Development of Reproductive System

Sex differentiation depends on the testis determining factor (TDF) gene on Y chromosome. In the presence of this factor, male sex organs develop, in its absence female sex organs develop**.**

GONADS

Gonads do not acquire male or female characteristics until week 7 of development.

Embryonic sources

Three sources share in development of gonads:

1-**Genital ridges** of the intermediate cell mss of mesoderm (urogenital ridge).
2-**Coelomic epithelium** of the genital ridge.
3-Endoderm of the **wall of the yolk sac.**

On the 5th week, **genital ridges** appear as a pair of longitudinal projections medial to the mesonephros. Primordial germ cells appear in the wall of the yolk sac and migrate by ameboid movements along the dorsal mesentery of the hindgut, arriving in the genital ridges at week 5-6. The primordial germ cells have an inductive influence on development of gonads. During the arrival of germ cells, the coelomic epithelium of the genital ridges proliferates and penetrates the underlying mesoderm forming primitive **sex (gonadal) cords** in both male and female embryos (fig.1). The indifferent gonads consist of an outer cortex and inner medulla. At this stage (week 7) it is impossible to differentiate between male and female gonads (fig.2).

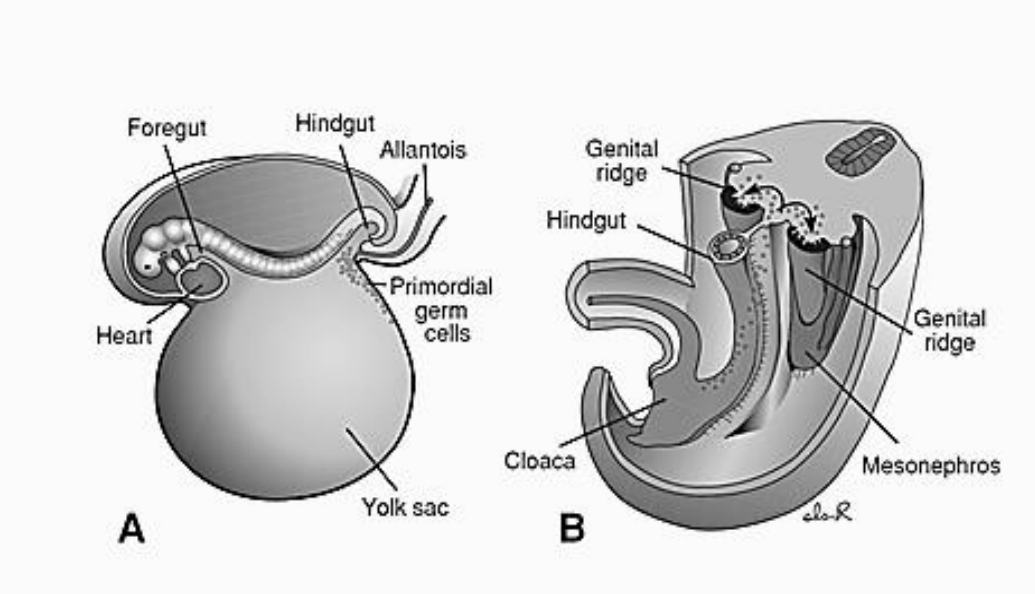

Fig.1. Embryonic sources of gonads.

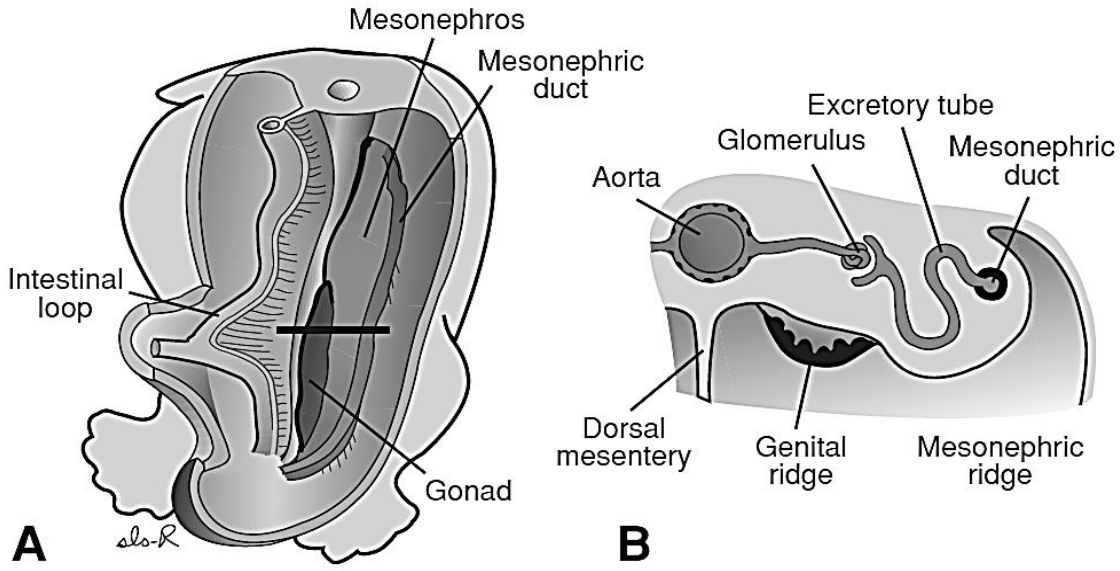

Fig.2.Relationship between mesonephros and genital ridge at 6-weeks, indifferent gonads.

TESTES

If the embryo is genetically male, primordial germ cells carry XY sex chromosomes. Under the influence of Y chromosome whose genes encode testis determining factor (TDF), the primitive sex cords penetrate deep toward the hilum of the gonad to form medullary cords. These cords break up into a network which gives rise to the ***rete testis***.

In the 12th week, other sex cords proliferate and lose contact with the surface epithelium. They become U-shaped and enclose germ cells. Their ends become continuous with rete testis through tubuli recti (fig.3). **Testis cords** are now composed of primitive germ cells and Sertoli cells. ***Interstitial cells of Leydig*** are derived from mesoderm of the genital ridge. They lie between testis cords and start secreting testosterone which reaches peak at 8-12 weeks. Testes now become able to influence sexual differentiation of the genital ducts and external genitalia.

Testis cords remain solid until puberty, when they acquire a lumen, thus forming the seminiferous tubules. Seminiferous tubules will join the rete testis and in turn the efferent tubules. These efferent ductules are remnants of the mesonephric tubules and they function as the link between the rete testis and the ductus deferens (derivative of the mesonepohric or Wolffian duct).The genital ridge mesoderm forms a dense layer of fibrous connective tissue, tunica albuginea, around the testis. Tunica albuginea sends trabeculae to divide the testis into compartments.

