THE PLACENTA AND FETAL DEVELOMPENT

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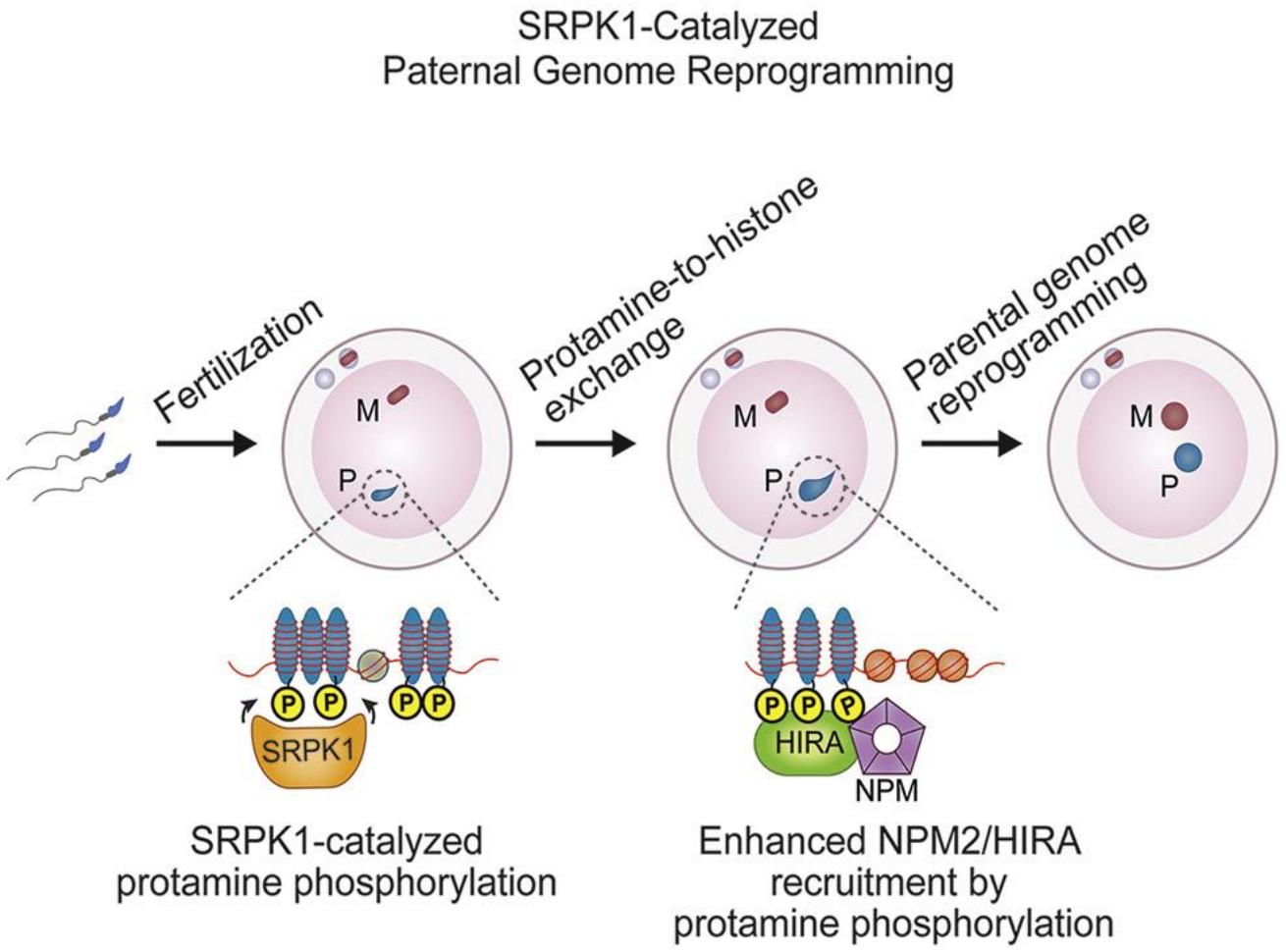
Fertility

- The LH surge occurs at the midpoint of the menstrual cycle in 30% of women.
- In 60%, it occurs within a1 day window of the midpoint
- In 95%, it occurs within a 3 day window of the midpoint.
- Spermatozoa are largely viable for only 24 hours (though they may be found for days in the vagina).
- In a woman with a 26-32 day cycle, days 8-19 encompass the period of fertility.

Fertility

- Clomiphene activates estrogen receptors in the pituitary gland.
- Fertility drug.
- Mifepristone inhibits progestins at progesterone receptor (abortifacient).



Lan-Tao Gou et al, Initiation of Parental Genome Reprogramming in Fertilized Oocyte by Splicing Kinase SRPK1-Catalyzed Protamine Phosphorylation, *Cell* (2020). DOI: 10.1016/j.cell.2020.02.020 Accessed 03/13/2020

Mechanism

- The paternal genome undergoes a massive exchange of histone with protamine for compaction into sperm during spermiogenesis.
- Upon fertilization, this process is potently reversed, which is essential for parental genome reprogramming and subsequent activation.
- Splicing kinase SRPK1 initiates this life-beginning event by catalyzing site-specific phosphorylation of protamine, thereby triggering protamine-to-histone exchange in the fertilized oocyte.

Mechanism

- Protamine undergoes a DNA-dependent phase transition to gel-like condensates and SRPK1-mediated phosphorylation opens up such structures to enhance protamine dismissal by nucleoplasmin (NPM2) and enable the recruitment of HIRA for H3.3 deposition.
- Selective chromatin accessibility in both sperm and MII oocytes is largely erased in early pronuclei in a protamine phosphorylation-dependent manner.
- SRPK1-catalyzed phosphorylation initiates a highly synchronized reorganization program in both parental genomes.

Fertilization

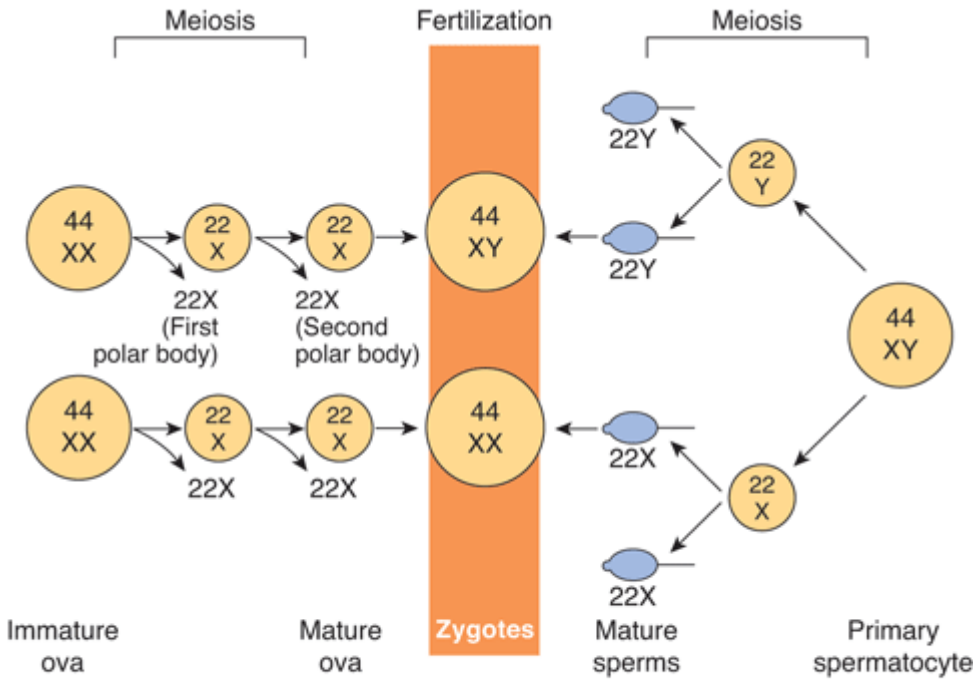


Fig. 25-2 Accessed 07/01/20102000.)

Fertilization

- On day 0, the ovum is released into the fallopian tube.
- In phase 1, the acrosome of the spermatozoön is capacitated and is able to penetrate the corona radiata cells that are on the exterior of the ovum.
- In phase 2, the inner acrosome membrane dissolves and fusion of the speramatozoön with the oöcyte occurs.
- Following fusion, the second meiotic division of the oöcyte occurs.
- The male pronucleus is formed; pronuclear membranes are then broken down.

Embryonic development

- On day 3, dividing cells (blastomeres) form cell ball (morula).
- On day 5, blastocyst forms. Implantation by day 7 (usually on posterior uterine wall surface).
- Implantation in the fallopian tube or abdomen may lead to ectopic pregnancy (symptoms related to fetal growth).
- Implantation at cervical os leads to abruptio placentae.
- Placenta accreta occurs with adherence to myometrium
- Percreta if penetrates myometirum.

Embryonic development

- The embryoblast forms a compact mass at one end of the cavity (inner cell mass) and the outer cell mass is organized into a thin single layered epithelium.
- There is a hypoblast and an epiblast at the 8th day.
- Formation of the bi-laminar disk.
- The layer of hypoblast is called the extra-embryonic endoderm and the exo-coelomic cavity is now called the primary yolk sac.
- The entire lining of the cavity is called Heuser's membrane.
- Extra-embryonic reticulum is secreted between the extra-embryonic endoderm and the cytotrophoblast.

Embryoblast

- Extra-embryonic vessels form initially from the yolk sac.
- Embryonic vessels form shortly after the extra-embryonic vessels.
- Cytotrophoblast and syncytiotrophoblast form amniotic and chorionic cavities.
- Definitive secondary yolk sac.
- Within the chorionic cavity the extra-embryonic mesoderm consists of somato-pleuric and splanchno-peluric divisions.
- The syncytiotrophoblast invades the uterine wall at implantation and induces blood vessel formation.

Embryonic development

- During the first week the embryo receives nutrients and eliminates waste products through simple diffusion.
- On day 9, the uteroplacental circulation begins to form (primary stem villi).
- On day 16, the extra-embryonic mesoderm extends into the primary stem villi making them secondary stem villi.
- By the end of the third week, the villus has formed blood vessels that connect to forming fetal blood vessels (tertiary stem villi).

Embryonic development

- The embryonic disk becomes elongated and is broader at the cephalic end.
- Gastrulation.
- On day 15 epiblast cells begin to migrate toward the midline forming a groove (primitive streak).
- Cells invaginate and give rise to endoderm, mesoderm, and ectoderm. (Tri-laminar embryo).
- Neuralation.
- Cells that migrate cranially form notochord.
- Induce neural tube.

Embryonic development

- The notochordal process develops as a hollow tube-like invagination from the primitive pit and extends from the primitive pit to the prechordal plate.
- It fuses with endoderm and becomes a notochordal plate.
- The notochordal plate detaches and forms a solid cord (notochord).
- The notochord is composed of mesodermal and endodermal cells.
- Tri-laminar embryonic disk.

Embryonic development

- Ectoderm thickens to form the neural plate.
- Fusion continues in both cranial and caudal directions.
- The fusion of the neural folds results in the formation of the neural tube.

Embryonic development

- At day 20, the paraxial mesoderm begins to form somitomeres, in a rostral to caudal sequence.
- The somitomere consists of mesoderm cells arranged in concentric whirls around a center.
- In the head, somitomeres form neuromeres.
- From the occipital region caudally, somitomeres form somites.
- These are arranged segmentally.
- The first occipital and the coccygeal segments are lost.

Embryonic development

- On day 22, the neural plate invaginates to form the neural tube and neural crest.
- Neural folds make contact in the area of the four occipital somites and first cervical somite.

Embryonic development

- Neural tissue stratified. Migration occurs in waves.
- Wave 1: Neuro-epithelial cells near the ventricle (ventricular layer) continually divide and give rise to neuroblasts.
- Cell bodies and astrocytes are found in middle layer.
- Marginal (sub-pial) layer contains nerve fibers and oligodendrocytes.
- Wave 2: Macroglioblasts will form most glia cells (microglia come from mesenchyme not ectoderm).
- Failure of migration leads to multiple cysts or smooth cerebral convolutions or even heterotopic tissue.

