"GUBERNACULUM ANOMALIES"- EMBRYOLOGICAL BASIS AND ITS CLINICAL SIGNIFICANCE

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ABSTRACT

As the scrotum and labia majora form in males and females, respectively; the gubernaculum aids in the descent of the gonads. This being both testes and ovaries. The testes would descend to a greater degree than the ovaries and thus passing through the inguinal canal. The gubernaculum connects the gonad to the inguinoscrotal region and is involved in testis descent. In the male fetus it rapidly develops, whereas in the female fetus, development is lacking.

Introduction

The paired Gubernaculum are embryonic structures which begin as undifferentiated mesenchyme attaching to the caudal end of the gonads (testes in males and ovaries in females) [1]. As the scrotum and labia majora form in males and females, respectively, the gubernaculum aids in the descent of the gonads (both testes and ovaries). The testis descends to a greater degree than the ovary and ultimately passes through the inguinal canal. Testicular descent is a complex process that only occurs in mammals. The location of the scrotum varies between species, as does the scrotal development. In the human, however, baby boys are born with fully descended testes in a pendulous scrotum, which reaches half way down the thigh. The laxity of the tissues is related to prenatal hormones, as a few weeks later the scrotum appears smaller. Postnatal testosterone levels are high between 2–4 months, but after this the scrotum shrinks and the testes are quite retractile until the onset of puberty in the second decade [2]. Given the complexity of the developmental process, it is no surprise that undescended or cryptorchid testes are common anomalies. Orchidopexy is one of the most common operations in childhood, and this is a significant financial as well as emotional burden for parents. Long-term outcomes after orchidopexy also remain problematic, with decreased fertility and increased risk of testicular cancer still serious public health issues. [1-3]

Up to the 7th week the internal genital organs in both sexes on both sides consist of two canal systems: a)The mesonephric duct and the mesonephric tubules, which first form on the dorsal side of the nephrogenic cord at the level of the 9th somite in the form of solid, cellular mesenchymal cords. They detach themselves from the nephrogenic cord and are located below the coelomic epithelium that is thickened at this place. b) The paramesonephric duct (Müller) is formed from a finger-shaped invagination of the coelomic epithelium on the upper pole of the mesonephros.

Here, it forms a funnel that opens into the coelomic cavity (future ampulla of the fallopian tube).

The paramesonephric duct invades on both sides - laterally to the mesonephric duct - into the mesonephros and grows in the caudal direction. At the lower end of the mesonephros the paramesonephric duct crosses over the mesonephric duct in order to grow further medially. There, the paramesonephric ducts meet on both sides and fuse to form a canal (the future uterus).They then push on the urogenital sinus, forming a small protrusion, the paramesonephric tubercle.[3-4]

Incidence

Because the testis descends into the scrotum during the last month of pregnancy, many premature boys are delivered before the descent process is completed. Cryptorchidism occurs in about 3% of full term boys and 30% of boys born at 30 weeks of gestational age. Most undescended testes will spontaneously descend within the first six months of life. [4]

Ontogenesis for the normal development gubernaculum in males:

Normally, the testis descent is thought to have 2 phases:
1)Transabdominal descent - dependent on insulin-like hormone 3 (INSL3).
2)Inguinoscrotal descent - dependent on androgens.

The regulation of testis descent is still being investigated and several different factors have been identified that may have roles in descent. The first stage of testicular descent occurs 10–15 weeks of gestation with the testes moving to the inguinal region.[4-5]

The gubernaculum (gubernaculum Hunteri) is the caudal inguinoscrotal ligament that connects the testis to the lower abdomen. The cranial suspensory ligament (mesonephric ligament) is the cranial ligament that connects the testis to the posterior abdominal wall.[5]