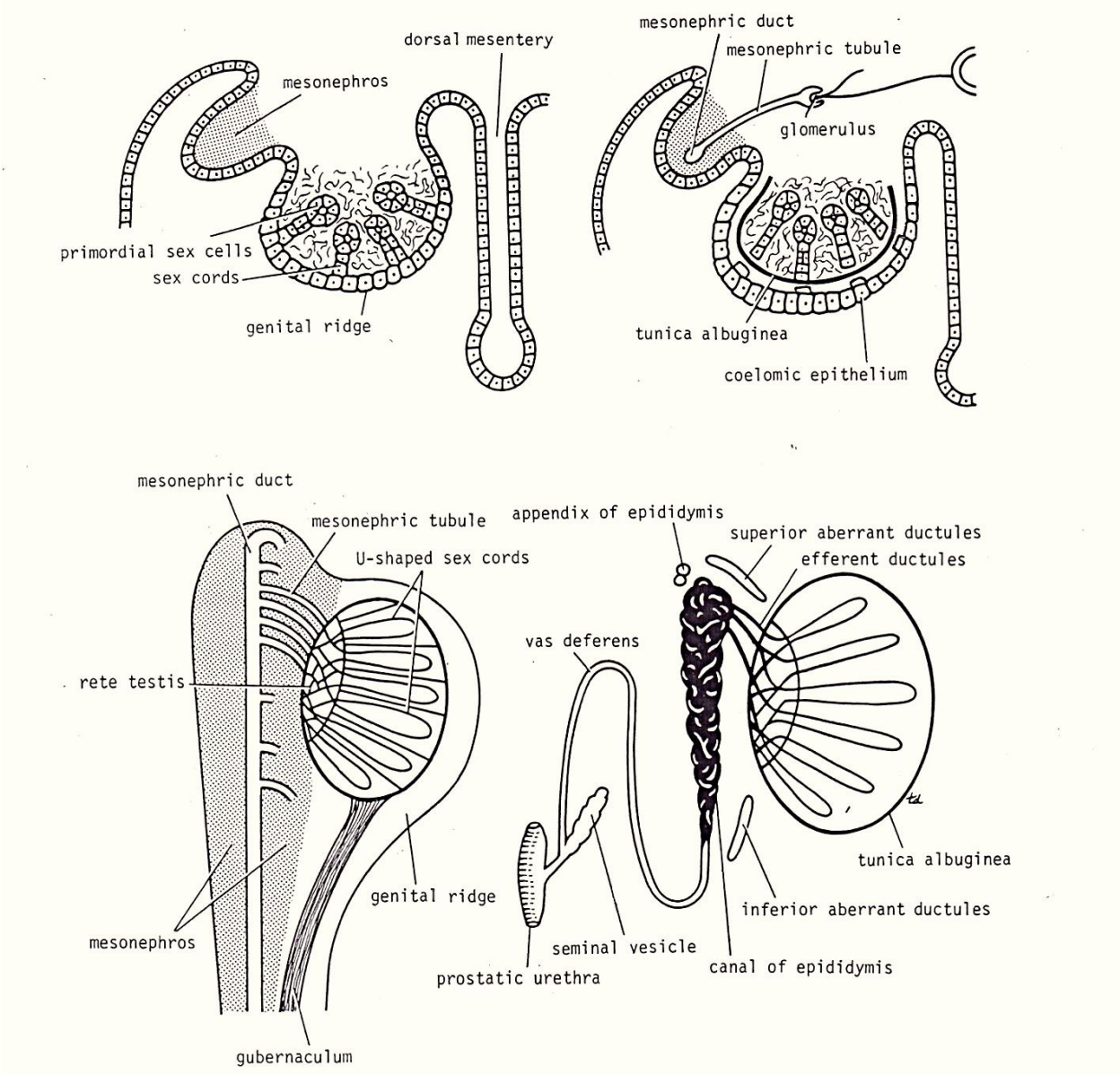

Fig.3. Development of the testis.

Descent of the testes

Early in development the testis was high in the abdomen and is attached together with the mesonephros by a urogenital mesentery to the posterior abdominal wall. With degeneration of the mesonephros the attachment serves as a mesentery for the testis-, ***mesorchium***. Extending from the caudal pole of the testis is a mesodermal condensation known as **gubernaculum** which terminates in the scrotal swelling. As gubernaculum reaches the inguinal region it passes between the differentiating internal and external oblique muscles. Meanwhile, a peritoneal sac, **processus vaginalis**, forms an evagination which follws the course of the gubernaculum and lies in front of it toward the scrotum. Shortening of gubernaculum assisted by hormones (androgens and gonadotrophins) and differential growth of the posterior abdominal wall help descent of the testis. Shortening of gubernaculum pulls and guides the testis through the anterior abdominal wall into the inguinal canal to the scrotum (fig.4). The testes reach the deep inguinal ring by the 7^{th} month and superficial inguinal ring by the 8^{th} month of pregnancy. After birth and up to one year the narrow canal connecting the processus vaginalis with the peritoneal cavity is obliterated leaving ***vestigue of processus vaginalis***. The testis is then covered by the two layers (parietal and visceral) of the ***tunica vaginalis***. In addition the testis become ensheathed in layers derived from the anterior abdominal wall through which it passes. Fascia transversalis forms ***internal spermatic fascia***, internal oblique forms ***cremasteric muscle and fascia***, and external oblique forms ***external spermatic fascia***.

Factors which help descent of the testes

1-Hormones (androgens and gonadotrophins).

2-Shortening of gubernaculums.

3-Atrophy of the mesonephros allows caudal movements of the testis.

4-Atrophy of the paramesonephric ducts in male enables the testes to move trans abdominally to reach the inguinal canal.

5-Enlagement of the fetal pelvis.

6-Elongation of the trunk.

7-Increased abdominal pressure from growth of abdominal viscera.