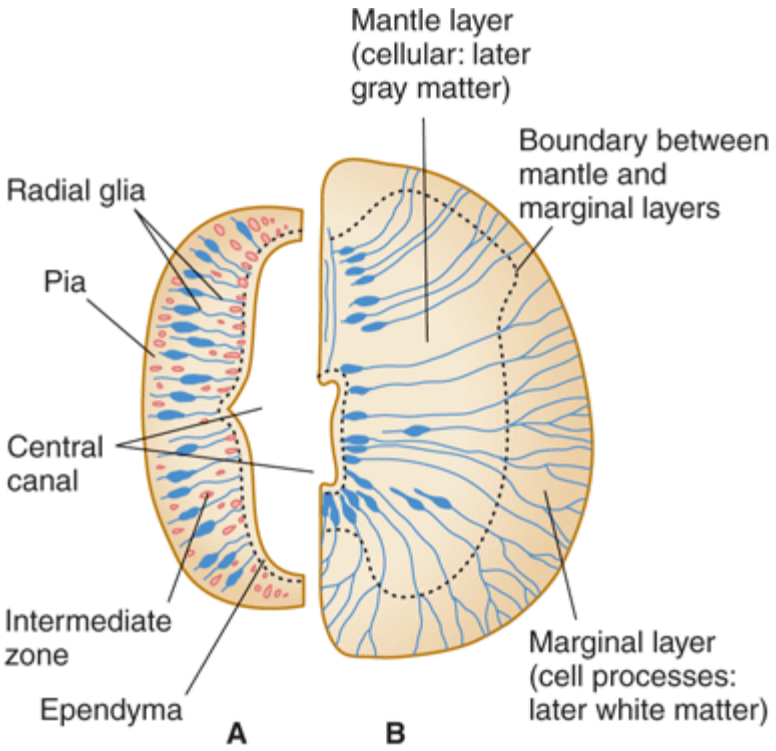
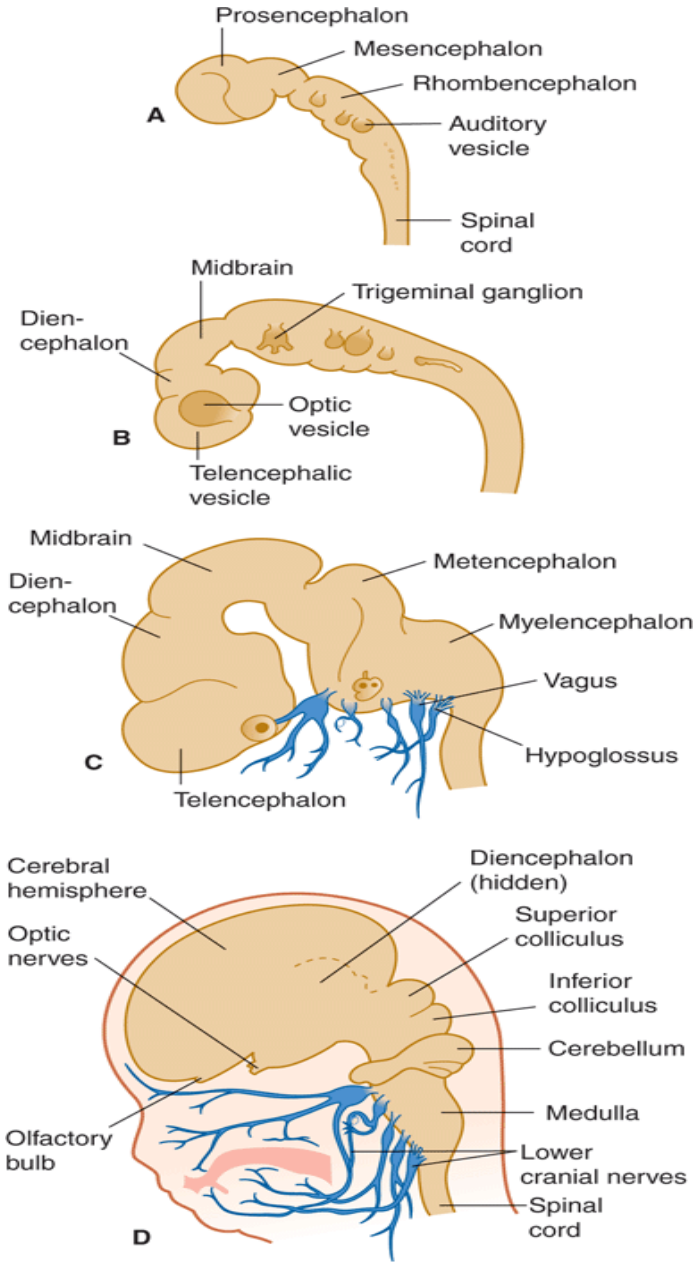


Fig. 2-1 Accessed 05/01/2010

Embryonic development

- The brain is derived from the neural tube rostral to the 4th somite pair.
- Three primary vesicles form:
- Prosencephalon (evolves to telencephalon and diencephalon)
- Mesenchephalon
- Rhombencephalon (metencephalon and myelencephalon).
- Longitudinal fold (head-tail fold) occurs in the sagittal plane and is due to the rapid growth of the CNS as well as differential growth within the embryo.
- As a result of folding the flat tri-laminar embryo becomes a tubular embryo.

Embryonic development (overview)

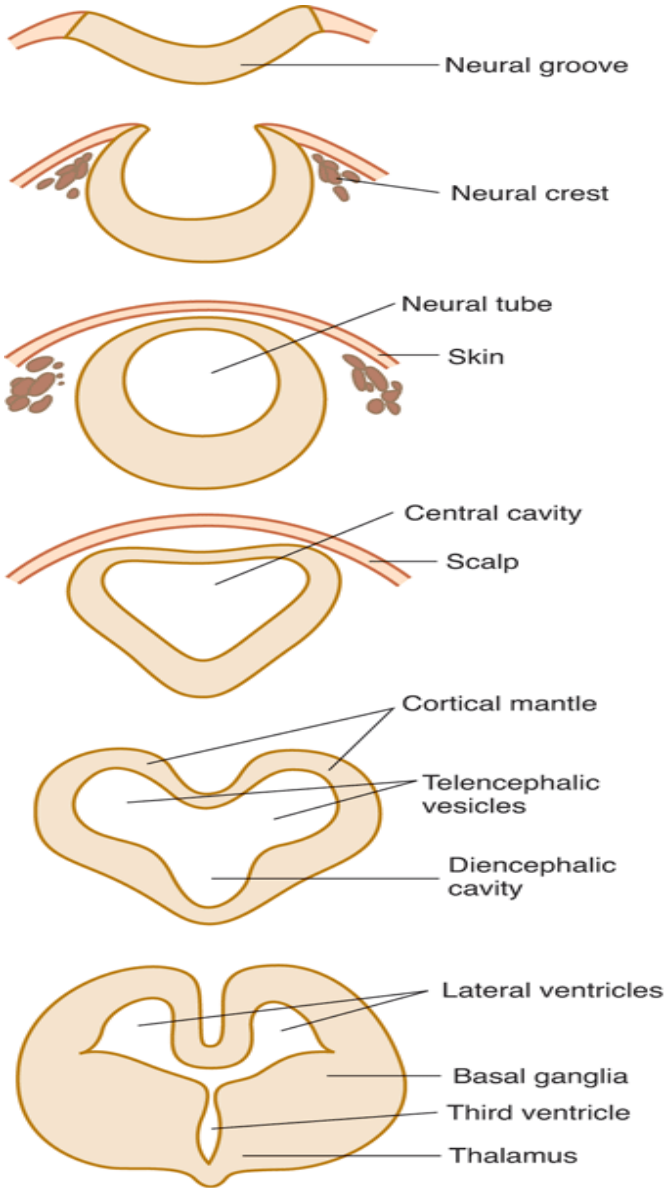


Source: Waxman SG: *Clinical Neuroanatomy, 26th Edition*: http://www.accessmedicine.com

A: 3½ weeks
B: 4½ weeks C: 7 weeks
D: 11 weeks

Fig. 7-1
Accessed 05/01/2010

Embryonic development (overview)



Source: Waxman SG: *Clinical Neuroanatomy, 26th Edition*: http://www.accessmedicine.com

Cross sections showing early development from neural groove to cerebrum.

Fig. 10-1 Accessed 07/01/2010

Embryonic development

- The mantle zone differentiates into an alar plate, which contains mostly sensory neurons, and a basal plate, which is primarily composed of motor neurons.
- These two regions are demarcated by the sulcus limitans, a groove on the wall of the central canal.
- The alar plate differentiates into a dorsal gray column; the basal plate becomes a ventral gray column.
- The processes of the mantle zone and other cells are contained in the marginal zone, which becomes the white matter of the spinal cord

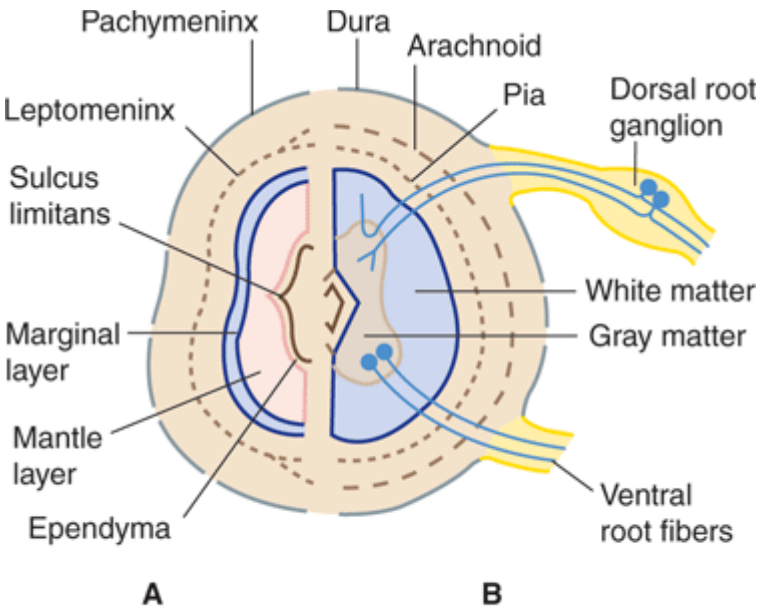
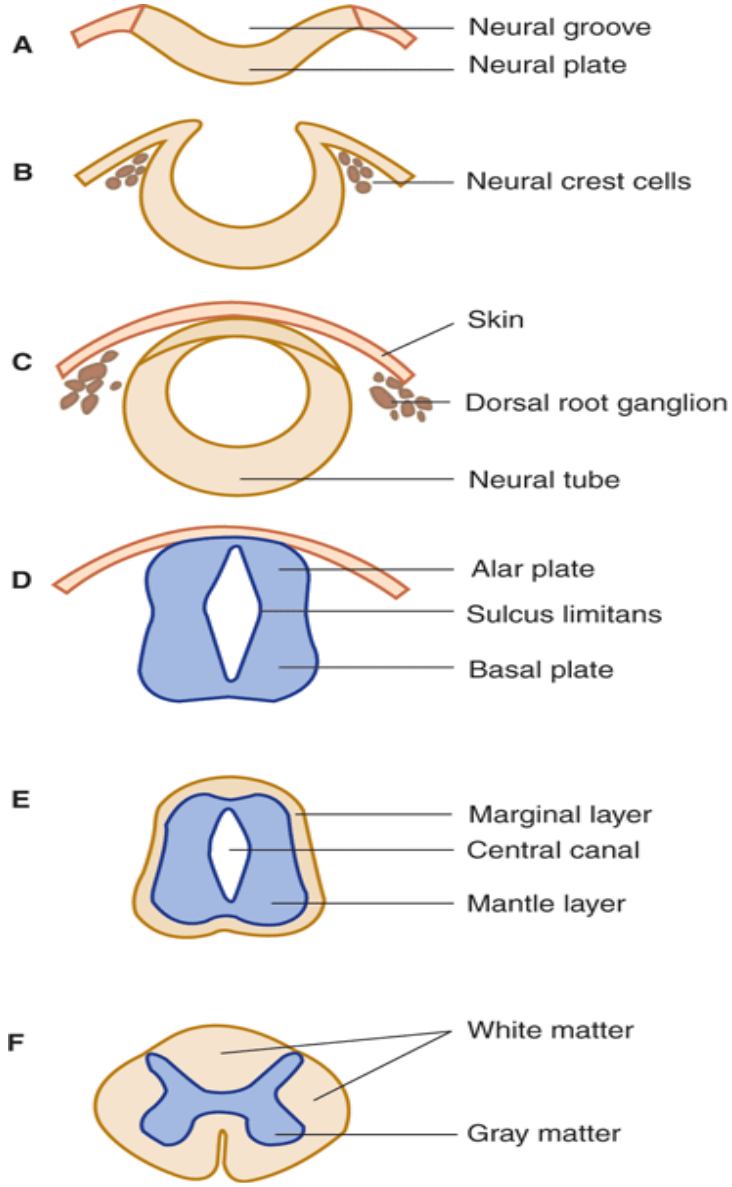