Normally the testes will descend through the inguinal canal during the 9th fetal months and if they do not lie in the

scrotum by the age of one year, spontaneous later descent is unlikely. The development of the gubernaculum and much of the process of testicular descend are under the influence of fetal androgens [6]. These androgens and the interstitial cells secreting them have regressed by the 4th week after birth. Most testes will lie in the scrotum by 3 months of age. In premature babies full descent may occur up to 6 months after birth. At 3 weeks of development, the germ cells migrate from the yolk sac to the genital ridge. From the 4th to the 8th week, in male embryos with a normal sex determining region on the short arm of the Y chromosome, the germ cells coalesce to form the primordial testis [5-7]. Under the influence of human chorionic gonadotropin, the Leydig cells of the developing testis begin to secrete testosterone. At about 9 weeks of development, the labioscrotal swellings fuse to form the scrotum (see movie). Testosterone also induces development of the mesonephric (Wolfian) duct to form the epididymis, vas deferens and seminal vesicles.[7] During this stage of development, the testis moves from the genital ridge across the pelvis to lie at the internal inguinal ring.[7-9]

The processus vaginalis appears at about 13 weeks of development as an outpouching of the parietal peritoneum. This developing tunnel moves medial and caudal between the internal and external abdominal oblique muscles and into the scrotum [9]. The testis stays at the opening of the processus vaginalis, the internal inguinal ring, for 10 to 12 weeks. This herniation of the patent processus is at least partially dependent on the abdominal wall musculature to generate an elevated intra-abdominal pressure [9-10]. If the abdominal muscles cannot increase intra-abdominal pressure, the patent processus vaginalis may not progress through the inguinal canal and the testis may not descend into the scrotum [10]. At 26 to 36 weeks of development the epididymis precedes the testis into the processus vaginalis. These structures descend into the scrotum and become fused with the posterior layers of the scrotum, providing an anchor which prevents the testis from rotating. At 37 to 40 weeks (full term), the processus vaginalis closes, eliminating any communication between the peritoneum and the inguinal canal or scrotum [11]. Between the 3rd month of pregnancy and its end the testes become transferred from the lumbar area (ventro-medial to the mesonephros) into the future scrotum. This transfer is due to a combination of growth processes and hormonal influences [12]. The gubernaculum testis also plays a decisive role in this phenomenon.

The gubernaculum testis arises in the course of the 7th week from the lower gubernaculum, after the mesonephros has atrophied. Cranially it has its origin at the testis and inserts in the region of the genital swelling (future scrotum) [11-12].

At the same time, at the inguinal canal along the lower gubernaculum, an evagination of the peritoneum arises, the vaginal process, on which the testes will slide through the inguinal canal [13]. In that the vaginal process lengthens downwardly, it takes the muscle fibers of the oblique internal muscle and the transverse muscle with it. The muscle fascia of the transverse muscle is the innermost layer and in the scrotal region, it forms the internal spermatic fascia of the spermatic cord and the scrotum. The muscle layer of the musculus cremaster is formed from fibers of the oblique internal and transverse muscles [14]. Externally, the external spermatic fascia is formed from the superficial aponeurosis of the oblique external abdominal muscle [13-14].

The region, where the testes pass through the abdominal wall, is called the inguinal canal.

Between the 7th and the 12th week the gubernaculum shortens and pulls the testes, the deferent duct and its vessels downwards. Between the 3rd and 7th month the testes stay in the area of the inguinal canal so they can enter into it. They reach the scrotum at roughly the time of birth under the influence of the androgen hormone[14-15].

While in the first year of life the upper part of the vaginal process becomes obliterated, there remains only the peritoneo-vaginal ligament. The lower portion persists as the tunica vaginalis testis, which consists of a parietal and a visceral layer [15].

The differentiation of the male sex organ canals is influenced by the testosterone hormone that is produced from the 8th week in the fetal testis by Leydig's interstitial cells.