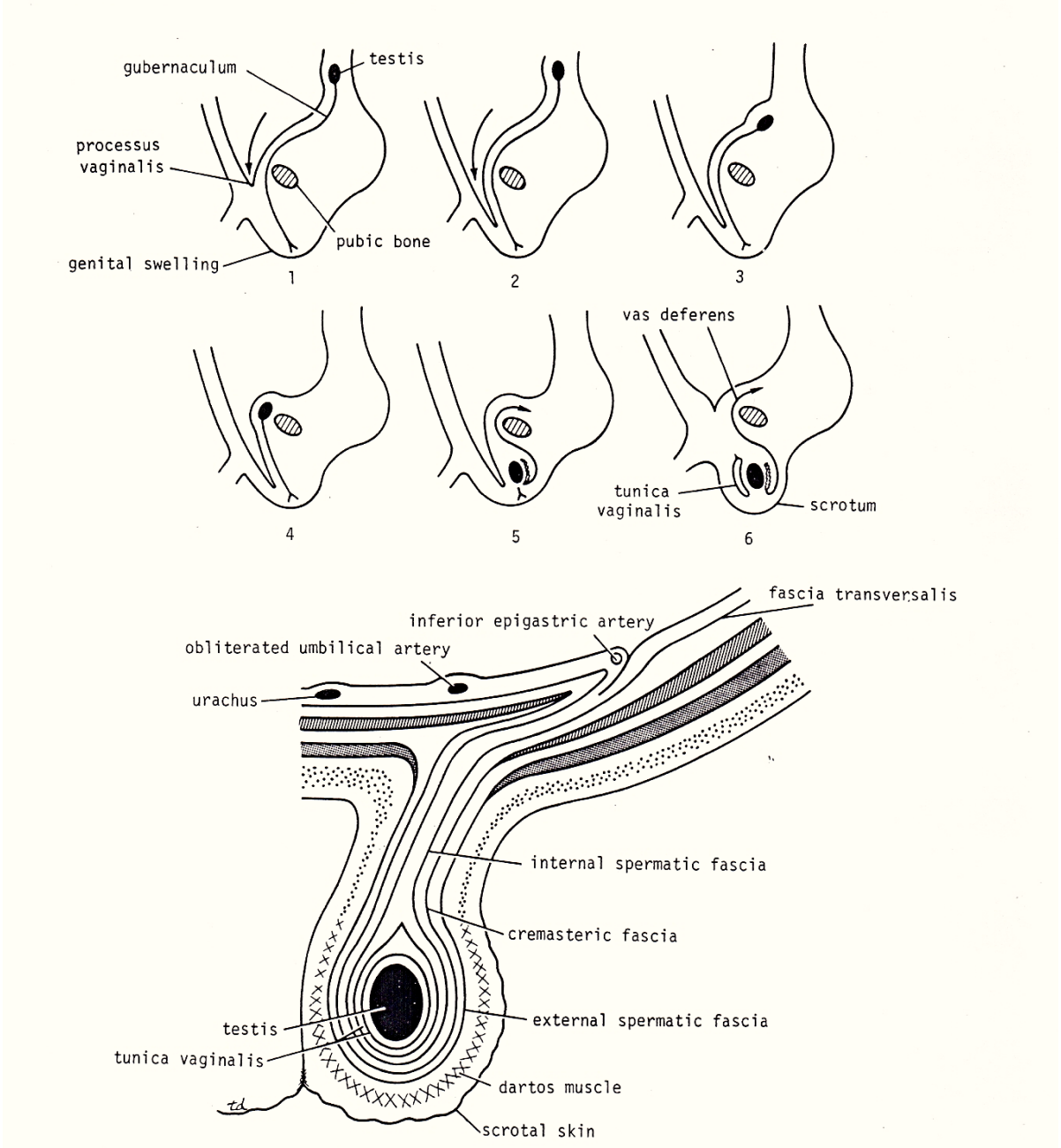

Fig.4. Descent of the testis and formation of the inguinal canal.

Anomalies of the testes

1-**Inversion** of the testis which may be polar or anterior.

2- **Ectopic testis** is maldescended testis due to abnormal path guided by abnormal band of gubernaculum. It may be in the anterior abdominal wall, femoral triangle, perineum or at root of penis (fig.5).

3- **Cryptorchism** is failure of descent of one or the two testes. During the 1st postnatal year most of the undescended testes descend into the scrotum. Cryptorchism is the commonest anomaly in the neonate that occurs in about 30% of premature male babies and in 3% of full term male babies. It is due to abnormal androgen production. The testis remains in the abdomen, pelvis, inguinal canal or is retractile (fig.6). An undescended testis is unable to produce mature sperms because of the higher temperature in the abdominal cavity. It is advised to surgically correct the anomaly before 18 months to avoid later infertility and possibility of tumor formation.

4- **Congenital hydrocele** (fig.7.A & B) is due to irregular obliteration of the passageway between the peritoneum and the processus vaginalis leaving a small cyst along its course. These cysts may secrete fluid resulting in hydrocele of the testis or spermatic cord.

5- **Congenital inguinal hernia** (fig.7 C) is descent of a loop of intestine into the scrotum due to failure of obliteration of the connection between the peritoneal cavity and the processus vaginalis.

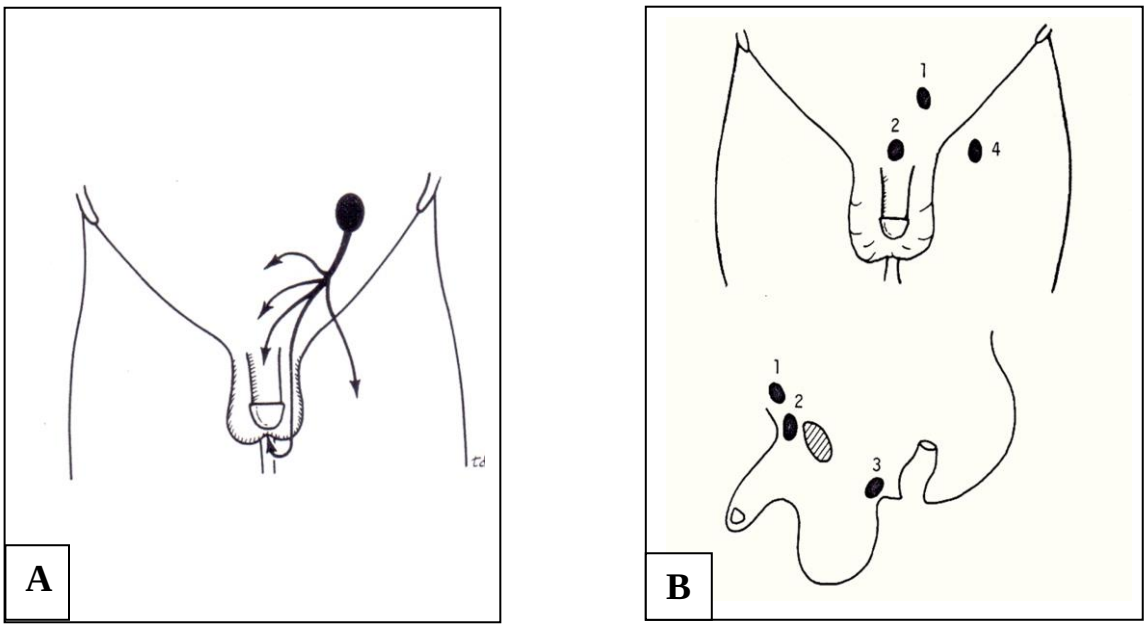

Fig.5.A. Split gubernaculum leading to B. Ectopic sites of testis; 1) abdominal, 2) root of penis, 3)perineum, 4) femoral triangle

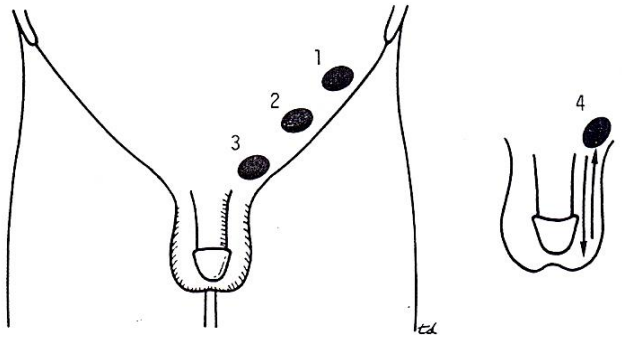

Fig.6.Common sites of incomplete descent of testis: 1) abdominal, 2) inguinal, 3) superficial ring, 4) retractile testis.