Fig. 5-2 Accessed 05/01/2010

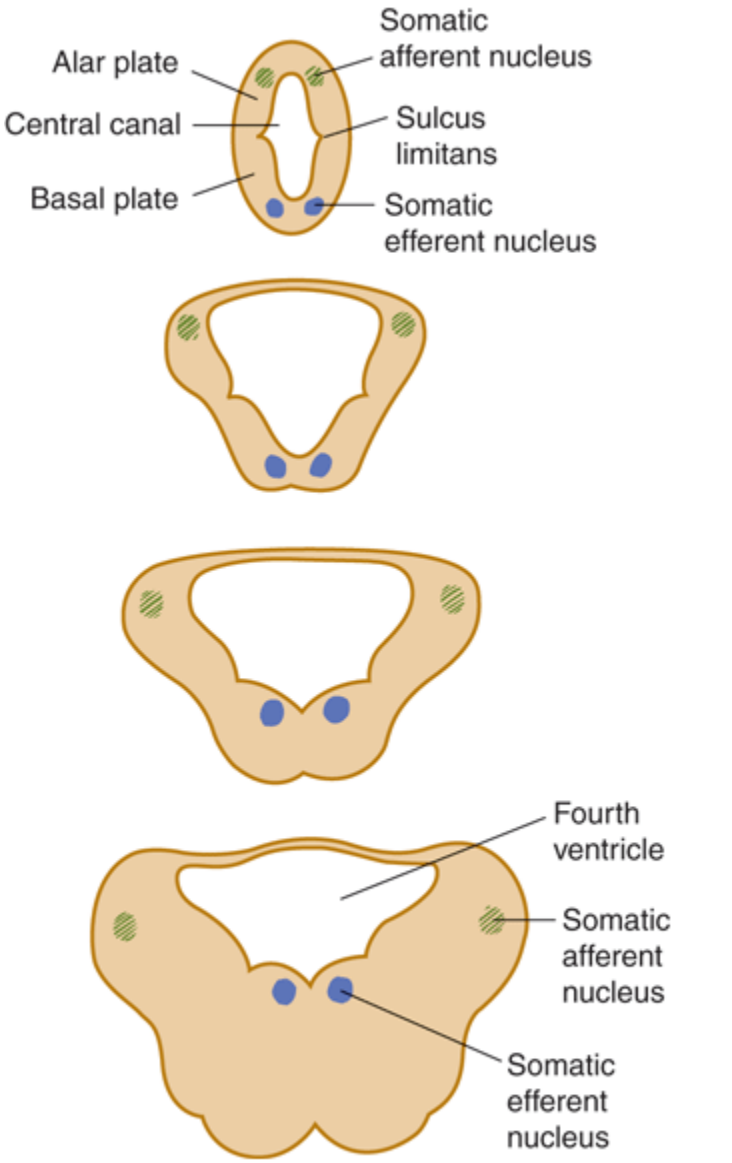
Embryonic development (overview)



Source: Waxman SG: *Clinical Neuroanatomy, 26th Edition*: http://www.accessmedicine.com

Fig. 5-1 Accessed 05/01/2010

Embryonic development (overview)



Source: Waxman SG: *Clinical Neuroanatomy, 26th Edition*: http://www.accessmedicine.com

A similar arrangement occurs in the brainstem. However in the upper medulla and pons, structures are shifted by the development of the fourth ventricle.

Fig.7-2 Accessed 05/01/2010

Embryonic development

- The migration of cells from the primitive streak continues to week 4 after which the streak regresses.
- The primitive streak and primitive node play essential roles in the determination of body axes.
- At the 4^{th} week of gestation, the body cavity forms in the space between somatic and splanchnic layers of the lateral plate mesoderm.
- The rostral and caudal ends of the embryo gut tube end blindly.

Embryonic development

- The yolk sac and allantois remain outside the embryo. (Secondary yolk sac)
- The yolk sac functions to transfer nutrients during second and third weeks.
- The central opening of the gut tube remains in communication with the yolk sac through the vitelline duct .
- Hematopoiesis and germinal cell formation begin in the yolk sac.
- The allantois also participates in hematopoiesis.
- Vessels persist as umbilical veins and artery.
- Urachus connected to bladder.

Embryonic development

- Diverticulum from pharynx gives rise to the larynx, trachea, bronchi, and lungs.
- At week 4, organogenesis begins. Limb buds form.
- Optic and otic placodes begin eye and ear formation

Embryonic development

- Cardiac precursor cells arise from the epiblast.
- They are associated with splanchnic mesoderm.
- The underlying endoderm induces these cells to form cardiac myoblasts.
- At the same time blood islands are forming nearby.
- Cardiac cells surround the blood islands, forming a horseshoe shaped tube (the cardiogenic field).
- Two laterally situated tubes are present by day 19.
- The heart is beating.

Embryonic development

- Initially the cardiac tube is suspended by a dorsal mesentery.
- At this point the heart consists of endothelium and splanchnic mesoderm.
- The splanchnic mesoderm develops into two layers (the myocardium and the cardiac jelly).
- Cells from the splanchnic mesoderm also migrate and give rise to epicardium.
- The result is a three layered tube.

Embryonic development

- By day 21, the bulbus cordis moves anteriorly, inferiorly and to the right.
- The ventricle moves anteriorly, inferiorly and to the left.
- The atrium shifts posteriorly and superiorly.
- Rotation at the 5^{th} week permits the right sinus horn to be incorporated into the right atrium (sinus venarum).
- Valves form for the inerfior vena cava and the coronary sinus.
- The crista terminalis divides the trabeculated part of the right atrium from the sinus venarum.
- The moderator band (septomarginal trabecula) is located in the right ventricle.

Embryonic development

- At the 5th week, the coelom fuses, separating the embryo from the yolk sac, creating the intracoelomic space.
- It partitions further with the formation of the cardiac and pulmonary systems.
- Paired lateral ridges fuse to separate the respiratory from the digestive system.
- At the 5th week, the transverse septum gives rise to the central tendon of the diaphragm
- A small area lateral to the central tendon arises from the pleuroperitoneal membrane
- The somatic mesoderm gives rise to the muscular part of the diaphragm while the mesentery of the esophagous forms the crura of the diaphragm.

Embryonic development

- During the 4th and 5th weeks of development, pharyngeal arches form at the cranial end of the embryo and each of the arches receives a blood vessel.
- Endoderm.
- The first of four paired pouches gives rise to the tympanic cavity, mastoid antrum, and the auditory tube.
- The first pharyngeal cleft forms the external auditory meatus.
- The first membrane forms the tympanic membrane.
- The other clefts and membranes regress.

Embryology

- The pharyngeal arches arise from the mesoderm.
- The first pair of arches receives CN V.
- Muscles of mastication.
- The second pair of arches receives CN VII.
- Muscles of facial expression.
- The third pair of arches receives CN IX.
- Stylopharyngeus.

Embryology

- The fourth pair of arches receives CN X.
- Palatal and pharyngeal muscles as well as the cricothyroid muscle.
- There is no fifth pair of arches.
- The sixth pair of arches receives CN X.
- Muscles of the larynx.

Embryology

- Parietal and occipital bones derived from paraxial mesoderm.
- All other bones of skull and face are derived from neural crest.
- The neural crest within the arches gives rise to cartilage and arteries.
- At the first arch pair, Meckel’s cartilage gives rise to the malleus and incus.
- The maxillary artery is at the first arch.
- At the second arch pair, Reichert’s cartilage gives rise to the stapes.
- At the third arch pair arise the common carotid arteries.

Embryonic development

- The fourth arch pair results in the right subclavian artery and the arch of the aorta on the left.
- The sixth arch pair give rise to the pulmonary arteries.
- The ductus arteriosus arises from the left arch only.
- During the 5th week of development, three systems of veins can be observed:
- Vitelline (omphalomesenteric)
- Umbilical
- Cardinal.

Embryonic development

- The ductus venosus bypasses the sinusoids of the liver.
- After birth the left umbilical vein obliterates to form the ligamentum teres hepatis.
- After birth the ductus venosum obliterates to form the ligamentum venosum.

Early limb development

- The ventral and medial parts of the somite dissociate and shift position (during the 4th week) and are known as the sclerotome.
- Cells of the sclerotome surround the neural tube and notochord and migrate laterally to form limb precursors.
- The remaining part of the somite gives rise to a dermato-myotome.
- Somites stimulate the somatic layer of lateral plate mesoderm to evaginate.
- The somatic layer of lateral plate mesoderm forms a core of mesenchyme covered by surface ectoderm.

Early limb development

- The earliest sign of limb development are the limb buds.
- Buds appear low on the embryo because of the large developing head.
- The upper limb bud (cervical, thoracic) appears by day 26; the lower limb bud (lumbar, sacral), by day 28.
- The distal ends of the limb buds flatten into paddle like plates, called hand and foot plates and by the end of the 6^{th} week, the mesenchyme in the hand plate has condensed to form digital rays (finger buds).

Early limb development

- By the end of the 7th week, the mesenchyme in the foot plate has condensed to form digital rays (toe buds).
- At the tip of each ray the apical ectodermal ridge (AER) induces bone formation.
- Loss of connective tissue between rays leads to separation of digits.
- Upper limbs rotate medially 90°; lower limbs, laterally 90° to reach anatomical position.

Embryonic development

- At 4-8 weeks gestation, secondary and tertiary bronchi form
- At 5-16 weeks, conducting bronchi.
- At week 8, organogenesis complete.
- At week 9, the face is developing; ears are low set, and the eyelids are fused.
- External genitalia can be distinguished.
- The liver is the major site of hematopoiesis.
- At week 10, the fetus is producing urine.
- At week 10, sexual differentiation noted.

Fetal development

- At week 11, the intestines have returned to the abdomen. (270° rotation about superior mesenteric artery.)
- At week 12, the spleen is the major site of hematopoiesis.
- At week 13, the eyes face forward; eye movements are noted. Hair is present on skin and scalp.
- At 16-25 weeks, respiratory bronchioles form
- The production of surfactant from type II cells begins at week 24.

Fetal development

- By weeks 17-20, the limbs have reached their final relative proportions and there are increased limb movements.
- The skin is covered in a waxy secretion (vernix caseosa) consisting of secretions from sebaceous glands and dead epithelial cells.
- There is an extensive covering of hair (lanugo) that helps to hold the vernix caseosa on the skin.
- Brown fat is formed.

Fetal development

- Primary ovarian follicles are formed in females; testes are descending in males.
- By week 25, blink and startle reflexes are present.
- Surfactant is beginning to be secreted in lungs. Fingernails are present.
- By week 26, the lungs are capable of breathing. The CNS is able to maintain breathing and body temperature.
- Fat is beginning to accumulate.
- The fetus is viable.
- By week 28, hematopoiesis begins to shift to the bone marrow.