Two phenomena mark the differentiation of the canals of the internal male sex organs:
- The atrophy of the paramesonephric duct (Müller)
- The development and differentiation of the mesonephric duct (Wolff)

The mesonephric duct (Wolff) atrophies cranially and leaves behind only the epididymal appendage as an embryonic rudiment. On both sides the parts of the mesonephric duct, which lie across from the testes, form the epididymis. The testis and the epididymis of both sides are partially enveloped by the tunica vaginalis testis (serous bilaminar membrane with a periorchium [= outermost layer] and epiorchium [= inner layer]). In the part of the epididymis are end the efferent ductules [15-16]. They originate from the mesonephric tubules and so form the beginning of the epididymis. Immediately afterwards it coils tightly and finally goes into the lower part of the epididymis (its tail) and over into the deferent duct. This is a musculo-epithelial tube that, during ejaculation, dispatches the sperm cells from the epididymis into the urethra [17].

In the male fetus - between the 8th and 11th week - the paramesonephric duct atrophies due to the effects of the antimüllerian hormone (AMH), which is formed by precursors of Sertoli's supporting cells (cells that surround the primordial germ cells and come from the primitive gonadal cords) [17-18]. Despite the effects of this hormone, embryonic remnants of the paramesonephric duct remain behind in males. These are the testicular appendage at the cranial pole of the testis and the prostatic utricle at its caudal pole [18].

The accessory sexual glands originate from two epithelial tissues. They either come from the epithelial mesodermal origin of the mesonephric duct (Wolff) or from the epithelial endodermal origin of the urogenital sinus [19].

The seminal vesicle differentiates itself during the 12th week from a protrusion on the deferent duct, near where it opens at the back wall of the urogenital sinus (future prostatic part of the urethra) [18-20]. They thus have a mesodermal origin. These paired glands produce a viscous, fructose-rich secretion that serves as a source of energy for the sperm cells. The portion of the mesonephric duct that lies between the junction of the seminal vesicle and the prostatic part of the urethra is called the ejaculatory duct [20]. Between the two ejaculatory duct junctions the prostatic utricle (remainder of the paramesonephric duct) has its opening. This location is called the seminal colliculus [21].

The prostate develops from a protrusion on the dorsal wall of the prostatic part of the urethra during the 12th week. The prostate's glandular epithelium develops, therefore, from cells that have their origin in the endoderm, while the stroma and smooth muscle develops from cells with a mesodermal origin - under the inducing influence of DHT [22-23].

The glands become active after the 15th week and surround the two ejaculatory ducts and the prostatic utricle as well as the prostatic part of the urethra [23].

Over the course of the 12th week and parallel to the development of the prostate, bulbourethral (Cowper's) and urethral (Littre's) glands form, originating in pairs of endodermal protrusions of the spongy part of the urethra, which follow from the prostatic membranous parts [24]. Finally, the seminal fluid is augmented by secretions from the seminal vesicle, the prostate, the bulbourethral and urethral glands [23-25].
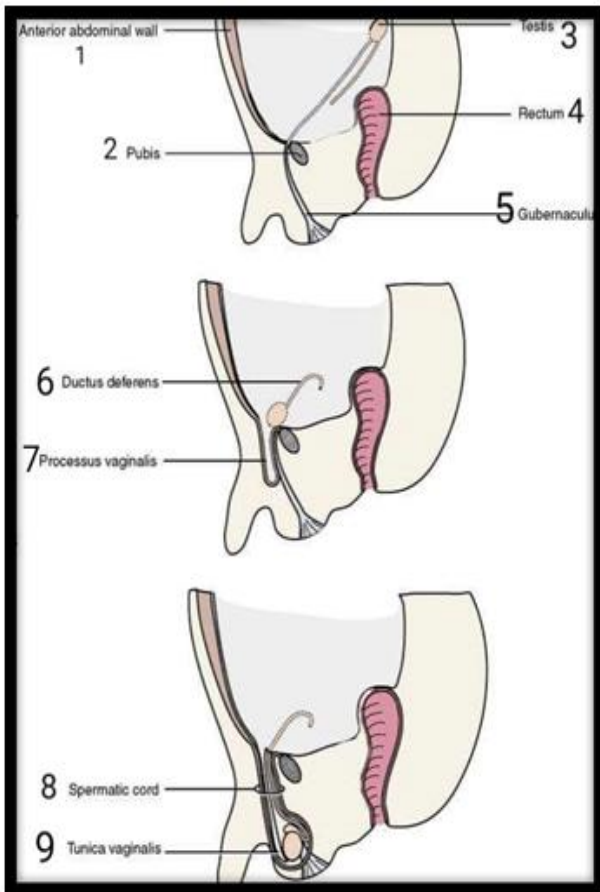

