

EMBRYOLOGY

Course Description and Rationale

Birth defects are the leading cause of infant mortality and, together with prematurity, account for approximately 50% of all infant deaths. Furthermore, 3-6% of children will be born with a major congenital defect, many of which could have been prevented. As a health care professional, you will encounter women of childbearing age or who are already pregnant. Therefore, it is imperative that the care giver realize that she or he may be providing care to two people not one and that whatever procedures or medications are prescribed may have a serious impact on the unborn child. It is also imperative to understand what types of health care measures can be used to prevent birth defects. This course will describe the classical embryological events from fertilization to birth that result in a newborn child and that provide the rationale for improving maternal and infant health. It will also focus on clinical problems associated with birth defects and their means of prevention.

Textbook

Langman's Medical Embryology by T.W. Sadler, 13th ed. Lippincott, Williams and Wilkins, 2010.

Additional Teaching Aids

Syllabus: The syllabus is designed to focus your studying, especially the sections labeled **The Bottom Line** _____. Knowing the material in **The Bottom Line** _____ will enable you to pass the course.

CD-ROM: Simbryo: A collection of 6 animations showing embryological development

Lectures

- Lecture 1:** From fertilization to gastrulation
- Lecture 2:** Derivatives of the Germ Layers and Origin of the Body Cavities
- Lecture 3:** Musculoskeletal
- Lecture 4:** Heart Development
- Lecture 5:** Vascular Development: Fetus and Placenta
- Lecture 6:** Respiratory System and Digestive System
- Lecture 7:** Kidneys
- Lecture 8:** Gonads and Genitalia
- Lecture 9:** Head and Neck
- Lecture 10:** Central Nervous System
- Lecture 11:** Ear and Eye
- Lecture 12:** Fetal Growth, Birth Defects, and Prenatal Diagnosis

Syllabus

Lecture 1: From Fertilization to Gastrulation (pp 34-70)

Objectives:

- 1) Trace the period of development from zygote to blastocyst formation
- 2) Understand the derivation of the cytotrophoblast and syncytiotrophoblast
- 3) Know the origins of the epiblast and hypoblast
- 4) Know the origins of the amniotic and yolk sac cavities
- 5) Understand the importance of extraembryonic mesoderm in forming the chorionic cavity
- 6) Describe primary villus formation in the placenta and the role of the cytotrophoblast and syncytiotrophoblast
- 7) Define the term ectopic pregnancy and know where this phenomenon usually occurs
- 8) Describe the process of gastrulation and distinguish it from the process of neurulation
- 9) Name the 3 germ layers and describe their origins
- 10) What is the organizer and what does it organize
- 11) Define the term notochord and describe its significance
- 12) When is laterality established

Terms to define: morulla, blastomeres, blastocyst, embryoblast, trophoblast, inner cell mass, outer cell mass, embryonic stem cells, cytotrophoblast, syncytiotrophoblast, hypoblast, epiblast, extraembryonic mesoderm, chorionic cavity, primary villi, connecting stalk, ectopic pregnancy, hydatidiform mole, imprinting, gastrulation, primitive streak, primitive node, primitive pit, notochord, prechordal plate,

cloacal membrane, buccopharyngeal membrane, endoderm, ectoderm, mesoderm, anterior visceral endoderm, situs inversus, laterality sequences, primary villi, secondary villi, tertiary villi,

The Bottom Line_____:

Fertilization usually occurs in the ampulla of uterine tube

Infertility affects 15-30% of couples = use assisted reproductive technology (ART): 1% of all births in the USA = by ART = increase in prematurity, low birth weight and birth defects even among singleton births

After fusion of pronuclei, division of the blastomeres forms a morula (mulberry)
Compaction of the blastomeres by formation of tight junctions allows fluid to be pumped into the center of the morula: results in formation of the blastocyst consisting of a fluid filled cavity and an inner cell mass = embryo, and an outer cell mass = trophoblast (fetal contribution to the placenta)

If pregnancy occurs, then syncytiotrophoblast secretes hCG that maintains the corpus luteum that makes progesterone to maintain pregnancy.

No fertilization = no hCG = corpus luteum regresses = no more progesterone = menstruation leaving the basal layer to regenerate endometrial glands for next cycle.

Second week:

Trophoblast consists of 2 layers: 1) cytotrophoblast(makes cells); 2) syncytiotrophoblast: forms syncytium = responsible for invasion of the blastocyst into the uterine endometrium and production of hormones

Inner cell mass lies at one pole of the blastocyst and forms the germ disc that has 2 layers: epiblast and hypoblast

Two cavities form: amniotic = dorsal to epiblast; yolk sac = ventral to hypoblast

syncytio; Tertiary villi = blood vessels in mesoderm core with most of cyto degenerated covered by syncytio: = Vessels in tertiary villi are formed by extraembryonic mesoderm; these vessels will connect Extraembryonic mesoderm formed around the outside of the amnion and yolk sac splits into two layers = somatic and splanchnic. Cavity between = chorionic cavity

2 layers of extraembryonic mesoderm continuous at the connecting stalk (umbilical region)

About 12-14 days, the embryo penetrates uterine vessels = some bleeding = may misdiagnose as menstrual bleeding = misdiagnose pregnancy and age of embryo
Ectopic pregnancy = abnormal implantation sites: Most common is in the ampullary region of the uterine tube (tubal pregnancy); Most common site in the abdominal cavity is

the Rectouterine (Douglas') pouch

Week 2 is the week of 2s:

- 2 layers to trophoblast: syncytio- and cytotrophoblast
- 2 layers to embryoblast: epiblast and hypoblast
- 2 cavities: amniotic and yolk sac (actually 3 since the chorionic cavity forms later in the week)
- 2 layers of extraembryonic mesoderm somatic and splanchnic

Third week:

Gastrulation = the process of making 3 germ layers: ectoderm (skin, CNS), mesoderm (blood, bones, connective tissue), endoderm (gut, , gut derivatives, parenchyma of glands).

Epiblast = Forms all 3 germ layers = all of the embryo. Hypoblast disappears

Primitive streak forms at the caudal end of embryo at the beginning of the 3rd week: Epiblast cells migrate toward and through the streak and node to form mesoderm and endoderm; Node = organizer = cranial end of streak
Cells that migrate through the cranial region of the node form the prechordal plate followed by the notochord: these 2 structures induce the CNS; eventually, the notochord forms the nucleus pulposus in intervertebral discs.

Cranial-caudal axis established by Anterior Visceral Endoderm (AVE): Secretes genes essential for head formation

Head mesoderm (dorsal mesoderm = paraxial mesoderm) is organized by Goosecoid and other genes that antagonize BMP-4.

BMP-4 secreted throughout the embryonic disc = ventralizes mesoderm = forms intermediate and lateral plate mesoderm: Antagonized by Goosecoid and other genes expressed by the node; hence the node is the organizer

Brachyury (T gene) controls formation of dorsal mesoderm in regions caudal to the head: Expressed by the node and notochord: If decreased T gene, then results in caudal dysgenesis.

PITX2 = master gene for laterality = establishes left sidedness: Upregulated by serotonin (5HT), nodal and FGFs

Caudal dysgenesis (Sirenomelia; Mermaid syndrome) = insufficient mesoderm formed by gastrulation = missing kidneys, fused lower limbs.

Situs inversus = transposition of the viscera = usually no other defects

Laterality sequences = incomplete situs inversus such that organ reversal only involves a few organs = often have other defects. Antidepressants causing laterality problems

Trophoblast = forms villi for placenta: Primary villi = core of cytotrophoblast covered by syncytiotrophoblast; Secondary villi = core of extraembryonic mesoderm, covered by cyto, covered by with each other and to umbilical vessels to form the fetal circulation.

Week 3 = week of 3s:

3 germ layers: ectoderm, mesoderm, endoderm

3 cavities: amniotic, yolk sac, chorionic

Ectoderm: skin, CNS, PNS, eyes, internal ear, neural crest cells(bones & connective tissue of the face and part of the skull)

Mesoderm: bones, connective tissue, urogenital system, cardiovascular system

Endoderm: gut and gut derivatives(liver, pancreas, lungs, etc.)

