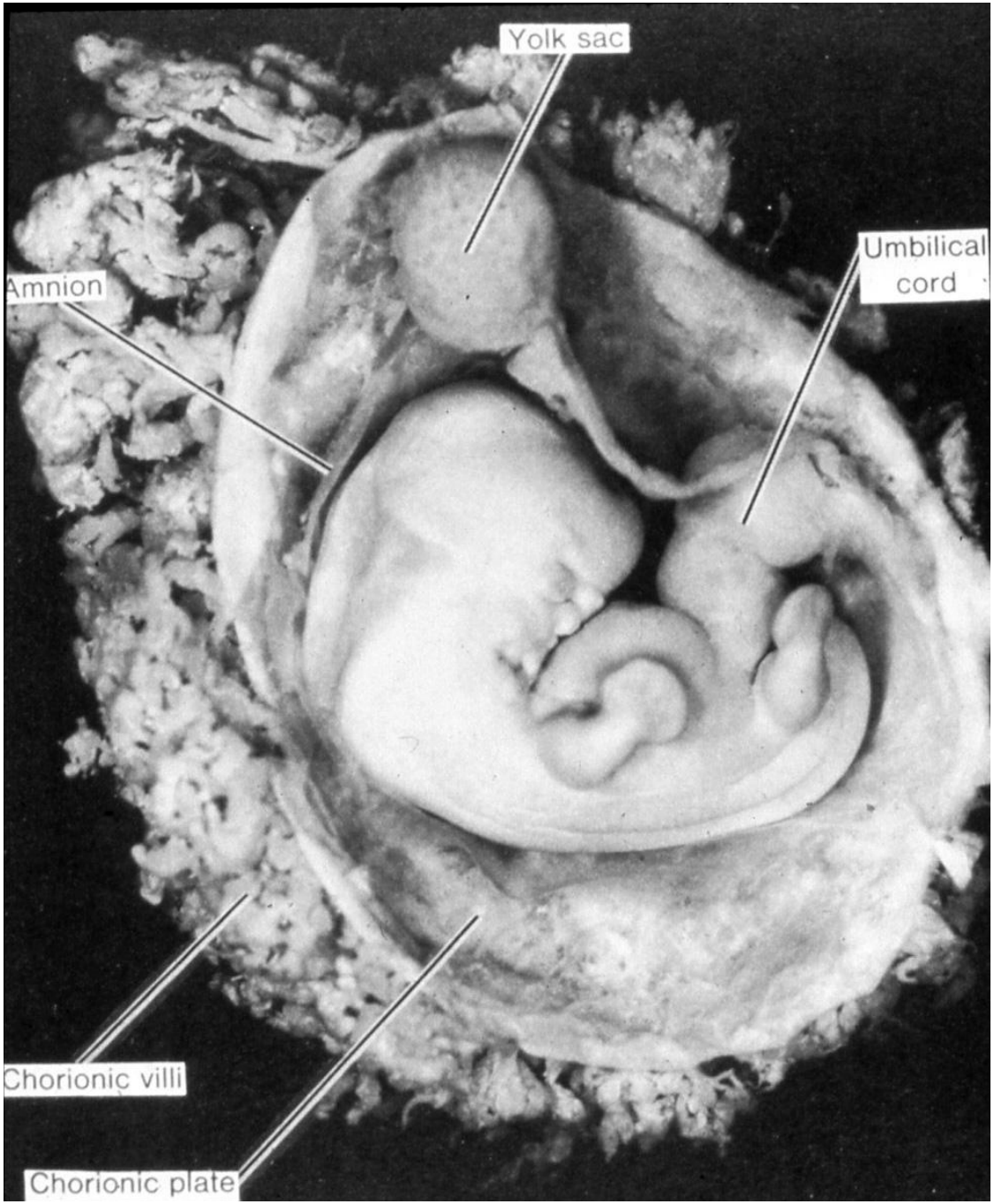
Fetal Development as Vulnerable Periods

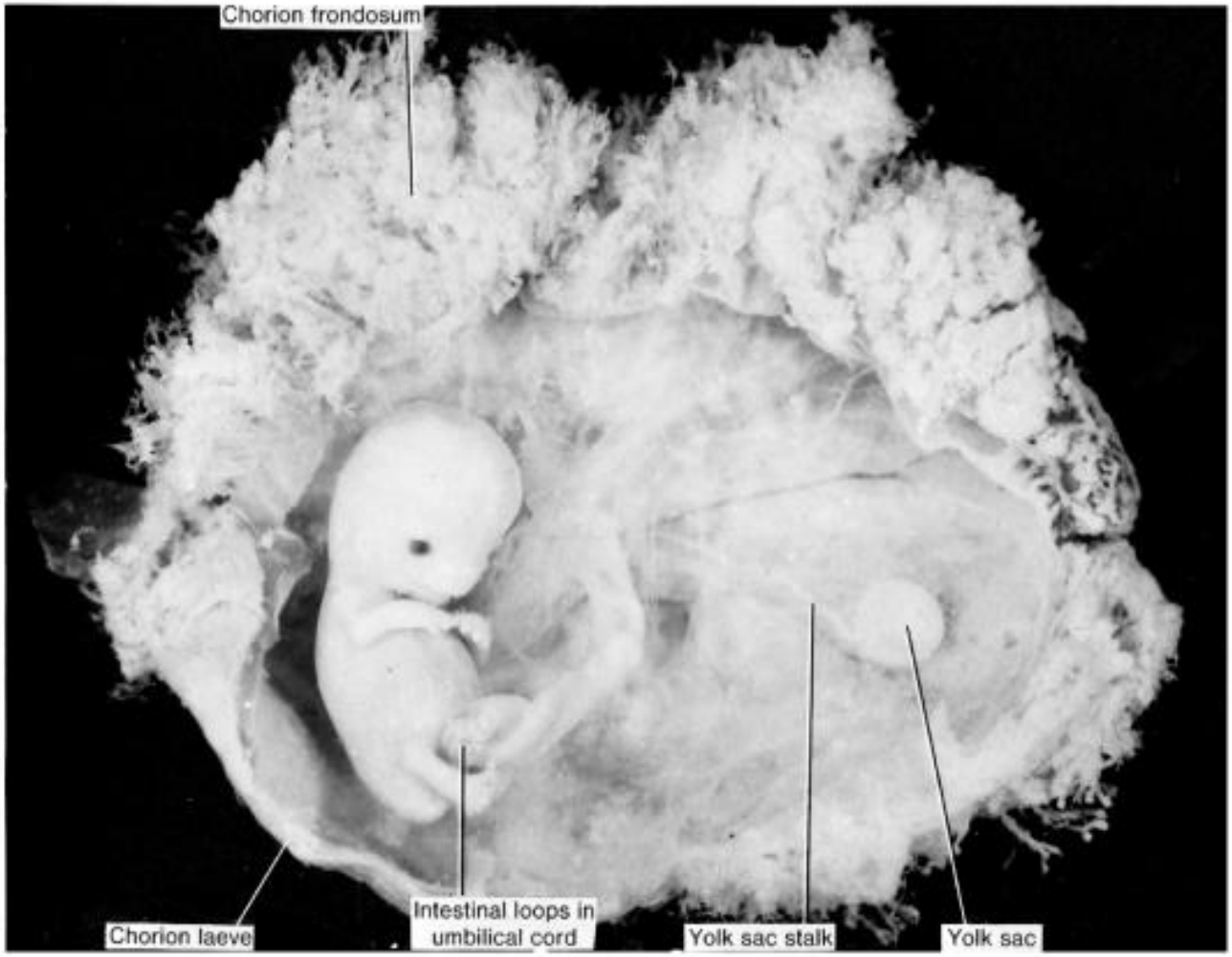
*When does the fetal period begin?