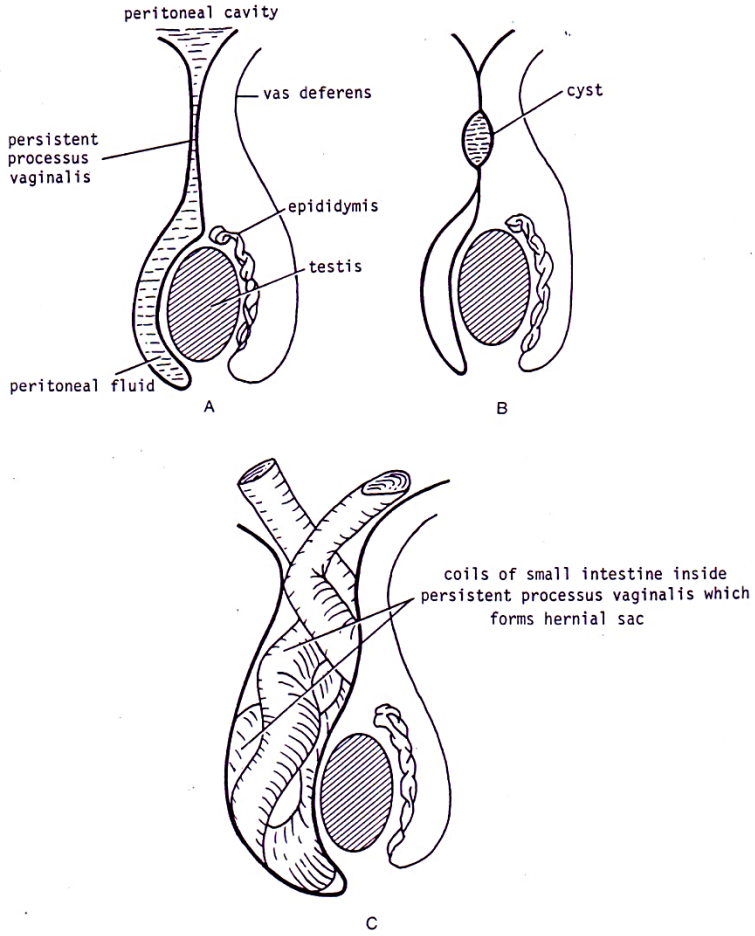

Fig.7. A) Congenital hydrocele, B) Encysted hydrocele, C) Congenital inguinal hernia.

OVARY

In female embryo with an XX genotype and an absence of Y, primitive sex cords dissociate into clusters of cells which contain primitive germ cells. These clusters are located in the medulla forming rudimentary rete ovari and later disappear replaced by vascular stroma or ovarian medulla. Coelomic epithelium proliferates and by week 7 gives a second generation of sex cords named cortical cords which penetrate the underlying mesoderm but remain close to the surface. These cords form isolated cell clusters surrounding primitive germ cells, Primitive germ cells develop into oogonia and the cell clusters around it form follicular cells. By this the primordial ovarian follicles form. By week 16, as the ovary separates from the regressing mesonephros it will be suspended by a mesentrery- the ***mesovarium***.

Descent of the ovary

As the ovary develops in the middle part of the genital ridge, the cranial genital ligament forms the suspensory ligament of the ovary while the caudal genital ligament forms gubernaculum ovari. Gubernaculum ovari travels the inguinal canal toward the genital swelling (labia majora) followed by small processus vaginalis. At that time the uterus is developing and attaches to the gubernaculums (fig.8). This attachment prevents further traction on the ovary, so the ovary does not reach the inguinal canal. The part of gubernaculums between the ovary and uterus forms ovarian ligament and the part between the uterus and labia majora forms the round ligament of the uterus.

Anomalies of the ovary

1-**Ovarian dysgenesis** as in Turner syndrome.
2-**Imperfect descent** of the ovary.
3-Peristence of the processus vaginalis (hydrocele of the canal of Nuck).

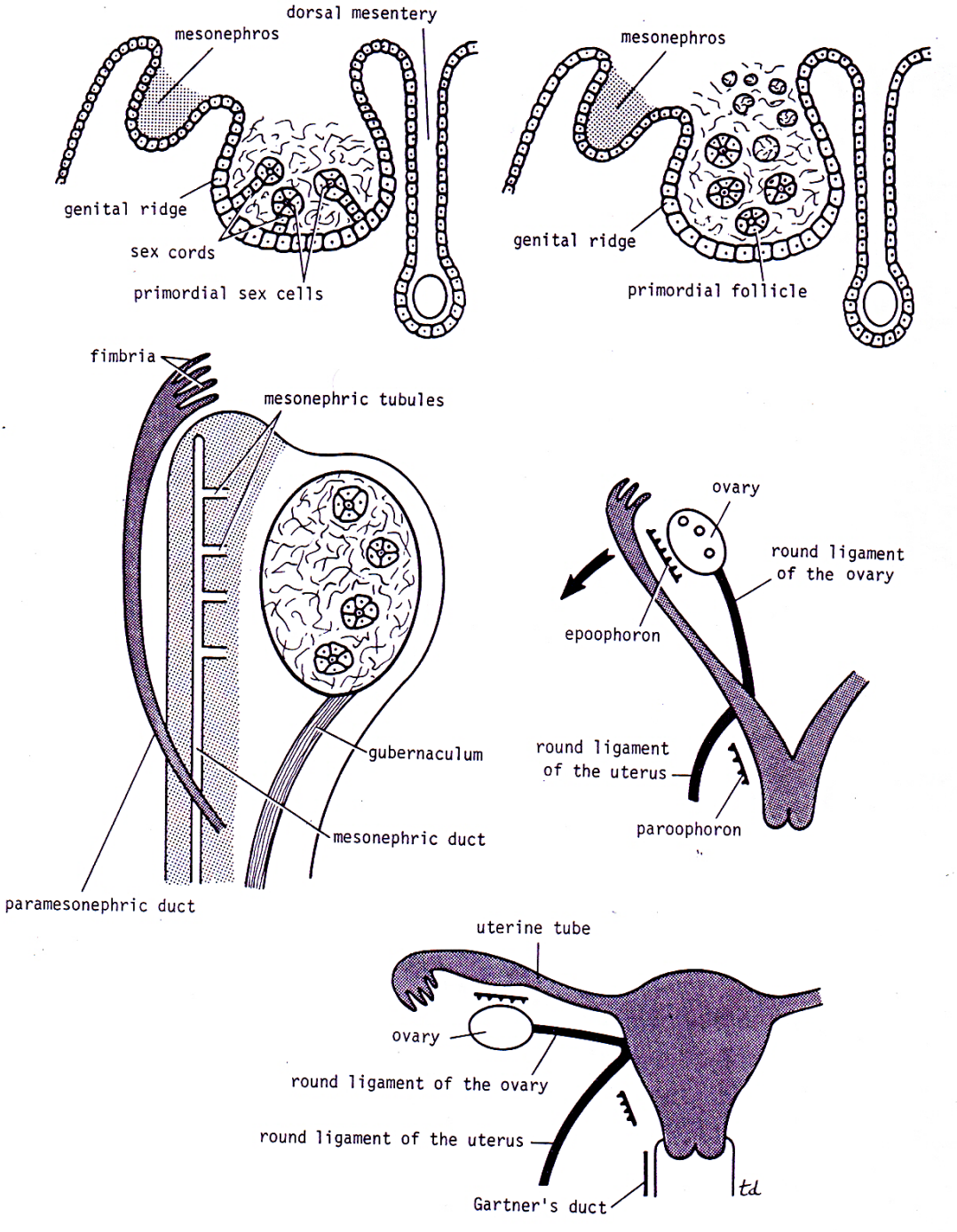

Fig.8.Formation of the ovary and its relation to the developing uterus.