Lecture 2: Derivatives of the Germ Layers and Origin of the Body Cavities (pp 71-104)

Objectives:

- 1) Name the major derivatives of the three germ layers
- 2) Explain why the embryonic period is considered the most critical time in human development for the induction of birth defects
- 3) Describe the process of neurulation and understand that it overlaps with the period of gastrulation
- 4) What is a homeobox gene? What role do they play in specifying the craniocaudal axis?
- 5) What is the embryological basis for caudal dysgenesis (sirenomelia) and sacrococcygeal teratomas
- 6) Determine the origin of the intraembryonic cavity
- 7) Describe the processes of cephalocaudal and lateral folding of the embryonic disc and their significance with respect to establishment of body form
- 8) What is the embryological basis for gastroschisis versus omphalocele and ectopia cordis?
- 9) Describe the subdivisions of the intra-embryonic mesoderm and the role this tissue plays in development of the intra-embryonic coelomic cavity
- 10) Describe the role of the pleuropericardial folds in establishing the pericardial and pleural cavities
- 11) Describe the formation of the diaphragm and explain the origins of diaphragmatic hernias

Terms to define: neural plate, neural tube, neuropores, neural crest, placode, mesenchyme, paraxial mesoderm, intermediate mesoderm, lateral plate mesoderm, somite, dermamyotome, sclerotome, vasculogenesis, angiogenesis, head fold, tail fold, cloaca, vitelline duct, crown rump length, intraembryonic coelom (cavity), visceral and parietal mesoderm, Homeobox genes, serous membrane, septum transversum

The Bottom Line_____:

face and skull, spinal ganglia, sympathetic and enteric ganglia, melanocytes, adrenal medulla, cranial nerve ganglia (V, VII, IX, X)

Ectoderm: skin, CNS, PNS, eyes, internal ear, neural crest cells(bones & connective tissue of the face and part of the skull)

Mesoderm: bones, connective tissue, urogenital system, cardiovascular system

Endoderm: gut and gut derivatives(liver, pancreas, lungs, etc.)

Ectoderm: forms neural plate = induced by upregulation of FGFs while the node (organizer), notochord, and prechordal mesoderm block BMP 4 activity: Combination of increased FGFs and decreased BMP4 activates a neural pathway = fore and midbrain regions only: Hindbrain and spinal cord induction = dependent upon FGFs and WNT3a
Neural plate forms neural folds that elevate and fuse in the midline to form the neural tube = CNS

Cells at top (crest) of the neural folds = neural crest = migrate to form bones and connective tissue of the

Neural Tube Defects (NTDs)

Spina bifida = open neural tube anywhere from cervical to lumbosacral area:
lumbosacral = most common = results from non closure of neural folds = 70%
can be prevented by taking folic acid (400 ug/day) for at least 3 months
preconceptionally and throughout pregnancy

Spina Bifida Occulta = tube closes, but vertebra do not = covered by skin

There is an increased risk of having a child with an NTD if have one child with the defect or a family history

Anencephaly = cranial neural folds fail to close causing brain tissue to degenerate;
death results = folic acid works as preventative

Mesoderm: paraxial (dorsal mesoderm) = somites = vertebral column, muscles, dermis.

Somitomeres form in head region and contribute to the skull and muscles of the face

Intermediate (ventral) mesoderm = urogenital structures

Lateral plate (ventral) mesoderm = splits into splanchnic (visceral, surrounds organs) and somatic (parietal, lines body cavities)

Blood vessels form in 2 ways: 1) Vasculogenesis = in situ = form blood islands first, then these cells coalesce into endothelial tubes = establishes major vessels = aorta and cardinal veins; 2) Angiogenesis = sprouting from existing vessels: Both processes regulated by Vascular Endothelial Growth Factor (VEGF) and its receptors

Mesenchyme = any loose connective tissue regardless of origin

Mesoderm = derived from mesodermal germ layer

4 body folds: Cephalocaudal (head and tail folds) and lateral folding (2 lateral folds)closes gut tube around the umbilical region

Vitelline duct (yolk sac duct) connects gut tube to yolk sac

Gut divided into pharyngeal, fore, mid, and hind gut = closed at the cranial

(buccopharyngeal membrane) and caudal (cloacal membrane) ends: Cloaca = expanded portion of hind gut = later forms urogenital sinus and part of anal canal

Body cavity = same as intraembryonic cavity (coelom) = eventually becomes the cardiac, pleural, and peritoneal cavities = all 3 cavities derived from space between the 2 layers of the lateral plate mesoderm:

1) splanchnic (visceral) layer = surrounds gut tube, heart, and lungs; 2) somatic (parietal) layer = lines body wall

2 sides of cavity are brought together by embryonic folding = caudal and cranial folds and 2 lateral folds = draws everything around the umbilical region: Failure of the folds to close = ventral body wall defects = ectopia cordis, gastroschisis, and bladder and cloacal extrophy

Omphalocele = ventral body wall defect, but is not due to a closure problem; it is due to a failure of bowel loops to return to the abdominal cavity following umbilical herniation

2 layers of lateral plate mesoderm form serous membranes that secrete fluid for lubrication. 2 layers continuous at the root of each organ

Gut is suspended by dorsal mesentery = double layer of peritoneum = where 2 layers are continuous

Division of cavities:

Septum transversum = block of mesentery derived from splanchnic mesoderm around the heart: moves to the region between the thoracic and peritoneal cavities due to cranial folding that curved the heart into the thoracic region.

Pericardioperitoneal canals = posterior to septum transversum = connect primitive pleuropericardial and peritoneal cavities

Pleuroperitoneal membranes close pericardioperitoneal canals

Pleuropericardial folds (membranes) grow around the heart and separate the pleural and pericardial cavities = form the fibrous pericardium

Diaphragm formed by

Pleuroperitoneal membranes

Septum transversum = central tendon

Muscular components = from cervical myotomes C3, 4, 5 = carry phrenic nerve with them

Mesentery of the esophagus = crura

Diaphragmatic hernia = usually on left = failure of pleuroperitoneal membrane to close pericardioperitoneal canal = abdominal organs may compress lungs and heart

Homeobox genes = contain conserved DNA binding motif from the homeotic gene complex of *Drosophila*; grouped into 4 clusters; regulate anterior-posterior (craniocaudal) patterning of the embryo

Period of organogenesis = 3rd to 8th weeks = most sensitive to teratogenic insult because organ primordia are forming

Lecture 3: Musculoskeletal (pp 143-174)

A. Muscular System

Objectives:

- 1) Describe the regions of a somite that give rise to muscle cells
- 2) Describe the muscular derivatives of the epimeres and hypomeres
- 3) Describe the origins of the innervation of the segmental musculature
- 4) Know the origins of head, body, limb, smooth, and cardiac musculature

Terms to define: dermomyotome, epimere, hypomere, dorsal primary ramus, ventral primary ramus, Poland anomaly

The Bottom Line _____:

Muscles:

Skeletal muscle: from paraxial mesoderm = myotomes form from somites and somitomeres

Myotome: formed by cells at the ventrolateral lip (VLL) of the prospective myotome region and by cells from the dorsomedial lip (DML)

DML contributes cells to the primaxial domain of mesoderm (also includes sclerotome and dermatome cells).

VLL contributes cells to both the primaxial and abaxial domains of mesoderm.

Abaxial and primaxial domains are separated by the Lateral Somitic Frontier = border between each somite and lateral plate mesoderm.

Primaxial domain contains only cells from paraxial mesoderm: forms muscles of the back, shoulder girdle (rhomboids, levator scapulae, and Latissimus dorsi), and intercostals.

Abaxial domain forms limb and abdominal wall (obliques and transversus abdominus) muscles.

Regardless of their final position, migrating muscle cells receive innervation from their spinal segments of origin and carry these spinal nerves with them as they migrate.

Paraxial cells also form dermis on the back (from dermatomes), vertebrae, and bony parts of the ribs (from sclerotome)

Abaxial cells form dermis in the body wall (from lateral plate mesoderm) and rib cartilages (from sclerotome cells that migrate across the lateral somitic frontier).