1. 6 weeks
2. 9 weeks
3. 10 weeks
4. 16 weeks

*Add 2 weeks if calculating from the last menstrual cycle

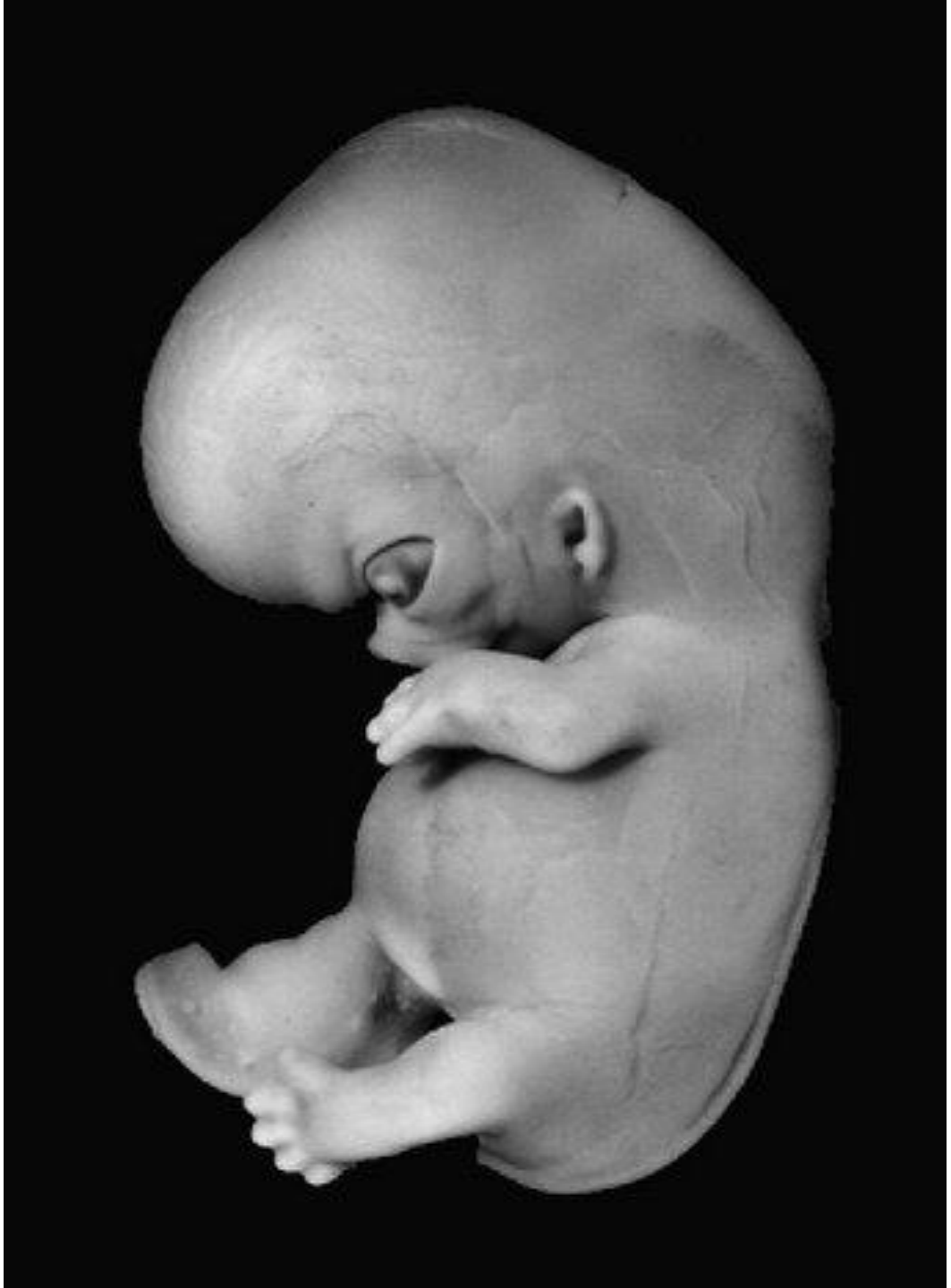
6 weeks

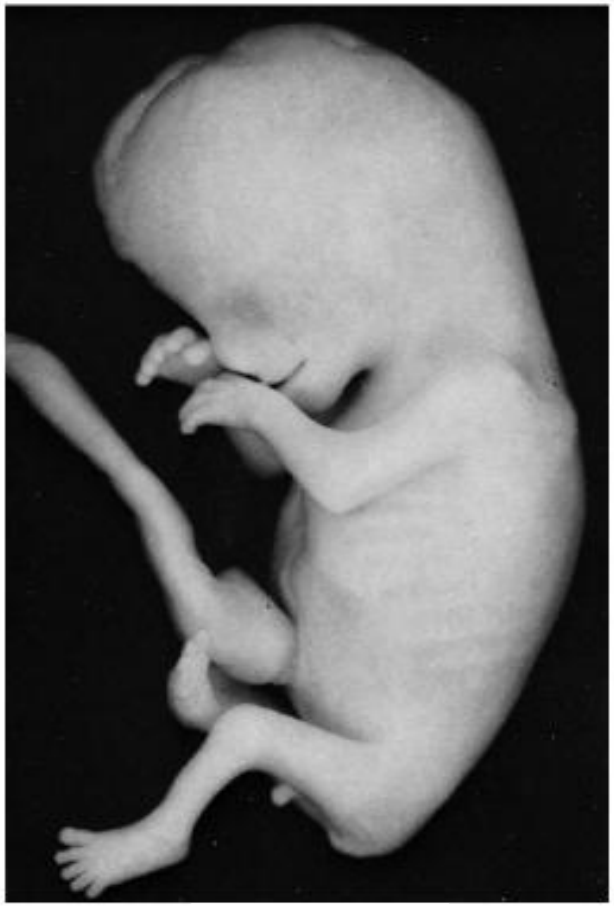

Yolk sac
Umbilical cord
Amnion
Chorionic villi
Chorionic plate



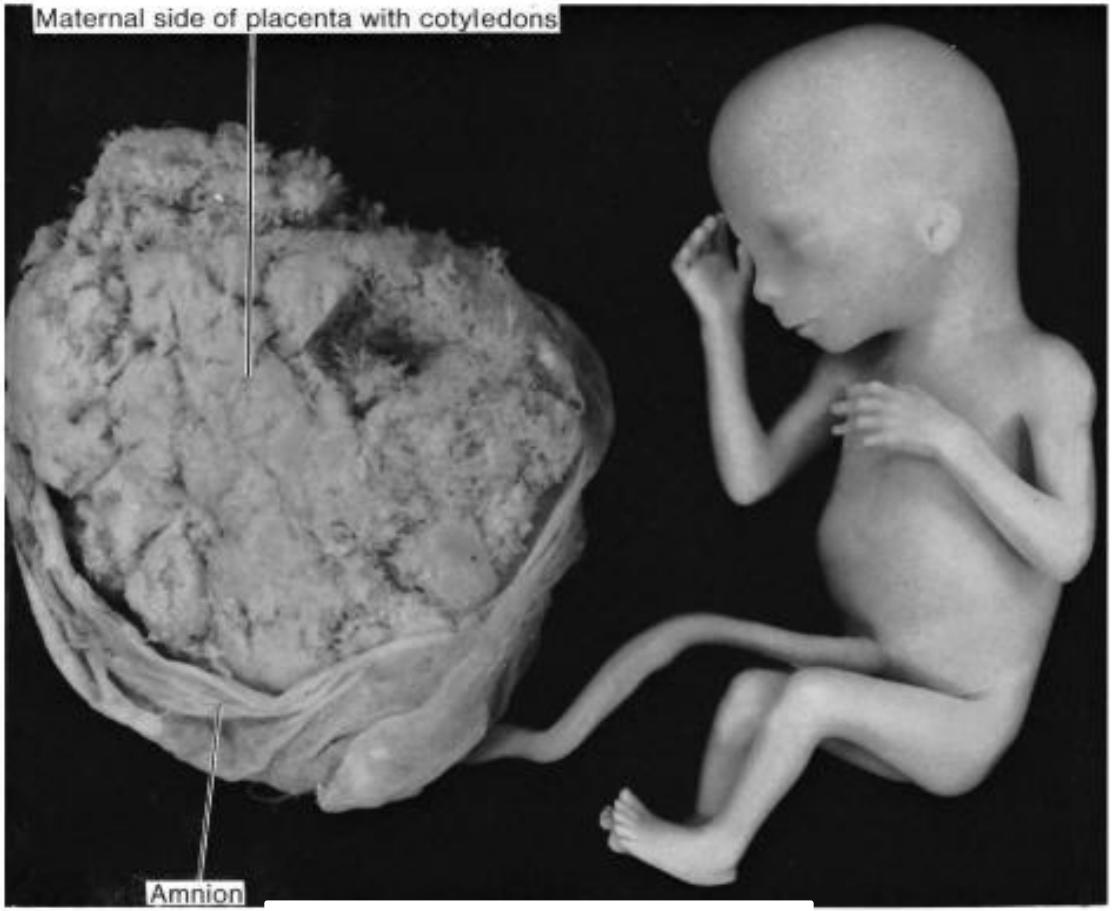
