infertility (azoospermia or severe oligospermia) [42].

On the other hand, chromosomal abnormalities have been found to be associated with severe male factor infertility. The Y chromosome-specific structural abnormalities that may be detected upon cytological analysis include pericentric inversion, dicentric, ring, and truncated Y chromosome [31]. The X-autosome and Y-autosome translocations in men are usually associated with azoospermia.

- The XX male syndrome (means translocation of the SRY to X-chromosome) is another rare type of structural chromosome abnormality seen in azoospermic men, i.e. failure of spermatogenesis.

- Autosomal chromosome abnormalities are usually structural (rather than numeric) in infertile males [43]. In the oligozoospermic population, autosomal anomalies, especially Robertsonian and Reciprocal translocations, are more frequent than sex chromosome abnormalities. Robertsonian translocations are mostly fusions between chromosomes 13 and 14. Additionally, autosomal inversions are 8-fold more frequent in infertile men than in normal population. Particularly, inversions in chromosome 9 are associated with azoospermia [31].

- Xp22 contiguous syndrome (deletion of area of short arm of X-chromosome): the deletion affect several genes as DAX-1 gene and gene can cause deficiency of gonadotrophin with hypogonadis and failure of spermatogenesis [32].

- Deletion of DAZ and DAZ2 genes on Yq chromosome interfere with spermatid maturation [32].

- Autosomal chromosome translocation with sex chromosome could interfere sex chromosome pairing and segregation during early pachytene stage of spermatogenesis. This could interfere with X chromosome inactivation that required for proper meiosis, and so, causing interruption of the meiotic cycle and defected spermatogenesis [32].

Other factors that affect spermatogenesis
- Primary endocrine failure involving either gonadotrophin releasing hormone or gonadotrophin deficiency is associated with severe disorders in spermatogenesis [32].
- Dietary deficiencies (such as vitamins B, E and A), anabolic steroids, metals (cadmium and lead), x-ray exposure, dioxin, alcohol, and infectious diseases will also adversely affect the rate of spermatogenesis [33].
- Follicle stimulating hormone (FSH) stimulates both the production of androgen binding protein by Sertoli cells, and the formation of the blood-testis barrier. Androgen binding protein is essential for concentrating testosterone in levels high enough to initiate and maintain spermatogenesis. 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 follicle stimulating hormone will increase the production of spermatozoa by preventing the apoptosis of type A spermatogonia [33].
- Seminiferous epithelium is sensitive to elevated temperature in humans and will be adversely affected by high temperatures [33].

CAUSES OF SPERM CHROMOSOMAL DISORDERS

The causes of chromosomal disorders are actually not well defined. Evidence has been presented to implicate such things as ionizing radiation, autoimmunity, virus infections and chemical toxins in the pathogenesis of certain disorders. It's easy to understand how, for example, radiation could break DNA and lead to deletions [34] (Matrin, 1996). Most cases of simple aneuploidy - monosomy or trisomy - are likely due to meiotic non-disjunctions. X chromosome monosomy (Turner’s syndrome) is the only lesion compatible with life; while other chromosome monosomy are not survive, and can be seen frequently in aborted material. That is mean; cells should contain at least one X chromosome for survival. On the other hand, chromosome trisomy is commonly seen; and can affect both sex chromosomes (XXX, XXY, XYY), and autosomal chromosomes (13, 18, 21) [35]. These are errors made in chromosome segregation during meiosis. If pairs of homologous chromosomes fail to separate during the first meiotic division or if the centromere joining sister chromatids fails to separate
during the second meiotic division, gametes, and hence offspring, will be produced that have too many and too few chromosomes [36].

MECHANISMS OF OTHER TYPES OF CHROMOSOME ANOMALIES

DNA is continually subjected to damage, and repair. Double-strand breaks (DSBs) can arise normally during DNA replication in meiosis, where human cells are thought to repair ~10 breaks per cell cycle. Multiple enzymes and proteins contribute to this process, so mutation/s of these proteins and/or enzymes could be lethal to cells or embryo. DNA DSBs rejoining or recombination is the fundamental mechanism for genomic repair.

Non-homologous end joining (NHEJ) is another pathway for DSBs repair. NHEJ can result in multiple chromosomal rearrangements; for example, intra-chromosomal deletion if rejoining occurred following the process of DSB. Also, reciprocal translocation may occur if ligation of two DNA ends located on non-homologous chromosomes took place. In higher eukaryotes, crossovers between homologous chromosomes are essential for proper disjunction of homologues during meiosis.

Therefore, failures of performing DSBs, and/or DSB repair can result in random disjunction of homologous chromosomes, and thus chromosome aneuploidy will result. Taken together, multiple forms of chromosomal aberration could arise spontaneously in meiosis during foetal development, such as loss of heterozygosity, unequal chromatid exchanges, or non-allelic exchanges [37].

Uniparental disomy (UPD) refers to the situation in which both copies of a chromosome pair have originated from one parent. In humans, it can result in clinical conditions by producing either homozygosity for recessive mutations or aberrant patterns of imprinting. Furthermore, UPD is frequently found in conjunction with mosaicism for a chromosomally abnormal cell line, which can also contribute to phenotypic abnormalities. It appears that errors in transmission of a chromosome from parent to gamete and during early somatic cell divisions are remarkably common, but that embryo and cell selection during early embryogenesis help to ensure the presence of a numerically balanced chromosome complement in the developing fetus. UPD is also likely to occur within a portion of cells in all individuals simply as a consequence of somatic recombination occurring during mitotic cell divisions. This can be an important step in cancer development as well as a contributing factor to other late onset diseases. The following diagram showing the way by which UPD can occur [38].

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