# INTRODUCTION

The Ancient Egyptian papyri (2000 BC) says, "Man is the source of life, through his seeds and woman is a reservoir of these seeds".

The classic definition of infertility is the absence of conception after 12 months of regular, unprotected intercourse ***(Evenson et al., 2002)***.

The (WHO) definition of infertility is the absence of conception after 24 months of unprotected intercourse ***(Evenson et al., 2002)***.

Pregnancy rates by intercourse in normal couples are approximately 20–25% per month, 75 % by six months, and 90% by one year ***(Lipshultz et al., 2009)***.

Etiology of 20% of cases of infertility is attributed to purely male factor etiology, while an additional 30% to 40% involve both male and female factor pathology ***(Donohue et al., 1990)***.

The goal of the infertility evaluation is to cause a successful pregnancy in the safest, most natural, expeditious, and cost-effective manner possible ***(Sabanegh and Agarwal, 2012)***.

Evaluation of infertility require a methodic approach involving a comprehensive medical history, review of systems,

targeted physical examination and basic laboratory tests. An effective initial approach should be rapid, cost-effective, and non-invasive ***(Kolettis and Sabenegh, 2001)***.

According to the classic definition of infertility the evaluation is deferred till 12 months of unprotected intercourse.

However, infertility evaluation can be recommended before 1 year if male infertility risk factors are known to be present (such as a history of bilateral cryptorchidism), female infertility risk factors are suspected (including female age older than 35 years) or the couple questions the male partner's fertility potential. Early evaluation provides early identification and correction of factors that may reduce fertility, as well as reassurance of anxious couple ***(Evenson et al., 2002)***.

The basic test to evaluate a man's fertility is semen analysis. Other tests include: Post-Ejaculatory Urine Sample, Blood Tests, Ultrasound, and Sperm Penetration Tests ***(Levine et al., 2008)***.

Initial male factor evaluation may suggest the need for more advanced evaluation including additive semen, genetic, endocrine, or radiologic tests to arrive at the correct diagnostic and treatment plan ***(Evenson et al., 2002)***.

A new category of investigation for cases of persistent infertility is the detection of male chromosomal abnormalities

by complete DNA sequencing of a patient's Y chromosome which is the gold standard test for genetic mutation that detects Y chromosome microdeletion ***(Evenson et al., 2002)***.

Medical treatment of male infertility is indicated when a specific contributing factor that is potentially amenable to attempts at medical treatment is identified. This routinely includes the recommendation to remove any environmental toxins or drugs affecting fertility potential and management of endocrine abnormalities by administration of a deficient hormone or blocking an excessively secreted hormone ***(Brugh et al., 2003)***.

Surgical management of male infertility has evolved and expanded over years leading to more precise diagnosis and tailored treatments with diminished morbidity and greater success.

Surgeries for male infertility are divided into four major categories: (i) diagnostic surgery; (ii) surgery to improve sperm production; (iii) surgery to improve sperm delivery; and (iv) surgery to retrieve sperm for use with *in vitro* fertilization and intracytoplasmic sperm injection (IVF–ICSI) ***(Diamond, 2009)***.

Assisted reproductive techniques (ART) have become increasingly popular for the management of idiopathic male infertility, unexplained infertility, or in cases in which no therapy is available nor has effectively resulted in conception.

These techniques involve the manipulation of sperm, ova, or both in an attempt to improve the chances of conception ***(Sabanegh and Agrawal, 2012)***.

Retrieval of sperms for ART can be done by many techniques.

Percutaneous epididymal sperm aspiration (PESA) for intracytoplasmic sperm injection offers a relatively quick, minimally invasive and inexpensive method for sperm retrieval in patients with obstructive azospermia. Epididymal sperm offers the advantage of great maturity and motility relative to testicular sperm ***(Buffat et al., 2006)***.

Testicular sperm aspiration (TESA) performed under local anesthesia or open epididymal approach for sperm retrieval can be used for the occasional cases where insufficient quantity of sperm is obtained by PESA.

Microscopic epididymal sperm aspiration (MESA) is a new efficient technique but requires an operating microscope and proficiency in micro surgical skills ***(Diamond, 2009).***

However, comparison between IVF–ICSI using sperm retrieved from the epididymis *vs.* testis has not shown significantly different fertilization or embyo transfer rates ***(Pasqualotto et al., 2002)***.