End of 8 Weeks

9 Weeks



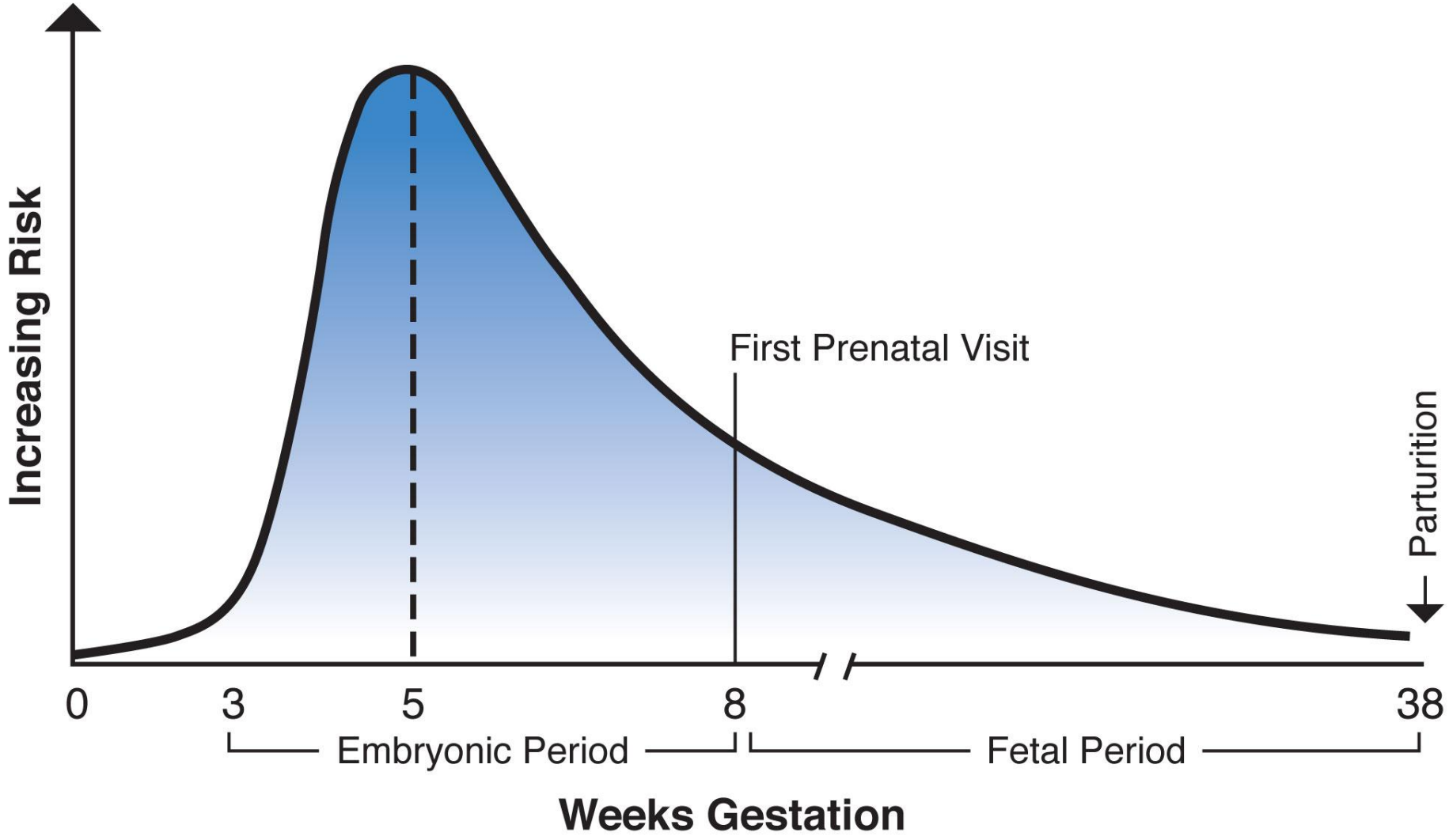


11-12 Weeks

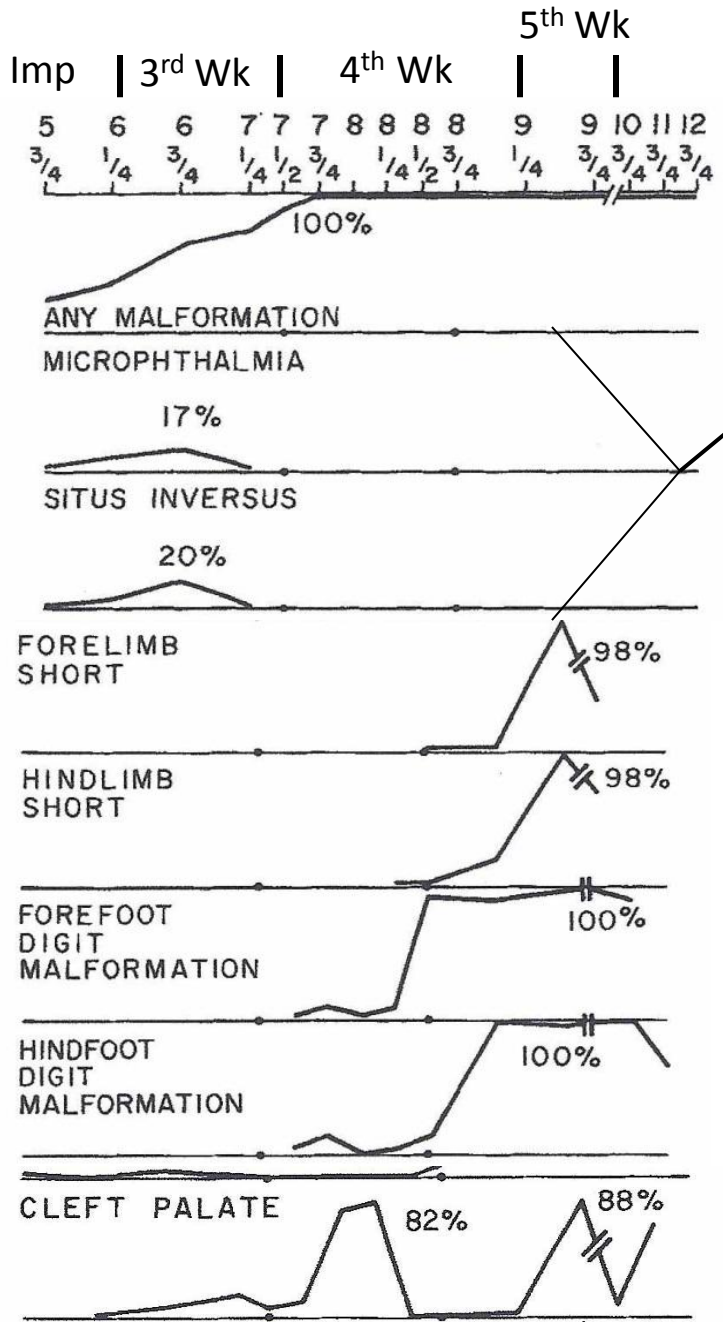


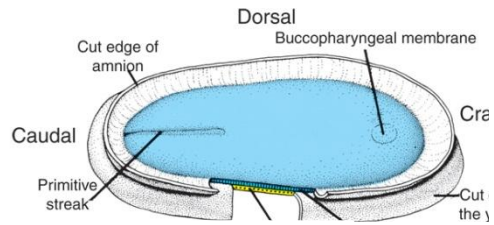
18 Weeks

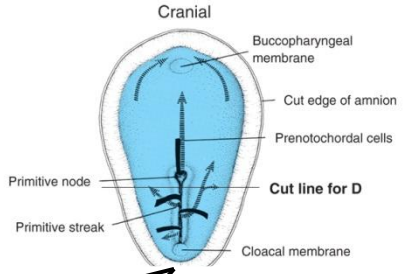
Risk of Birth Defects Being Induced

