INTRODUCTION

Testosterone plays a key role in the development of male reproductive tissues such as the testis and prostate as well as promoting secondary sexual characteristics such as increased **muscle**, bone mass, and the growth of body hair **(Browne, 2002***)*

Testosterone effects can be classified as virilizing and anabolic, though the distinction is somewhat artificial, as many of the effects can be considered both.

- *Anabolic effects* include growth of muscle mass and strength, increased **density and** strength, and stimulation of linear growth and bone maturation.
- *Androgenic effects* include maturation of the sex organs, particularly the penis and the formation of the scrotum in the fetus, and after birth (usually at puberty) a deepening of the voice, growth of the beard and axillary hair. Many of these fall into the category of male secondary sex characteristics. **(Brown, 2002)**

The *prenatal androgen effects* occur during two different stages. Between 4 and 6 weeks of the gestation.

- Genital virilization (midline fusion, phallic urethra, scrotal thinning and rugation, phallic enlargement); although the

role of testosterone is far smaller than that of dihydrotestosterone.

- Development of prostate and seminal vesicles.

During the second trimester, androgen level is associated with gender formation **(Swaab et al., 2009)** This period affects the femininization or masculinization of the fetus and can be a better predictor of feminine or muscular behaviors such as sex typed behavior than an adult's own levels **(Browne, 2002)**

In the first weeks of life for male infants, testosterone levels rise. The levels remain in a pubertal range for a few months, but usually reach the barely detectable levels of childhood by 4-6 months of age (**Corbier et al., 1992)**. The function of this rise in humans is unknown. It has been speculated that "brain masculinization" is occurring since no significant changes have been identified in other parts of the body **(Dakin et al., 2008**) Surprisingly, the male brain is masculinized by testosterone being aromatized into estrogen, which crosses the blood-brain barrier and enters the male brain, whereas female fetuses have alpha-fetoprotein which binds up the estrogen so that female brains are not affected **(Kalat et al., 2009)**.

Testosterone is secreted by the testicular Leydig cells and, to a minor extent, by the adrenal cortex. In premenopausal

women, the ovaries are the main source of testosterone with minor contributions by the adrenals and peripheral tissues. After menopause, ovarian testosterone production is significantly diminished. Testosterone production in testes and ovaries is regulated via pituitary-gonadal feedback involving luteinizing hormone (LH) and, to a lesser degree, inhibins and activins **(Morley et al., 2000).**

Most circulating testosterone is bound to sex hormone-binding globulin (SHBG), which in men also is called testosterone-binding globulin. A lesser fraction is albumin bound and a small proportion exists as free hormone. Historically, only the free testosterone was thought to be the biologically active component. However, testosterone is weakly bound to serum albumin and dissociates freely in the capillary bed, thereby becoming readily available for tissue uptake. All non-SHBG-bound testosterone is therefore considered bioavailable.

Decreased testosterone levels indicate partial or complete hypogonadism. Serum testosterone levels are usually below the reference range. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure **(Dumesic et al., 1995**).

Primary testicular failure is associated with increased luteinizing hormone (LH) and follicle stimulating hormone

(FSH) levels, and decreased total, bioavailable, and free testosterone levels Secondary/tertiary hypogonadism, also known as hypogonadotrophic hypogonadism, shows low testosterone and low, or inappropriately "normal, " LH/FSH levels.

Increased testosterone levels:

- In prepubertal boys, increased levels of testosterone are seen in precocious puberty. Further workup is necessary to determine the cause (s) of precocious puberty.

- In adult men, testicular or adrenal tumors or androgen abuse might be suspected if testosterone levels exceed the upper limit of the normal range by more than 50% **(Kalat et al., 2009**).

AIM OF THE WORK

The aim of this work was to determine a normal reference ranges of total and free serum testosterone in normal Egyptian male neonates. Also, measurement of stretched penile length was done and correlated to each of weight, length and free & total testosterone level.

DEVELOPMENT OF MALE GENITAL SYSTEM

The development of the reproductive system is a part of the prenatal development, and concerns the sex organs. Because its location to a large extent overlaps the urinary system, their development can also be described together as the development of the urinary and reproductives organs which are developed from the intermediate mesoderum **(Larsen, 2001)**.

