A decorative wreath of various botanical specimens, including ferns, leaves, and flowers in shades of green, red, orange, and purple, framing a central white circle.

Development of Female Reproductive System

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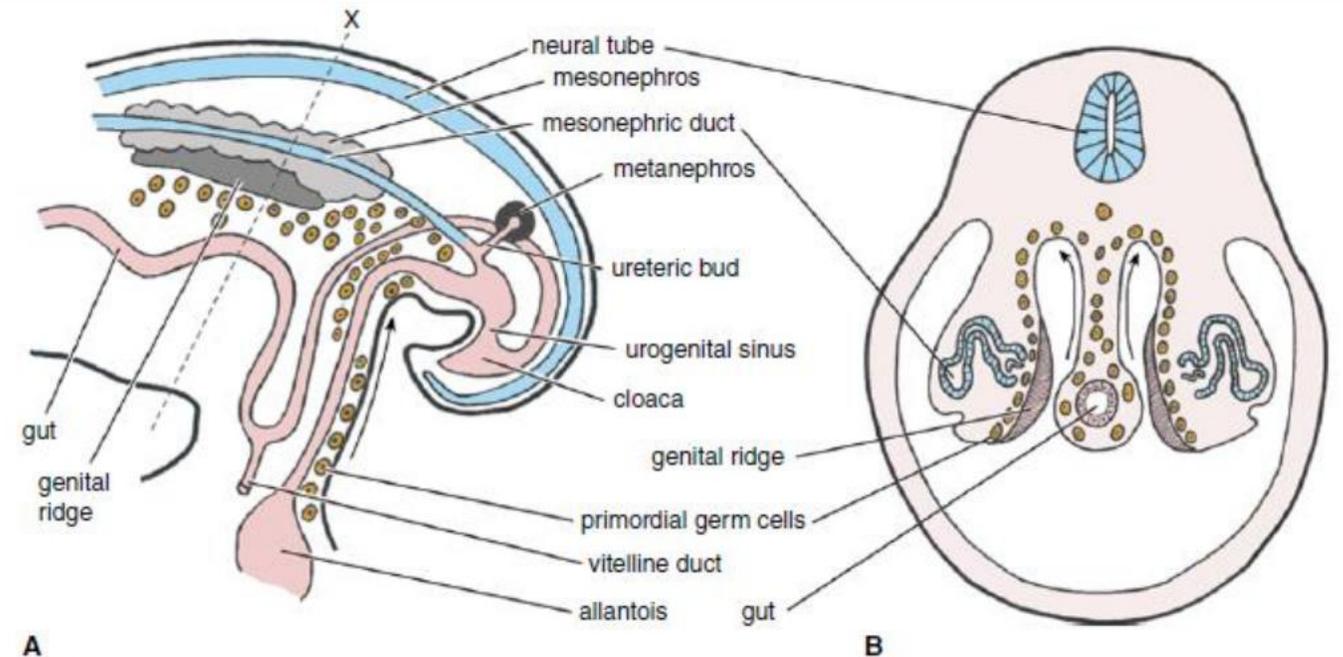
Introduction to Embryology of Genital System

Although the sex of an embryo is determined chromosomally at fertilisation, an undifferentiated stage of development initially occurs in which the primordia of both male and female genital organs are present.

Depending on the genetically-determined sex of the individual, the genital organs appropriate for that sex develop while the genital organs for the other sex regress. Sexual identity is not confined solely to the reproductive organs but is evident also in other anatomical features and in physiological and behavioural characteristics.

Primordial Germ Cells

- At an early stage in embryological development, primordial germ cells, which eventually populate the undifferentiated gonad, can be detected in the epiblast by specific staining methods.
- These cells, which migrate through the primitive streak and then to the yolk sac and allantois, move along the wall of the hindgut to the genital ridge, a structure destined to become the undifferentiated gonad.



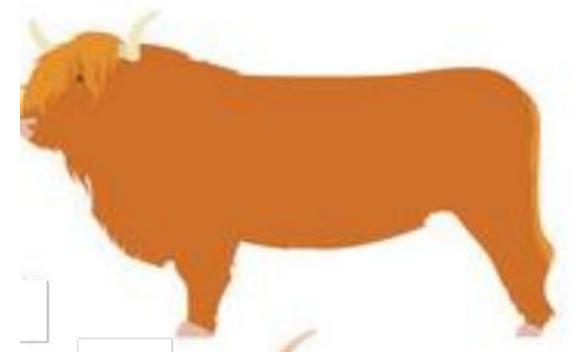
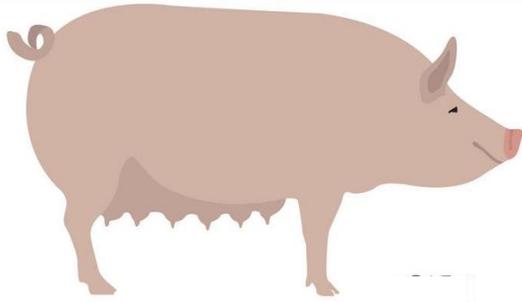
A. Route of migration of primordial germ cells from the allantois to the genital ridge, their site of differentiation. B. Transverse section through an embryo at the level indicated showing the migratory pathway of primordial germ cells along the dorsal mesentery to the genital ridge (arrows).

Primordial Germ Cells

❖ In mammals, primordial germ cells arrive at their site of differentiation by active migration, whereas in avian species they reach the genital ridge via the blood stream.

❖ It has been suggested that germ cells may be attracted to the genital ridge by chemotaxis.

❖ Primordial germ cells can be detected in the genital ridge by day 18 in pigs, by day 21 in dogs, by day 22 in sheep and by day 28 in cattle.