GENITAL DUCTS

Development of the genital ducts and external genitalia occurs under the influence of hormones.

In male, Sertoli cells of the fetal testis produce **mullerian inhibiting substance (MIS)** that causes regression of the paramesonephric ducts. The testes produce androgens (testosterone and dihydrotestesterone) that mediates virilization of the mesonephric ducts (vas deferens and epididymis) and modulate differentiation of male external genitalia (growth of penis, scrotum and prostate).
In female, absence of anti-mullerian hormone stimulates the paramesonephric ducts to develop into uterine tubes and uterus. In absence of male androgens, estrogen produced by the placenta and fetal ovaries stimulates differentiation of external genitalia into labia majora, labia minora , clitoris and vagina.

Development of uterine tubes, uterus and vagina

Paramesonephric (Mullerian) ducts appear as a pair of longitudinal invaginations of coelomic epithelium anterolateral to the mesonephric ducts (fig.9). Edges of these grooves approach each other and fuse to form mullerian ducts. Cranially the ducts open into the coelomic cavity. The ducts run lateral to the mesonephric ducts but further caudally at the level of the pelvis they cross in front of the mesonephric ducts and genital ducts to become medial to them. Three parts can be recognized in each paramesonephric duct:

a)**Cranial vertical** portion that opens in the coelomic cavity.
b)**Horizontal** part that crosses the mesonephric duct.
c)**Caudal vertical** part that fuses with its partner from the opposite side to form the uterus. The caudal fused tip of the fused ducts is called mullerian tubercle that projects into the posterior wall of the urogenital sinus producing an elevation,- the **sinus tubelcle.**

With descent of the ovaries the caudal and horizontal parts of the mullerian duct form the ***uterine tube*** in both sides. The caudal vertical parts of the two sides fuse to form the ***uterus*** and the ***cervix,*** and the septum inside disappears. The surrounding mesenchyme gives the muscle and peritoneal covering of the uterus (myometrium and perimetrium). As the horizontal parts of the mullerian ducts move mediocaudally, a broad transverse fold, ***-broad ligament***, is established. The broad ligament invests the uterus and uterine tubes.

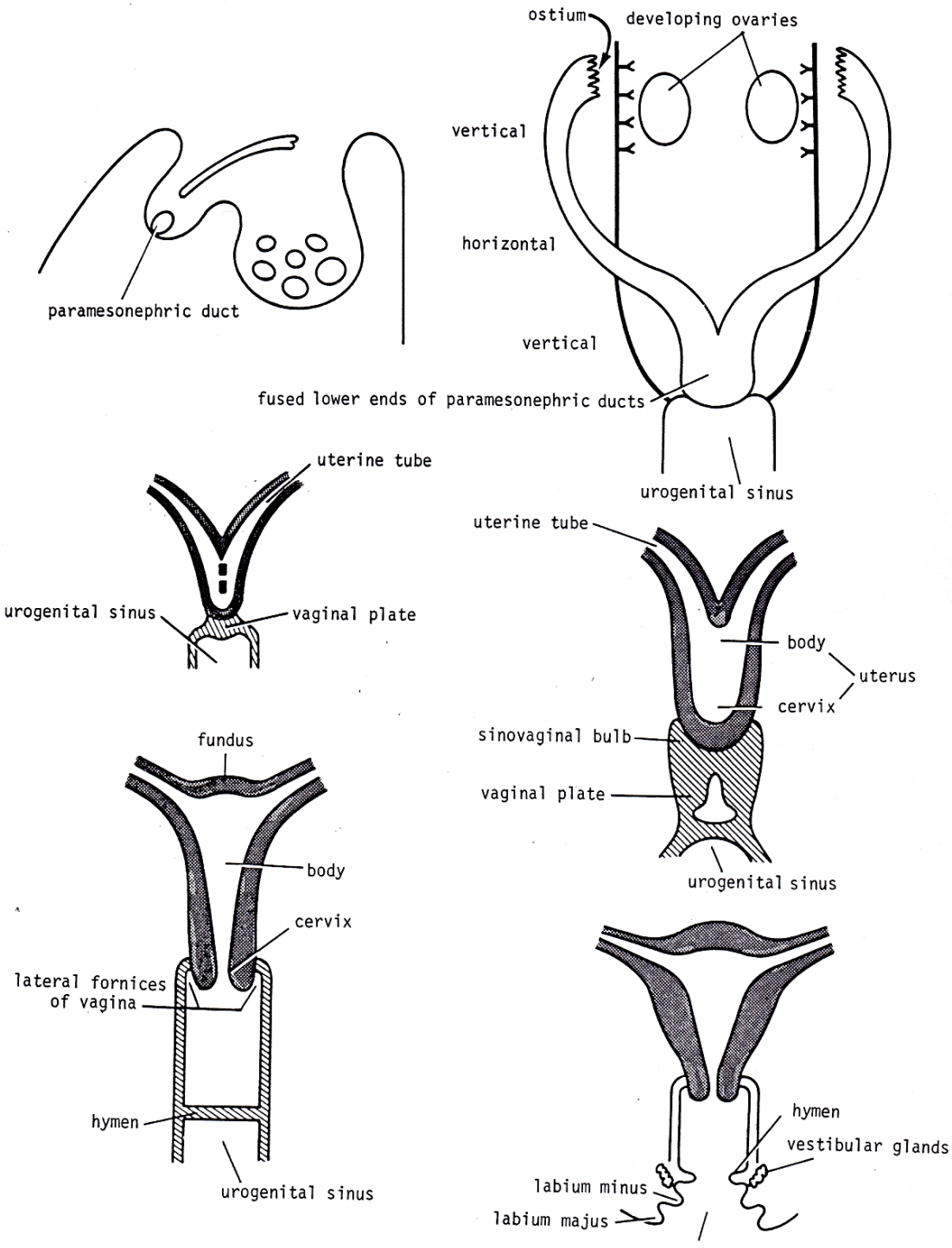

Fig.9. Development of the uterine tubes, uterus and vagina

Development of vagina

Shortly after the mullerian tubercle has reached the urogenital sinus, two solid outgrowths arise from the pelvic part of the UG sinus called **sinovaginal bulbs**. These bulbs fuse to form a solid **vaginal plate**. By the 5^{th} month the vagin is canalized. The wing expansions of the vagina, -vaginal fornices, are of paramesonephric origin. Thus the vagina has a dual embryonic origin, with the upper portion derived from the uterine canal and the lower portion from the urogenital sinus. The lumen of the vagina remains separated from that of the UG sinus by a thin plate known as the hymen. The hymen consists of epithelial lining of the UG sinus and a thin layer of vaginal cells. It develops a small central opening during the perinatal life.