Fig 1. Development and descent of testes and formation of spermatic cord. A- Two months in utero. B- Three months in utero. C-At birth.
1- anterior abdominal wall. 2-pubis. 3-testis. 4-rectum. 5-gubernaculum. 6-dctus deferens. 7-processus vaginalis. 8—spermatic cord. 9-tunica vaginalis.

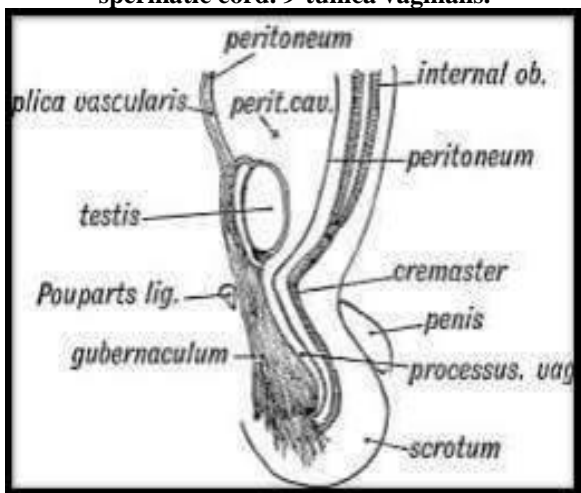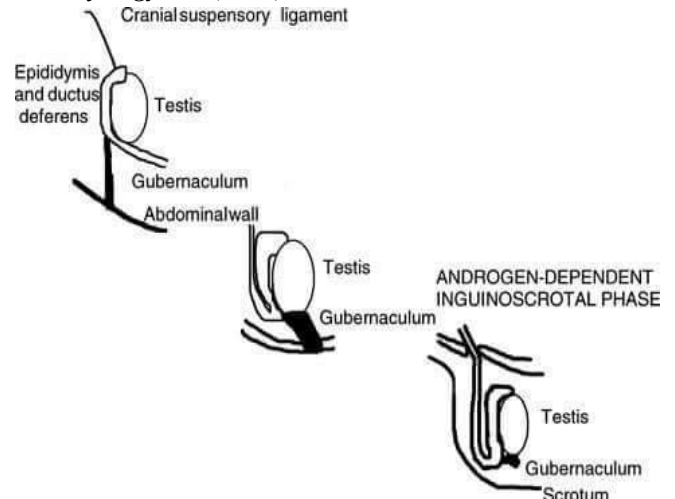**Fig 2. Formation of the gubernaculum testis.**

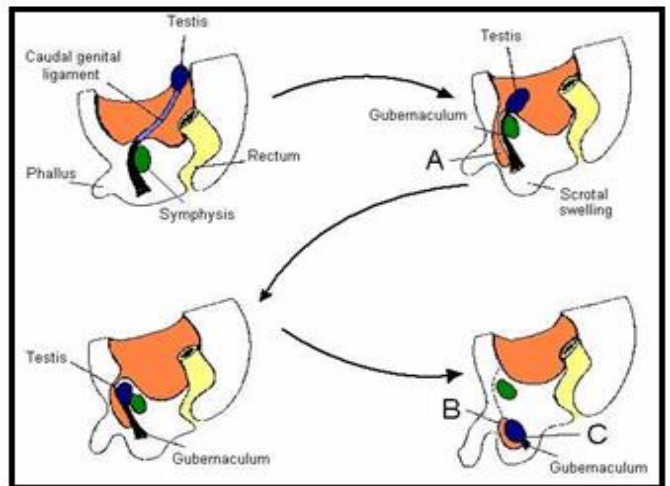**Fig 3. Schematic figure of the phases of testicular descent.**

Fig 4. Schematic diagram showing the normal descent of testis.