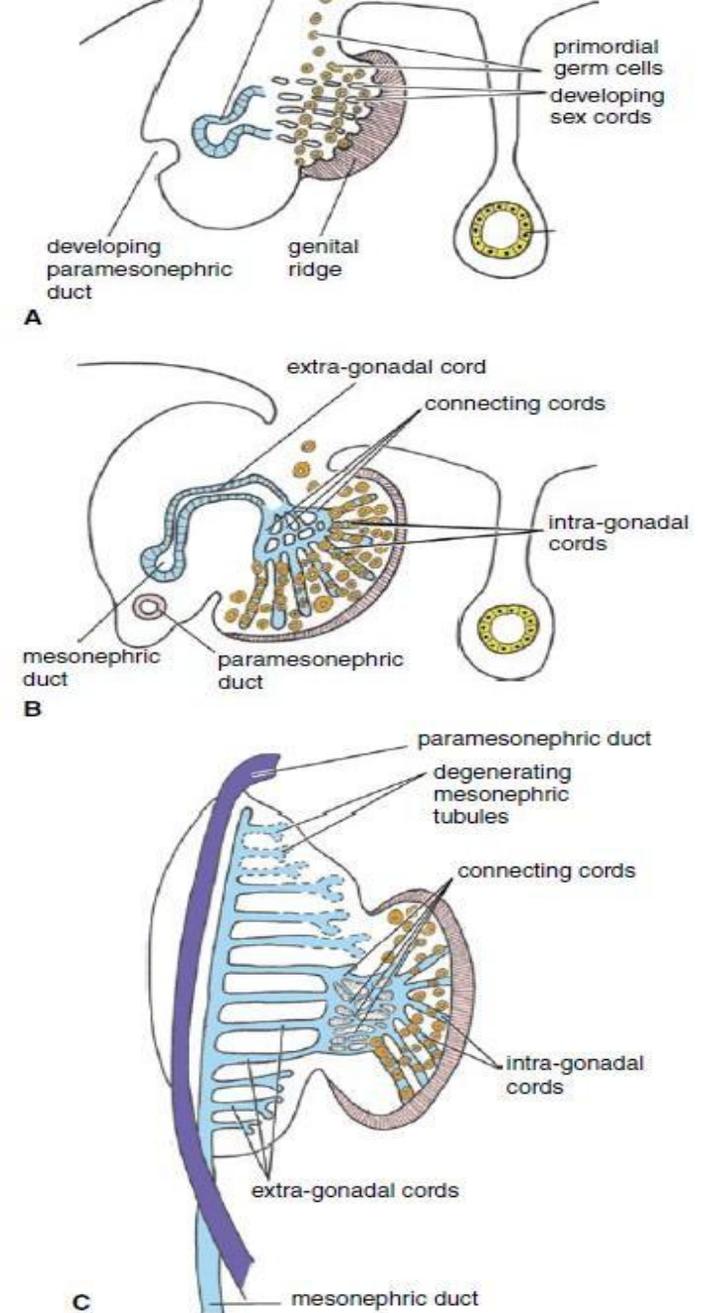


Primordial Germ Cells

- Primordial germ cells divide mitotically during migration to the developing gonads. Soon after entering the primordial gonad, the germ cells become enclosed in specific germ cell compartments, primordial follicles in the female embryo. Both the proliferation and differentiation of primordial germ cells in these particular locations are strongly influenced by locally-secreted soluble factors.
- Only germ cells which reach the undifferentiated gonad differentiate and survive. Most germ cells outside the gonadal region undergo apoptosis but some which survive outside this region may form germ cell tumours referred to as teratomata.

Undifferentiated stage of gonad formation

- ❑ Although the origin of the somatic gonadal cells is unresolved, three cellular sources have been proposed: a) local mesenchymal cells, b) coelomic epithelium and c) cells derived from the mesonephric tubules.
- ❑ The outline appearance of the gonadal ridges precedes the arrival of the primordial germ cells in the area. The undifferentiated gonads consist of primordial germ cells and mesodermal cells.
- ❑ The invading mesonephric cells and the mesonephric tubules form a tubular network called the rete system which consists of extra-gonadal cords, connecting cords and intra-gonadal cords.



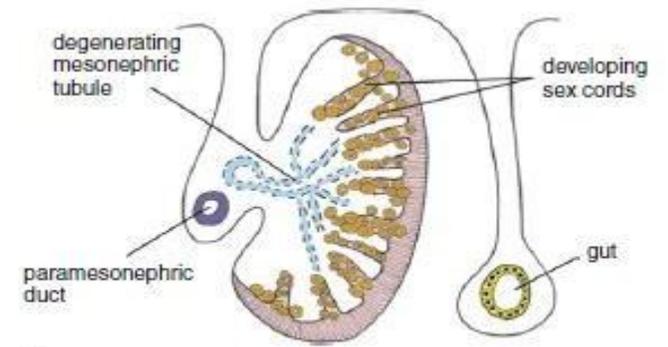
Sequential stages in the development of the undifferentiated gonad. A. Formation of sex cords in the genital ridge. B. Relationship between the mesonephric duct and the developing sex cords. C. Ventral view of the developing gonad shown in B.

Undifferentiated stage of gonad formation

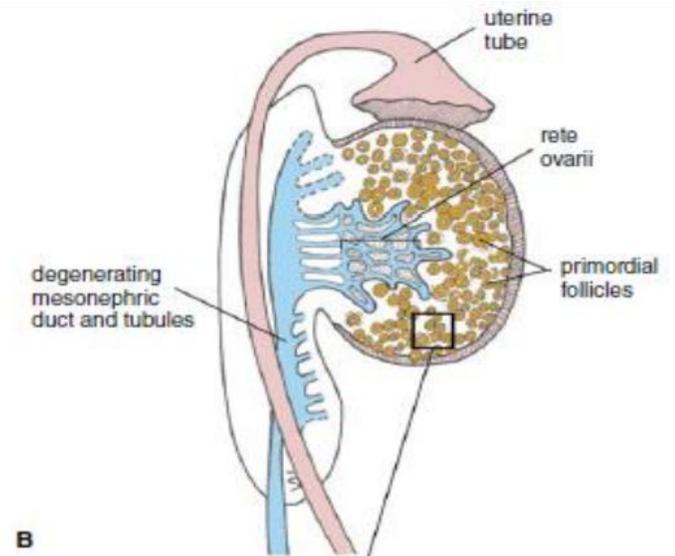
- During development, as a consequence of proliferation in its mid-region, the developing gonadal ridge assumes a globular appearance and remains attached to the mesonephros by a fold of mesothelium. Because of their morphological similarity, it is not possible to distinguish male primordial gonads from female primordial gonads at an early stage of development using histological methods. However, using modern molecular techniques, the sex of an embryo can be reliably confirmed at an early stage of development.