The reprodctive organs are developed from the intermediate mesdoderm. The permenant organs of the adult are preceded by a set of structurs which are purely emberyonic, and which with the exception of the ducts disappear almost entirely before the end of fetal life. These embryonic structures are the wolffian and Mullerian ducts. The Wolffian duct remains as the duct in males, and the Mullerian as that of the female (**Larsen, 2001**).

The genital ridge:

The gonads appear on the fifth week as a pair of longitudinal ridges located on the medial sides of mesonephros between it and dorsal mesentery. They develop due to proliferation of the coelomic epithelium together with condensation of the underlying mesoderm. The coelomic

epithelium proliferates and its cells penetrate the underlying mesoderm forming a number of solid cords, the primary sex cords. In both male and female embryos, these cords are connected to the surface epithelium. Sex cords appear in the 8th week in male **(Sadler, 2006)**.

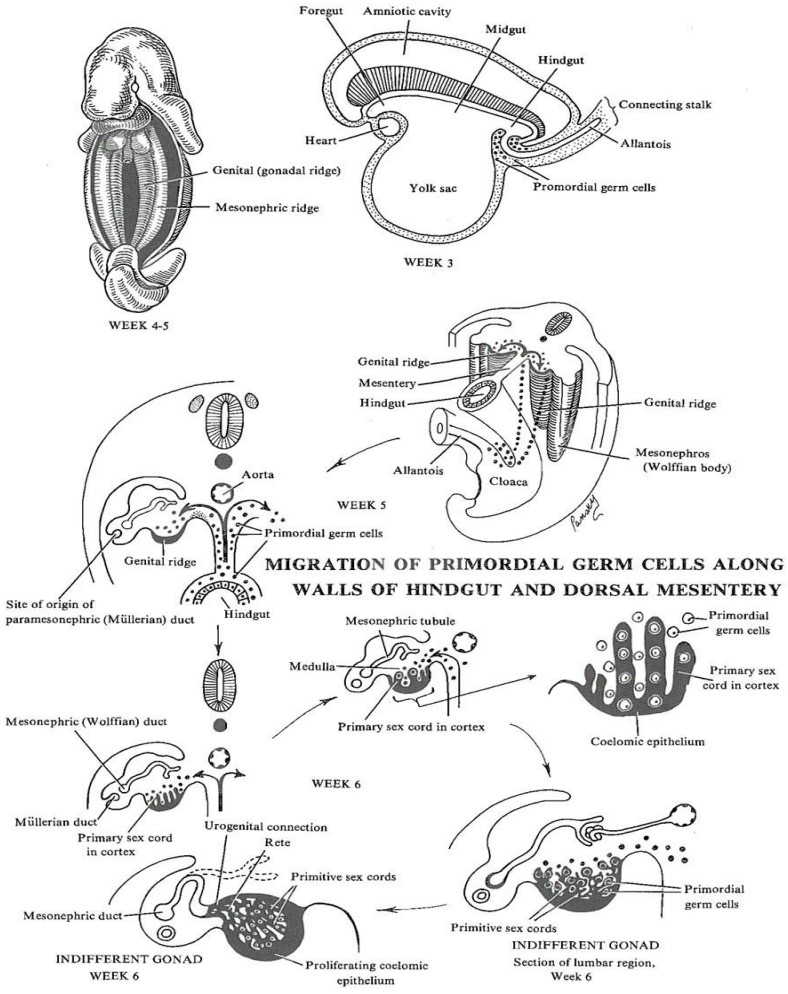

Figure (1): Migration of primoridal germ cells along walls of hindgut and dorsal mesentery **(Salder, 2006).**

The germ cells:

In human embryos, the primordial germ cells appear at an earlier stage (4^{th} week) of development among the endoderm of the wall of yolk sac close to allantois. This part of the yolk sac becomes incorporated in hindgut after folding. The germ cells do not appear in the genital ridges until the sixth week of development, they migrate by amoeboid movement along the dorsal mesentery of hindgut to reach the genital ridges in the sixth week, where they become incorporated in the sex cords, if the germ cells fail to reach ridges, the gonads do not develop. Hence, the primordial germ cells have an inductive influence on the development of the gonads **(Moore et al,2000)**.