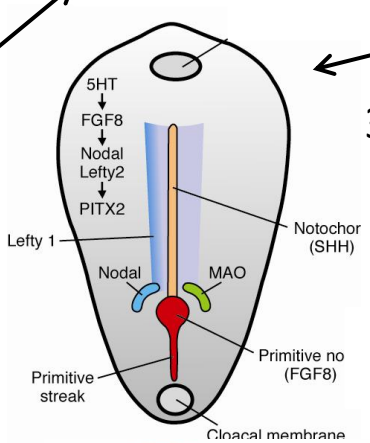


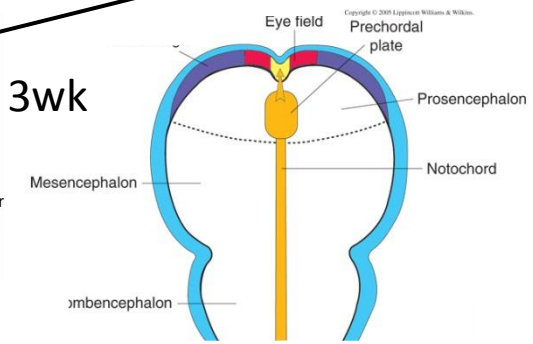
Shenefelt: Teratology; 5: 103-118, 1972. Retinoic acid as a teratogen in hamsters

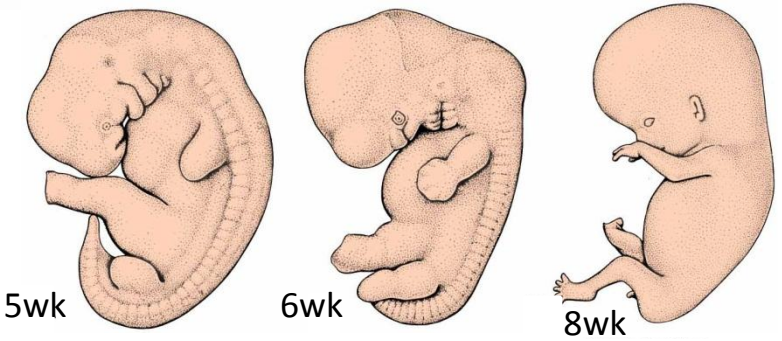


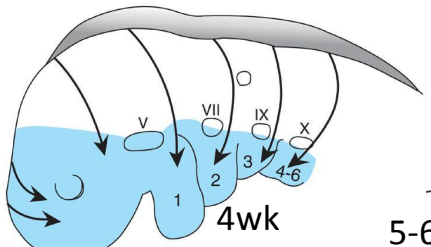


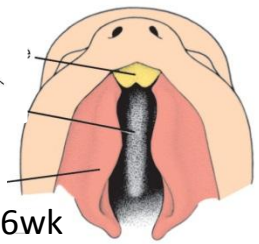