Head musculature formed by somitomeres = tongue, eye (except those of the iris = pupillary muscles = derived from the optic cup) and pharyngeal arches. Muscles in the head are patterned by connective tissue that is formed by neural crest

Limb muscles formed by VLL cells: patterned by connective tissue formed by lateral plate mesoderm regulated by Myo D genes = transcription factors

Cardiac muscle formed from splanchnic mesoderm around heart tube

Smooth muscle formed from splanchnic mesoderm around gut tube

Poland anomaly = absence of pectoralis major (and sometimes minor)

B. Skeletal System

Objectives:

- 1) Describe the bony derivatives of the sclerotome, somatic mesoderm of the body wall, and the neural crest
- 2) Contrast development of the membranous versus the cartilaginous neurocranium
- 3) Define the terms suture and fontanelle and describe their locations and functions
- 4) Define craniosynostosis and its leading genetic cause

- 5) Describe the basic processes of limb development and define apical ectodermal ridge, hyaline cartilage model, and epiphyseal plate
- 6) What genes control proximal-distal, anterior-posterior growth, and bone patterning in the limbs?
- 7) Describe vertebral formation and determine the origin of the intersegmental arrangement of the vertebral column

Terms to define: somitomeres, somites, neurocranium, viscerocranium, suture, fontanelle, cranioschisis, craniostenosis (craniosynostosis), apical ectodermal ridge(AER), zone of polarizing activity(ZPA), progress zone, epiphyses, diaphyses, meromelia, polydactyly, syndactyly, resegmentation, scoliosis, spina bifida

The Bottom Line_____

Paraxial mesoderm forms somites along the spinal cord and somitomeres in the head

Somites have 3 components: 1) dermatome (skin); 2) myotome (muscle); 3) sclerotome (bone)

Mesoderm refers to tissues derived from the mesodermal germ layer; mesenchyme = any loose connective tissue regardless of origin: for example from neural crest cells

Skull

Neurocranium = skull= has 2 parts: 1) membranous = flat bones = intramembranous ossification;

2) chondrocranium: formed in a cartilage model first followed by ossification = bones of base: the prechordal portion is derived from neural crest = cranial to pituitary: Rest = paraxial mesoderm

Sutures = coronal, sagittal, etc., form seams that allow molding of the head during birth:

Larger spaces between bones = fontanelles = “soft spots”
Craniosynostosis = early fusion of the sutures = abnormal skull = many of these defects result from mutations in fibroblast growth factor receptors (FGFRs).

Viscerocranium = face = mostly from the frontonasal prominence and the 1st and 2nd pharyngeal arches = neural crest cells
1st arch = maxilla, mandible, malleus, incus; 2nd arch = stapes, part of hyoid bone

Limbs = buds form during 4th and 5th weeks at positions specified by HOX genes
Forelimb structures specified by TBX5; hindlimb by TBX4
AER = apical ectodermal ridge = proximodistal growth = FGFs maintain a rapidly proliferating population of cells adjacent to the ridge = the progress zone
Cell death in ridge = digits; cell death between digits separates each finger
ZPA = zone of polarizing activity = cranial to caudal(anterior-posterior) patterning, thumb to little finger = *sonic hedgehog* (SHH) and retinoic acid = morphogens
Bone patterning = HOX genes
Amelia = no limbs; meromelia = short limbs;
Thalidomide = limb defects, now an anticancer, anti AIDS drug so seeing thalidomide type limb defects again
Polydactyly = too many digits, syndactyly = fused digits; brachydactyly = short digits

Vertebral Column: derived from somites(sclerotome) and from notochord(nucleus pulposus of intervertebral disc). Caudal part of one sclerotome fuses with cranial part of another = intersegmental so that muscles bridge the vertebra to act on them = resegmentation

Lecture 4: Heart Development (pp 175-201)

Objectives:

- 1) Determine the identity of the tinman
- 2) Explain the role of cephalocaudal and lateral embryonic folding in positioning of the heart tube
- 3) Define the term cardiac looping and describe its formation
- 4) Identify the bulbus cordis, conus cordis, and truncus arteriosus and name their derivatives
- 5) Describe the contributions of the sinus venosus to atrial development
- 6) Describe the processes involved in septation of the atria, ventricles, and truncus arteriosus, including the role of the endocardial cushions
- 7) Explain the embryological origins of ventricular septal defects (VSD), atrial septal defects (ASD), and transposition defects of the great vessels
- 8) Understand that heart defects may arise very early during the establishment of laterality or later during cardiac looping and septation
- 9) Explain the roles of the primary (PHF) and secondary (SHF) heart fields in normal and abnormal cardiac development

Terms to define: epicardium, endocardium, myocardium, cardiac loop, bulbus cordis, dextrocardia, sinus venosus, endocardial cushions, septum primum, septum secundum, ostium primum, ostium secundum, foramen ovale, heart-hand syndromes, tetralogy of Fallot, transposition of the great vessels

The Bottom Line_____:

Heart development starts during gastrulation when cells migrating through the lateral edges of the primitive node move in a cranial direction to establish the primary heart field (PHF). The PHF is a horseshoe shaped collection of splanchnic mesoderm cells that unite to form a tube cranial to the cranial neural folds. Later, the tube is moved to the thoracic cavity by cranial folding; lateral folding causes fusion of the 2 sides of the horseshoe shaped tube so that a single heart tube forms.

BMP-2 (TGF- β family) induces NKX 2-5 (tinman gene) that establishes the cardiogenic field. TBX5 (T Box transcription factor) regulates septation.

The horseshoe shaped region of cardiac mesoderm represents the primary heart field and contains cardiac progenitor cells responsible for forming the atria, left ventricle, and part of the right ventricle. These cells are patterned during the establishment of left-right symmetry as the form the PHF. The rest of the heart, including the remainder of the right ventricle and the outflow tract, are formed by the secondary heart field (SHF), a region of splanchnic mesoderm at the posterior aspect of the pharynx. These cells are responsible for lengthening the outflow tract and are regulated by FGFs secreted by neural crest cells.

Endocardium = lines heart cavity = same as the endothelial wall of blood vessels

Myocardium = muscle cells = from surrounding splanchnic mesoderm

Epicardium = same as visceral pericardium: parietal pericardium lines inside of fibrous pericardium. Fibrous pericardium comes from pleuropericardial folds

Cardiac looping = cranial end of the heart tube grows ventrally and to the right; caudal end grows dorsally and to the left; as this process occurs regions of the tube begin to differentiate into atria, ventricles, and outflow tract: Looping helps delineate these regions and sets the stage for septation

Dextrocardia: Looping occurs in opposite direction. Can be induced during patterning of the PHF (Days 16-18) or during cardiac looping (4th week)

Atrioventricular junction = canal = will be separated into 2 channels = right and left AV canals

Outflow tract = conus cordis into truncus arteriosus = will become pulmonary and aortic channels

Sinus venosus = primitive venous receiving end of the heart that has right and left sinus horns: Each horn receives umbilical, vitelline, and common cardinal veins. Veins shift to right = left sinus horn diminishes, right increases in size and is incorporated into the wall

of the right atrium to form smooth-walled portion of the right atrium (trabeculated part of right atrium is derived from the original primitive right atrium). Crista terminalis = dividing line between smooth [sinus venarum] and trabeculated parts of the right atrium. Valves guard opening into smooth portion of right atrium = valve of the inferior vena cava and valve of the coronary sinus.

Left sinus horn = forms oblique vein of left atrium and the coronary sinus

Septum formation: key = endocardial cushions = areas of expanded matrix production between the endocardium and myocardium = form in AV canals (4 of them: 2 lateral, superior and inferior) and in conotruncal region. The key to the origin of some heart defects involves problems with endocardial cushions

Atrial Septum: Septum primum grows from the roof of the atrium toward AV endocardial cushions as these cushions (superior and inferior) grow toward each other to divide the AV canal. However, before the septum contacts the AV cushions programmed cell death (apoptosis) creates a hole = ostium secundum (ostium primum was the space between the septum primum and the AV endocardial cushions). Simultaneously a second septum grows from the roof of the atrium, the septum secundum, and it grows toward the AV cushions, but it never gets there: Septum secundum overlaps septum primum and ostium secundum. The new opening between the 2 atria is the foramen ovale. Septum primum = valve of the foramen ovale. Probe patency of the foramen ovale = valve does not close completely = 10% of population

Left atrium = smooth part = from pulmonary vessel that forms in the cardiac mesentery from cells in the SHF, gets positioned by the atrial septum, and incorporated into the posterior atrial wall. Trabeculated part derived from the original left atrium.

AV valves = superior and inferior endocardial cushions grow together: the AV valves are formed by thinning of all 4 cushions: right AV valve = tricuspid; left AV valve = bicuspid (mitral)

Conus and truncus septation = conotruncal cushions grow from sides of the channel, spiral 180° and fuse in midline to create pulmonary and aortic vessels. Neural crest cells help form conotruncal cushions: insults to crest cells = basis for some heart defects. Often, heart and craniofacial abnormalities go together because crest cells contribute to craniofacial development so both types of defects result from insults to neural crest.

Ventricular septation: created by growth of the muscular portion (expansion of the ventricular chambers) and membranous portion: growth of the inferior endocardial cushion downward toward the muscular portion completes the membranous portion of the septum

Heart defects:

Atrial septal defects (ASDs) = may be due to problems with patterning the PHF or with septum formation and growth, i.e. with excessive cell death in formation of the ostium secundum = ostium secundum defect

Ventricular septal defects (VSDs) = most common: Most (80-90%) occur in muscular portion of the septum, but disappear postnatally. More serious ones usually in the membranous portion. Due to effects on PHF or with endocardial cushion growth.