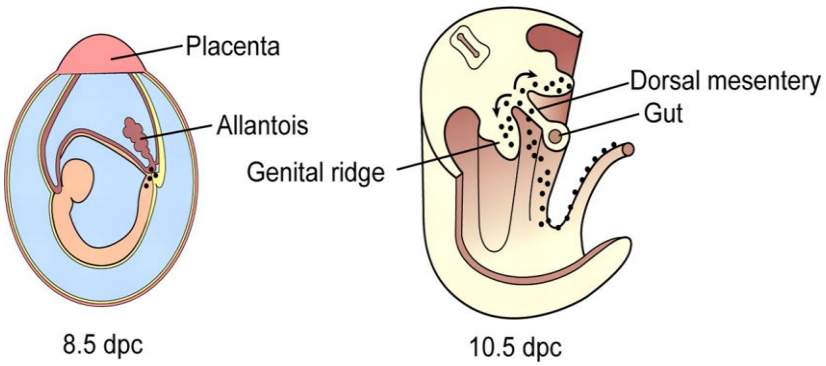

Figure (2): The migratory pathway of primordial germ cells. Schematic representation of the localization of PGCs (black dots) at the base of the allantois around the hindgut pocket in an 8.5 dpc mouse embryo (*left*) and their migration along the hindgut, dorsal mesentery, and into the genital ridges in a 10.5 dpc embryo (*right*) (**Bendel-Stenzel M et al., 1998).**

Development of the gonads:

If the embryo is a male, the primordial germ cells carry XY sex chromosomes. Under influence of the gene on the Y chromosome, which encodes the Testis-Determining Factor (TDF), the undiffrentiated gonad develops into a testis **(Sadler, 2006)**.

The TDF induces the primitive sex cords to proliferate and penetrate deeply into medulla to form the testis or medullary cords. Near the hilum of the gonads, the cords break and anastomose into a network called rete testis. Later, a dense layer of fibrous connective tissue, the tunica albuginea develops from the surrounding mesoderm, isolating the testis cords from the surface epithelium. The development of a dense tunica albuginea is the characteristic diagnostic feature of testicular development **(Moore et al., 2000)**.

In the fourth month, the testis cords become horseshoe-shaped and develop into the seminiferous cords that contain two kinds of cells, perimodial germ cells which are endodermal in origin and supporting cells which are derived from the surface epithelium (mesodermal) which constitute most of the seminiferous epithelium in the fetal testis **(Sadler, 2006)**.

The interstitail cells of leyding develop from the mesoderm located between the cords. During the eighth week, these cells begin to produce testosterone, which induces mascline differntiation of the mesonephric ducts and the external

genitalia. Testosterone production is stimulated by the chorionic gonadotophins. In addition to testosterone the fetal testes produce mullerian inhibiting factor (MIF), which is produced by Sertoli cells. MIF suppresses development of the paramesonephric ducts (**Moore et al., 2000**).

The cords remain solid until puberty, then become canlized to form the seminiferous tubles. Once the semineiferous tubules and rete testis are canalized, they establish an open communucation with the mesonephric tubules that form the vasa efferentia (**Larsen, 2001**).

During later development, the surface epithelium flattens to form the mesotheliumon the external surface of the adult testis (**Larsen, 2001**).