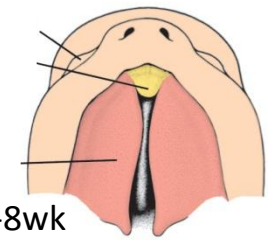






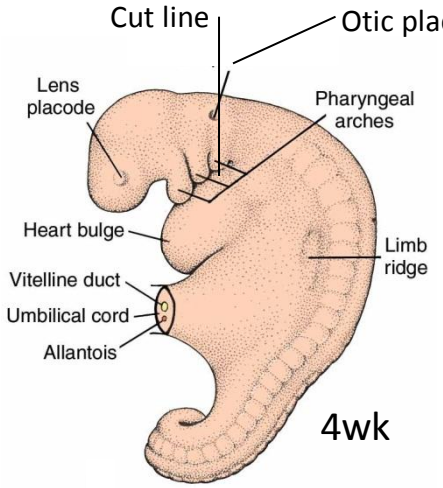




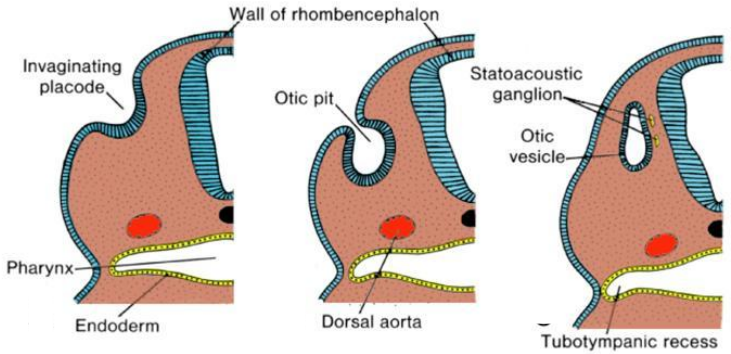


Teratogenicity of Rubella Infection

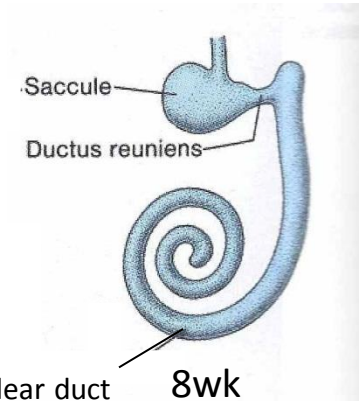
Prior to 8 weeks: 100% of infected infants had heart defects and/or deafness.