Differentiation and maturation of the ovaries

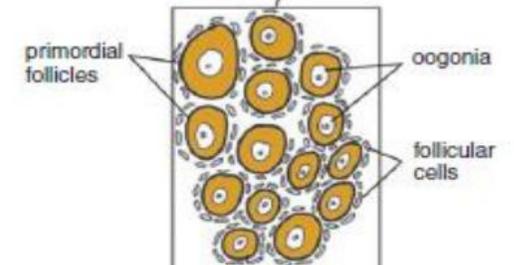
- The sex cords form irregular recognisable structures into which germ cells become incorporated. Following breakdown of the sex cords, germ cells undergo a period of enhanced mitotic activity in the developing ovaries. The germ cells are organised into nests, which contain numerous oogonia linked by cytoplasmic extensions. Irrespective of the duration of oogonial mitosis within a species, in the majority of mammals it ceases before or shortly after birth.
- As individual oogonia complete their period of mitotic activity, the germ cell nests degenerate and the oogonia become surrounded by a layer of squamous somatic cells of mesothelial origin, termed follicular cells. A germ cell enclosed in a basal lamina and surrounded by follicular cells constitutes a primordial follicle. The follicular cells induce the enclosed oogonium to enter the prophase of meiosis I.



A



B



C

Cross-section A, and ventral view B, of differentiation of the ovary from the undifferentiated gonad, showing the formation of primordial follicles and the uterine tube. C. Primordial follicles.

Differentiation and maturation of the ovaries

- At this stage the germ cells, which are referred to as primary oocytes, undergo a prolonged resting or dictyate stage. Although some maturation of primary oocytes may occur, these germ cells do not progress to the tertiary stage of development until stimulated by gonadotrophic hormones at the onset of puberty.

Differentiation and maturation of the ovaries

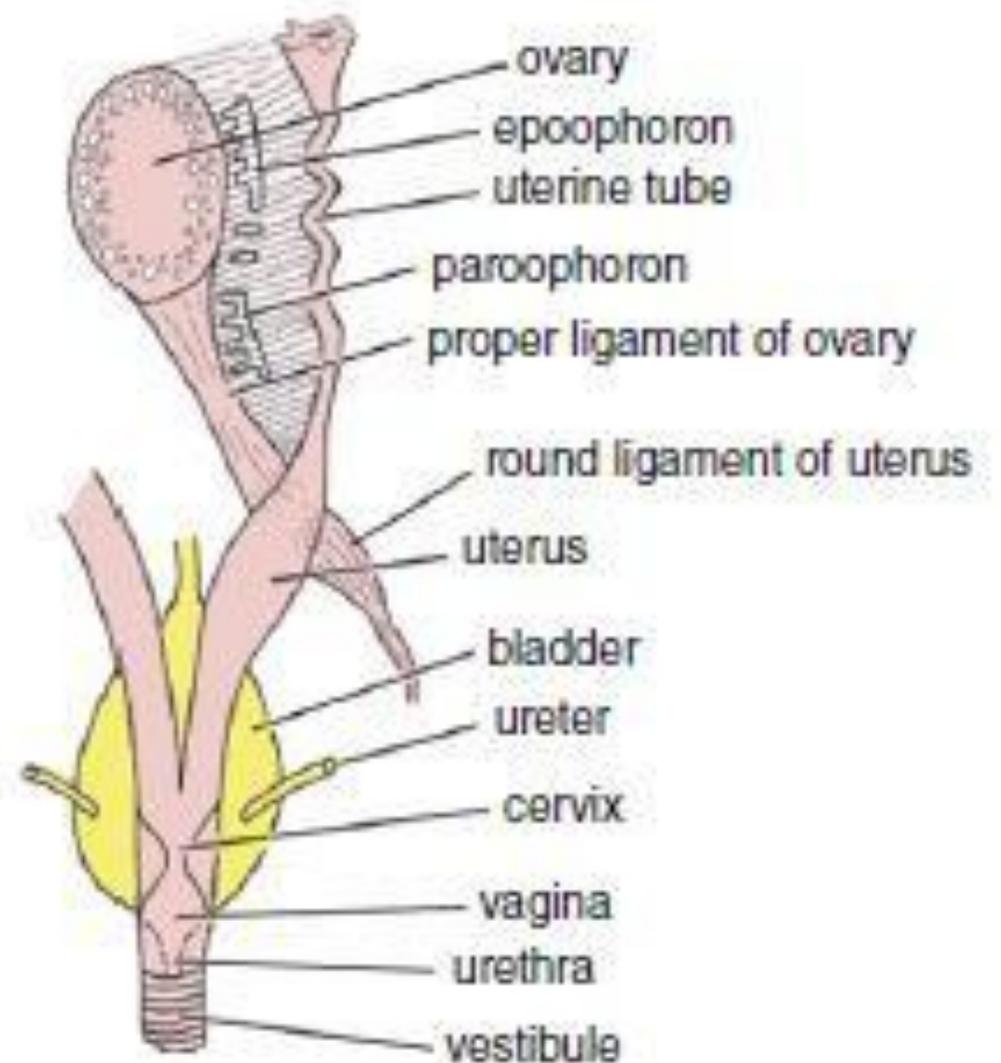
- ✓ Following the advent of puberty, recurring cyclical stages of follicular maturation occur in response to gonadotrophic hormones. As folliculogenesis proceeds, the squamous follicular cells, which become cuboidal, form stratified layers and are referred to as granulosa cells.
- ✓ Female mammals have their full complement of primary oocytes before or shortly after birth. In the ovary, germ cell proliferation and follicular development are confined to the peripheral areas of the developing gonad.
- ✓ By the end of this developmental period in domestic species, with the exception of horses, the ovary consists of a dense outer cortex which contains the follicles and a less dense central medulla composed of degenerating intra-gonadal tubules, the rete ovarii.
- ✓ In cattle, sheep and pigs, follicles are randomly distributed in the cortex while, in dogs and cats, they occur in clusters. In mammals, a high percentage of oogonia and primary oocytes undergo degenerative change referred to as atresia, during prenatal and postnatal life.

Features of equine gonadal development

- Development of follicles in the equine ovary is concentrated in the central area corresponding to the medulla in other species, while the non-follicular area is located peripherally. During *in utero* development, the unattached surface of the ovary becomes concave and, because it is from this site that ovulation occurs, the concavity is referred to as the ovulation fossa.
- The equine foetal gonads exhibit remarkable growth from approximately day 110 to day 220 of gestation. This enlargement, which occurs in both the developing ovary and testis, is attributed to hyperplasia and hypertrophy of interstitial cells.