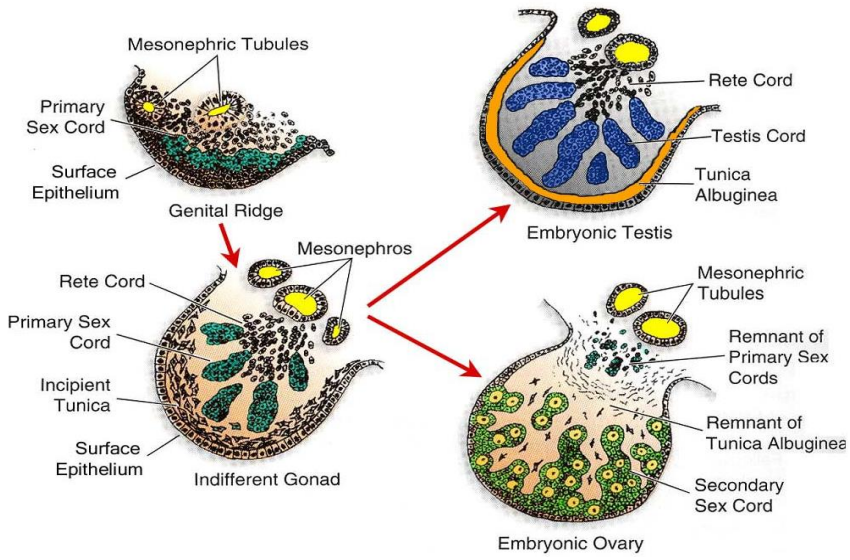

Fig. (3): Development of mamalian testies and ovary **(Sadler, 2006).**

Descent of the testes:

The testis develops on the posterior abdominal wall opposite the first lumbar vertebra; later, it descends to the scrotum pulling after it the testicular artery of the abdominal aorta. The testis and the mesonephros are attached to the posterior abdominal wall by the urogenital mesentery **(Moore et al., 2000)**.

Opposite the testis is the mesotestis or mesorchium, carnial to the testis is the suspensory ligament of the testis, which degenerates, caudal to the testis, it becomes fibromuscular forming the gubernaculum testis. In the inguinal region, the gubernaculum passes obliquely through the developing anterior abdominal wall to reach the genital (scrotal) swelling, the gubernaculum guides the testis during its descent. The testis descends in two stages; internal descent and external descent. In the internal descent, the testis descends till it reaches the deep inguinal ring in the 3rd month. This stage of decent is caused by relative elongation of the posterior abdominal wall in an upward direction, without corresponding elongation of the gubernaculum. Thus, it is a growth dispalcement rather than active migration. The external descent through the inguinal canal starts in the 7th month and reaches the scrotum in the 8th month under the effect of gonadtrophins and androgens, increased intra-abdominal pressure by the growing viscera and a shortening of

the gubernaculum due to atrophy of its fibrous elements and contraction of its muscular elements **(Sadler, 2006)**.

The processus vaginalis is a pouch derived from the coelomic cavity on each side of the midline. It penetrates the anterior abdominal wall, running ventral to the gubernaculum to reach the genital swellings. It pushes the layers of body wall forming the inguinal canal. The testis descends dorsal to and outside the processus vaginalis. The proximal part is obliterated after birth to form the vestige of the processus vaginalis peritonii. The distal part is invaginated by the testis to form the visceral and parietal layers of the tunica vaginalis **(Sadler, 2006)**.

In addition to being covered by peritoneal layers derived from the processus vaginalis, the testis becomes ensheathed in layers derived ftom the anterior abdominal oblique wall through which it passes. Thus, the transverse fascia forms the internal spermatic fascia, the internal abdminal oblique muscle gives rise to the cremasreric fascia and muscle, and the external abdominal oblique muscle forms the extenal spermatic fascia. The transverses abdominis muscle does not contribute alayer, since it arches over this region and does not cover the path of migration (**Moore et al., 2000**).