Ontogenesis of normal development of gubernaculum in females

Just as in the male, there is a gubernaculum in the female, which effects a considerable change in the position of the ovary, though not so extensive a change as in that of the testis [26]. The gubernaculum in the female lies in contact with the fundus of the uterus and adheres to this organ, and thus the ovary can only descend as far as to this level [25-26]. The part of the gubernaculum between the ovary and the uterus ultimately becomes the proper ovarian ligament, while the part between the uterus and the labium majorus forms the round ligament of the uterus [27]. A pouch of peritoneum analogous to the processus vaginalis in the male accompanies it along the inguinal canal: it is called the canal of Nuck. The ovaries are also moved slightly - from the location where they are engendered in the middle of the abdomen to the pelvis. This migration results partially from the massive growth of the upper abdominal region in comparison with the pelvic area [28]. The influence of the lower gubernaculum in this process is not entirely clear [27-28].

The mesonephros atrophies in the 7th week. Only the ovary with its mesovarium medially and the paramesonephric duct (later fallopian tube) with the mesosalpinx lateral to the meso of the original urogenital tract remain [29]. They are connected with the dorsal abdominal wall of the embryo via the meso of the original urogenital tract. Through atrophy of the mesonephros the upper gubernaculum connects the ovary directly with the upper rear body wall and becomes designated as the suspensory ligament of ovary [28-30].

The lower gubernaculum has its origin in the bottom side of the ovary and forms the ovarian ligament and, further down, the round ligament of uterus that reaches the genital swelling (labia majora) through the inguinal canal [30].

The nephrogenic cord is originally vertical. The fallopian tube, which forms from the upper part of the paramesonephric duct (Müller), finally takes on a horizontal position in that it is drawn medially by the joining of the lower part of the paramesonephric duct (Müller) as the uterus is being formed [31]. The ovary, which initially lies medially to the fallopian tube (paramesonephric duct) in front of the atrophying mesonephros, slides backwards as a result.

The peritoneal mesos passively follow these movements. Finally the broad ligament of uterus forms with three sections:
▪ Upper section: mesosalpinx with the fallopian tube
▪ Ventral section: mesometrium with the round ligament of uterus
▪ Dorsal section: mesovarium with the ovarian ligament

During the 7th week the canal system of the female sex organs differentiates [32]. The mesonephric duct and its tubules atrophy and out of the paramesonephric duct (Müller) arises the future fallopian tube, the uterus and the upper part of the vagina. Sometimes, a few embryonic remnants of the mesonephric duct remain in the form of the Epoophoron, the Paroohoron at the level of the mesovarium, and a row of small cysts of Gartner. Out of the upper, non-fused portion of the paramesonephric duct (Müller) arises the fallopian tube and its ampulla [31-32]. The lower section fuses after it crosses medially on both sides of the inferior ovarian gubernaculum and forms the utero-vaginal canal. The medial septum in between disappears at the end of the 3rd month [32-33].

To be observed is the development of the ligaments. The ovarian gubernaculum gets attached on the developing utero-vaginal canal there where it goes over into the fallopian tube. Above it forms the ovarian ligament and below the round ligament of uterus, which goes through the inguinal canal and inserts in the female genital swelling (labia majora) [33].

If the separating wall beyond the fusion location of the two paramesonephric ducts is not resorbed, various utero-vaginal abnormalities result. The blind end of the utero-vaginal canal forms the sinu-vaginal eminence and ends at the back wall of the urogenital sinus (SUG) [34]. The sinu-vaginal eminence becomes thicker due to epithelial proliferation and retracts, while the wall of the SUG also thickens there. These epithelial layers, which form at the lower end of the utero-vaginal canal, are known as the vaginal plate. At their cranial end they form a circular protrusion, the location of the future vaginal fornix [34-35].

Through canalization of the vaginal plate the utero-vaginal canal opens itself towards the outside. The upper 3/4 of the vagina comes from the mesoderm and the lower fourth from the endoderm [35]. The fibromuscular walling forms from the neighboring mesenchyme. The vagina is separated from the SUG by the hymen. Its origin is not entirely clear. Discussed is a passive invagination of the back wall of the SUG [35-36].