Fetal development

- By week 30, hematopoiesis chiefly occurs in the bone marrow.
- Fat then comprises 8% of body weight.
- Alveolar increase begins at week 32.
- By weeks 35-38, fat will increase, to comprise 16% of body weight.
- Testes will have descended into scrotum in males.
- Lungs and kidneys mature.
- Head proportion normalized.

Fetal development

- Rapid increase in fetal size outpaces the growth of the uterus (and volume of amniotic fluid).
- May constrain growth and compress fetus, leading to deformation.

Ectoderm

- The surface ectoderm gives rise to the epidermis, hair, nails, sweat (and mammary) glands, lining of the mouth and anorectum; the anterior pituitary; enamel of the teeth; internal ear; lens of the eye.
- The neural crest is also ectoderm.

Neural crest derivatives

- Parasympathetic ganglia of CN III, VII, IX and X
- Sensory ganglia of CN V, VII, VIII, IX and X
- Autonomic and dorsal root ganglia
- Connective tissue around the eye; optic nerves; muscles of the pupil and ciliary body
- Pia mater and arachnoid of the occipital lobe
- Mesenchyme of the head; bones of nose, face, middle ear, and neck
- Dermis, smooth muscle, fat of the face; odontoblasts
- Schwann cells
- Chromaffin cells of the adrenal medulla as well as neurosecretory cells of the heart and lungs.

Endoderm

- The endoderm of the embryo contributes to the yolk sac.
- The primitive gut tube is bound at each end by the bucco-pharyngeal and cloacal membranes.
- The lateral folding of the embryo results in the incorporation of the allantois (forms the cloaca).
- Endoderm also forms the epithelium of the respiratory tract, bladder, urethra, tympanic cavity and auditory tube
- The parenchyma of the thyroid, parathyroid, liver and pancreas; the stroma of the tonsils and thymus.

Mesoderm

- The paraxial mesoderm forms the axial skeleton, voluntary musculature and part of the dermis.
- The intermediate mesoderm forms the urinary system and parts of the genital system
- The lateral plate mesoderm splits into two layers.
- The splanchnic mesoderm is associated with the endoderm and the somatopleuric mesoderm is associated with the ectoderm.

Common teratogens

- Alcohol (leading cause of mental retardation)
- ACE inhibitors (renal damage)
- Cocaine (abnormal fetal development)
- Iodide (congenital goiter)
- 13-cis-retinoic acid (multiple anomalies)
- Thalidomide (limb defects). Employed in treatment of myeloma
- Warfarin (multiple anomalies)

Pattern formation

- General body plan laid down in embryo.
- Regional separation, patterns for organs and appendages are established in stages.
- Define cells in the region.
- Establish signaling centers to provide positional information (relative positions of cells).
- Differentiation of cells in response to cues.

Types of genetic mediators

- Paracrine signaling molecules.
- Secreted into intercellular spaces.
- Diffuse to nearby cells.
- Mediates interactions between nearby cells.
- Four major families are fibroblast growth factor (FGF), hedgehog (SHH) proteins, wingless family (WNT), and transforming Growth Factor-β (TGF-β).

Types of genetic mediators

- DNA transcription factors.
- Bind DNA, activate or repress gene expression.
- Control gene expression in cell.
- Respond to external stimuli.
- Targets may be transcription factors.
- Cascade effect.
- Major families include Homeobox (HOX, PAX, EMX, MSX), High-mobility group (HMG, SOX), T-box (TBX).

Types of genetic mediators

- Extracellular Matrix Proteins.
- Serve as scaffolding for tissues and organs.
- Facilitate cell migration.
- Secreted proteins that form scaffold for tissues (Collagens, fibrillins, elastins, laminins, fibronectins, tenascins).
- Fibrillin–1 and elastin coordinate microfibril assembly in extracellular matrix.
- Laminin important in anchoring cells to extracellular matrix.
- Separate cells.
- Provide matrix for migration.

Extracellular matrix proteins

- Cells bind to extracellular matrix using specific proteins.
- Integrins are the link between extracellular matrix and cytoskeleton.
- Glycosyltransferases bind glycosyl residues on the extracellular matrix.

Telos

- Cell type, function, longevity is established during development.
- Sonic hedgehog (SHH) involved in process. Produced at base of limbs in zone of polarizing activity.
- Affect neural tube, somites, limbs.
- Affect left-right axis.
- Defects disrupt midline brain development.
- Holoprosencephaly is severe form. Severe mental retardation and early death.

Axis specification

- Vertebrate body plan has three axes:
- Anterior-posterior axis is first to form.
- Derives from growth of primitive streak.
- Patterning along the axis is due to HOX genes.
- Clusters of four similar genes (A-D) on different chromosomes.
- HOX genes expressed from anterior boundary rearward in embryo in specific temporal order.
- Similar rules for each cluster.
- Segment transforms, called homeotic transformation.
- Valproic acid disrupts homeobox transcription.

Dorsal-ventral axis.

- Wnt-7 is produced at apical ectodermal ridge.
- Necessary for proper organization along dorsal-ventral axis.
- Noggin and chordin are dorsalizing signals.
- Bmp4 is ventralizing signal.
- Noggin and chordin bind Bmp4, prevent binding to receptor.
- Antagonistic pattern common in development.

SOX family

- Prototype is SRY, the sex-determining region of the Y chromosome.
- Regulate SOX9 expression in genital ridge.
- SOX9 regulates chondrogenesis and COL2A1.
- Mutation causes camptomelic dysplasia.
- Short limbs, sex-reversal of XY fetuses.
- Sox10 abnormality is one of neural crest. Hirschsprung disease.

Left-right axis

- Laterality defects can be random (situs ambiguus) or reversed (situs inversus), and involve one or many organs.
- Asymmetric SHH from notochord causes left side expression of primitive node (TGFβ).
- Palatogenesis affected as well via TGFβ
- Rightward looping of heart tube results.
- Mutation in dynein, the motor protein for cilia.

Left-right asymmetry

- Zinc-finger protein of the cerebellum (zic3). GLI transcription factor family on X chromosome.
- GLI family regulated by forming complex with protein similar to dynein.
- Randomization defects; males affected.
- Heterozygote females, left-right reversal.
- More common in conjoined than normal twins.
- Inadequate signaling from left-side twin.

Anterior-posterior limb

- Anterior defects in Holt-Oram syndrome.
- Thumb, radius defects most common.
- T-box gene TBX5 mutated.
- Posterior defects in ulnar-mammary syndrome.
- Posterior digits, ulna most affected.
- TBX3 mutated, closely linked to TBX5.
- Have similar but complementary roles.

Limb development

- Second only to heart defects in human newborns.
- FGF8 is candidate for inductive signal.
- Produced at apical ectodermal ridge. S
- timulates mitosis of underlying mesoderm, providing for lengthening of limbs.
- Can induce entire limb program.
- Signal mediated by FGF10 expression in mesoderm.
- WNT2b and WNT8c maintain FGF10 expression.

Proximal-distal axis

- Proximal-distal growth stimulated by FGF2, FGF4 and FGF8.
- Stimulate proliferation of mesodermal cells in progress zone.
- The zone of proliferating activity uses SHH to maintain the apical ectodermal ridge. Also used in dorsal-ventral and left-right axis.
- The zone of proliferating activity also signals positional information along the proximal-distal axis.

Proximal-distal axis

- Skeletal dysplasias caused by FGFR mutations. Increased activity inhibits chondrocyte growth.
- Most common due to autosomal dominant FGFR3 mutations.

Placental hormones

- Human chorionic gonadotropin interacts with the luteal HCG receptor and promotes the maintenance of the corpus luteum during the beginning of pregnancy, causing it to secrete progesterone.
- HCG is upregulated by cAMP.
- Due to its highly-negative charge, HCG may repel the immune cells of the mother, protecting the fetus during the first trimester.
- The hormone is produced by villous syncytiocytotrophoblasts.
- HCG is heterodimeric.
- The α unit resembles LH, FSH, TSH. The β unit is unique to HCG.

Placenta

- The maternal part of the placenta is called the decidua and is the endometrium in pregnant women.
- It is called decidua because it falls away from the rest of the uterus after birth.
- The decidua basalis lies at the base of the placenta
- The parietalis is the remainder of the endometrium
- The capsularis surrounds the placenta.

Placenta

- Composed of chorionic villi that sprout from the chorion to provide a large contact area between the fetal and maternal circulations.
- In the mature placenta, the maternal blood enters the intervillous space through endometrial arteries (spiral arteries) and circulates around the villi to allow gas and nutrient exchange.
- The deoxygenated blood flows back from the intervillous space to the decidua and enters the endometrial veins.
- Maternal vessels connect with villi but not with fetal vessels.
- Maternal blood lies in the intervillous spaces.

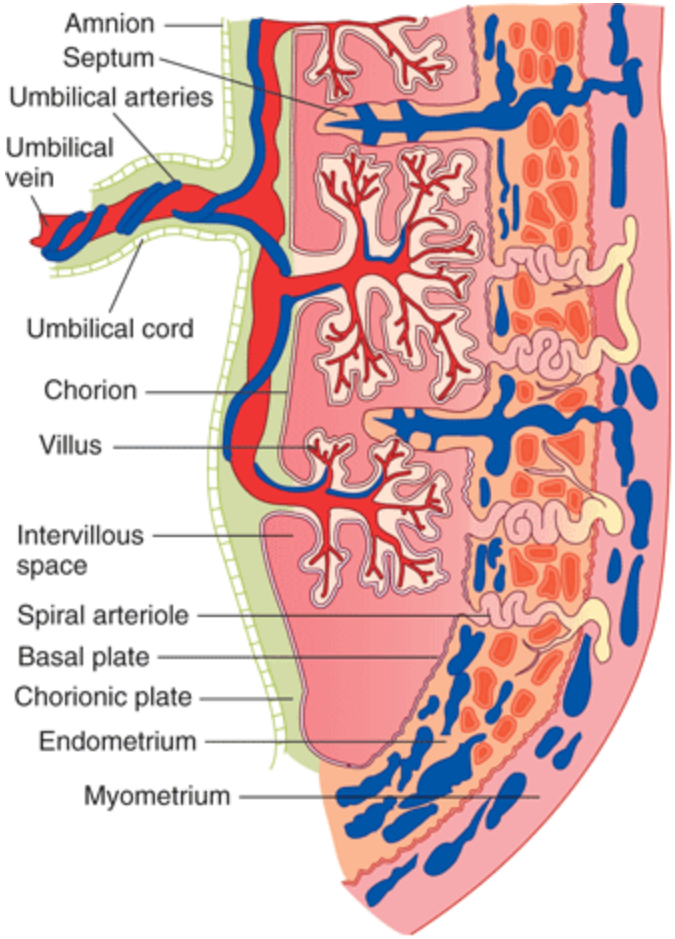
Placenta

- Deoxygenated fetal blood enters the placenta through two umbilical arteries that branch radially to form chorionic arteries.
- Chorionic arteries branch further as they enter the villi. In the chorionic villi they form an extensive capillary system.
- Blood oxygenated in the placenta returns to the fetus through the single umbilical vein
- The umbilical cord connects with placental vessels through the chorionic plate.
- The amnio-chorionic membrane lies outside the mother's circulation.

Placenta

- The placental membrane is a composite structure.
- After 20 weeks of development, the cytotrophoblast becomes markedly reduced.
- In some regions only the syncytiotrophoblast and the vascular endothelium remain.

Placenta



(Reproduced with permission from Benson RC: *Handbook of Obstetrics and Gynecology,* 8th ed. Originally published by Appleton & Lange. Copyright © 1983 McGraw-Hill.)