Microscopic epididymal sperm aspiration (MESA), requires an operating microscope and proficiency in micro surgical skills. It is appropriate for men who have unreconstructable epididymal or vasal obstruction or in the setting of multiple prior surgeries and extensive scarring ***(Robinson et al., 2010)***.

Inspite of all of these methods and techniques of treatment there is no current treatment available for most types of male infertility. For example, there is no known treatment for cases in which the sperm-producing structures of the testes have been severely damaged or abnormal ***(Cochrane, 2007).***

# AIM OF THE WORK

To spotlight the recent approaches used for management of male infertility.

# SPERMATOGENESIS

Spermatogenesis is a specialized process of DNA reduction and germ cell metamorphosis, by which male primordial germ cells called spermatogonia undergo meiosis and produce a number of cells termed spermatozoa ***(Smith, 2009).***

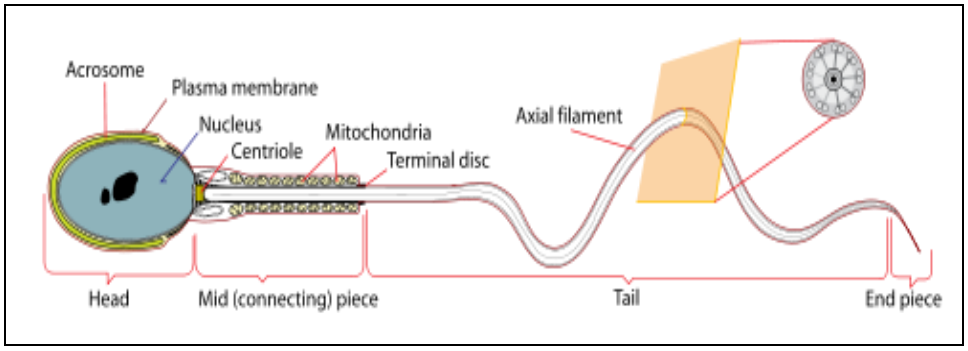


**Fig. (1):** Simplified spermatozoon diagram ***(Smith, 2009).***

The initial cells in this pathway are called primary spermatocytes. The primary spermatocyte divides into two secondary spermatocytes; each secondary spermatocyte then divides into two spermatids. These develop into mature spermatozoa, also known as sperm cells. Thus, the primary spermatocyte gives rise to two cells, the secondary spermatocytes, and the two secondary spermatocytes by their subdivision produce four spermatozoa ***(Smith, 2009).***

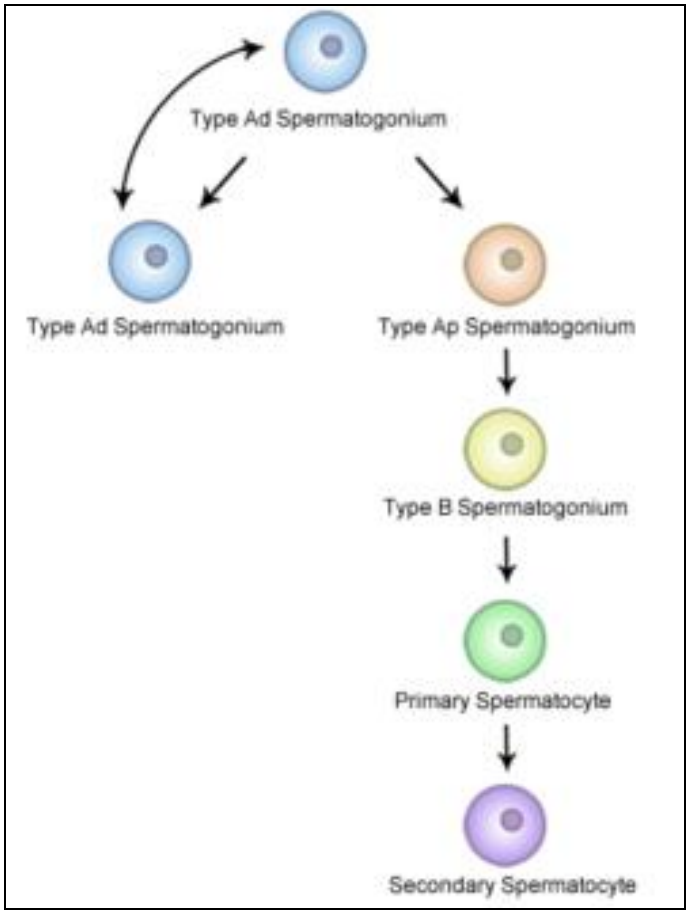


**Fig. (2):** Spermatocytogenesis ***(Smith, 2009).***

A cycle of spermatogenesis involves the division of primitive spermatogonial stem cells into subsequent germ cells. Several cycles of spermatogenesis coexist within the germinal epithelium at any one time, and they are described morphologically as stages. Spermatogenesis involves:

(1) **A proliferative phase** as spermatogonia divide to replace their number (self-renewal) or differentiate into daughter cells that become mature gametes.