4wk

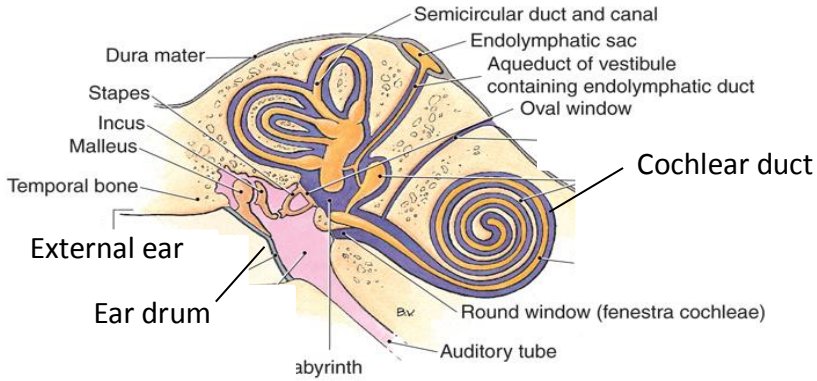


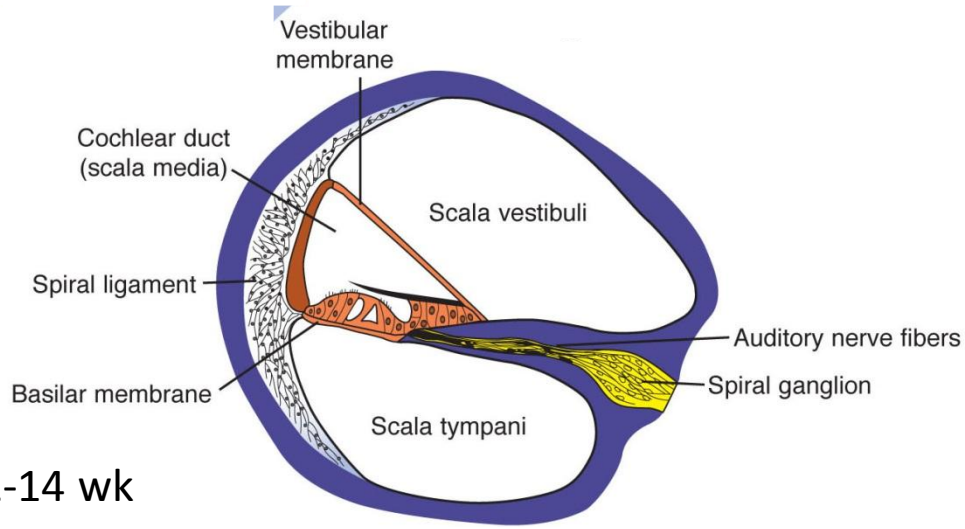
4-5wk



8wk

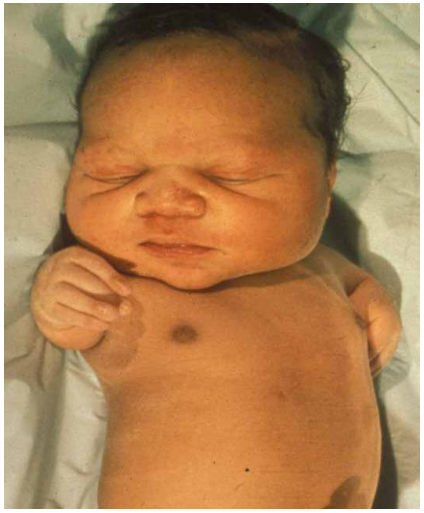
At 11-14 weeks : 35% of infected infants had deafness and none had heart defects.





12-14 wk

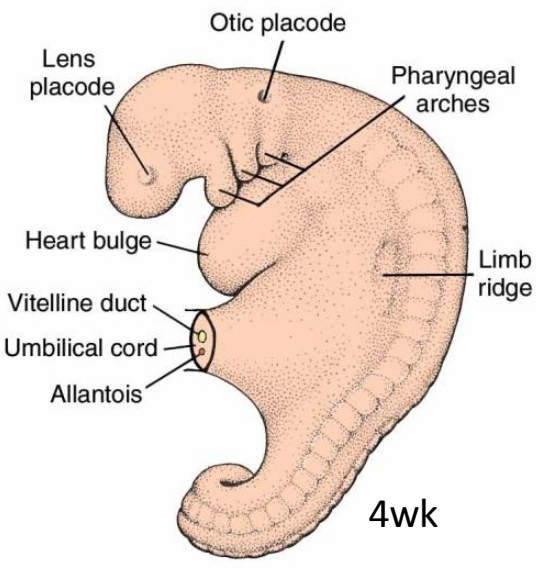
Thalidomide and Birth Defects

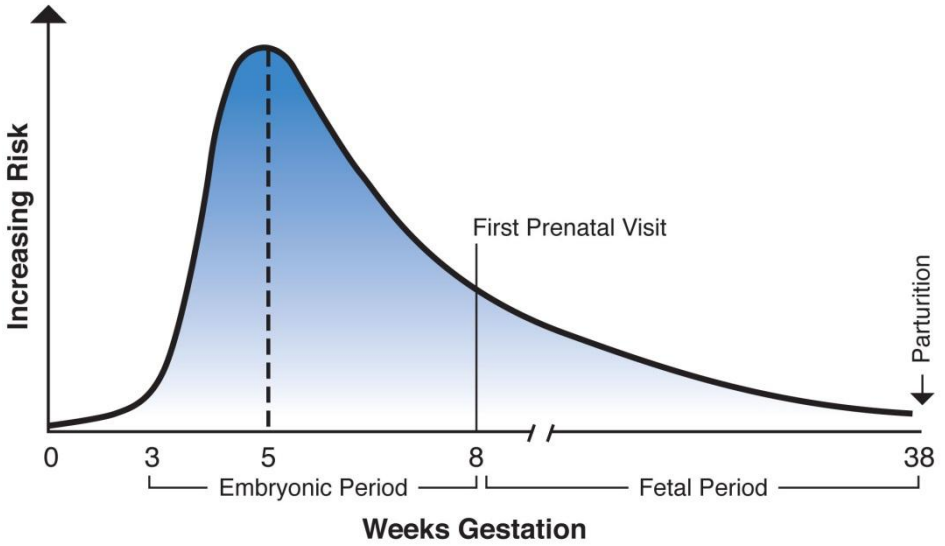


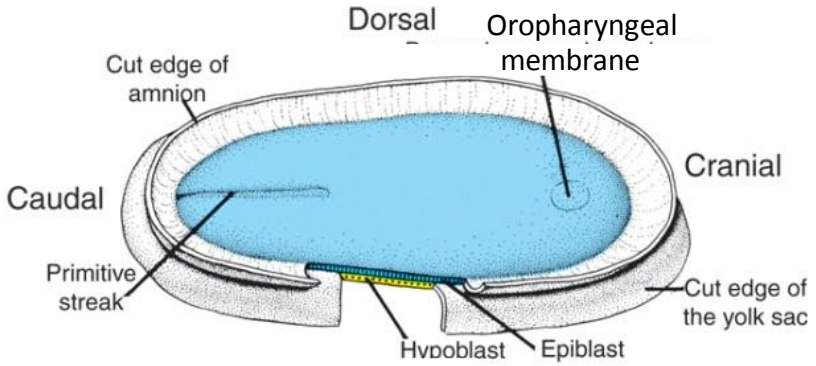
Forelimbs if started the drug in the 4th week