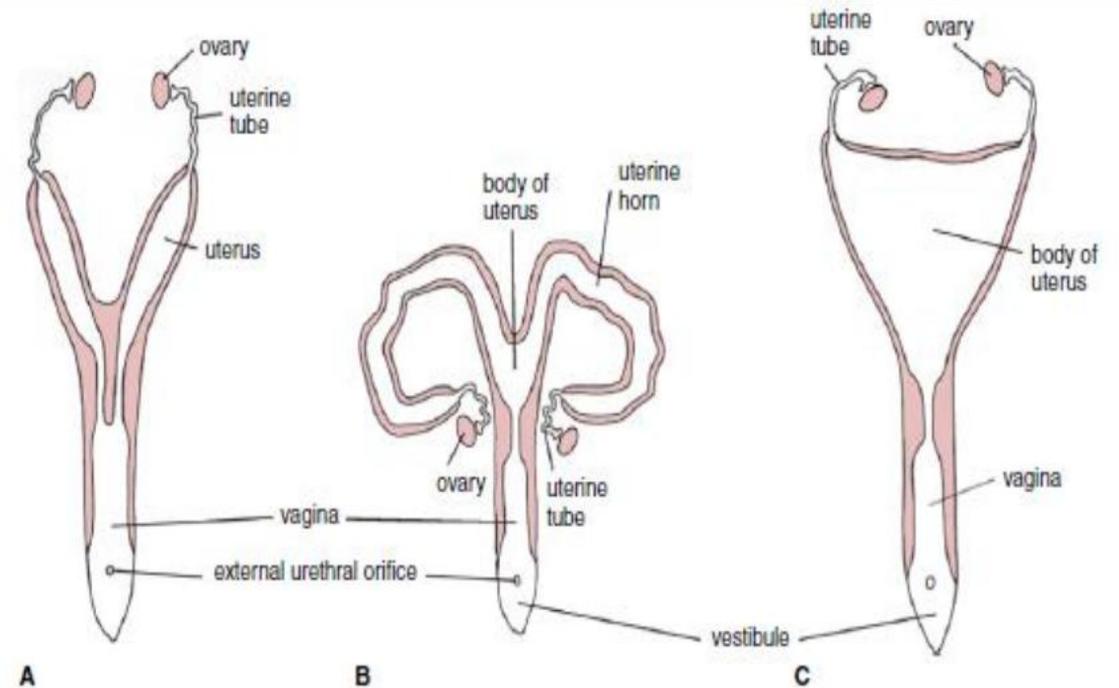
GENITAL DUCTS

- Irrespective of the genotype of the developing embryo, both male and female genital ducts form during the undifferentiated stages of gonadal formation. Differentiation of the female genital duct systems from the undifferentiated duct system is outlined in figure.
- In the female embryo, paramesonephric ducts contribute to the formation of the genital duct system, while the mesonephric ducts atrophy except for vestiges. The paramesonephric ducts are located lateral to the mesonephric ducts.



Differentiation of the female duct system in mammals

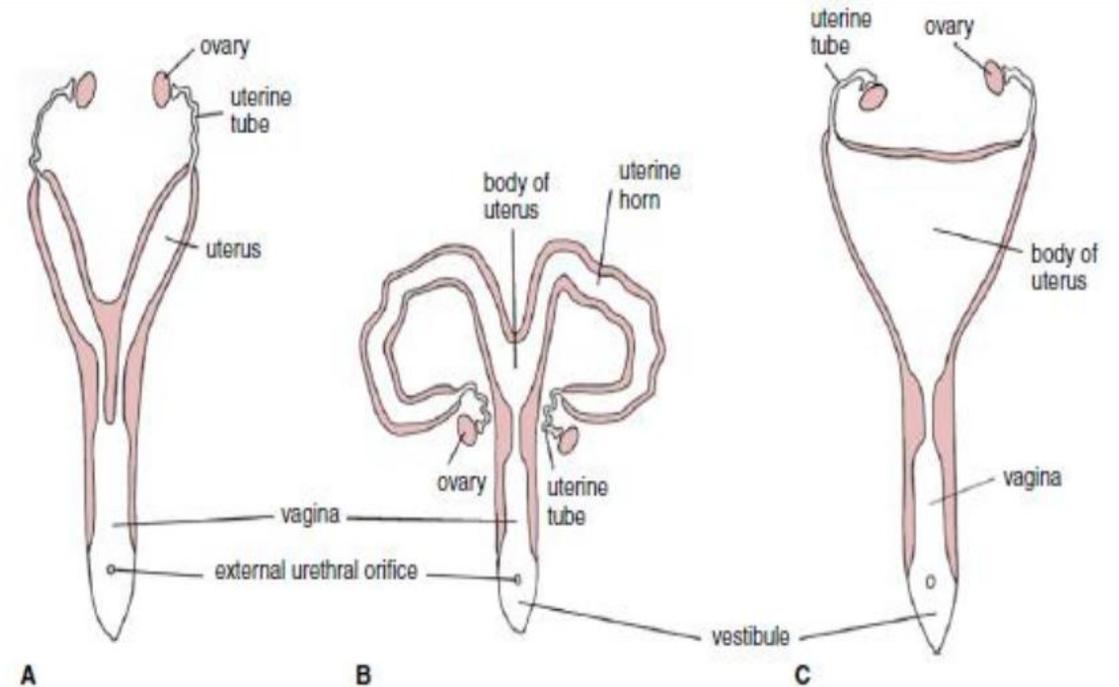
- The primordia of the paramesonephric ducts arise from intermediate mesoderm lateral to the cranial ends of the mesonephric ducts. Initially, grooves which form in the coelomic epithelium give rise to paramesonephric ducts which move deeper into the mesenchyme adjacent to the related mesonephric ducts.
- The cranial portions of the paramesonephric ducts form the uterine tubes, while the caudal portions of the ducts give rise to the uterine horns, uterine body and cervix. At their cranial aspects, the uterine tubes remain open and communicate with the coelomic cavity. Postnatally, this communication persists as the abdominal ostium. At first, the portions of the ducts which are closed elongate caudally, lateral to the mesonephric duct.



Final anatomical arrangement of the reproductive tracts in selected mammals. The extent of paramesonephric duct fusion determines the shape of the body of the uterus and the nature of its relationship with the vagina. A. Rodent reproductive tract, showing a uterus duplex. B. Porcine reproductive tract, showing a bicornuate uterus. C. Primate reproductive tract, showing a uterus simplex.

Differentiation of the female duct system in mammals

- Close to the urogenital sinus, each duct occupies a position ventral to the mesonephric duct and fuses in the midline with its corresponding duct from the opposite side. The closed end of the fused ducts continues to grow caudally and makes contact with the urogenital sinus and then the formation of the vaginal plate.
- i. In rodents and rabbits, fusion is confined solely to the outer portions of the walls of the ducts while the lumina remain distinct. This results in a separate opening for each uterine lumen into the vagina (uterus duplex).
- ii. In domestic species, the caudal ends of the ducts fuse. Subsequently, the medial fused walls atrophy resulting in the formation of a single tube, the body of the uterus, which has a single opening into the vagina. Those portions of the ducts cranial to the region of fusion remain distinct and are the primordia of the horns of the uterus and the uterine tubes. Thus, in domestic animals the uterus which consists of two horns and a body is referred to as a bicornuate uterus.