Outflow tract defects due to effects on: 1) PHF (Double outlet right ventricle [DORV], transposition of the great vessels [TGA]; 2) SHF (DORV, Tetralogy of Fallot [pulmonary stenosis, over-riding aorta, VSD, and right ventricular hypertrophy]; 3) Neural crest cells [common truncus arteriosus]

Dextrocardia: heart loops the opposite way, usually associated with transposition of other organs = situs inversus = loss of left/right symmetry. May be caused during establishment of laterality or during looping.

Almost any type of heart defect can be produced by selective serotonin reuptake inhibitors (SSRIs) used as antidepressants.

Lecture 5: Vascular Development: Fetus and Placenta (pp 109-119; 202-217)

Objectives:

- 1) Know the derivatives of the 3rd, 4th, and 6th aortic arches
- 2) Understand that arteries shift to the left and veins to the right during development
- 3) Describe the origin of the umbilical vein, the portal system, and the inferior vena cava
- 4) Trace the patterns of pre- and postnatal blood flow and describe the changes that occur at birth
- 5) Understand the importance of extraembryonic mesoderm in forming the chorionic cavity
- 6) Describe primary villus formation in the placenta and the role of the cytotrophoblast and syncytiotrophoblast
- 7) Understand the structure and function of the term placenta
- 8) Know the relationship between the amnion, chorion, and uterine cavity

Terms to define: aortic arches, ductus arteriosus, double aortic arch, coarctation of the aorta, ductus venosus, cytotrophoblast, syncytiotrophoblast, primary villi, chorion, chorion frondosum, decidua, decidua basalis, amniochorionic membrane, cotyledons, hemolytic disease of the newborn, erythroblastosis fetalis

The Bottom Line_____:

Vascular development: Fetus

Arterial System

Arterial arches (5 prs.) associated with pharyngeal arches = arise from aortic sac off the heart outflow tract, course through pharyngeal arches, undergo modification:

aortic sac splits into brachiocephalic and 1st part of the aortic arch

1st arch = mostly disappears, leaves maxillary artery

2nd arch = mostly disappears, leaves hyoid and stapedial arteries

3rd arch = carotid system

4th arch = persists on both sides = subclavian on the right and part of the aortic arch on the left

6th arch = forms pulmonary arteries = on left, the distal part persists and connects to the aorta as the ductus arteriosus = allows for circulation to bypass the lungs

Vitelline arteries supply the gut: celiac = foregut; superior mesenteric = midgut; inferior mesenteric = hindgut

Umbilical arteries: Form in mesoderm in the connecting stalk and make connections with the common iliac arteries: ultimately become internal iliac and superior vesicular arteries and medial umbilical ligaments

Arterial Defects:

- 1). Patent ductus
- 2). Coarctation of aorta: preductal and postductal (80%) = blood finds ways around the block.
- 3). Double aortic arch = difficulty swallowing = both parts of dorsal aorta remain

Venous system

Vitelline v = gut and liver, left disappears; right forms hepatic sinusoids, hepato cardiac portion of inf vena cava, portal v., sup mesenteric v.

Umbilical v: right disappears; left connects placenta to inf vena cava= ductus venosus = bypasses Liver: right umbilical v ultimately becomes the ligamentum teres; ductus venosus becomes ligamentum venosum

Cardinal v: drain body wall bilaterally: As organs form, new veins develop to drain these organs and primary vessels form on the right so that left to right connections are made to the right side

Anterior and post cardinal v drain to common cardinals to primitive atrium

A left to right anastomosis occurs between ant card v = left brachiocephalic v: Ant card v on both sides form jugular system

Post card v disappear and are replaced by: 1) supracardinals = body wall via intercostals; right forms the azygous v, left forms hemiazygous v: left to right connection forms between them; 2) subcardinals = kidneys; left to right connection = left renal v; 3) sacrocardinals = lower limbs = left to right connection = left

common iliac v

Sup vena cava is formed by the right common cardinal v and the right ant cardinal v

Inferior vena cava = 1) hepatic portion from the right hepatocardiac channel a part of the right vitelline v; 2) Renal segment from the right subcardinal v; 3) sacrocardinal segment from the right sacrocardinal v

Prenatal and postnatal circulatory patterns:

Before Birth: blood flow in fetus = umbilical v from placenta (oxygenated) to ductus venosus (contains mechanisms to regulate blood flow to the fetal heart and bypasses liver) to inf vena cava to R atrium to L atrium through foramen ovale (guided by valve of the inferior vena cava in the right atrium) to L ventricle to aorta to umbilical arteries to placenta (little blood goes to R ventricle because pulmonary circulation not functional = lungs not working. Most blood that does enter the R ventricle goes out pulmonary vessel and bypasses the lungs by going through the ductus arteriosus into aorta)

After birth: Sphincter regulating flow in ductus venosus closes (ligamentum venosum), umbilical arteries close (medial umbilical ligaments), umbilical v closes (lig teres), ductus arteriosus closes (bradykinin from lungs causes closure = lig arteriosum), foramen ovale closes: closure of the foramen ovale is due to a drop in blood pressure in the right atrium (mostly due to reduced flow by clamping the umbilical cord) and an increase in the left due to increased blood flow from the lungs

Vascular development: Placenta

Trophoblast consists of 2 layers: 1) cytotrophoblast (makes cells); 2) syncytiotrophoblast: forms syncytium = responsible for invasion of the blastocyst into the uterine endometrium and production of hormones

Extraembryonic mesoderm formed around the outside of the amnion and yolk sac splits into two layers = somatic and splanchnic. Cavity between = chorionic cavity

2 layers of extraembryonic mesoderm continuous at the connecting stalk (umbilical region)

Extraembryonic (chorionic plate) mesoderm gives rise to blood vessels for the fetal portion of the placenta

About 12-14 days, the embryo penetrates uterine vessels = some bleeding = may misdiagnose as menstrual bleeding = misdiagnose pregnancy and age of embryo

Placenta: Fetal portion = chorion frondosum = villi

Maternal portion = decidua basalis of the uterus

Implantation site grows = amnion fuses with chorion = amniochorionic membrane = forms a hydrostatic wedge and ruptures during labor

Chorion fuses with outer wall of uterus obliterating uterine cavity

Cotyledons = septa from deciduas basalis that separate villi into clusters: total = 15-20

Placental circulation: fetal separate from maternal, but still get some fetal cells into maternal circ
= can lead to an

antibody response by mother against fetal red blood cells = erythroblastosis fetalis (hemolytic disease of the newborn)

Placental functions: Exchange gases, nutrients etc., transmission of antibodies, hormone production = progesterone

Lecture 6: Respiratory System & Digestive System (pp 218-249)

A. Respiratory System

Objectives:

- 1) Know how the lung bud forms and is separated from the gut tube
- 2) Understand the origin of tracheoesophageal fistulas
- 3) Understand the origin and relationships of the visceral and parietal pleura and the pleural cavity
- 4) Describe the factors involved in lung maturation, including the role of alveolar type I and II cells
- 5) Define the terms respiratory distress syndrome and hyaline membrane disease

Terms to define: respiratory diverticulum, tracheoesophageal septum, pleural cavity, visceral and parietal pleura, alveoli, type I and II alveolar cells, respiratory distress syndrome, hyaline membrane disease, surfactant

The Bottom Line _____:

Lung bud (respiratory diverticulum) grows off foregut: endoderm forms lung cells, splanchnic mesoderm surrounding gut tube forms connective tissue and bronchial cartilages

Tracheoesophageal septum = separates esophagus and trachea

Tracheoesophageal atresia with or without fistulas results from abnormal septation

Lung bud divides = bronchial buds = divides and branches into lungs to create bronchopulmonary segments and ultimately alveoli. Lungs keep making divisions (6) postnatally

Cells in lungs = alveolar cells = derived from endoderm:

Type I alveolar cells form the blood air barrier = very thin

Type II alveolar cells make surfactant, a phospholipid, that decreases surface tension = essential to keep alveoli open = not made until 28 weeks = premature

babies have trouble breathing because they have not made enough surfactant = respiratory distress syndrome (hyaline membrane disease): Treat with steroids and artificial surfactants

Pleura: visceral (around lung, derived from splanchnic mesoderm); parietal = around body wall. Two are continuous at hilus area: space between layers = pleural cavity

B. Digestive System

Objectives:

- 1) Understand the relationship of the visceral and parietal peritoneum, mesenteries, and the peritoneal cavity
- 2) Know the location and ultimate fate of the ventral mesentery
- 3) List the derivatives of the fore-, mid-, and hindgut regions and briefly describe their morphogenesis
- 4) Describe the formation of the liver and its function during fetal life
- 5) Describe the process of gut rotation and its role in producing retroperitoneal versus intraperitoneal structures
- 6) Describe the origin of the lesser sac and epiploic foramen (of Winslow)
- 7) Describe the vascular supply of the primitive gut tube. How does this arrangement compare to that in the adult?
- 8) Define the term physiological umbilical herniation and the time and reasons for its occurrence
- 9) Describe the embryological origin of the following defects: congenital umbilical hernia, left sided colon, Meckel's diverticulum, gut atresia and stenosis, gastroschisis, and omphalocele