Fig. 34-16 Accessed 05/01/2010

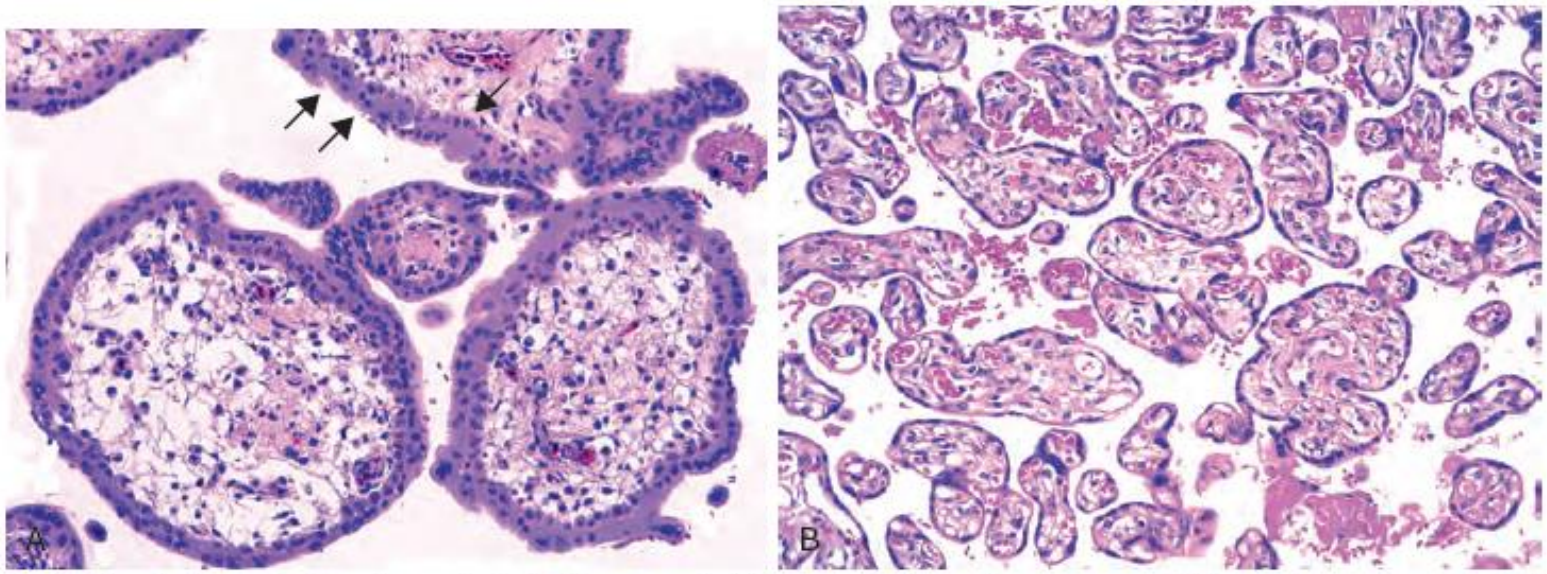


Figure 22-46 Normal placenta. **A,** First-trimester chorionic villi composed of delicate mesh of central stroma surrounded by two discrete layers of epithelium—the outer layer consisting of syncytiotrophoblast *(two arrows)* and the inner layer consisting of cytotrophoblast *(arrow)*. **B,** Third-trimester chorionic villi composed of stroma with dense network of dilated capillaries surrounded by markedly thinned-out syncytiotrophoblast and cytotrophoblast (same magnification as **A.**)

Fetal circulation

- Two parallel circulations with 3 shunts.
- Eustachian valve directs oxygenated blood from inferior vena cava across foramen ovale into left atrium .
- Ductus arteriosus directs blood from pulmonary arteries to aorta.
- Ductus venosus directs oxygenated blood from umbilical vein to inferior vena cava.

Fetal circulation

- Pulmonary veins hypertrophied from chronic vasoconstriction
- Prevents blood from entering the lungs, pulmonary capillaries, and left atrium
- Chorionic villus is major site of gas exchange

Fetal circulation

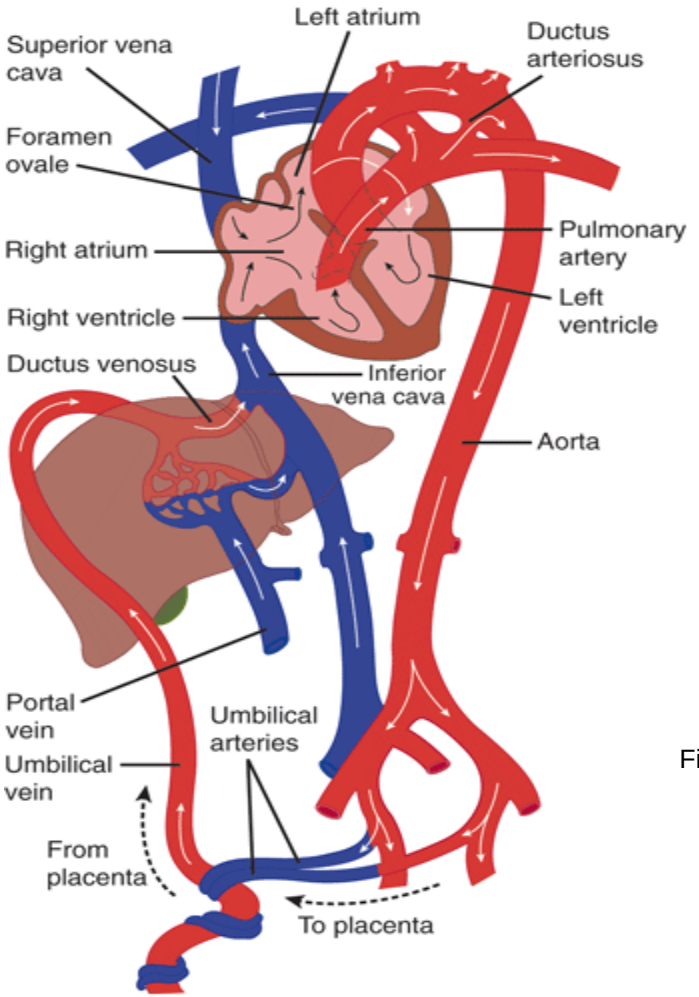


Fig. 34-18 Accessed 02/01/2010

Placental hormones

- Epithelial growth factor, HCG , cAMP, and β-adrenergic agonists stimulate further HCG production as well as differentiation of cytotrophoblasts (anchoring, invasion).
- HCG is degraded by villous macrophages (Hofbauer cells) and kept from fetal circulation.
- By the third trimester, the placenta is producing sufficient estrogen and progesterone to sustain the pregnancy.
- Estrogen is produced from dehydroisoandrosterone from the fetal adrenal gland as the placenta lacks a means of converting C21 to C19 steroids (thus, the placenta produces aromatase).

Placental hormones

- The placenta also produces cytokines, pituitary and hypothalamic (releasing) hormones, renin, PTH, and uterine activation and inhibition hormones.
- Human placental lactogen (chorionic somatotropin) has a structure and function similar to that of growth hormone and (to a large extent) prolactin.

Human placental lactogen

- HPL decreases maternal glucose utilization (by decreasing sensitivity to insulin).
- More glucose is available to the fetus.
- The mother responds by upregulation of pancreatic hormone production
- HPL induces lipolysis with the release of free fatty acids.
- In the fasting state, HPL production is stimulated.

Human placental lactogen

- Fatty acids are used as fuel by the mother; relatively more glucose is available to the fetus.
- Ketones produced are also available to the fetus.
- This mechanism serves to protect fetal development in the face of calorie restriction.

Table 10-4 Abnormalities Suggesting Inborn Errors of Metabolism

General
Dysmorphic features
Deafness
Self-mutilation
Abnormal hair
Abnormal body or urine odor ("sweaty feet"; "mousy or musty"; "maple syrup")
Hepatosplenomegaly; cardiomegaly
Hydrops
Neurologic
Hypotonia or hypertonia
Coma
Persistent lethargy
Seizures
Gastrointestinal
Poor feeding
Recurrent vomiting
Jaundice
Eyes
Cataract
Cherry red macula
Dislocated lens
Glaucoma
Muscle, Joints
Myopathy
Abnormal mobility

Adapted from Barness LA, Gilbert-Barness E: Metabolic diseases. In Gilbert-Barness E, et al (eds): Potter's Pathology of the Fetus, Infant, and Child. St. Louis, Mosby, 2007.

Spontaneous abortion

- “Miscarriage” is loss of fetus before 20 weeks gestation.
- Most occur before 12 weeks.
- 35% of all pregnancies
- Causes:
- Fatal chromosomal abnormalities
- Luteal phase defect
- Physical defects of the uterus
- Antiphospholipid syndrome
- Toxoplasma, Mycoplasma, Listeria infections (particularly in second trimester losses)

Ectopic pregnacy

- Implantation of the fetus in a site other than the normal intrauterine location
- 90% in the extrauterine fallopian tube
- 35-50% associated with PID
- Most common cause of hematosalpinx
- Initially the embryonal sac, surrounded by immature chorionic villi, implants within the lumen of the fallopian tube. Trophoblastic cells and chorionic villi then invade the wall of the fallopian tube.
- The growth of the gestational sac distends the fallopian tube, causing thinning of the wall and rupture.

Ectopic pregnacy

- The clinical course of ectopic tubal pregnancy is characterized by the onset of moderate to severe abdominal pain and vaginal bleeding 6 to 8 weeks after last menstrual period, correlating with distention and then rupture of the fallopian tube
- Rupture is a medical emergency (hemorrhagic shock)
- 4-10% mortality
- Less commonly the tubal pregnancy may undergo spontaneous regression and resorption, or be extruded through the fimbriated end of the tube into the abdominal cavity (tubal abortion).

Placental hormones

- Human chorionic gonadotropin interacts with the luteal HCG receptor and promotes the maintenance of the corpus luteum during the beginning of pregnancy, causing it to secrete progesterone.
- HCG is upregulated by cAMP.
- Due to its highly-negative charge, HCG may repel the immune cells of the mother, protecting the fetus during the first trimester.
- HCG is produced by villous syncytiocytotrophoblasts.
- HCG is heterodimeric.
- The α unit resembles LH, FSH, TSH. The β unit is unique to HCG.

Placental hormones

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Human placental lactogen

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- More glucose is available to the fetus.
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- HPL induces lipolysis with the release of free fatty acids.
- In the fasting state, HPL production is stimulated. Fatty acids are used as fuel by the mother; relatively more glucose is available to the fetus.
- Ketones produced are also available to the fetus.
- This mechanism serves to protect fetal development in the face of calorie restriction.

Twin placentas

- Twin pregnancies arise from fertilization of two ova (dizygotic) or from division of one fertilized ovum (monozygotic).
- There are three basic types of twin placentas:
- Diamnionic dichorionic (which may be fused)
- Dichorionic placentation may occur with either monozygotic or dizygotic twins
- Diamnionic monochorionic
- Monoamnionic monochorionic.
- Monochorionic placentas imply monozygotic (identical) twins, and the time at which splitting of the developing embryo occurs determines whether one or two amnions are present.