The accessory glands arise from the endoderm of the SUG:
a. The greater vestibular glands (Bartholini) are paired glands that form in the course of the 12th week from the endoderm of the SUG. The outflow canals empty sideways in the vaginal vestibule. They correspond to the bulbourethral gland (Cowper) in males.
b. The lesser vestibular glands (Skene) or paraurethral glands also form from epithelial buds (endoderm) of the SUG and

grow into the neighboring mesenchyma. They are distributed over the whole vaginal vestibule and - in males - correspond to the prostate.

In females the cranial portion of the pelvic part of the definitive SUG remains narrow and forms the female urethra, which is very short. With the progressing development the caudal portion of the pelvic part shrinks and becomes included in the phallic part (vaginal vestibule) [37]. Therein discharge the urethra and the vagina. The phallic part of the definitive SUG enlarges to become the vaginal vestibule that is caudally closed off externally by the urogenital membrane. It then tears in the course of the 7th week [36-37].
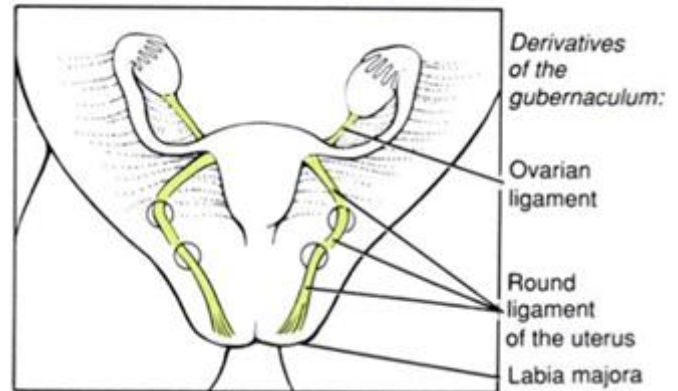

Fig 5. schematic diagram showing gubernaculum in female.

Ontogenesis of the abnormal development of testis

Cryptorchidism is the absence of one or both testes from the scrotum. It is the most common birth defect of the male genitals.[38-40] About 3% of full-term and 30% of premature infant boys are born with at least one undescended testis. However, about 80% of cryptorchid testes descend by the first year of life (the majority within three months), making the true incidence of cryptorchidism around 1% overall. Cryptorchidism may develop after infancy, sometimes as late as young adulthood, but that is exceptional [41-42]. Cryptorchidism is distinct from monorchism, the condition of having only one testicle. The condition may occur on one or both sides; it more commonly affects the right testis [42-43].

A testis absent from the normal scrotal position may be:
1) Anywhere along the "path of descent" from high in the posterior (retroperitoneal) abdomen, just below the kidney, to the inguinal ring;
2) In the inguinal canal;
3) Ectopic, having "wandered" from the path of descent, usually outside the inguinal canal and sometimes even under the skin of the thigh, the perineum, the opposite scrotum, or the femoral canal;
4) Undeveloped (hypoplastic) or severely abnormal (dysgenetic);
5) Missing (also see anorchia).

About two thirds of cases without other abnormalities are unilateral; most of the other third involve both testes [44-45]. In 90% of cases an undescended testis can be felt in the inguinal canal. In a small minority of cases missing testes may be found in the abdomen or appear to be nonexistent (truly "hidden") [45].

Undescended testes are associated with reduced fertility, increased risk of testicular germ cell tumors and psychological problems when the boy is grown. Undescended testes are also more susceptible to testicular torsion (and subsequent infarction) and inguinal hernias [46]. Without intervention, an undescended testicle will usually descend during the first year

of life, but to reduce these risks, undescended testes can be brought into the scrotum in infancy by a surgical procedure called an orchiopexy Although cryptorchidism nearly always refers to congenital absence or maldescent, a testis observed in the scrotum in early infancy can occasionally "reascend" into the inguinal canal [45-47]. A testis which can readily move or be moved between the scrotum and canal is referred to as retractile.