Terms to define: parenchyma, mesentery, intraperitoneal, retroperitoneal, omental bursa, lesser omentum, epiploic foramen (of Winslow), falciform ligament, portal triad, primary intestinal loop, vitelline duct, physiological umbilical herniation, annular pancreas, mobile cecum, volvulus, omphalocele, gastroschisis, Meckel's diverticulum, gut atresia and stenosis, urorectal septum, urorectal fistula, rectovaginal fistula

The Bottom Line_____:

Mesentery = double layer of peritoneum

Visceral peritoneum = around the organ, derived from splanchnic (visceral) mesoderm surrounding the gut tube; parietal peritoneum = on body wall, derived from somatic (parietal) mesoderm

Both visceral and parietal layers are continuous where parietal layer leaves body wall = forms a mesentery in this region

Mesenteries = suspend organs from body wall = allow for passage of blood and lymph vessels and nerves

Dorsal mesentery extends from the caudal region of the esophagus to the end of the hind

gut

In stomach area = dorsal mesogastrium = forms greater omentum
also have dorsal mesoduodenum and dorsal mesocolon
dorsal mesentery to jejunum and ileum = mesentery proper

Ventral mesentery is derived from thinning of the septum transversum: Only exists from the caudal end of the esophagus to upper part of duodenum

Lesser omentum = ventral mesentery extending from the gut tube to liver;
Falciform ligament = ventral mesentery extending from the liver to ventral body wall = contains umbilical v that becomes the ligamentum teres

Peritoneal ligaments = mesenteries joining organs or attaching organs to the body wall

4 parts to gut: Pharyngeal, foregut, midgut and hindgut; fore mid and hind are specified early during their formation during body folding: SOX2 = esophagus and stomach; PDX1 duodenum; CDXC = small intestine; CDXA large intestine: Additional signals are used for differentiation of specific regions and for gut derivatives + epithelial-mesenchymal interactions between gut epithelium and visceral mesoderm surrounding it: Sonic hedgehog secreted by gut establishes a nested expression pattern of HOX genes in the mesoderm; mesoderm directs the differentiation of specific gut regions

Foregut characterized by outgrowth of organs = lungs, pancreas, gall bladder, liver.
Endoderm forms parenchyma (cells) of these tissues; splanchnic mesoderm around gut tube forms connective tissue

Stomach also derived from foregut: rotates 90° degrees around a longitudinal axis and 90° around an anterior-posterior axis and pulls mesenteries with it (ventral and dorsal).

Dorsal grows down from the greater curvature = greater omentum: Ventral = lesser omentum connected to liver; free margin of the lesser omentum = roof of epiploic foramen(of Winslow) = entrance to the (omental bursa) lesser sac. Free margin also contains portal triad = bile duct, portal v, hepatic artery. Greater sac = rest of peritoneal cavity.

Celiac artery = artery to foregut

Liver is induced by FGFs secreted by cardiac mesoderm = inhibit inhibitors of liver development; BMPs from septum transversum make liver region responsive to FGFs and upregulate liver specific genes= hepatocyte nuclear transcription factors: once established the liver serves as an hematopoietic organ during most of fetal life

Duodenum = fuses to posterior body wall except cap(secondarily retroperitoneal)

Duodenal atresias are due to problems of recanalization

Pancreas = 2 buds = 2 ducts: accessory (of Santorini) and main (of Wirsung).

Buds fuse to form the gland, but if the ventral bud grows in the wrong direction pancreatic tissue may surround the duodenum causing stenosis = annular pancreas

Midgut = forms primary intestinal loop with mesenteric artery as axis. Rotates 270°(counterclockwise around axis and herniates out umbilicus (6th week); gut returns to cavity in 10th week: Herniates 90° as it herniates and another 180° as it returns

Omphalocele = gut fails to return = usually associated with other defects, also with increased AFP
Gastroschisis = gut herniates directly through the body wall due to failure of the body wall to close = usually few other defects
Vitelline duct = connects yolk sac to midgut = if remains = Meckel's diverticulum
Atresias and stenosis of midgut = vascular accidents

Hindgut extends from left third of the transverse colon to upper two thirds of anal canal ends in cloaca

Urorectal septum separates cloaca from hindgut: Hindgut portion forms rectum and upper part of the anal canal (lower portion of the anal canal is derived from proliferation of ectoderm to form the anal pit); Remainder of cloaca becomes the urogenital sinus

Anal canal supplied by superior and middle rectal arteries (upper two thirds) and inferior rectal artery (lower third, because the lower part is derived from ectoderm)

Failure of the urorectal septum to separate hindgut from cloaca results in urorectal fistulas (males) and rectovaginal fistulas (females)

Imperforate anus = ectoderm from anal pit fails to contact caudal end of the hindgut

Congenital megacolon (Hirschsprung's disease = no ganglia in smooth muscle of gut = no neural crest = no mobility)

Lecture 7: Kidneys (pp 250-260)

Objectives:

- 1) Describe the role of the intermediate mesoderm in development of the urinary system
- 2) Define the terms pronephros, mesonephros, and metanephros
- 3) List the derivatives of the ureteric bud and the metanephric mesoderm
- 4) Understand the importance of epithelial mesenchymal interactions in kidney development
- 5) Describe the embryological origin of congenital cystic kidney, renal agenesis, double ureter, and horseshoe and pelvic kidneys
- 6) Describe the formation of the urinary bladder and the urogenital sinus

Terms to define: pronephros, mesonephros, metanephros, urogenital ridge, ureteric bud, calyces, nephron, glomerulus, renal corpuscle, Bowman's capsule, pelvic kidney, horseshoe kidney, urachus, urorectal septum, bladder extrophy

The Bottom Line_____:

Urogenital system = mostly from intermediate mesoderm

3 kidneys in succession:

pronephros = cervical = non-functional

mesonephros = thoracolumbar; may function for a short time: duct = mesonephric

duct

metanephros = definitive kidney; begins to function in the 12th week

Collecting system = ureteric bud off mesonephric duct grows into and induces metanephric blastema = (intermediate) mesoderm. Bud continues to divide = forms ureter, renal pelvis, major and minor calyces, collecting tubules

Metanephric mesoderm induced by ureteric bud forms filtration system = glomerulus, Bowman's capsule, proximal convoluted tubule, loop of Henle, and distal convoluted tubule.

WT 1 gene is the master gene for kidney development and it allows mesoderm to be induced by the ureteric buds: Development continues to be dependent upon an interaction between branches of the ureteric bud and the metanephric blastema: Mutations in WT1 cause Wilm's tumor

Renal agenesis occurs when induction between the epithelium of the ureteric bud and mesoderm from the metanephric blastema fails (another example of an epithelial-mesenchymal interaction)

Congenital polycystic kidney = cysts = form from collecting ducts (= autosomal recessive form of the disease, which is progressive and usually causes renal failure in infancy or early childhood); or from all parts of the nephron = autosomal dominant form = less progressive and more common

Kidneys form in pelvis: Differential growth moves them into lumbar region. If kidneys fuse = horseshoe kidney = gets stuck on inferior mesenteric artery

Urorectal septum, a wedge of mesoderm, grows caudally and divides the cloaca into the anorectal canal (hindgut), posteriorly and urogenital sinus, anteriorly:

Bladder forms from upper part of urogenital sinus: Expansion of this region causes an incorporation of the mesonephric ducts into the posterior wall of the bladder (the trigone) and causes the ureters to enter the posterior wall: Expansion of the posterior wall causes the mesonephric ducts to move lower to enter urethra where prostate forms. In the female the portion of the mesonephric ducts that is not incorporated into the bladder degenerates

Urachus (old allantois) extends from the urogenital sinus to the umbilicus: Normally it degenerates to become the median umbilical ligament; if it stays open = urachal fistula

Lecture 8: Genital System (pp 261-277)

Objectives:

- 1) Define the terms genital ridge and indifferent gonad and describe the changes that occur when the primordial germ cells arrive carrying either an XX or XY chromosome complement
- 2) Contrast the development of the mesonephric and paramesonephric duct systems and their derivatives in the male and female
- 3) Describe the formation of the vagina

- 4) Contrast the fate of the genital tubercle, urethral folds, and genital swellings in the male and female
- 5) Describe the process involving descent of the testes from the abdominal cavity into the scrotum and understand the origin of a congenital inguinal hernia