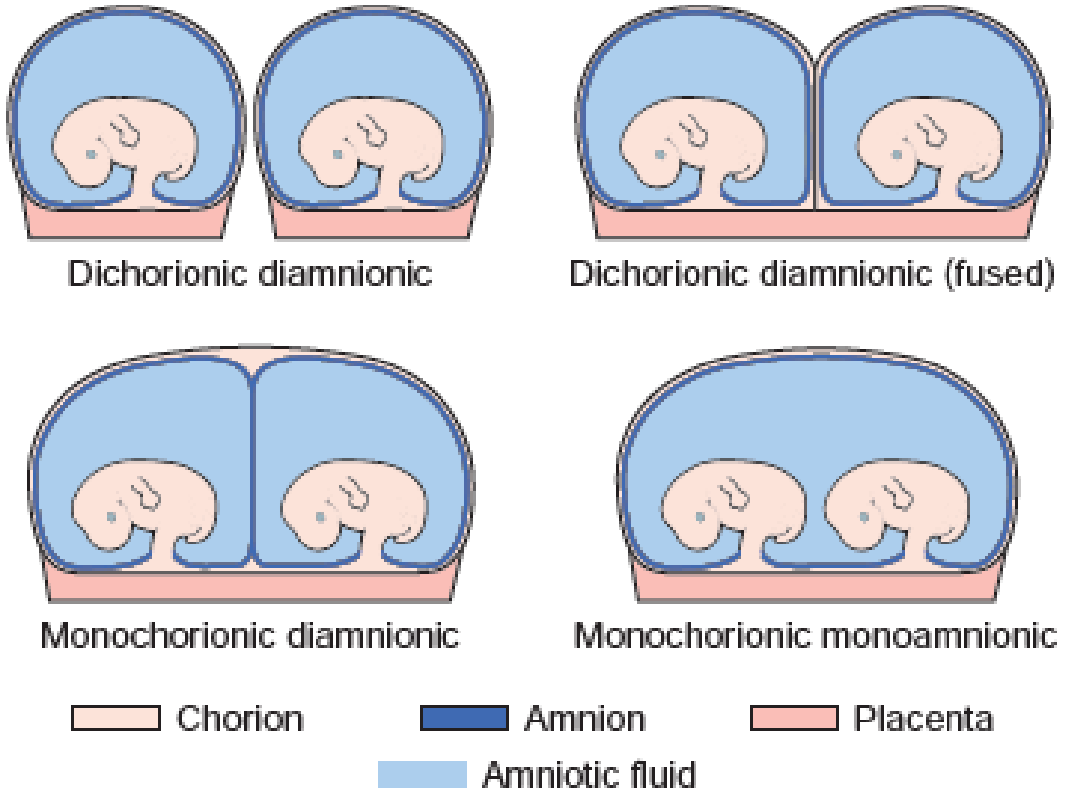


Figure 22-48 Diagrammatic representation of the various types of twin placentation and their membrane relationships. (Adapted from Gersell D, et al: Diseases of the placenta. In Kurman R (ed): Blaustein's Pathology of the Female Genital Tract. New York, Springer-Verlag, 1994.)

Twin-twin transfusion syndrome.

- Monochorionic twin placentas have vascular anastomoses that connect the circulations of the twins
- In some cases these connections include one or more arteriovenous shunts.
- If these shunts preferentially increase blood flow to one twin at the expense of the second, one twin will be underperfused, while the second will be fluid overloaded (high output failure).
- May lead to fetal death

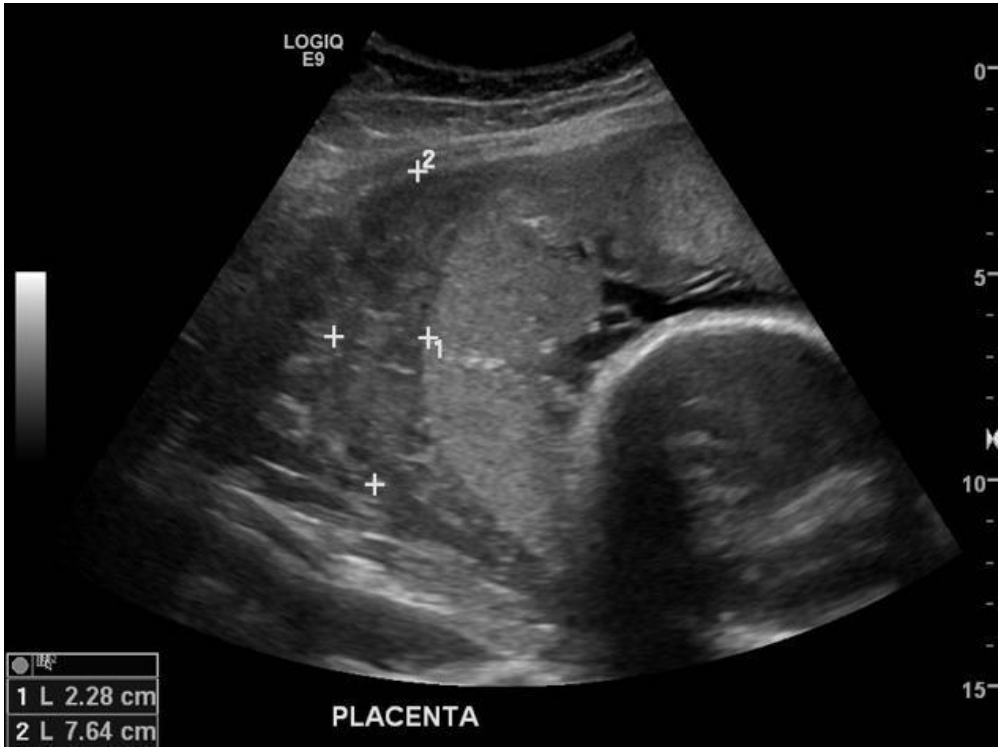
Placental implantation

- Placenta previa
- The placenta implants in the lower uterine segment or cervix
- Often leading to serious third trimester bleeding.
- A complete placenta previa covers the internal cervical os.
- Placenta accreta
- Partial or complete absence of the decidua
- The placental villous tissue adheres directly to the myometrium, which leads to a failure of placental separation at birth.

Placental implantation

- It is an important cause of severe, potentially life-threatening postpartum bleeding
- 60% associated with previous placenta previa
- Abruptio placentae
- Retroplacental hemorrhage at the interface of placenta and myometrium threatens both mother and fetus.

Abruptio placenta



Hematoma present laterally (marginal separation)

https://radiopaedia.org/articles/placental-abruption
Accessed 01/20/2020

Chorioamnionitis

- Ascending infections from the vagina
- Most common
- Bacterial
- Localized infection of the membranes produces premature rupture of membranes and preterm delivery.
- The amniotic fluid may be cloudy with purulent exudate, and histologically the chorionamnion contains an infiltrate of neutrophils accompanied by edema and congestion of the vessels.
- Fetal response consists of a “vasculitis” of the umbilical and fetal chorionic plate vessels.

Chorioamnionitis

- Hematogenous infections:
- Toxoplasma gondii
- Treponema pallidum
- Mycobacterium tuberculosis
- Listeria
- Rubella
- Cytomegalovirus
- Herpes simplex
- They give rise to chronic inflammatory cell infiltrates in the chorionic villi (chronic villitis)

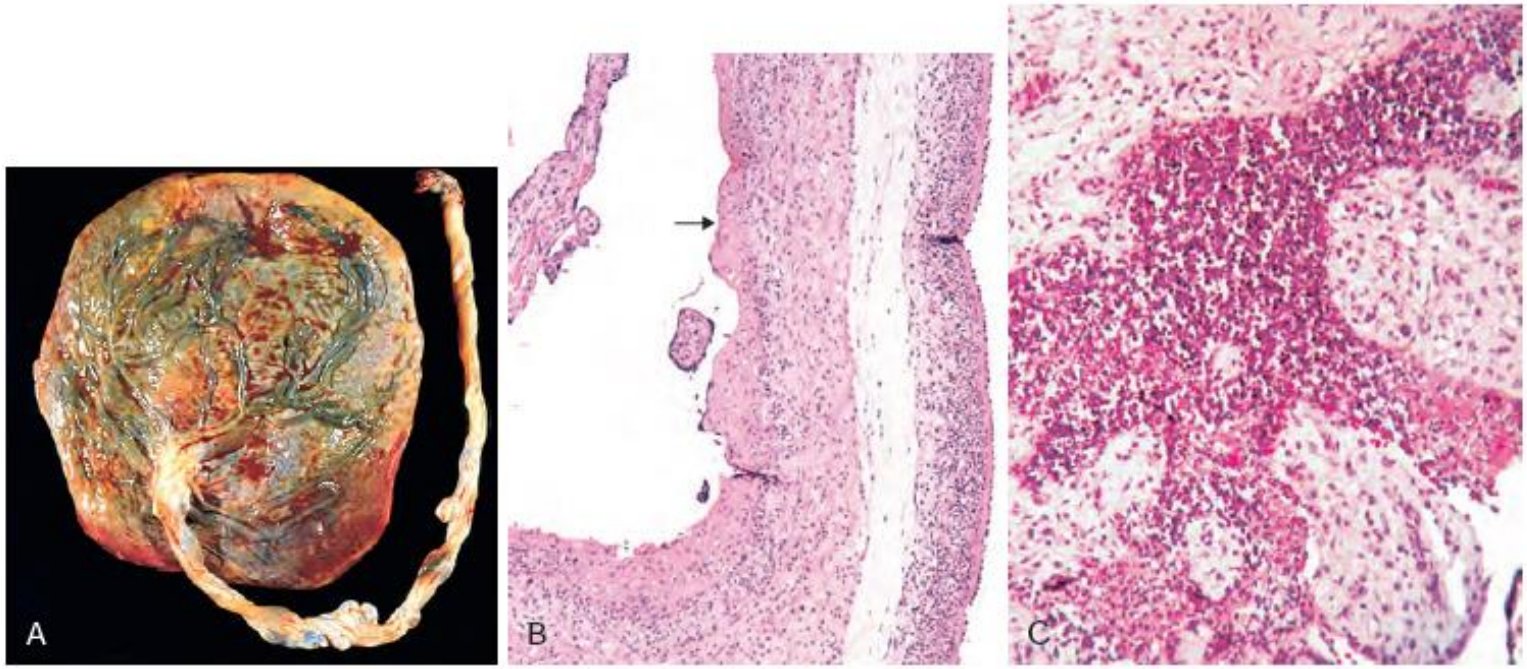


Figure 22-49 Placental infections derived from ascending and blood-borne routes. Acute chorioamnionitis. **A,** On gross examination the placenta contains greenish opaque membranes. **B,** A photomicrograph illustrates a dense bandlike inflammatory exudate on the amniotic surface *(arrow)*. **C,** Acute necrotizing intervillositis, from a fetal-maternal infection by *Listeria*.

Pre-eclampsia

- Systemic syndrome characterized by widespread maternal endothelial dysfunction that presents during pregnancy with hypertension (vasoconstriction), edema and proteinuria (increased vascular permeability).
- 3-5% of pregnancies
- Primiparas
- Last trimester
- Symptoms remit following delivery of the placenta

Pre-eclampsia

- May lead to convulsions (eclampsia)
- Other complications stemming from systemic endothelial dysfunction include hypercoagulability, acute renal failure, and pulmonary edema.
- 10% of women with severe preeclampsia develop microangiopathic hemolytic anemia, elevated liver enzymes, and low platelets (HELLP syndrome)
- 20% will develop hypertension and microalbuminuria 7 years following pre-eclampsia
- Twice the risk of vascular disease of the heart and brain

Pre-eclampsia

- Normally, fetal extravillous trophoblastic cells (trophoblastic cells not associated with chorionic villi) at the implantation site invade the maternal decidua and decidual vessels, destroy the vascular smooth muscle, and replace the maternal endothelial cells with fetal trophoblastic cells (forming hybrid fetomaternal blood vessels).
- This process converts the decidual spiral arteries from small-caliber resistance vessels to large capacity uteroplacental vessels lacking a smooth muscle coat.

Pre-eclampsia

- The precipitating events in the pathogenesis of preeclampsia are:
- (1) Abnormal trophoblastic implantation and a failure of physiologic remodeling of the maternal vessels, which is required for adequate perfusion of the placental bed.