(2) **A meiotic phase** when germ cells undergo a reduction division, resulting in haploid (half the normal DNA complement) Spermatids.

(3) **A spermiogenesis phase** in which spermatids undergo a profound metamorphosis to become mature Time to make and ejaculate human sperm.

Spermatozoa are the mature male. Thus, spermatogenesis is the male version of gametogenesis. In mammals it occurs in the male testes and epididymis in a stepwise fashion, and for humans takes approximately 64 days ***(Smith, 2009).***

Spermatogenesis is highly dependent upon optimal conditions for the process to occur correctly, and is essential for sexual reproduction. DNA methylation and histone modification have been implicated in the regulation of this process. It starts at puberty and usually continues uninterrupted until death, although a slight decrease can be discerned in the quantity of produced sperm with increase in age ***(Smith, 2009).***

Combined spermatocyte labeling curves for 11 individuals with normal semen quality who ingested 50 mL of 2H2O twice daily for 3 weeks. Note that new ejaculated sperm was found as soon as 42 days after ingesting the label, and that there is considerable interindividual variation in the time to make and ejaculate sperm among normal men ***(Smith, 2009).***

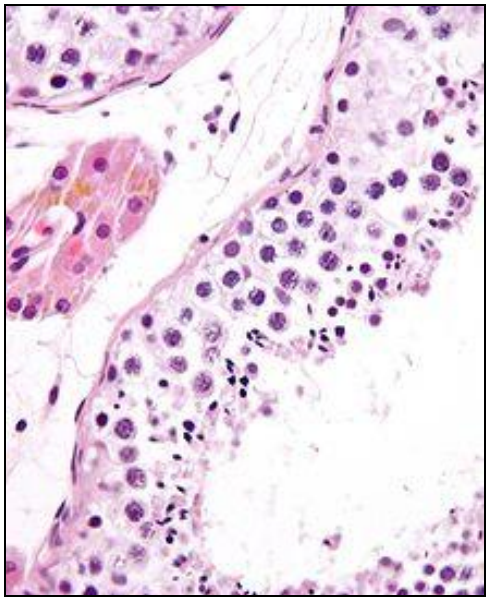

**Fig. (3):** Seminiferous tubule and sperm ***(Smith, 2009).***

If spermatogenesis is viewed from a single fixed point within a seminiferous tubule, six recognizable cellular associations or stages exist in a predictable and constant fashion in humans ***(Smith, 2009).***

In addition, there is also a specific organization of spermatogenic cycles within the tubular space, termed spermatogenic waves. The best evidence suggests that human spermatogenesis exists in a spiral or helical cellular arrangement that ensures sperm production is a continuous and not a pulsatile process ***(Smith, 2009).***