Terms to define: testis determining factor, genital ridge, primitive sex cords, Sertoli cells, Leydig cells, cortical cords, mesonephric (wolffian) ducts, paramesonephric (mullerian) ducts, testosterone, dihydrotestosterone, uterorectal pouch, genital tubercle, genital swellings, urethral folds, anal folds, hypospadias, pseudohermaphrodites, androgen insensitivity syndrome (testicular feminization), congenital adrenal hyperplasia, gubernaculum, processus vaginalis, indirect inguinal hernia, cryptorchidism

The Bottom Line_____:

Y chromosome = SRY gene (sex determining region of the Y chromosome) = transcription factor; its protein is called testis determining factor = regulates male development

Females have WNT4 gene that is the ovary determining gene = initiates a cascade that causes female differentiation

Genital ridges = intermediate mesoderm medial to the mesonephros = can form ovaries or testes

Germ cells from the yolk sac migrate to the ridges and arrive in the 6th week to enter the primitive sex cords: if germ cells are XY then testes develop; if XX then ovaries form

Males: Primitive sex cords remain to differentiate into the seminiferous tubules = lose contact with surface that gets covered by tunica albuginea

Sertoli cells form from cells in the cords and serve as nurse cells for sperm = similar to follicular cells in females

Interstitial cells (Leydig) differentiate from mesoderm surrounding the sex cords and make testosterone

Seminiferous tubules = old sex cords = canalize at puberty develop connections via the rete testes with some of the old mesonephric tubules that now form the efferent ducts

Females: primitive sex cords degenerate and are replaced by a second set of cords formed by the surface epithelium of the ovary = cortical cords: These cords break up into follicular cells that surround each germ cell (oogonia)

Both sexes have:

Mesonephric (Wolffian) duct = remains in male because it is stimulated by testosterone;

degenerates in females = remnants may form cysts

Paramesonephric duct (Mullerian): Degenerates in males because of mullerian

inhibiting substance (MIS; also called anti-mullerian hormone) made by Sertoli cells: In females the ducts remain because there are no Sertoli cells so therefore no MIS

Mesonephros contributes tubules for male ducts = efferent ducts (from old excretory tubules), epididymis, seminal vesical, ductus deferens (all from mesonephric duct))

Paramesonephric duct = uterine (Fallopian) tubes, uterus, upper part of vagina:
Remainder of vagina = from urogenital sinus: from the sinovaginal bulbs that are induced by the paramesonephric ducts where they contact the urogenital sinus

External genitalia: start the same in both sexes with a genital tubercle and cloacal folds around cloacal membrane

Urorectal septum separates region into urogenital (surrounded by urethral folds) and anal (surrounded by anal folds) areas

Genital swellings form lateral to the urethral folds

	In Male	In female
Genital tubercle	penis	clitoris
Urethral folds	fuse = urethra	no fusion = labia minora
Genital swellings	fuse = scrotum	no fusion = labia majora

Testosterone stimulates mesonephric ducts to differentiate into ductus deferens etc.

Dihydrotestosterone stimulates differentiation of the external genitalia

Testicular feminization (androgen insensitivity): Person is 46XY, but tissues unresponsive to testosterone

Estrogens stimulate female differentiation

Descent of testes = develop in abdomen, retroperitoneally and descend to scrotum through internal ring, inguinal canal, external ring: preceded by processes vaginalis that later surrounds each testis as the tunica vaginalis

Gubernaculum attaches to caudal pole of each testis and to scrotum = assists in descent and is stimulated by testosterone and MIS

As testes passes through the abdominal wall it picks up layers contributed by the muscles and fascia of the wall:

Fascia transversalis = internal spermatic fascia

Internal abdominal oblique = cremaster fascia and muscle

External abdominal oblique = external spermatic fascia

Cryptorchism = one or both testes do not descend

Inguinal hernia (indirect) = processus vaginalis fails to close and intestines pass through inguinal rings ; may enter the scrotum

Ovary also has a caudal ligament and gubernaculum that extend into the labia majora, but the uterus grows and makes contact with the ligaments = prevents ovary from descending: The part of the ligament from the ovary to the uterus becomes the proper ovarian ligament; the part from the uterus to the labia majora becomes the round lig of uterus

Lecture 9: Head and Neck (pp 278-302)

- 1) Define the terms pharyngeal arch, pouch, and cleft
- 2) Define the term "HOX code" and what it means with respect to arch development
- 3) Know the derivatives of the arches, the 1st cleft and pouch and that the remaining pouches give rise to the parenchyma of numerous glands
- 4) Know the nerves associated with each arch
- 5) Describe the origin of the tongue, including its nerve supply
- 6) Explain the origin of the thyroid gland, how it assumes its final position in the adult, and the formation of thyroglossal cysts
- 7) Define the term "facial prominences" and describe their role in formation of the face
- 8) Define the terms "primary" and "secondary palate" and explain the origins of clefts in these structures and the upper lip

Terms to define: ectodermal placodes, pharyngeal pouches, clefts, and arches, neural crest cells, facial prominences, branchial fistula, Treacher Collins syndrome, Robin sequence, DiGeorge anomaly, terminal sulcus, foramen cecum, thyroglossal duct, intermaxillary segment, primary and secondary palate, incisive foramen, median cleft lip, lateral cleft lip, oblique facial cleft

The Bottom Line_____:

Mesenchyme in head:

Paraxial mesoderm = somites and somitomeres = muscles, connective tissue, and parts of the skull

Lateral plate mesoderm = laryngeal cartilages and connective tissue

Neural crest cells (NCC) = bones of the face and part of the skull and connective tissues

Ectodermal placodes = thickenings of ectoderm posterior to the pharyngeal arches: Together with NCC they form the sensory ganglia for cranial nerves V, VII, IX,X

Pharyngeal arches (branchial arches), like gills around pharynx = mesenchymal core of mesoderm and NCC; endoderm (inside); ectoderm (outside); each arch receives its own

blood vessel (aortic arch) and cranial nerve.

First arch = maxillary and mandibular processes forms the maxilla and mandible
= muscles of mastication = trigeminal nerve (mandibular division)

Second arch = muscles of facial expression, stapes and hyoid bones, facial nerve

Third arch = remainder of hyoid bone and stylopharyngeus muscle =
glossopharyngeal nerve

Fourth - 6th arches = vagus (superior laryngeal) muscles of pharynx, laryngeal
cartilages: (recurrent branch) intrinsic muscles of larynx

Pouches are lined by endoderm; endoderm makes the cells of the glands (the
parenchyma) while the surrounding mesenchyme forms the connective tissue

one = auditory tube, middle ear

two = palatine tonsils

three = inf parathyroid and thymus

four = superior parathyroid

fifth = parafollicular cells of thyroid = calcitonin

Clefts lined by ectoderm: Only the first remains and forms the external auditory meatus;
Membrane between the first cleft and first pouch = the tympanic membrane = eardrum
Remainder of the clefts are covered by proliferation of tissue from the second arch: If
these clefts fail to disappear then lateral cervical fistulas or cysts may form anterior to the
sternocleidomastoid muscle

NCC migrate from segmented regions of hindbrain, called rhombomeres, into the arches
and carry their HOX code with them

Pharyngeal arch patterning is regulated by pouch endoderm (epithelium) that interacts
through signals with the HOX code in the mesenchyme to cause the characteristic
differentiation of each of the arches

NCC form all of the bones of the face = if insulted = facial clefts = neural crest also form
conotruncal septum in heart = explains why facial defects and heart defects often occur in
combination if crest cells are affected

Tongue = ant two thirds = 1st arch = mandibular nerve; post third = mostly 3rd arch =
glossopharyngeal n; line between the two = terminal sulcus. Intrinsic muscles = occipital
somites = hypoglossal n; taste = facial n (chorda tympani) and glossopharyngeal

Thyroid gland = forms at base of tongue at the foramen cecum; descends in midline along
thyroglossal duct: remnants of the gland or thyroglossal cysts may remain and will be
located in the midline

Facial prominences = maxillary, mandibular, frontonasal,

Nasal placodes form on both sides of the frontonasal prominence and these placodes are

surrounded by ridges = the medial and lateral nasal prominences: Later, placodes invaginate to form the nasal pits, eventually form openings into the nasal cavity

Upper lip = fusion of 2 medial nasal prominences in the midline and with each maxillary prominence laterally

Lower lip = merging of the 2 mandibular prominences

Nose = frontal prominence forms the bridge, medial nasal processes form the crest and tip, lateral nasal prominences form the alae

Nasolacrimal duct = between maxillary and lateral nasal prominences; if it fails to close = oblique facial cleft