Hindlimbs if started the drug in the 5th week

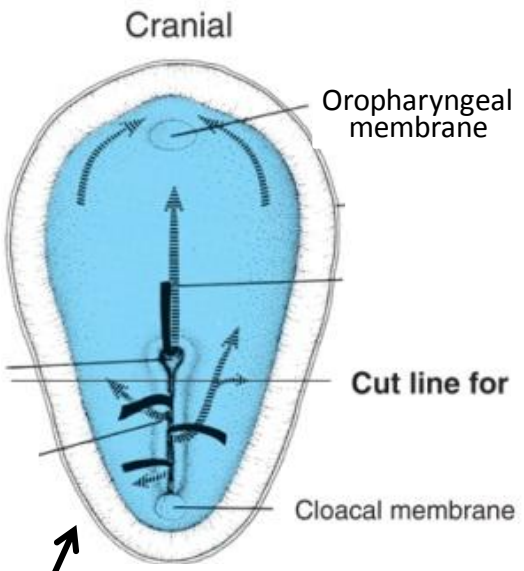
…But thalidomide also caused heart defects, ear defects, and GI tract defects!

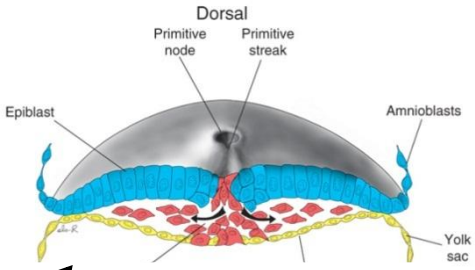




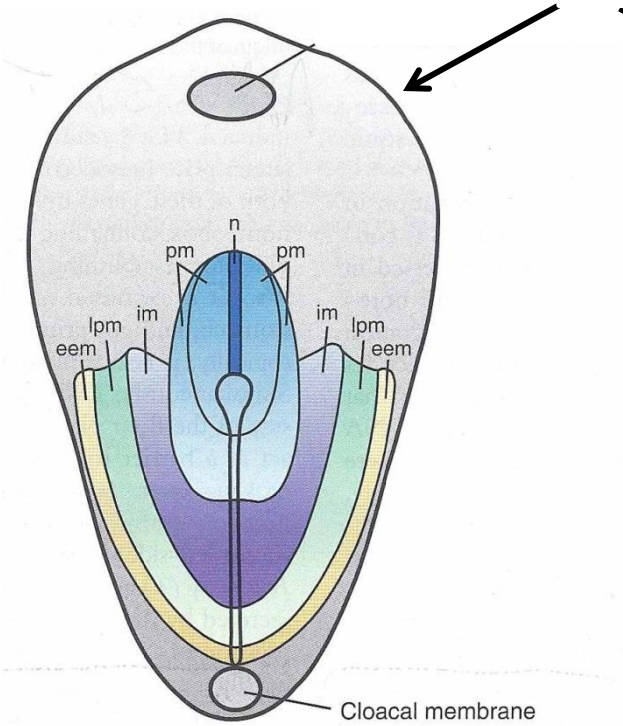


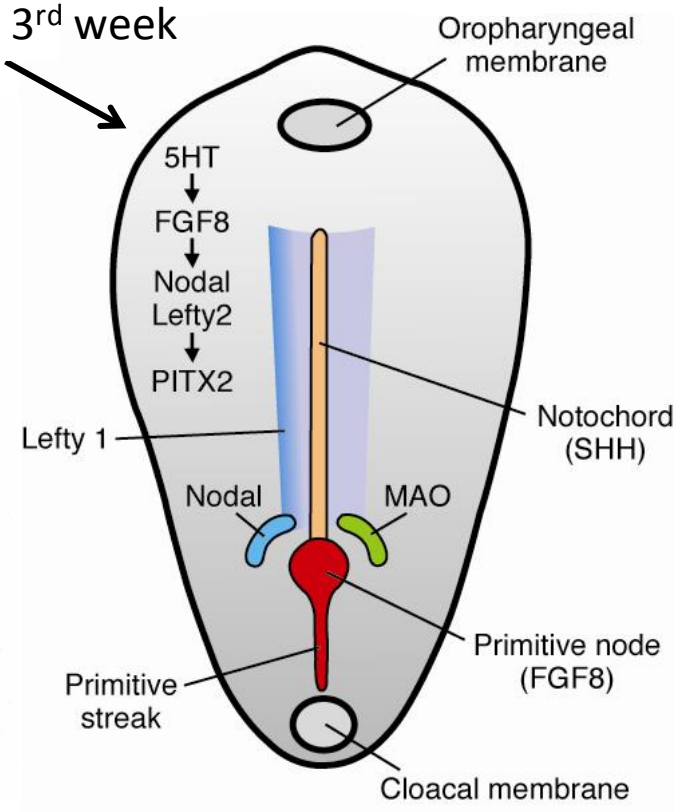
End of 2nd week