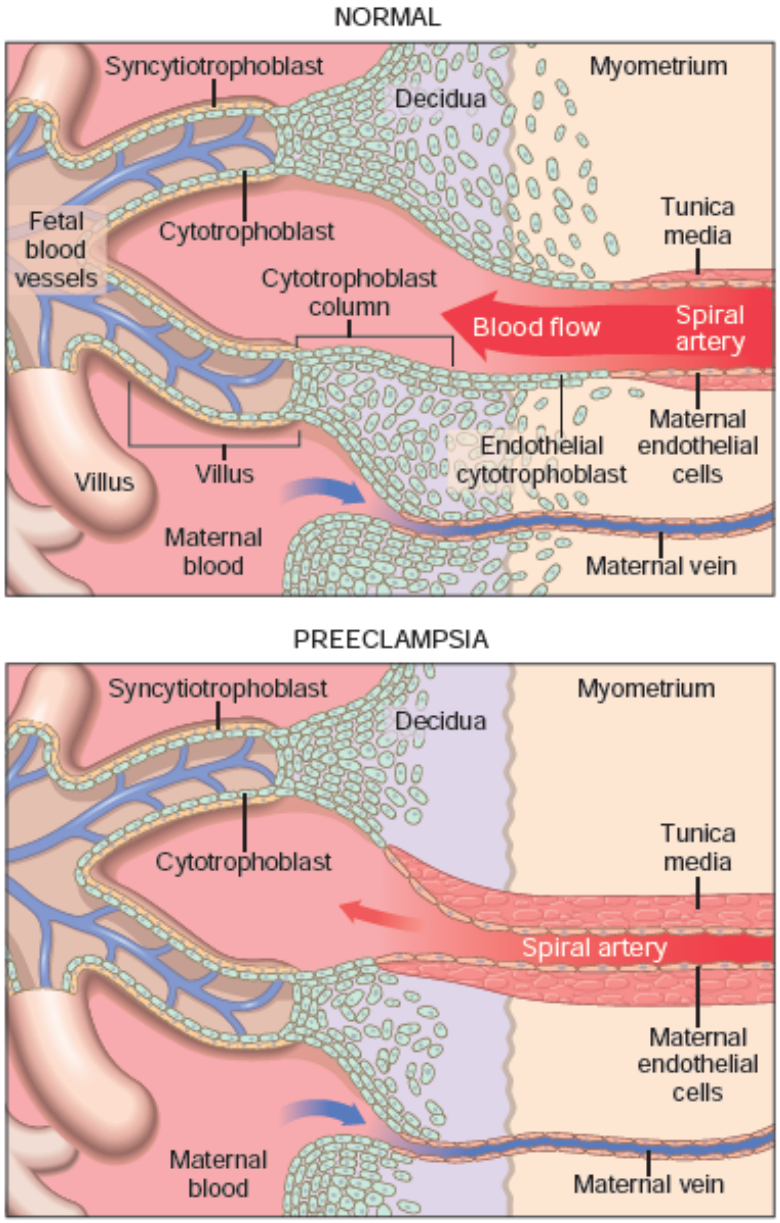


Figure 22-50 The physiologic alterations in the uterine spiral arteries and the failure of their remodeling in preeclampsia. (Modified from Maynard S, et al: Preeclampsia and angiogenic imbalance. Ann Rev Med 59:61, 2008.)

Pre-eclampsia

- (2) High levels of soluble FMS-like tyrosine kinase (sFlt1) and soluble TGFR (endoglin) bring about a decrease in angiogenesis much earlier than in normal pregnancy. The result is defective vascular development in the placenta.
- These are placentally derived.
- (3) TGFβ induces endothelial production of NO, a potent vasodilator
- Inhibition of TGFβ by endoglin may directly contribute to systemic vasoconstriction, hypertension, and tissue hypoperfusion.

Pre-eclampsia

- sFlt1 antagonizes VEGF
- VEGF stimulates endothelial production of PGI2 (antithrombotic)
- Reduced PGI2 associated with hypercoagulability
- In severe disease, endoglin levels higher than those of sFlt1.

Pre-eclampsia

- The placenta demonstrates:
- (1) infarcts, which are larger and more numerous that those that may be seen in normal full-term placentas,
- (2) exaggerated ischemic changes in the chorionic villi and trophoblast, consisting of increased syncytial knots,
- (3) frequent retroplacental hematomas due to bleeding and instability of uteroplacental vessels,
- (4) abnormal decidual vessels, which may show thrombi, lack of normal physiologic conversion, fibrinoid necrosis, or intra-intimal lipid deposition (acute atherosis)

Pre-eclampsia

- In the liver lesions, take the form of irregular, focal, subcapsular, and intraparenchymal hemorrhages.
- On histologic examination there are fibrin thrombi in the portal capillaries and foci of hemorrhagic necrosis.
- In the kidney, the glomeruli show marked swelling of endothelial cells, amorphous dense deposits on the endothelial side of the basement membrane, and mesangial cell hyperplasia.
- There is an abundance of fibrin in glomeruli. Fibrin thrombi may be present in the glomeruli and capillaries of the cortex.

Pre-eclampsia

- May produce complete destruction of the cortex (bilateral renal cortical necrosis)
- The brain may have gross or microscopic foci of hemorrhage along with small-vessel thromboses.
- Similar changes are often found in the heart and the anterior pituitary.

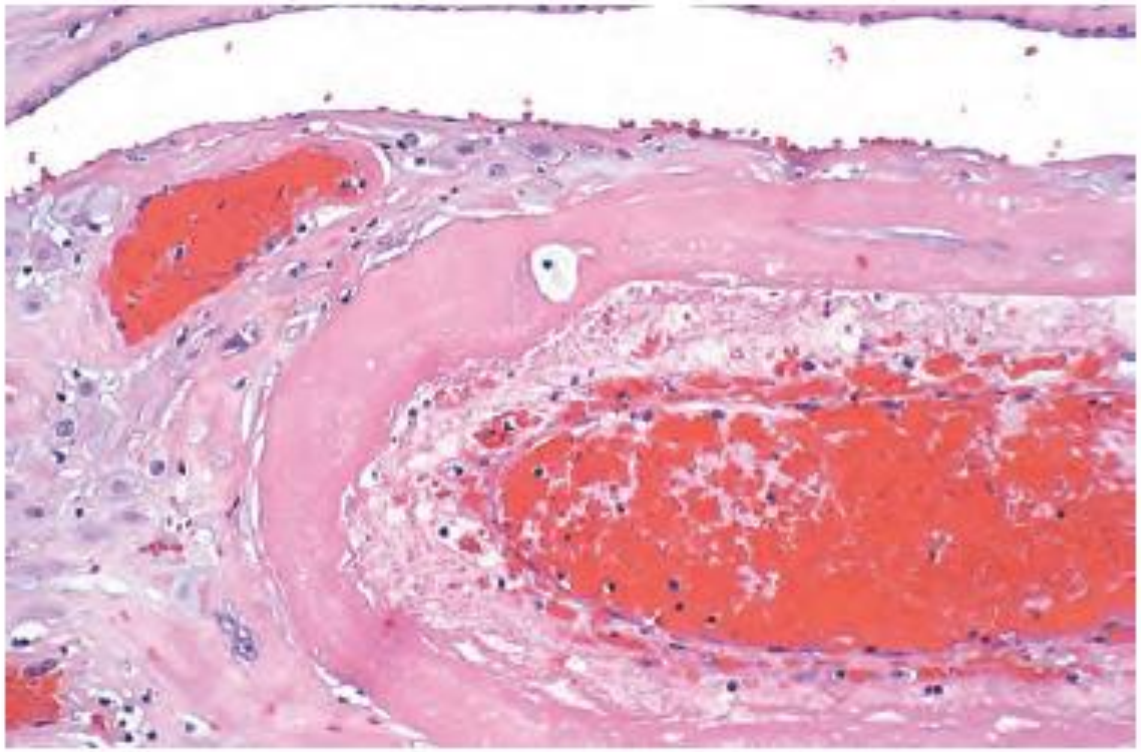


Figure 22-51 Acute atherosis of uterine vessels in eclampsia. Note fibrinoid necrosis of the vessel walls, subendothelial macrophages, and perivascular lymphocytic infiltrate. (Courtesy Dr. Drucilla J. Roberts, Massachusetts General Hospital, Boston, Mass.)

Molar pregnancy

- Usually seen in teenagers or in those >40 years old
- Identified about 9th week of gestation
- Presents with irregular or heavy bleeding
- Uterine contractions noted.
- May see hyperemesis.
- HCG elevated.
- Ultrasound shows a “snowstorm” pattern in uterus with no fetus present.
- Bilateral, large theca-lutein cysts.

Molar pregnancy

- Hydaditiform mole.
- Grape-like tissue clusters may be seen protruding from cervical canal.
- The classic appearance of hydatidiform moles is that of a delicate, friable mass of thin-walled, translucent, cystic, grapelike structures consisting of swollen edematous (hydropic) villi
- Chorionic villi are enlarged, scalloped in shape with central cavitation (cisterns), and are covered by extensive trophoblast proliferation

Molar pregnancy

- A complete mole arises from syncytiotrophoblast cells. No embryoblast.
- 90% results from fertilization of an öocyte that has lost maternal chromosomes.
- 46,XX karyotype stemming from the duplication of the genetic material of one sperm (androgenesis).
- 10% result from fertilization of an empty oocyte by two sperm
- Increased risk for invasive mole
- Increased risk for choriocarcinoma

Molar pregnancy

- An incomplete mole contains trophoblastic tissue with abnormal fetus.
- Fertilization of an öocyte by two sperm
- Usually triploid. (May be tetraploid)
- An invasive mole may penetrate the uterine wall
- Hydropic villi may embolize to distant sites
- Are not metastases and may regress spontaneously
- Trophoblastic tissue embolism may lead to ARDS.
- If trophoblastic tissue functional, may see hyperthyroid state.
- 5% will evolve to choriocarcinoma.

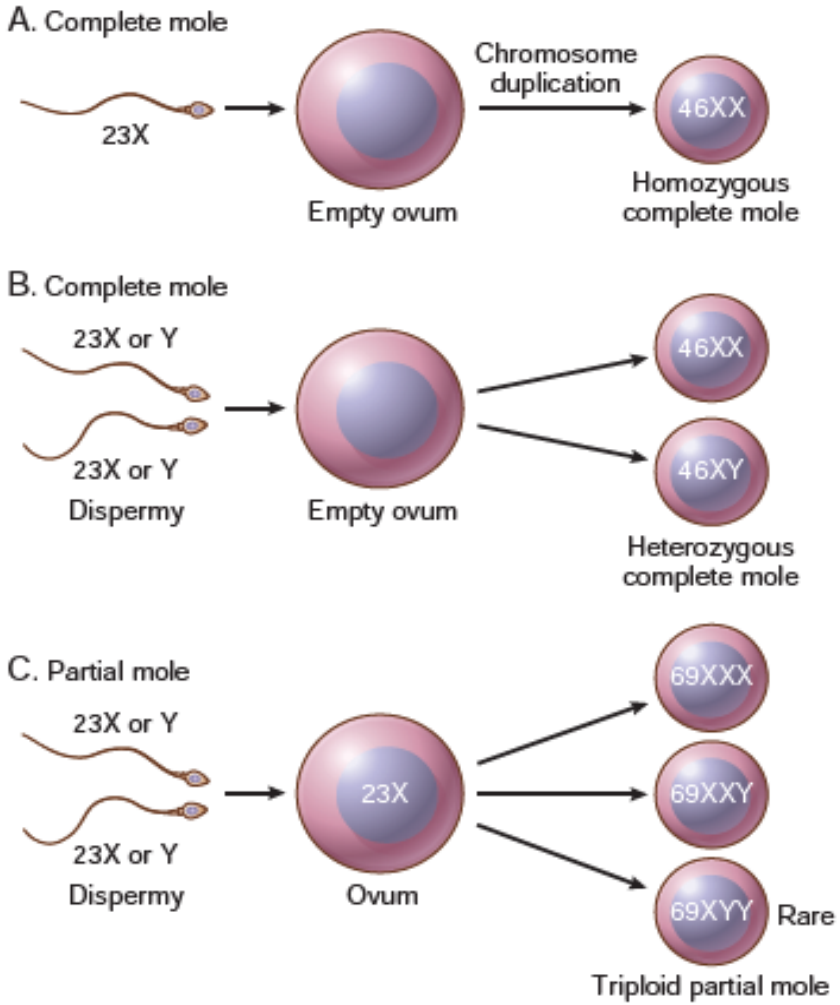
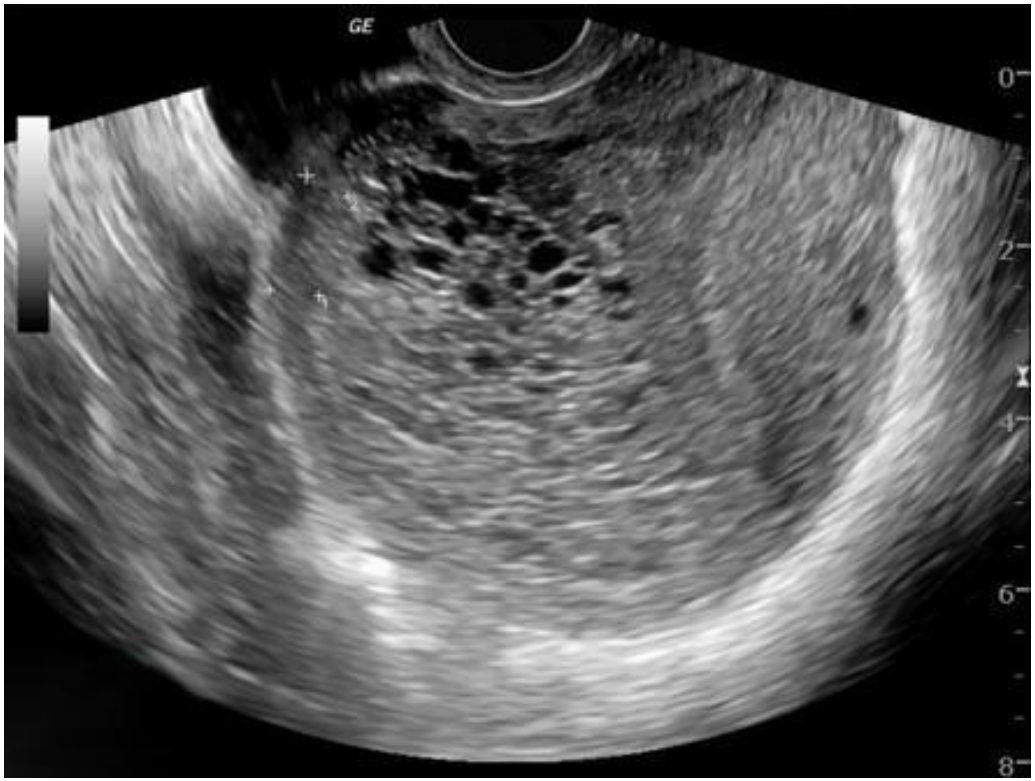