Urethral and paraurethral glands appear as outgrowths from the urethra. Greater vestibular glands form from as outgrowths from the UG sinus.

Paramesonephric ducts in male

Mullerian inhibiting substance (MIS) produced by Sertoli cells causes regtression of paramesonephric ducts in male leaving;

a)Appendix of the testis.

b)Prostatic utricle.

Development of seminal vesicles and prostate

Seminal vesicles appear as outgrowths from the caudal end of the mesonephric ducts. The part of the mesonephric duct between duct of the seminal vesicle and urethra becomes the ejaculatory duct.

Prostate appears as multiple outgrowths of the urethra that grow into surrounding mesenchyme. Prostatic glands are developed from endothelial outgrowths and the surrounding mesoderm forms capsule, stroma and smooth muscles.

Anomalies of paramesonephric ducts in female

Anomalies of uterine tubes

Anomalies of uterine tubes are rare

1-Accessory opening.

2-Duplication.

3-Absence.

4-Atresia.

Anomalies of the uterus (fig.10)

1-**Agenesis** of the uterus; failure of development of mullerian ducts.

2-**Rudimentery uterus** is a solid mass without a lumen.

3-**Infantile uterus** is a very small uterus.

The first three anomalies present with primary amenorrhea.

4-**Corneate uterus** is due to failure of development of one paramesonephric duct. Corneate uterus with rudimentary horn may be presented in some cases.

5-**Septate uterus** is non-disappearance of the septum between the fused ducts. The septum persists for variable extent.

In females with corneate or septate uterus pregnancy is possible but there is increased incidence of preterm delivary or recurrent abortions.

6-Failure of fusion of the mullerian ducts:

a)**Uterus didelphys** is a rare anomaly presented with duplication of uterus, cervix and vagina due to complete failure of fusion of the mullerian ducts.

b)**Uterus bicornis unicollis** is two uterine bodies and one cervix.

c)**Uterus bicornis bicollis** is two uterine bodies and two cervices.

d)**Arcuate uterus** is minor degree of imperfect fusion of mullerian ducts.

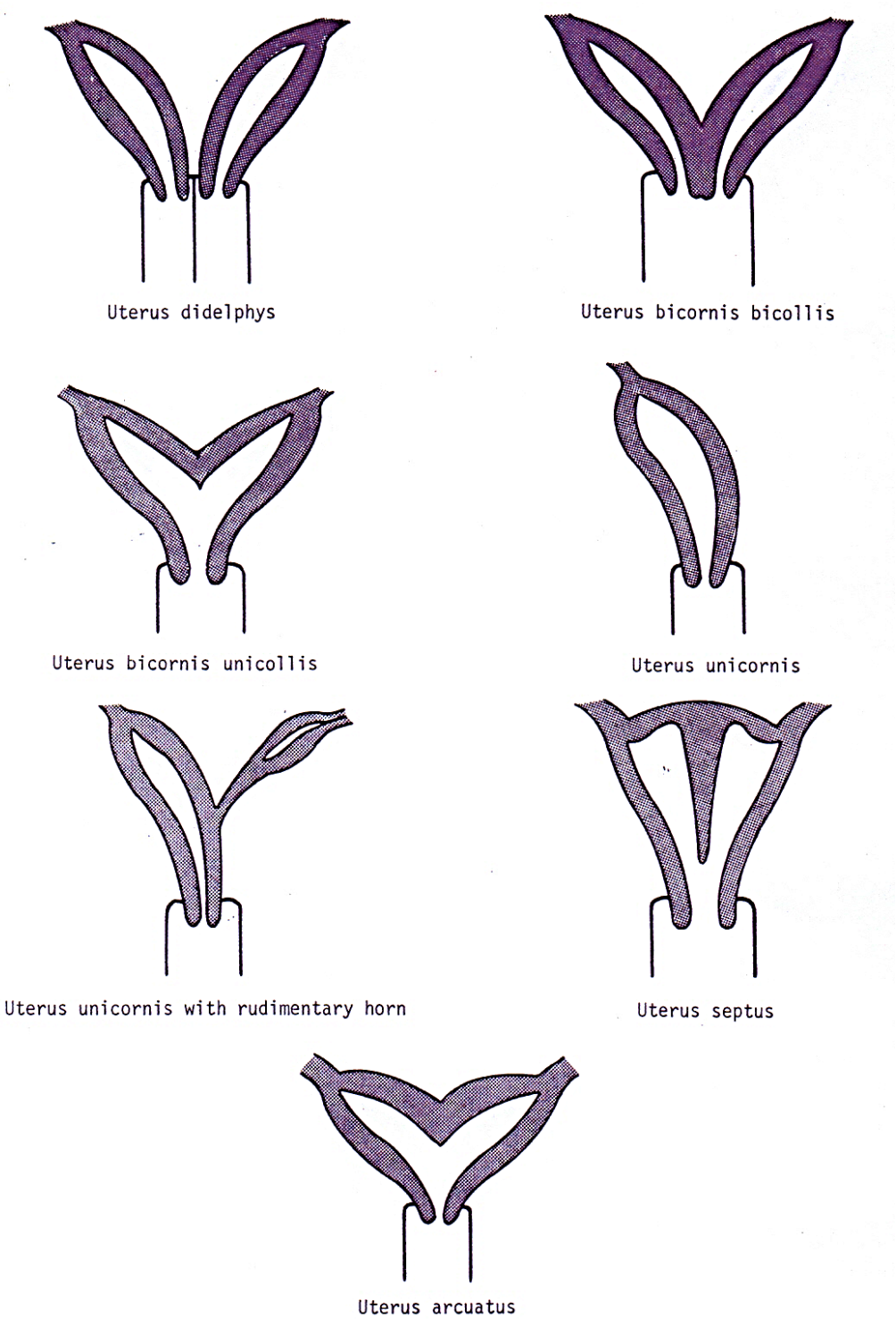

Fig.10. Anomalies of the uterus.

Anomalies of the vagina(fig.11)

1-**Vaginal agenesis** is failure of development of sinovaginal bulbs. This anomaly occurs 1/5000 cases.

2-Vaginal atresia (**Imperforate vagina)** is failure of canalization of the vagina.

3-**Vagina septum** is incomplete canalization of the vagina. Transverse septum usually is located at the junction of the upper and middle thirds.

4-**Imperforate hymen**.

5-Variable diameter of the vaginal orifice or may be more than one orifice.