Intermaxillary segment = medial nasal prominences merge = philtrum, incisor part of jaw, primary palate

Secondary palate = shelves off maxillary prominences elevate and fuse (incisive foramen at the point of fusion of primary and secondary palates)

Facial Clefts:

Median cleft lip = medial nasal prominences fail to merge together = often mentally retarded associated with holoprosencephaly = lacking midline of face and brain

Lateral cleft lip = between medial nasal and maxillary prominences

Oblique clefts = between maxillary and lateral nasal prominences

Cleft palate = maxillary prominences (palatal shelves)

Neural crest defects:

Treacher Collins syndrome: loss of zygomatic arch and part of maxilla

Robin Sequence: micrognathia and cleft palate; small mandible causes tongue to prevent fusion of the palatal shelves

DiGeorge Anomaly: small midface, immune problems because of deficient thymic tissue and cardiac defects; thymus problems due to fact that neural crest cells make connective tissue for the thymus = cannot form without epithelial (pouch endoderm) mesenchymal (neural crest cells) interaction

Occuloauriculovertebral Spectrum: Facial and vertebral defects

All of these embryopathies may have heart defects due to fact that crest cells also contribute to the endocardial cushions in the conotruncal region

Lecture 10: Central Nervous System (pp 306-317; 323-324 (pituitary); 329-342)

Objectives:

- 1) Describe the establishment of the neural tube from the neural plate and segregation of the primary brain vesicles and their subsequent subdivisions
- 2) Know the major derivatives of each of the 5 subdivisions of the brain
- 3) Define the terms mantle and marginal layers, and basal, alar, roof, and floor plates

- 4) Describe the origin of neuroblasts and glial cells
- 5) Understand the positional changes in the spinal cord relative to the vertebral column
- 6) Describe the origin of the cerebellum, the cerebral cortex, and hypophysis (pituitary)
- 7) Acquire a basic knowledge of the organization of the cranial nerves and their respective ganglia
- 8) Describe the origin of the sympathetic and parasympathetic nervous systems

Terms to define: prosencephalon, mesencephalon, diencephalon, cerebral aqueduct, mantle layer, marginal layer, roof and floor plates, intermediate horn, spinal ganglia, dorsal and ventral roots, dorsal and ventral primary rami, neuroepithelium, spinal nerve, choroid plexus, hydrocephalus, hypophysis, Rathke's pouch, infundibulum, holoprosencephaly, anencephaly, ectodermal placodes, epibranchial placodes, preaortic ganglia, sympathetic trunks, preganglionic and postganglionic fibers, congenital megacolon, Hirschsprung's disease

The Bottom Line_____:

Central nervous system = spinal cord and brain forms from the neural plate = rolls into neural tube during 4th week (neural folds fuse): Cephalic end of tube forms 3 primary brain vesicles that later subdivide:

- 1) Prosencephalon (forebrain) divides into the telencephalon, that forms the cerebral hemispheres, and the diencephalon that forms the optic vesicles, thalamus, hypothalamus, and neurohypophysis
- 2) Mesencephalon (midbrain) forms the anterior (visual) and posterior (auditory) colliculi; does not subdivide
- 3) Rhombencephalon (hindbrain) divides into the metencephalon, that forms the pons and cerebellum, and the myelencephalon that forms the medulla oblongata

Brain = alar and basal plates like spinal cord, but almost entirely alar in the forebrain (cerebral hemispheres)

Ventricles = interconnected spaces inside the brain that contain cerebrospinal fluid (CSF) connected via pathway from the lateral ventricles (cerebral hemispheres) through the interventricular foramen (of Monroe) into 3rd ventricle (diencephalon) into aqueduct of Sylvius (through midbrain) into 4th ventricle (hindbrain): CSF is made by choroid plexuses in the ventricles and circulates through these connections and escapes into the subarachnoid space through the foramina of Luschka (both sides of cerebellum) and Magendie (midline aperture posterior to the cerebellum): If the circulation of CSF is blocked the fluid continues to be made, but has nowhere to go causing the brain to swell = hydrocephalus; usually blocked at aqueduct in the mesencephalon

Pituitary gland originates from 2 sources: 1) the infundibulum from the diencephalon (neurohypophysis, posterior lobe); 2) Rathke's pouch off roof of stomadeum (adenohypophysis, anterior lobe). Pharyngeal hypophysis = remnants of Rathke's pouch

Hindbrain is organized into segments called rhombomeres whose identity is specified by HOX genes

Forebrain identity is established by an organizing center called the anterior neural ridge (ANR) = FGF8 Midbrain is directed by a center at the rhombencephalic isthmus

(between hind- and midbrain) = FGF8

Motor areas ventrally are specified by SHH; while dorsal sensory areas are specified by BMPs

SHH also establishes the midline and if this specification fails then part or all of the midline may be lost and lateral structures may merge; Holoprosencephaly = midline lost and 2 lateral ventricles merge into a single midline ventricle; the eyes also fuse = synophthalmia

Alcohol abuse can cause loss of the midline and is the leading cause of mental retardation

Spinal Cord = neuroepithelial cells = proliferative cells; leave the proliferative population to differentiate into neurons, ependymal cells and glioblasts

Mantle layer = grey matter

Marginal layer = outside of mantle layer = white matter = fiber tracts

Basal plates = motor horn cells

Alar plates = dorsal horns = sensory; separated from basal plates by sulcus limitans

Roof and floor plates = pathways for nerve fibers

Intermediate horn = from T1-L2 = sympathetic neurons

Molecular organization of the spinal cord is initiated by SHH secreted by the notochord and floor plate and by BMPs secreted by the roof plate and overlying ectoderm: Establishes a gradient across the cord; SHH induces motor region (ventral motor horns); BMPs induce sensory region (dorsal horns)

Neural crest cells make the spinal ganglia that house the neurons for the dorsal roots of spinal nerves

Spinal nerves have 2 components: 1) ventral roots = motor; nerve cell bodies are located in the ventral horns; and 2) dorsal roots = sensory; nerve cell bodies located in spinal ganglia

Ventral and dorsal roots come together at the intervertebral foramina to form spinal nerves; Spinal nerves split into dorsal and ventral primary rami = motor and sensory fibers mixed

Spinal Cord = full length of column at 3rd month. Thereafter vertebral column grows faster so cord ends at L2 - L3 = dorsal and ventral roots from caudal segments of the cord have to travel greater distances to get to their respective intervertebral foramina; these roots make up the cauda equinae

Spina bifida = open neural tube anywhere from cervical to lumbosacral area

Lumbosacral = most common = results from non closure of neural folds = 70% can be prevented by taking folic acid (400 ug/day) for at least 3 months preconceptionally and throughout pregnancy

Occulta = tube closes, but vertebra do not = covered by skin

Increase risk if have one child or a family history

Anencephaly = cranial neural folds fail to close causing brain tissue to degenerate; death results = folic acid works as preventative

Alcohol abuse can cause loss of the midline and is the leading cause of mental retardation

Cranial nerves: All but 2 (olfactory and optic) originate from the brainstem; one of these originates from the midbrain and the rest from the hindbrain where their motor components originate from specific rhombomeres: Motor neurons for cranial nerves originate in the brain; whereas sensory neurons originate outside the brain = similar to spinal nerves, although not all cranial nerves have both motor and sensory components
Sensory ganglia for cranial nerves originate from ectodermal placodes and neural crest cells: nasal, otic, and 4 epibranchial placodes

Autonomic system: sympathetic and parasympathetic

Sympathetic = neural crest = paravertebral ganglia (sympathetic trunk ganglia) para aortic ganglia (celiac, sup mesenteric, inf mesenteric); neural crest also contribute to the adrenal medulla

Parasympathetic = craniosacral = III, VII, IX, X, and S2, 3, 4: Ganglia of parasympathetic system derived from neural crest

Congenital megacolon (Hirschsprung disease) = no parasympathetic ganglia (enteric ganglia) in gut = no neural crest = no bowel movement

Lecture 11: Ear & Eye (pp 343-361)

Objectives

- 1) Define the terms external, middle, and internal ear and be able to describe their origins
- 2) Know the derivatives of the otic vesicle including the semicircular canals, saccule, utricle, and cochlea
- 3) Describe the development of the tympanic cavity and the ear ossicles
- 4) Know which pharyngeal arches contribute to formation of the external ear and why ear defects are so significant

Terms to define: otic placodes, otic vesicles, membranous labyrinth, semicircular canals, saccule, utricle, auricle

The Bottom Line _____:

Ear = internal, middle, external

Internal = otic placodes form otic vesicles = form saccule, utricle, cochlear duct, semicircular canals and membranous labyrinth