## Role of Sertoli cells

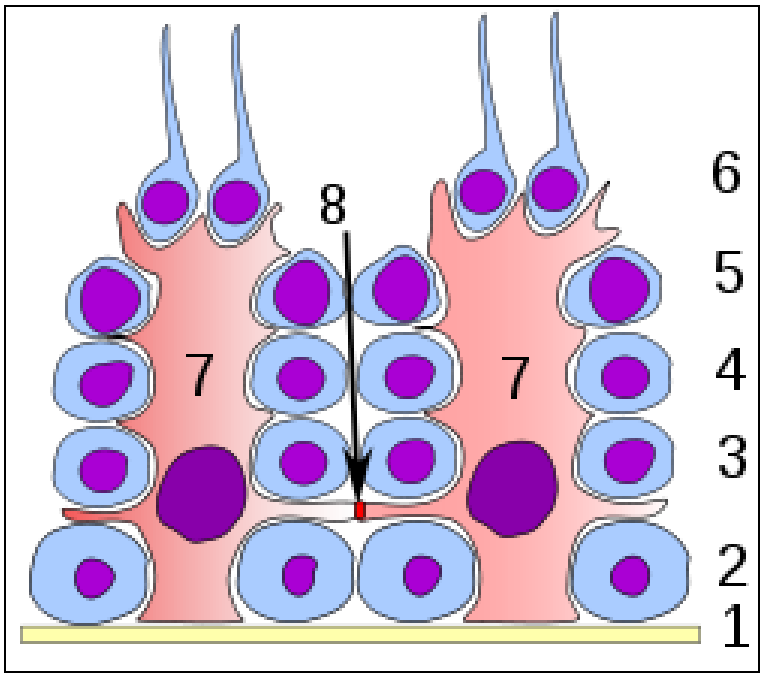


**Fig. (4)** Labelled diagram of the organisation of Sertoli cells (red) and spermatocytes (blue) in the testis. Spermatids which have not yet undergone spermination are attached to the lumenal apex of the cell ***(Pareek et al., 2007).***

**Description:** Germinal epithelium of the testicle. 1 basal lamina, 2 spermatogonia, 3 spermatocyte 1st order, 4 spermatocyte 2nd order, 5 spermatid, 6 mature spermatid, 7 Sertoli cell, 8 occlusive junctions ***(Pareek et al., 2007).***

At all stages of differentiation, the spermatogenic cells are in close contact with Sertoli cells which are thought to provide structural and metabolic support to the developing sperm cells ***(Pareek et al., 2007).***

A single Sertoli cell extends from the basement membrane to the lumen of the seminiferous tubule, although the cytoplasmic processes are difficult to distinguish at the light microscopic level ***(Pareek et al., 2007).***

Sertoli cells serve a number of functions during spermatogenesis, they support the developing gametes in the following ways:

- Maintain the environment necessary for development and maturation via the blood-testis barrier
- Secrete substances initiating meiosis
- Secrete supporting testicular fluid
- Secrete androgen- binding protein (ABP), which concentrates testosterone in close proximity to the developing gametes.
- Testosterone is needed in very high quantities for maintenance of the reproductive tract, and ABP allows a much higher level of fertility.
- Secrete hormones affecting pituitary gland control of spermatogenesis, particularly the polypeptide hormone, inhibin
- Phagocytose residual cytoplasm left over from spermiogenesis
- They release Antimullerian hormone which prevents formation of the Müllerian Duct / Oviduct.
- Protect spermatids from the immune system of the male.

***(Pareek et al., 2007).***

## Influencing factors

The process of spermatogenesis is highly sensitive to fluctuations in the environment, particularly hormones and temperature. Testosterone is required in large local concentrations to maintain the process, which is achieved via the binding of testosterone by androgen binding protein present in the seminiferous tubules. Testosterone is produced by interstitial cells, also known as Leydig cells, which reside adjacent to the seminiferous tubules ***(Lewis and Aitken, 2005).***

Seminiferous epithelium is sensitive to elevated temperature in humans and some other species, and will be adversely affected by temperatures as high as normal body temperature. The optimal temperature is maintained at 2 °C (man) below body temperature. This is achieved by regulation of blood flow and positioning towards and away from the heat of the body by the cremasteric muscle and the dartos smooth muscle in the scrotum ***(Lewis and Aitken, 2005).***

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 In addition, the male germ line is susceptible to DNA damage caused by oxidative stress, and this damage likely has a significant impact on fertilization and pregnancy ***(Lewis and Aitken, 2005).***

## Hormonal control

Hormonal control of spermatogenesis varies among species. In humans the mechanism is not completely understood, however it is known that initiation of spermatogenesis occurs at puberty due to the interaction of the hypothalamus, pituitary gland and Leydig cells. If the pituitary gland is removed, spermatogenesis can still be initiated by follicle stimulating hormone and testosterone ***(Pareek et al., 2007).***

Follicle stimulating hormone stimulates both the production of androgen binding protein by Sertoli cells, and the formation of the blood-testis barrier. Androgen binding protein is essential to concentrating testosterone in levels high enough to initiate and maintain spermatogenesis, which can be 20–50 times higher than the concentration found in blood ***(Pareek et al., 2007).***

Follicle stimulating hormone 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 ***(Pareek et al., 2007).***

The hormone inhibin acts to decrease the levels of follicle stimulating hormone ***(Pareek et al., 2007).***

The Sertoli cells themselves mediate parts of spermatogenesis through hormone production. They are capable of producing the hormones estradiol and inhibin. The Leydig cells are also capable of producing estradiol in addition to their main product testosterone ***(Pareek et al., 2007).***