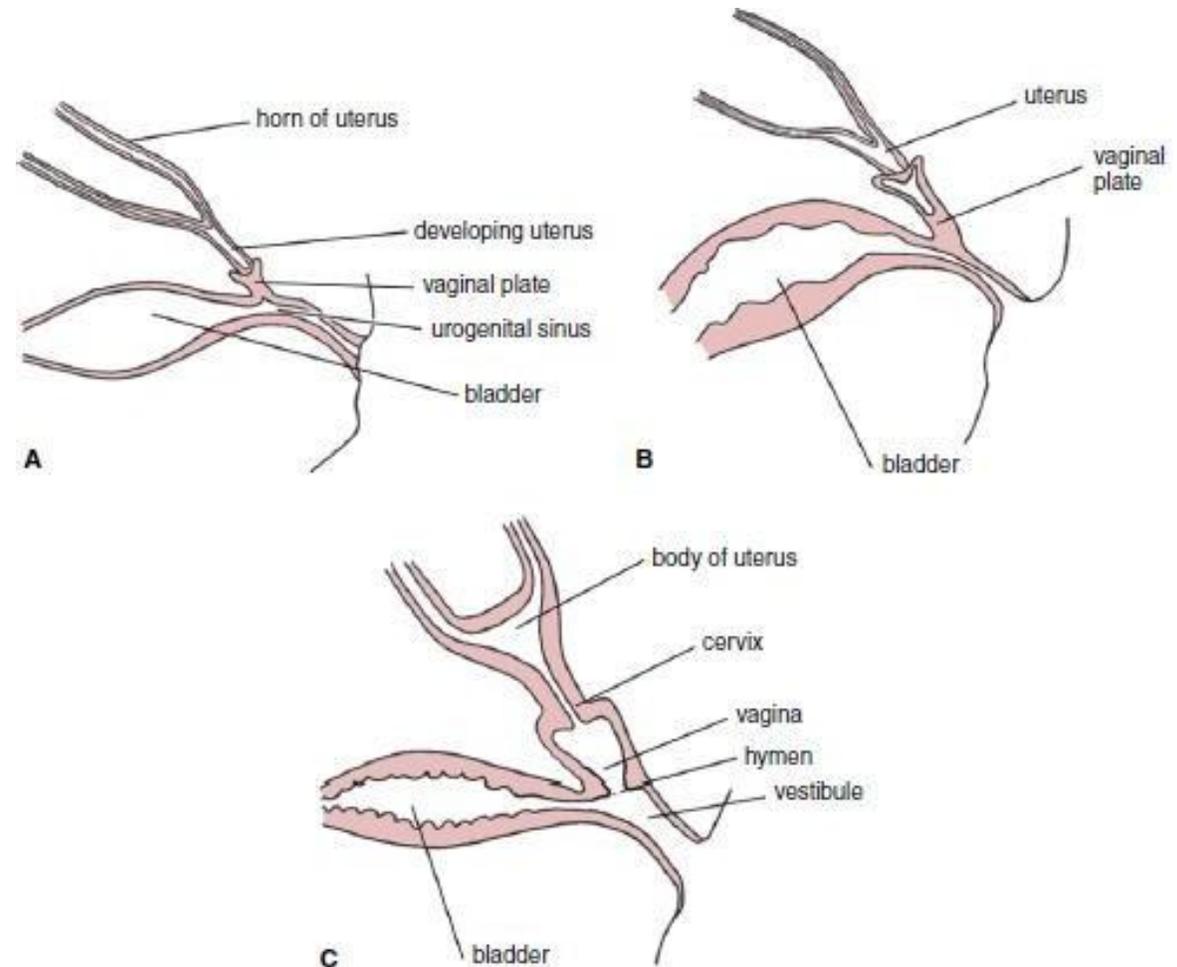
Final anatomical arrangement of the reproductive tracts in selected mammals. The extent of paramesonephric duct fusion determines the shape of the body of the uterus and the nature of its relationship with the vagina. A. Rodent reproductive tract, showing a uterus duplex. B. Porcine reproductive tract, showing a bicornuate uterus. C. Primate reproductive tract, showing a uterus simplex.

Differentiation of the female duct system in mammals

iii. In primates, including humans, extensive fusion of the paramesonephric ducts occurs with associated atrophy along the median line of fusion, resulting in the formation of a large uterine body termed a uterus simplex.