Middle = tympanic cavity = contains malleus and incus (1st arch) and stapes (2nd arch): Tensor tympani (malleus) = trigeminal nerve; Stapedius = facial nerve

External = auditory meatus from the first pharyngeal cleft; auricle forms from 6 auricular hillocks on the 1st and 2nd pharyngeal arches

Otic vesicle forms the membranous labyrinth which includes the saccule, utricle, endolymphatic duct, semicircular canals and cochlear duct
Cochlear duct is surrounded by a cartilaginous shell that becomes the bony cochlea;
Eventually the duct is suspended between 2 chambers: the scala vestibule and scala tympani

External ear defects (pits and tags, etc.) = common: since the external ear is derived from neural crest cells in the first 2 pharyngeal arches, external ear defects are often associated with other defects = good sign to look for additional birth defects: All frequently occurring chromosomal syndromes have ear abnormalities

C. Eye

Objectives:

- 1) Understand that the eyes originate as a direct outpocketing of the diencephalon
- 2) Describe how the optic cup forms and its relationship to lens formation
- 3) Know the origins of the different layers of the retina
- 4) Know the origins of the iris, pupillary muscles, and the ciliary body
- 5) Understand the origins of coloboma and synophthalmia

Terms to define: pigmented layer, neural layer, ciliary body, suspensory ligament, vitreous body, anterior chamber, posterior chamber, choroid fissure, coloboma, anophthalmia, synophthalmia, aniridia

The Bottom _____:

Eye = optic cup and lens

Cup = outpocketing of the diencephalon = invaginates to form 2 layers = neural (inner) and pigment (outer) layer of retina: Inner layer = 2 parts: 1) pars optica retinae = rods and cones and neurons; 2) pars ceca retinae = iris and ciliary body

Lens = from surface ectoderm induced by contact by optic cup

Optic stalk = outgrowth of diencephalon to cup: forms the optic nerve and has a groove on its ventral surface = the choroid fissure that contains the hyaloid artery that becomes the central artery of the retina

Coloboma = choroid's fissure fails to close; usually in the iris only

Sphincter and dilator pupillary muscles develop from optic cup ectoderm

Cornea forms from mesenchyme anterior to the eye = continuous with the sclera

Anterior chamber = between cornea and iris; Posterior chamber = between iris and the lens and ciliary body

Vitreous chamber = between lens and retina: filled with gelatinous substance = vitreous body

Pax6 = master gene for eye development = expressed in eye fields in anterior neural ridge: Initially there is only 1 eye field, but SHH secretion from the prechordal plate

upregulates PAX 2 in the middle of the eye field = separates the single field into 2: PAX 2 regulates differentiation of the optic nerves; PAX6 the eyes

Synophthalmia (cyclopia) = fused eyes (with holoprosencephaly) = SHH fails to establish the midline = no PAX2 expression and eye field does not separate: Mutations in SHH, abnormal cholesterol metabolism (Smith-Lemli-Opitz syndrome) and alcohol exposure can cause holoprosencephaly and synophthalmia

Microphthalmia = small eye (PAX6, cytomegalovirus)

Anophthalmia = (PAX6) = no eye = optic cup fails to form or make contact with ectoderm = usually associated with other brain defects

Aphakia (no lens) and aniridia (no iris) = PAX6

Lecture 12: Fetal Growth, Birth Defects, and Prenatal Diagnosis (pp 105-109; 120-140)

A. Fetal Growth

Objectives

- 1) Determine the duration of pregnancy
- 2) Understand what is meant by fetal period versus embryonic period
- 3) Know when in gestation most of the increase in fetal length versus fetal weight occurs
- 4) Know the relationship between the amnion, chorion, and uterine cavity
- 5) Understand the structure and function of the term placenta
- 6) Know the origin of dizygotic, monozygotic, and conjoined twins and the risks involved in twin and other multiple birth pregnancies
- 7) Know the 3 stages of labor

Terms to define: fetal period, crown-rump-length, premature, postmature, ultrasound, intrauterine growth restriction, preeclampsia, chorion, chorion frondosum, decidua, deciduas basalis, amniochorionic membrane, cotyledons, hemolytic disease of the newborn, erythroblastosis fetalis, hydramnios, polyhydramnios, oligohydramnios, amniotic bands, dizygotic twins, monozygotic twins, conjoined twins

The Bottom Line_____:

Fetal period = beginning of the 9th week to birth

Pregnancy = 40 weeks after onset of last normal menstrual period (LNMP) or 38 weeks after fertilization

Crown-rump-length = measurement of the embryo or fetus; also use crown-heel-length

Fetal length is mostly acquired during the 1st half of pregnancy; fetal weight is mostly added during the second half of pregnancy with 50% acquired in the last 2.5 months

Prematurity = born prior to 37 weeks of gestation (from LNMP) = 2nd leading cause of infant death

Low birth weight = Intrauterine growth restriction (IUGR) = infants who are at or below the 10th percentile for their expected birth weight= sometimes called small for gestational

age (SGA) = increased risk for birth defects, neurological deficiencies, respiratory distress syndrome, etc.

Twins are not a normal condition = increased risk of mortality and morbidity, especially prematurity

Dizygotic = 2 eggs; Monozygotic = 1 egg, usually splits at early blastocyst stage

Conjoined = splitting or duplication of primitive streak or ? overexpression of head forming genes

Birth (parturition): Labor has 3 phases: 1) effacement (thinning and shortening) and dilation of the cervix; 2) delivery of the fetus; 3) delivery of the placenta

B. Birth Defects and Prenatal Diagnosis

Objectives:

- 1) Estimate the percentage of liveborn infants that will have congenital malformations and provide reasons why this estimate will vary from one study and one region of the world to another.
- 2) Know the types of abnormalities that can occur: Malformations, Disruptions, Deformations
- 3) Define the most sensitive period to a teratogen
- 4) Have an appreciation for some of the factors that act as teratogens
- 5) Describe the factors determining the action of a teratogen (principles of teratology)
- 6) Gain an appreciation for the type of defects that can be diagnosed prenatally
- 7) Appreciate the problem of birth defects and learn what physicians can do to prevent them
- 8) Understand when and why prenatal diagnosis tests are conducted and the procedures employed

Terms to define: congenital malformation, dysmorphology, teratology, disruption, deformation, syndrome, amniocentesis, chorionic villus biopsy, ultrasound, alpha fetoprotein

The Bottom _____:

Teratology = study of congenital malformations (birth defects), 2 - 3% present at birth, 2 - 3% more diagnosed in 1st year of life: leading cause of infant deaths. Most are caused during the 3rd - 8th weeks = period of embryogenesis (organogenesis)

Abnormalities: 1) Malformations = occur during development of a structure; 2)

Disruptions = alterations after structures have formed normally; 3) Deformations = mechanical forces change a structure

Syndrome = groups of anomalies occurring together with a common etiology

Causes of birth defects:

Environmental factors:

viruses = either directly or by fevers

radiation

chemicals - thalidomide, alcohol (fetal alcohol syndrome) = leading cause of mental retardation, other drugs of abuse, lead

Antiepileptic agents = valproic acid, diphenylhydantoin

Pharmaceutical drugs = Accutane, SSRIs, antiepileptic drugs (valproic acid,

diphenylhydantoin)

Maternal disease = diabetes, PKU

Nutritional deficiencies

Susceptibility = dose, time of exposure, genetics (mother and fetus), duration of exposure

Male mediated teratogenesis = seminal fluid (not much evidence), household contamination from the work place, germ cell mutations

Prevention: 1) folic acid prevents up to 70% of all NTDs if given by 3 months preconceptionally and continued throughout pregnancy (also protects against facial clefts and heart defects and maybe others); 2) insulin dependent maternal diabetes = place under strict metabolic control; 3)antiepileptic agents = modify dosages and or change drugs; 4)PKU= keep mother on low phenylalanine diet; 5) avoid exposure to known teratogens = alcohol, SSRIs, environmental agents, etc.

Prenatal diagnosis:

Ultrasound: used to determine age, birth defects, sex, multiple births

Maternal serum screening can assess various markers such as alpha fetoprotein (AFP) = elevated in

neural tube and ventral body wall defects; decreased in Down syndrome and other chromosomal

abnormalities

Amniocentesis to assay (AFP) = in amniotic fluid = elevated in babies with neural tube

defects (NTDs) and abdominal wall defects. Done around 14 weeks to get enough amniotic fluid. Also

obtain cells for culture for genetic analysis.

Chorionic villus sampling (CVS) = obtain piece of villus to get cells for genetic analysis. Can be done earlier than amniocentesis, but cannot assess AFP

Diagnostic tests are done on high risk mothers = advanced age, previous problem, genetic history