In most full-term infant boys with cryptorchidism but no other genital abnormalities, a cause cannot be found, making this a common, sporadic, unexplained (idiopathic) birth defect [47].

A combination of genetics, maternal health and other environmental factors may disrupt the hormones and physical changes that influence the development of the testicles [47-48].

1) Severely premature infants can be born before descent of testes. Low birth weight is also a known factor.

2) A contributing role of environmental chemicals called endocrine disruptors that interfere with normal fetal hormone balance has been proposed. The Mayo Clinic lists "parents' exposure to some pesticides" as a known risk factor.

3) Diabetes and obesity in the mother.

4) Risk factors may include exposure to regular alcohol consumption during pregnancy (5 or more drinks per week, associated with a 3x increase in cryptorchidism, when compared to non-drinking mothers.

5) Cigarette smoking is also a known risk factor.

6) Family history of undescended testicle or other problems of genital development.

7) Cryptorchidism occurs at a much higher rate in a large number of congenital malformation syndromes. Among the more common are Down syndrome, Prader–Willi syndrome, and Noonan syndrome.

8) In vitro fertilization, use of cosmetics by the mother, and preeclampsia has also been recognized as risk factors for development of cryptorchidism.
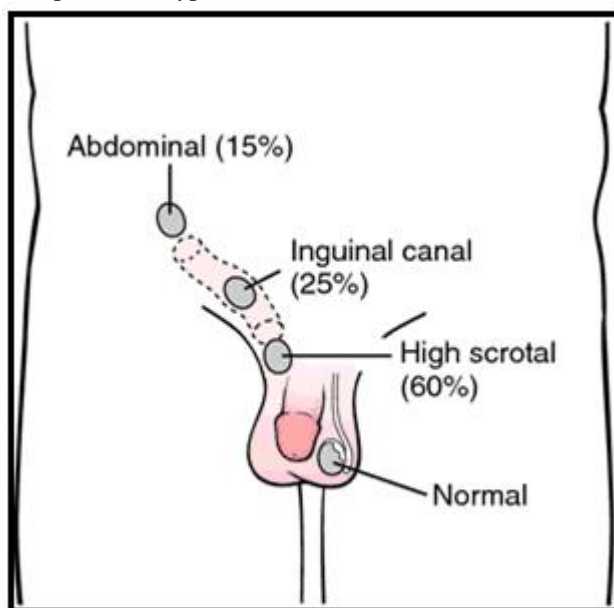

Fig-6: schematic diagram showing the different sites of un-descended testis

Discussion

The gubernaculum is only present during the development of the urinary and reproductive organs thus being replaced by distinct vestiges in both male and females [49-50].

The upper part of the gubernaculum degenerates in males, whereas the lower part persists as the gubernaculum testis (scrotal ligament). This ligament is acts in securing the testis to the most inferior portion of the scrotum. This causes it to fasten in place and limit the degree to which the testis can move within the scrotum [51].

The gubernaculum has two vestigial remnants in females, these includes the ovarian ligament and the round ligament of the uterus (ligamentum teres uteri) which respectively serve to support the ovaries and uterus in the pelvis [52].

Conclusion

The female gubernaculum is an embryonic structure that gives rise to the uterine round ligament and seems to be important in Müllerian development [53]. In the absence of androgens and anti-Müllerian hormone, the paramesonephric or Müllerian ducts complete their invagination and development, interfering with the connection of the tissue column that begins at the inguinal cone (the gubernaculum) and targets the mesonephric duct and caudal ligament of the gonad. The gubernaculum then grows over the Müllerian ducts, incorporating its muscular fibres [54]. Outside and above this point, the Müllerian ducts give rise to the Fallopian tubes, whereas medially to the point of insertion of the gubernaculum, the Müllerian ducts develop into the normal uterus, the adequate formation of which is also induced by the mesonephric ducts. Diverse human anatomical and physiological characteristics such as the simplex uterus, as well as pathological conditions and certain female genital malformations, could be related to gubernaculum dysfunction [54-55].

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