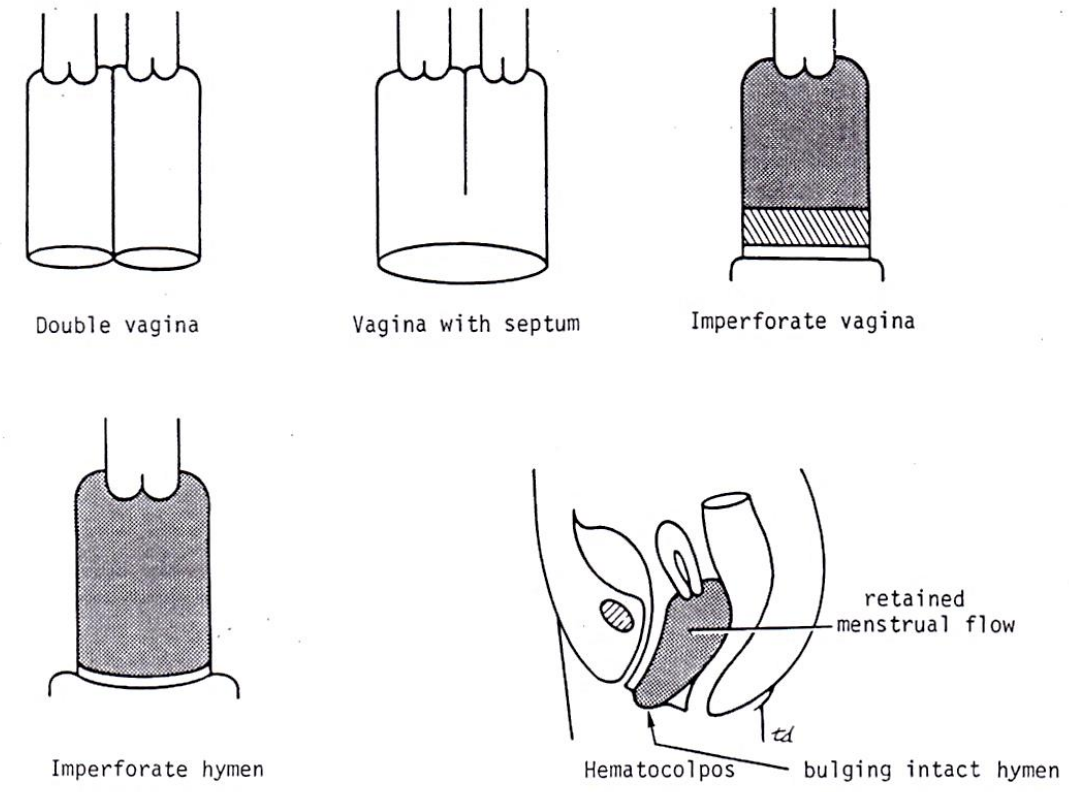

Fig.11. Anomalies of the vagina.

Development of external genitalia (fig.12)

Indifferent stage

In the 3rd week mesenchymal cells of the primitive streak migrate around the cloacal membrane to form a pair of elevated folds, the **cloacal folds**. Cranial to the cloacal membrane the folds fuse to form the **genital tubercle**.

During the 6th week, cloacal folds are subdivided into **urethral (genital) folds** anteriorly and anal folds posteriorly. In the mean time another pair of elevations, **genital swellings**, became visible on each side of the genital folds. By the end of the 6th week with appearance of genital tubercle, genital folds and genital swellings it is impossible to distinguish between male and female embryos. Distinguishing sexes appear during the 9th week but external genitalia are not fully differentiated until the 12th week.

Male external genitalia

Development of male external genitalia is under the influence androgens secreted by the fetal testes and is characterized by rapid elongation of the genital tubercle to form **phallus.** Enlagement of phallus forms the ***penis*** and mesenchyme in it develops into the ***corpora***. Phallus pulls urethral (genital) folds forward to form the lateral walls of the urethral groove, the floor of which is the urogenital membrane. Epithelial lining of the groove is endodermal and forms the **urethral plate**. The two urethral folds close over the urethral plate thus forming the ***penile urethra***. Ectdermal cells from the tip of phallus (glans) penetrate inward to form short epithelial cord. This cord later canalizes to for the ***external urethral meatus*** which fuses with the canalized penile urethra. The genital swellings move caudally and fuse to form the ***scrotum*** with a septum, scrotal septum, inside. A circular ingrowth of ectoderm at periphery of glans forms the ***prepuce.***

Female external genitalia

Estrogen plays an important role in development of female external genitalia. The genital tubercle elongates slightly to form the clitoris. Urethral folds do not fuse except posteriorly where they form frenulum of labia minora, and will form labia minora. Genital swellings fuse only cranially to form mons pubis and posteriorly to form labial commissure The rest of most of the genital swellings remain separate to form labia majora. The urogenital groove forms vestibule of the vagina.

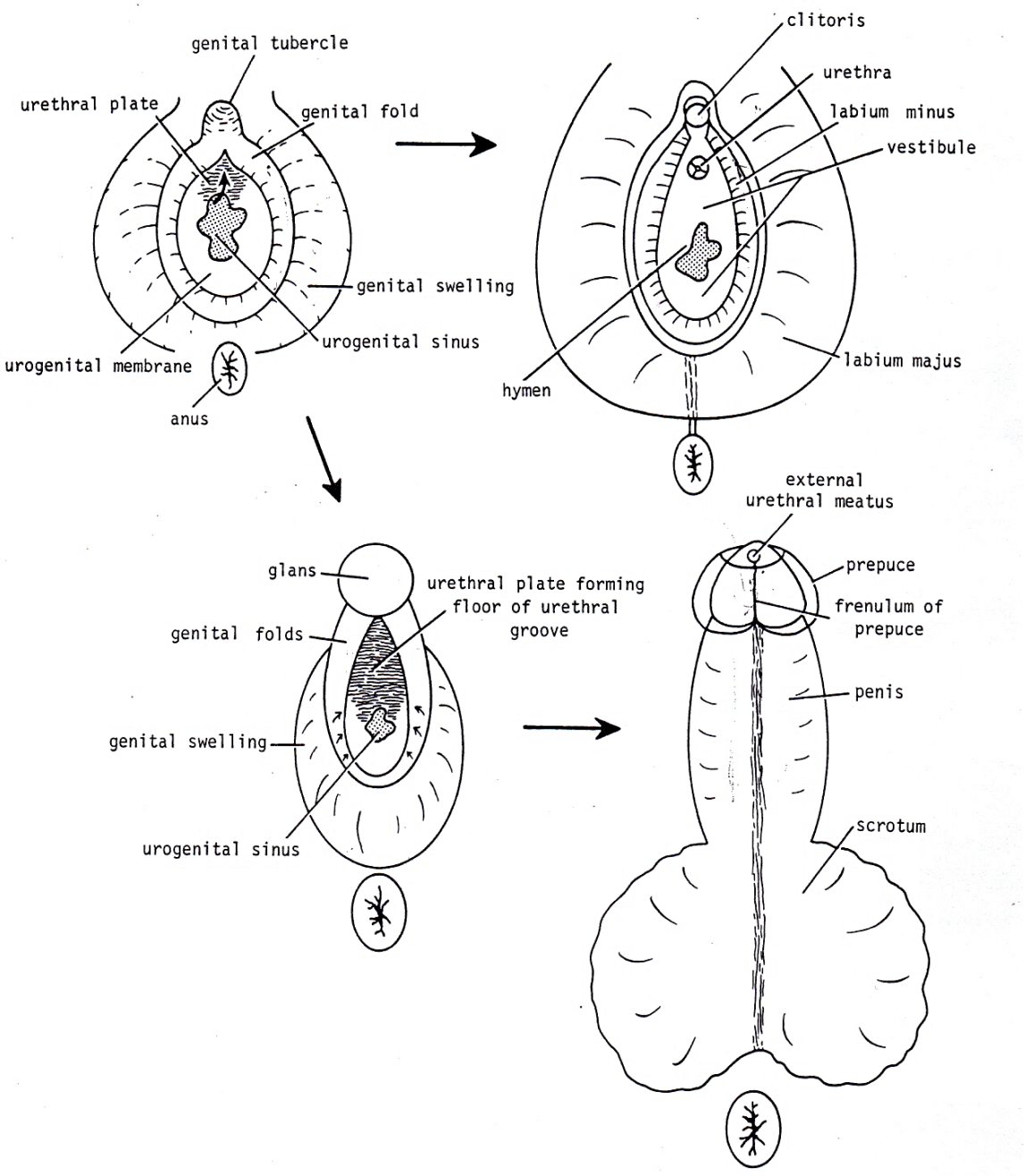

Fig.12. Development of external genitalia in female and male.