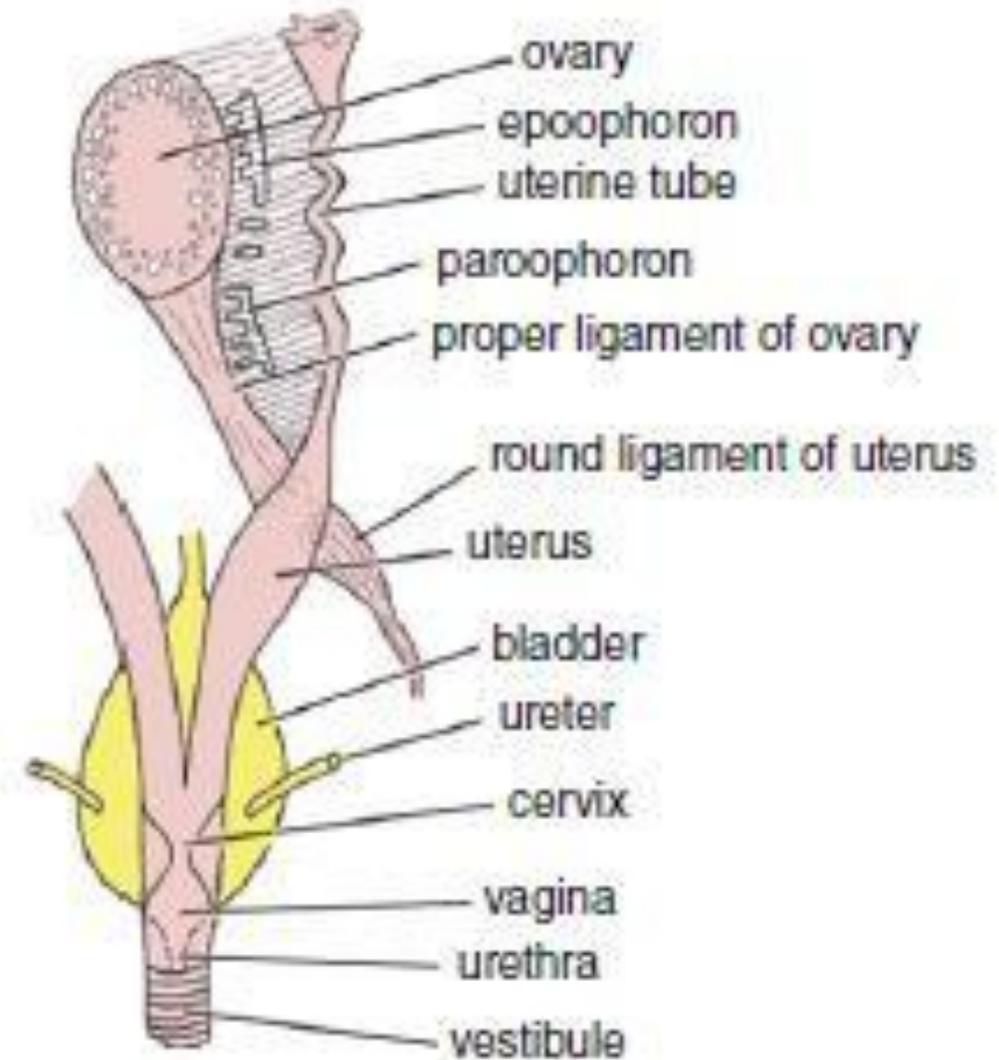
❖ The vagina is derived from both the vaginal plate and the fused ends of the paramesonephric ducts. Subsequently, cannulation of these fused structures occurs forming the lumen of the vagina. Initially, the lumen of the vagina is separated from the urogenital sinus by a thin membrane, the hymen, which subsequently breaks down. In domestic animals, persistence of hymen remnants is less evident than in primates. The caudal portion of the urogenital sinus forms the vestibule.

❖ Epithelial buds, which arise from the primitive urethra and definitive urogenital sinus, form the urethral and vestibular glands, the female homologues of the prostate and bulbourethral glands in the male embryo.



Differentiation of the female duct system in mammals

- Apart from some remnants of the excretory tubules and a small portion of the mesonephric duct, the female mesonephric system atrophies.
- The cranial remnants of the mesonephric tubules form the epoophoron.
- The mesonephric tubules caudal to the developing gonad become the paroophoron and the remainder of the mesonephric duct usually degenerates.
- Occasionally, a caudal portion of the duct persists as Gartner's duct, which may form a cyst in the vaginal wall.



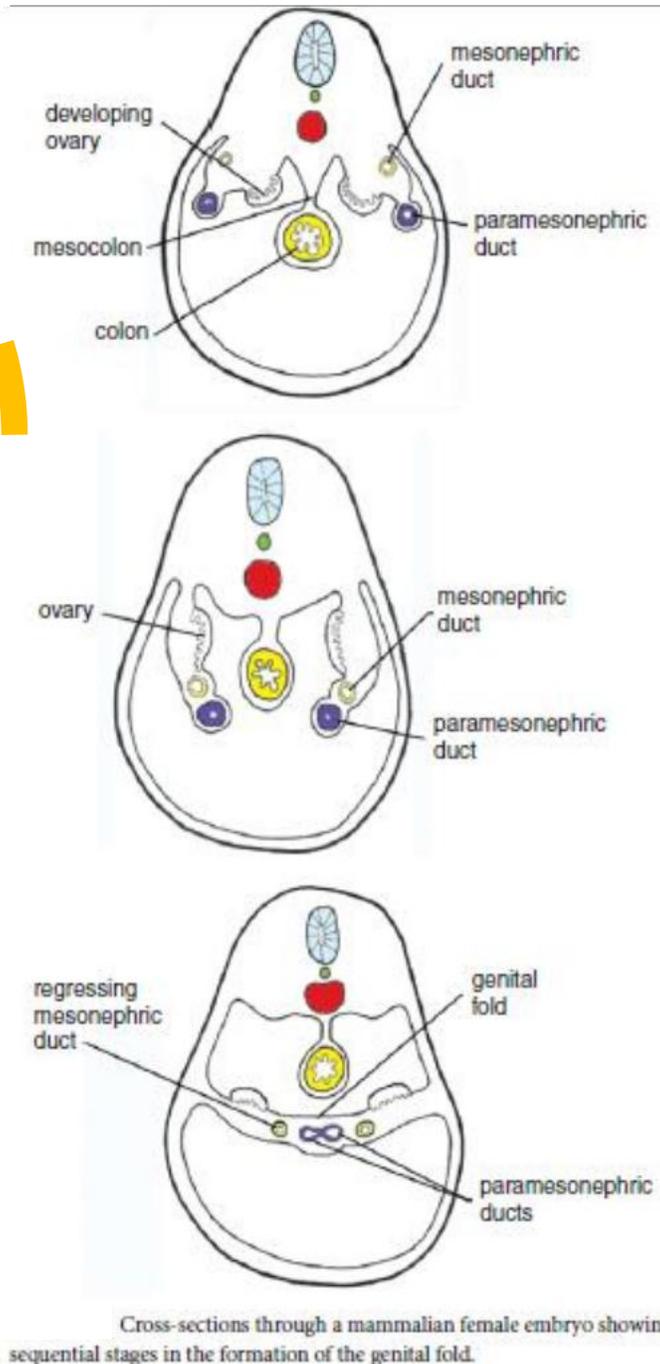
- Two primordial gonads and duct systems develop in avian embryos.
- In almost all genotypic female embryos, **the left gonad and its associated duct continue to develop into functional structures**, while **the right gonad and associated duct remain rudimentary**.
- The left paramesonephric duct gives rise to the different regions of the female reproductive tract from the ovary to the cloaca.



Avian gonads and associated ducts

Formation of the genital fold

- The urogenital system, which develops retroperitoneally, bulges into the peritoneal cavity. With the degeneration of the mesonephros, the gonads and genital ducts become suspended by thin folds of peritoneum. The caudal portions of the genital ducts meet and fuse in the midline. Fusion of their associated peritoneal folds forms the genital fold.
- In the female, this sheet of peritoneum is referred to as the broad ligament of the uterus and is composed of three segments, the mesovarium which suspends the ovaries, the mesosalpinx which suspends the uterine tubes and the mesometrium which suspends the uterus.