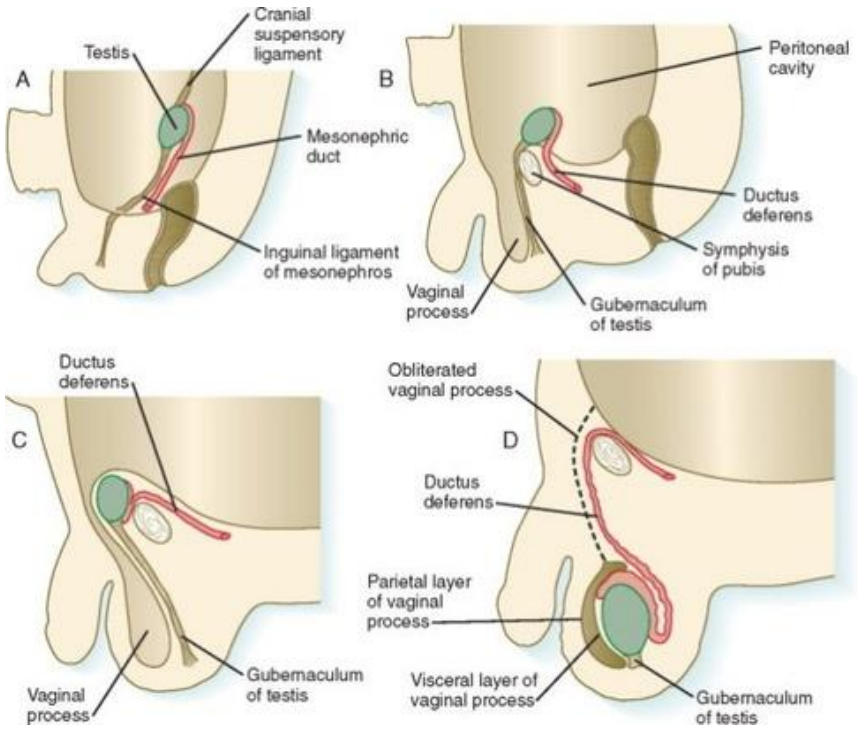

Figure (4): Desent of the testis. A. during the second month. B. in the middle of the third month. Peritoneum lining the coelmic cavity evaginates into scrotal swelling, where it forms the vaginal process (tnnica vaginalis). C. in the seventh month. D. shortly after birth. E.Scanning electron micrograph of a mouse embryo showing the primtive gonad (G), meonephric duct (arrowheads), and gubernaculum (arrows) **(Sadler, 2006).**

Wolffian duct:

It is present in the outer part of the intermediate mesoderm, immediately under the ectoderm, in the region from the fifth cervical segment to the third thoracic segment and extends caudally, fusing successively from before backwards to form the pronephric duct. This continues to grow caudalward until it opens into the ventral part of the cloaca; beyond the

pronephros. Thus, the Wolffian duct is what remains of the pronephric duct after the atrophy of the pronephros **(Sadler, 2006)**.

The mesonephric tubules:

The upper tubules form the superior aberrant ductule which joins the rete testis. The middle tubules from 6 to 12 forms the vasa efferentia and head of epididymis. The lower tubules form the inferior aberrant ductule which opens into the duct of epididymis plus the paradidymis which does not open into either the duct of epididymis or the rete testis **(Moore et al,2000)**.

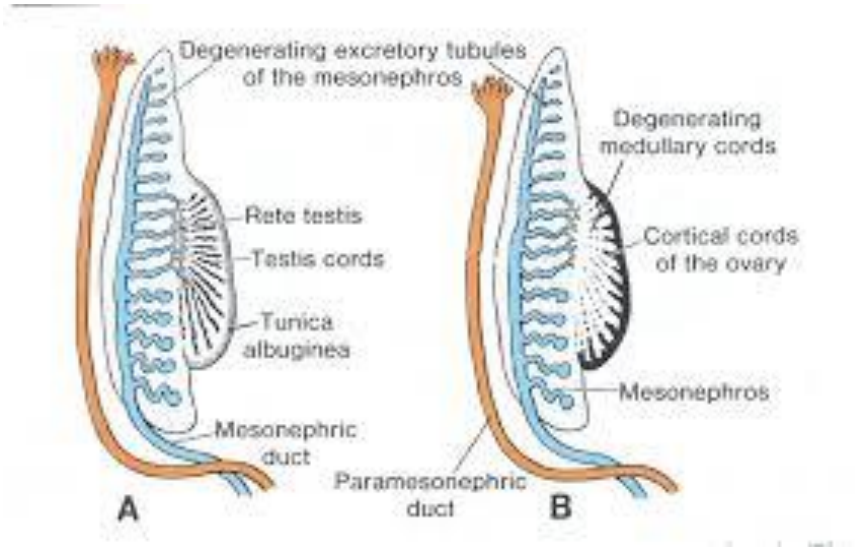

Figure (5):genital ducts in the sixth week in the male (A) and female (B). the mesonephric and paramesonephric ducts are present in both. Note the excretory tubule of the mesonephrons and their relation yo the developing gonad in both sexes **(Sadler, 2006).**