Urogenital homologues

Embryonic structure	Male	Female
Indifferent gonad	Testes	Ovaries
Cortex	Seminiferous tubules	Ovarian follicles
Medulla	Rete testis	Medulla
Gubernaculum	G testis	G ovary -Ovarian ligament -Round ligament
Mesonephros		
Mesonephric tubules	Efferent ductules Appendix epididymis	-Epoophoron -Paroophoron
Mesonephric ducts	Duct of epididymis Ductus deferens Seminal vesicles	-Duct of epoophoron -Gartner duct
	Ureteric bud	
Paramesonephric ducts	Appendix of testis Prostatic utricle	Uterine tubes Uterus, cervix, Vaginal fornices
Urogenital sinus	Urinary bladder Urethra Prostate	Urinary bladder Urethra Distal vagina Urethral,paraurethral Bartholin gland.
Genital tubercle	Penis	Clitoris
Genital folds	Ventral penis and Penile urethra	Labia minora
Genital swellings	Scrotum	Labia majora

Congenital abnormalities of the external genitalia

1-Agenesis of external genitalia is absence of penis or clitoris is very rare. It is due to failure of genital tubercle to develop.

2-Bifid penis and double penis is very rare, usually with ectopia vesica.

3-Micropenis is common with hypopituitarism.

4-Hypospadias.

5-Ep[ispadias.

6-Ambiguous genitalia (intersex, hermaphrodite) is a syndrome in which individuals have characteristics of both sexes.

i-**True hermaphrodite** (ovitesticular syndrome) is very rare. Individuals have both testes and overies and both are non functioning..

ii-**Psudohermaphrodite** is a syndrome in which the genotypic sex is masked by phenotypic appearance of the other sex. Male psudohermaphroditism is when the individual has testes while the external genitalia look like those of female. Female psudohermaphroditism is when the individual has ovaries and the external genitalia look like male.

a)**Female psudohermaphroditism**

Individuals are 46,XX and are mainly due to exposure of females to excessive androgens. A common cause is congenital adrenal hyperplasia. Administration of androgens or progesterone compounds during pregnancy may cause this syndrome. **Adrenogenital syndrome** is biochemical absence of hydroxylase enzyme which causes deficiency of hydrocortisone. In turn, there is increase in ACTH which causes hypertrophy of the adrenal cortex and overproduction of adrenal androgens. In female there will be enlarged clitoris and fused labia which look like male external genitalia (fig.13). Uterus, vagina and ovaries are usually present.

In male it causes precocious puberty.

b)**Male psudohermaphroditism** may result from inadequate production of androgens. Individual genotype is 46, XY. In the **Testicular feminization syndrome (Androgen insensitivity syndrome)** individuals are 46,XY but tissues of external genitalia are unresponsive to androgens and develop as females under the influence of estrogens. Since the individual is male and have MIS which suppresses Mullerian ducts, uterus and uterine tubes are absent. The vagina is short and ends blindly. Testes are usually in the inguinal canals with no signs of spermatogenesis (fig.14).

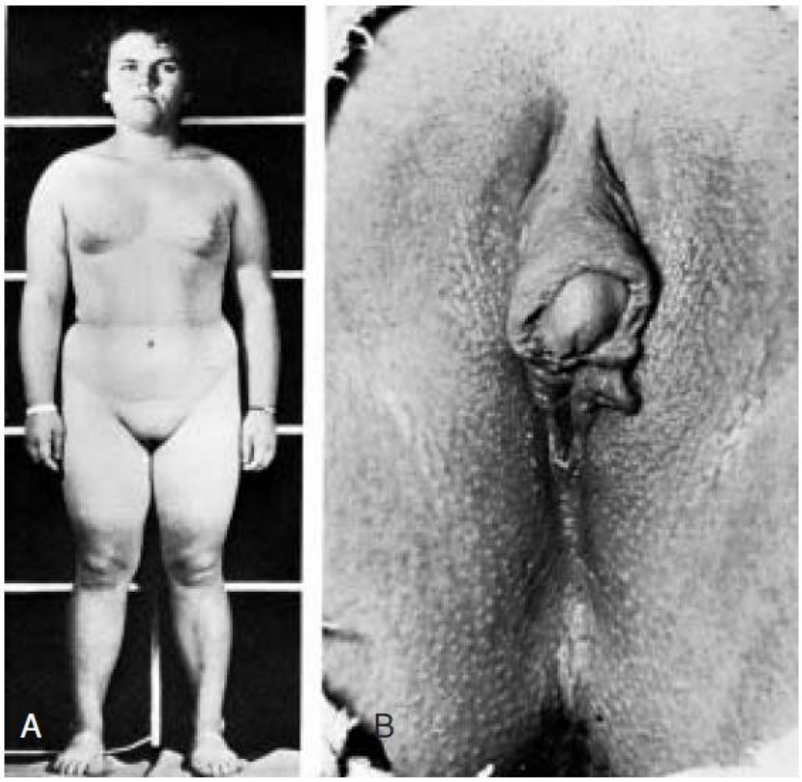

Fig.13.Female psudohermaphroditism (adrenogenital syndrome) ,notice fused labia and enlarged clitoris.

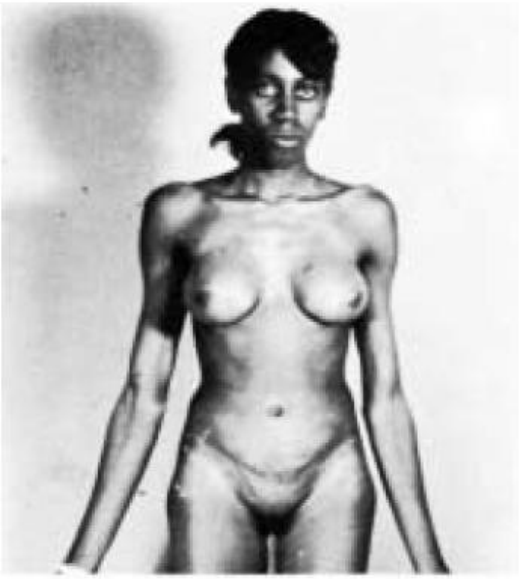

Fig.14. Testicular feminization syndrome. Notice feminine contour and enlarged breasts.