External genitalia

- During the undifferentiated phase of sexual development in the embryo, mesenchymal cells from the primitive streak migrate to the region around the cloacal membrane and form two elevated folds, the cloacal folds. These folds fuse ventrally and form the genital tubercle. Later in development, as a consequence of the formation of the urorectal septum, the cloacal membrane is subdivided into an anal and a urogenital membrane. The anal and urogenital membranes subsequently break down allowing communication between the rectum and urogenital sinus and the exterior. Endodermal cells from the urogenital sinus proliferate and grow into the mesoderm of the genital tubercle, forming the urethral plate. The cloacal folds are also divided into the anal folds dorsally and the urogenital folds ventrally. Proliferation of mesoderm lateral to each urogenital fold forms elevations which are termed the genital (labio-scrotal) swellings.

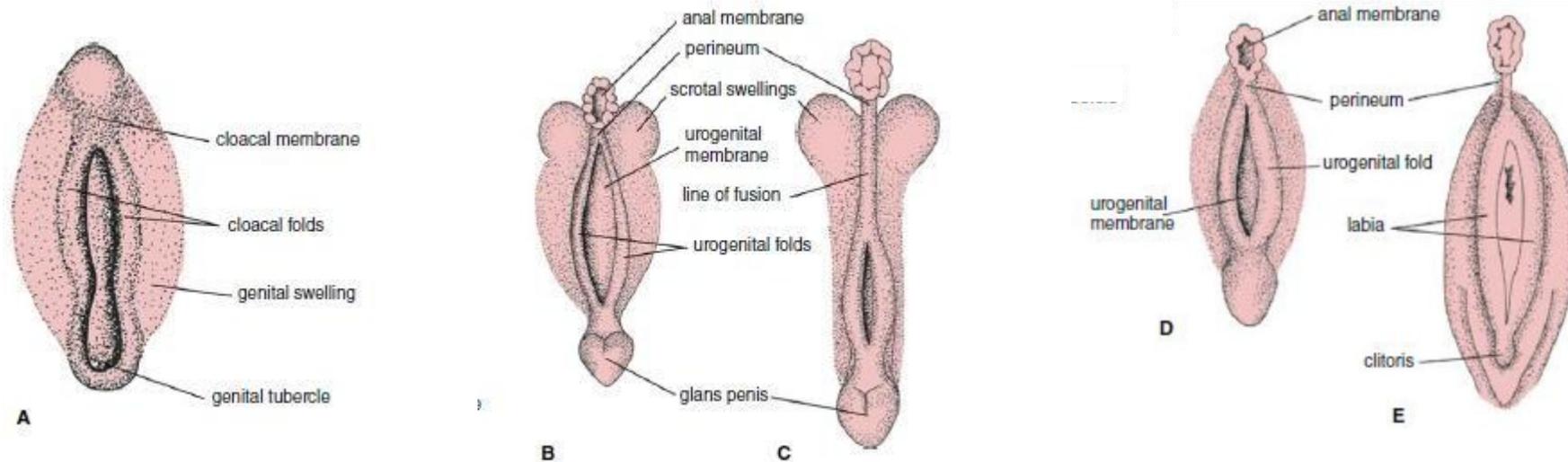


Figure 21.9 Development of the male and female external genitalia. Undifferentiated stage of the external genitalia, A, and sequential stages in the development of the male external genitalia, B and C, and of the female external genitalia, D and E.

Differentiation of the external genitalia

- In the female embryo, the vestibule arises from the caudal end of the urogenital sinus. The urogenital folds, which do not fuse, develop into the labia of the vulva. The genital tubercle, located on the floor of the vestibule, gives rise to the clitoris, which is covered by the labia at the point where these structures meet ventrally.

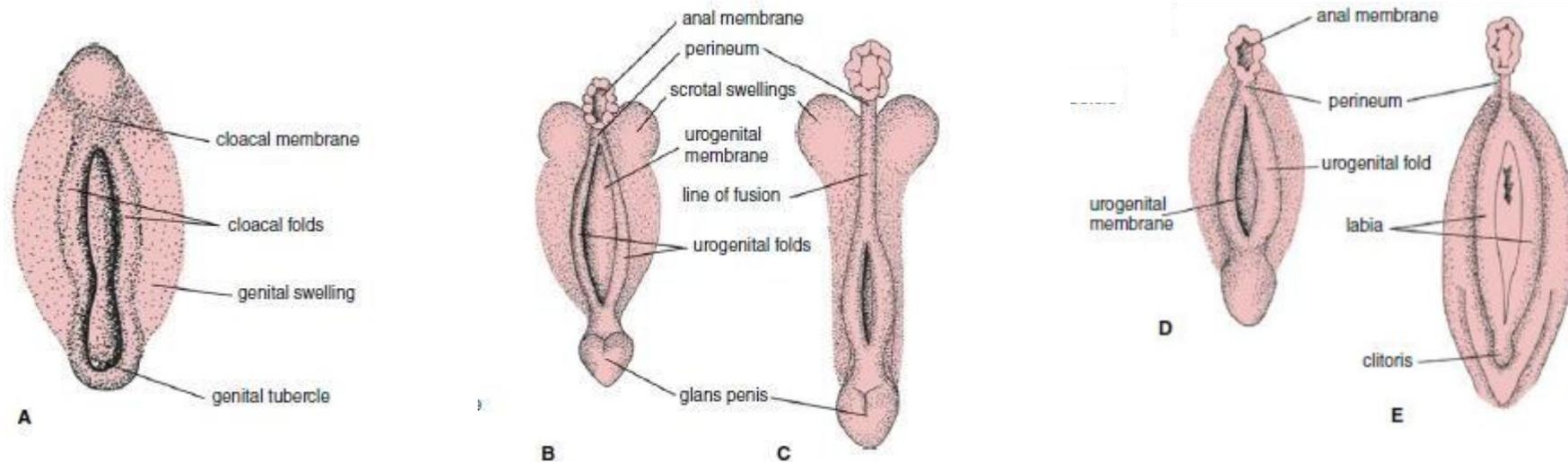


Figure 21.9 Development of the male and female external genitalia. Undifferentiated stage of the external genitalia, A, and sequential stages in the development of the male external genitalia, B and C, and of the female external genitalia, D and E.



Factors which influence sexual differentiation in mammals

- In fish, amphibians and reptiles, the sex of the offspring can be definitively determined by a number of environmental factors, including temperature and light.
- Although gonadal differentiation in mammals is largely determined by the genotype of the zygote, a range of modifying factors can influence gonadal differentiation. In turn, differentiation of the duct system and external genitalia is substantially determined by gonadal hormones.