Figure 22-52 Origin of complete and partial hydatidiform moles. **A,** Complete moles most commonly arise from fertilization of an empty ovum by a single sperm that undergoes duplication of its chromosomes. **B,** Less commonly, complete moles arise from dispermy in which two sperm fertilize an empty ovum. **C,** Partial moles arise from two sperm fertilizing a single ovum.

Hydaditiform mole



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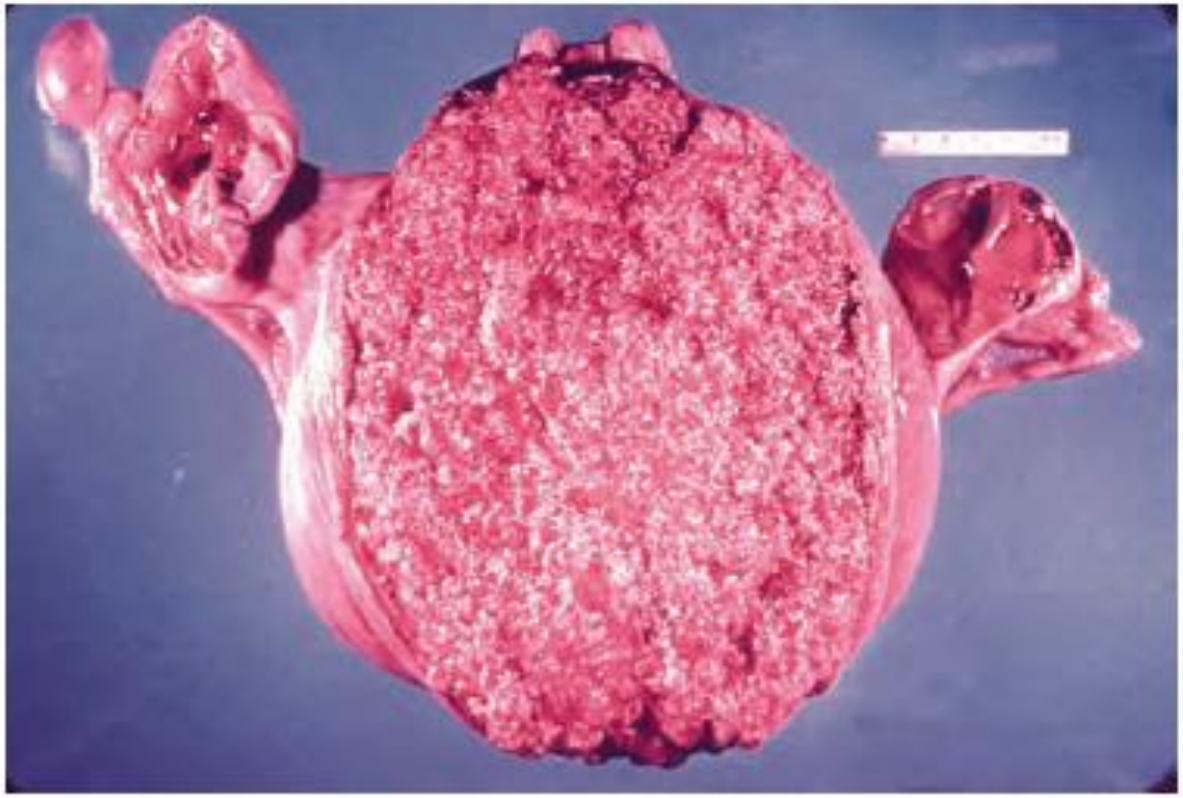

Figure 22-53 Complete hydatidiform mole. Note marked distention of the uterus by vesicular chorionic villi. Adnexa (ovaries and fallopian tubes) are visible on the *left* and *right side* of the uterus.

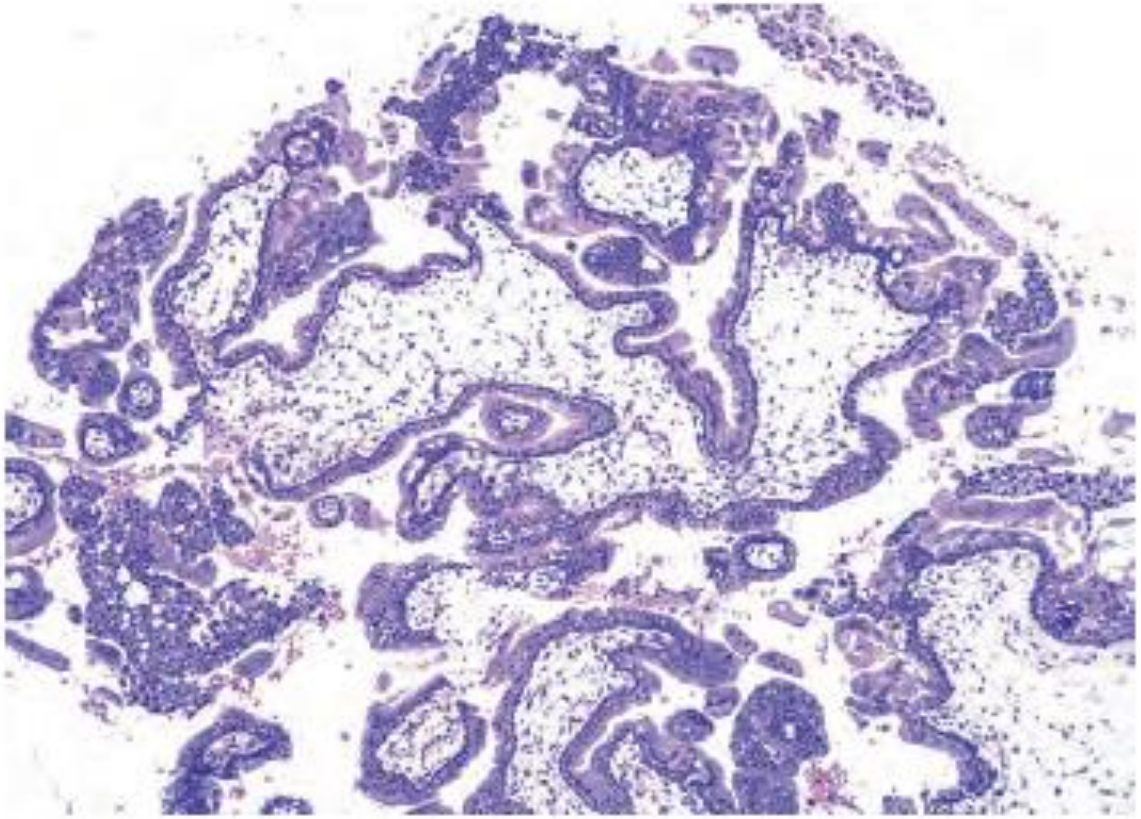

Figure 22-54 Complete hydatidiform mole demonstrating marked villous enlargement, edema, and circumferential trophoblast proliferation.

Choriocarcinoma

- Gestational choriocarcinoma is a malignant neoplasm of trophoblastic cells derived from a previously normal or abnormal pregnancy, such as an extrauterine ectopic pregnancy.
- Choriocarcinoma is rapidly invasive and metastasizes widely, principally to lungs and vagina
- Choriocarcinoma is a soft, fleshy, yellow-white tumor that usually has large pale areas of necrosis and extensive hemorrhage.
- Histologically, it does not produce chorionic villi and consists entirely of proliferating syncytiotrophoblasts and cytotrophoblasts

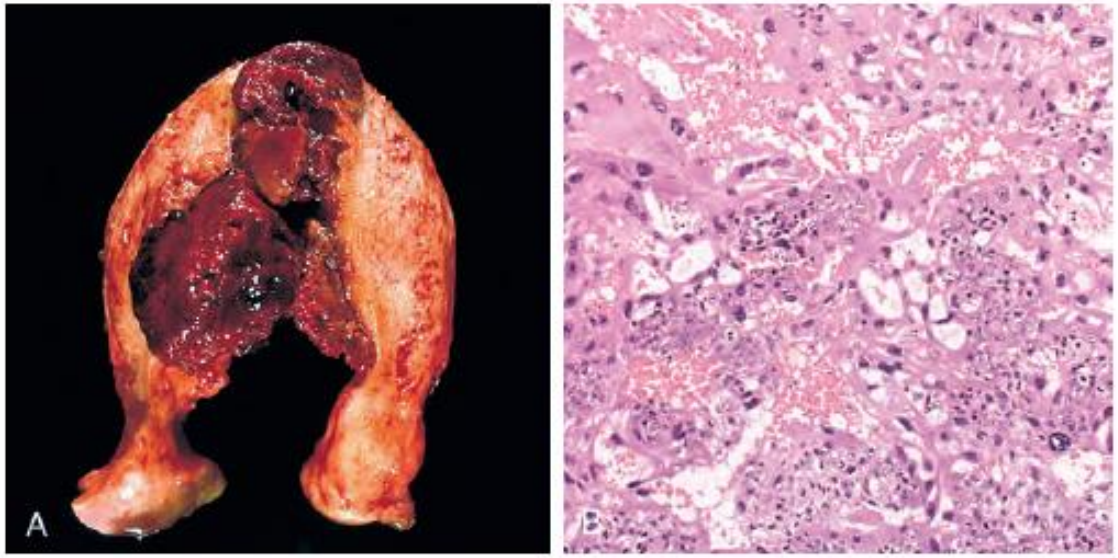

Figure 22-55 Choriocarcinoma. **A,** Choriocarcinoma presenting as a bulky hemorrhagic mass invading the uterine wall. **B,** Photomicrograph illustrating neoplastic cytotrophoblasts and syncytiotrophoblasts. (Courtesy Dr. David R. Genest, Brigham and Women's Hospital, Boston, Mass.)

Placental site trophoblastic tumor

- Neoplastic proliferation of extravillous (intermediate) trophoblasts
- PSTT presents as a uterine mass, accompanied by either abnormal uterine bleeding or amenorrhea
- Elevated HCG.
- Histologically, PSTT is composed of malignant trophoblastic cells diffusely infiltrating the endomyometrium.
- 50% follow a normal pregnancy
- Others follow spontaneous abortion or hydatidiform mole.
- 10% to 15% of women die of disseminated disease