Molecular aspects of sexual differentiation and gonadogenesis

- The growth factor Wnt-4 contributes to both ovarian differentiation and paramesonephric duct development. Accordingly, inactivation of *Wnt-4* early in embryonic development results in failure of the paramesonephric duct to extend caudally.

Influence of hormones on development of genital ducts and external genitalia

- In the female, under the influence of oestrogens, the paramesonephric ducts develop and differentiate into uterine tubes, uterus and the cranial portion of the vagina. During differentiation, oestrogens act on the external genitalia, inducing the formation of the clitoris, caudal portion of the vagina, vestibule and vulva. Although the sites of oestrogen secretion are not definitively established, it is probable that both maternal and foetal tissues secrete this hormone. Embryonic primordia from which structures in the female reproductive systems arise are presented in table.

Embryonic structure	Derivative in the female reproductive system
Primordial germ cells	Oocytes
Gonad	Ovary
Sex cords	Follicular cells
Mesonephric tubules	Epoophoron, paroophoron
Mesonephric duct	Gartner's duct
Paramesonephric duct	Uterine tube, uterus, cervix and cranial portion of vagina
Definitive urogenital sinus	Vestibule and associated glands
Genital tubercle	Clitoris
Urogenital folds	Labia of vulva
Genital swellings	None

SUMMARY

1. Chromosomal sex is determined at fertilisation.
2. Primordial germ cells migrate to the genital ridge, which subsequently develops into the appropriate gonad and duct system for that sex.
3. An indifferent stage of genital development occurs where primordia of the organs of both sexes co-exist.
4. Depending on the genetically determined sex of the individual, the organs appropriate for that sex develop, while the genital organs of the other sex regress, leaving only vestiges.
5. The sex cords of the gonads develop from intermediate mesoderm.
6. In the female embryo, the uterine tubes, uterus and cervix are derivatives of the paramesonephric duct.
7. External genitalia develop from the genital tubercle and the caudal portion of the urogenital sinus. Tissue differentiation is influenced by sex-specific hormones.

Ovarian migration

- In females, some intra-abdominal migration of the ovary occurs in particular species.
- In dogs and cats, the ovaries occupy a position in the sublumbar region caudal to the kidneys.
- The ovaries of mares migrate to a location midway between the kidneys and the pelvic inlet.
- In cattle and pigs, migration is more pronounced and the ovaries occupy a position at the pelvic inlet.
- The portion of the gubernaculum between the ovary and paramesonephric duct forms the proper ligament of the ovary; the remainder of the gubernaculum forms the round ligament of the uterus which occupies a position in the mesometrium.
- In bitches, the round ligament, which is a prominent structure, enters the deep inguinal ring and may predispose to inguinal herniation.

Anomalies of sexual development

- During the complex series of events involved in the development of the reproductive system, there are numerous opportunities for developmental defects to occur. These anomalies can occur at the chromosomal level, during gonadal differentiation, or at the stage of differentiation of the duct system or of the external genitalia.
- Manifestations of sexuality can be evaluated at a number of levels: genotypic, gonadal, phenotypic and behavioural. Based on collective conformity to these criteria an animal is considered to be male or female. An animal not conforming to these criteria and which exhibits some of the characteristics of both sexes is described as an intersex animal.

Turner syndrome (XO), which is due to non-disjunction, results in a phenotypic female with hypoplastic ovaries, small uterus and underdeveloped external genitalia. Delayed puberty and small stature are features of Turner syndrome. The condition, which is well recognised in humans, has been observed in horses, pigs, dogs and cats.

Ovarian dysgenesis, involving one or both ovaries, has been reported occasionally in domestic animals. A feature of this condition, which occurs in cattle, sheep and pigs, is that the ovaries, which are smaller than normal, have diminished gametogenic activity.

Hypoplasia of both testes and ovaries, which is usually associated with genetic or chromosomal abnormalities, also occurs in domestic animals.

Freemartinism in cattle

The freemartin syndrome is a form of intersexuality which occurs primarily in cattle. The freemartin is a genotypic female (XX) which is born co-twin to a male calf (XY). Although the basis of freemartinism is disputed, two hypotheses, a hormonal hypothesis and a cellular hypothesis, have been proposed to explain the morphological anomalies in affected animals.

a) In cattle, the vascular tips of adjacent chorioallantoic membranes fuse in over 90% of pregnancies involving twins, with resulting vascular anastomoses between the two embryonic circulations. If anastomosis occurs prior to sexual differentiation, the hormone hypothesis proposes that sex-determining factors from the male co-twin exert a marked influence on the undifferentiated reproductive system of the female twin. In such circumstances, the gonads of the female may have the appearance of normal ovaries or may resemble testes. Development of the paramesonephric duct system is partially inhibited and the mesonephric duct system may undergo varying degrees of differentiation. As a consequence of interference with paramesonephric duct development, the cranial portion of the vagina does not develop. However, the urogenital sinus does develop, giving rise to the caudal vagina closed at its cranial end, an enlarged clitoris and a characteristic tuft of hair at the ventral commissure of the vulva. In affected animals, mammary gland tissue and teats are underdeveloped.

b) The cellular hypothesis proposes that XY germ cells from the male co-twin alter the ovarian tissue of the female twin both morphologically and functionally. It is suggested that male germ cells reach the undifferentiated gonad of the female twin, where they subsequently promote a degree of differentiation of male gonadal tissue in the female gonad. Although obvious morphological abnormalities are not reported in male animals born as co-twins to freemartins, testosterone production in such animals is lower than in isosexual twins and these male animals have reduced fertility.

Transfer of cells between bovine dizygotic twins is not confined to germ cells alone, as haematopoietic stem cells are also exchanged between such twins. As a result of the exchange, each twin has a mixture of red blood cell types and they exhibit mutual immunological tolerance to tissue transplanted from one to the other. Freemartinism can be confirmed by clinical examination, by demonstration of chromosome chimerism (XX/XY), by blood typing and by the acceptance by one twin of skin grafts from the other.

Freemartinism in species other than cattle

- In sheep, dizygotic twinning occurs more frequently than in cattle. The occurrence of vascular anastomoses of the chorioallantoic blood vessels of ovine twins is reported to range from 1 to 65%. However, cytogenetic tests on heterosexual twins suggest that exchange of cells *in utero* is minimal and the incidence of freemartinism in sheep is approximately 1%. Freemartinism is reported infrequently in pigs and goats.



Thank you for your attention.