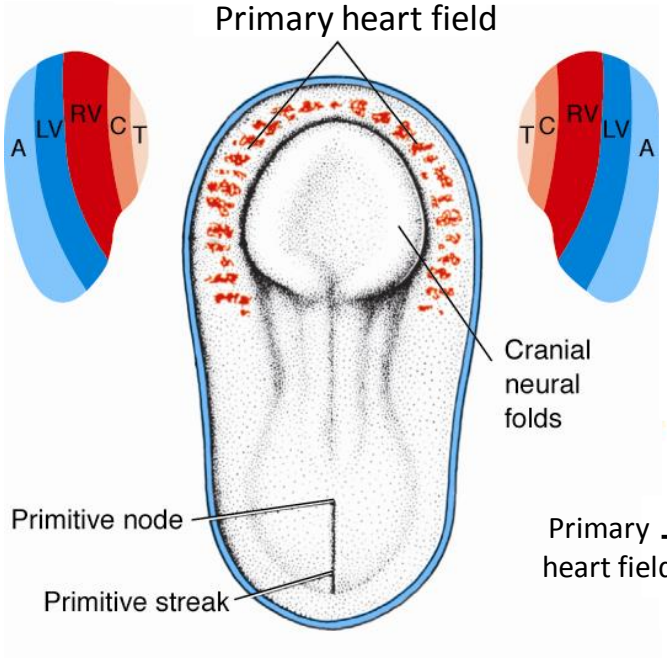


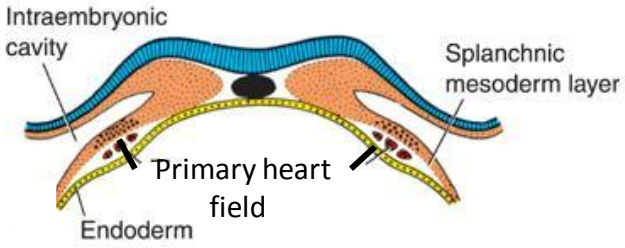
Beginning of 3rd week

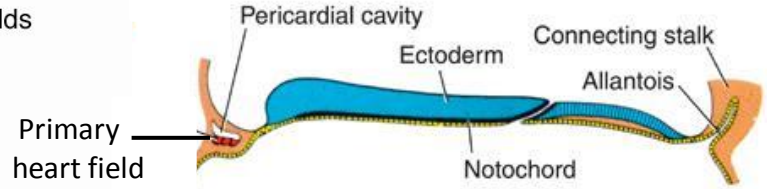


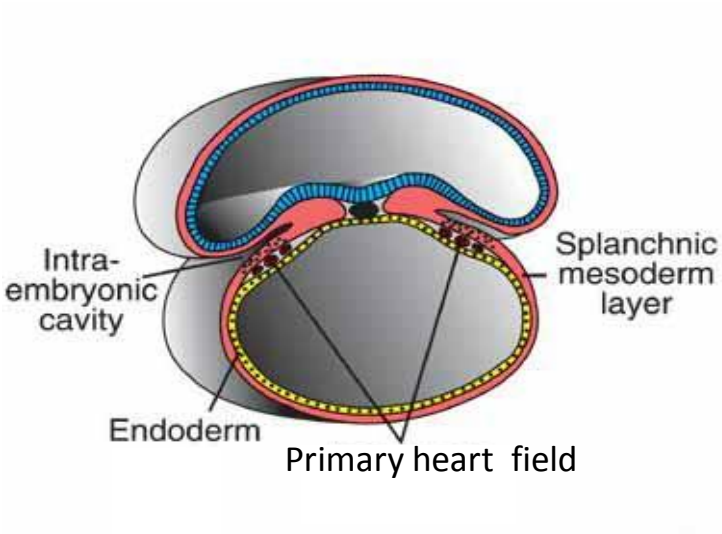


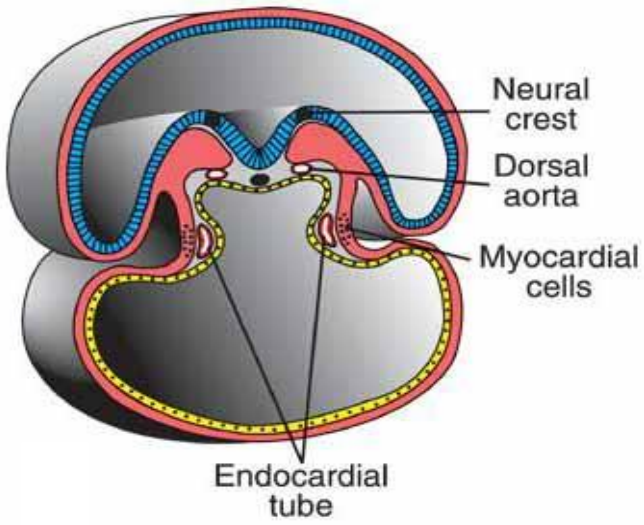
Heart Development late 3rd and early 4th weeks



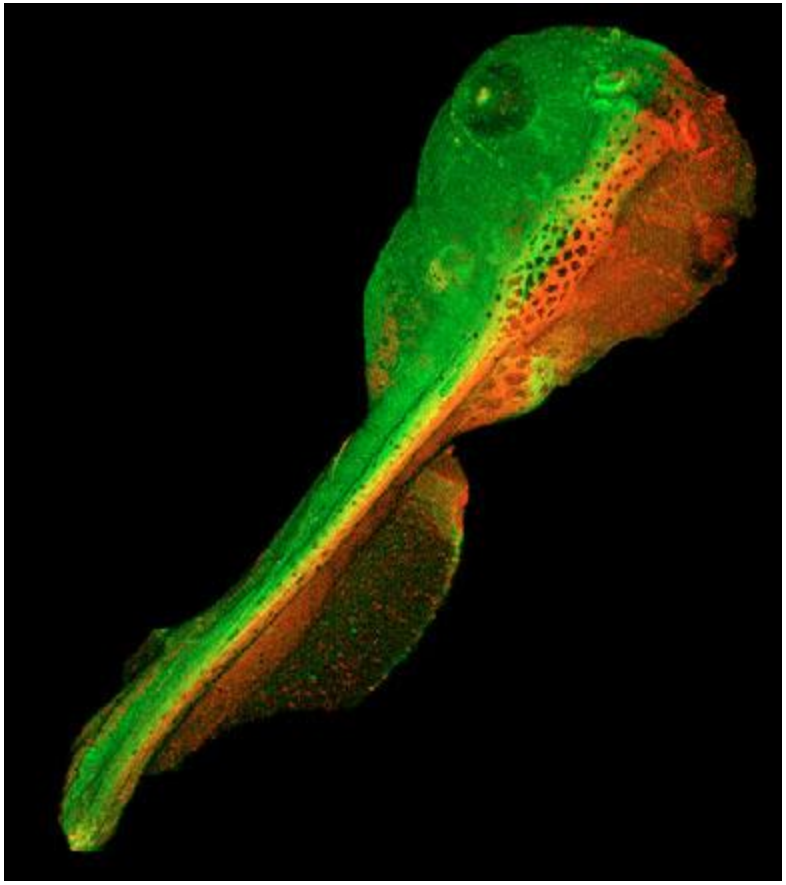


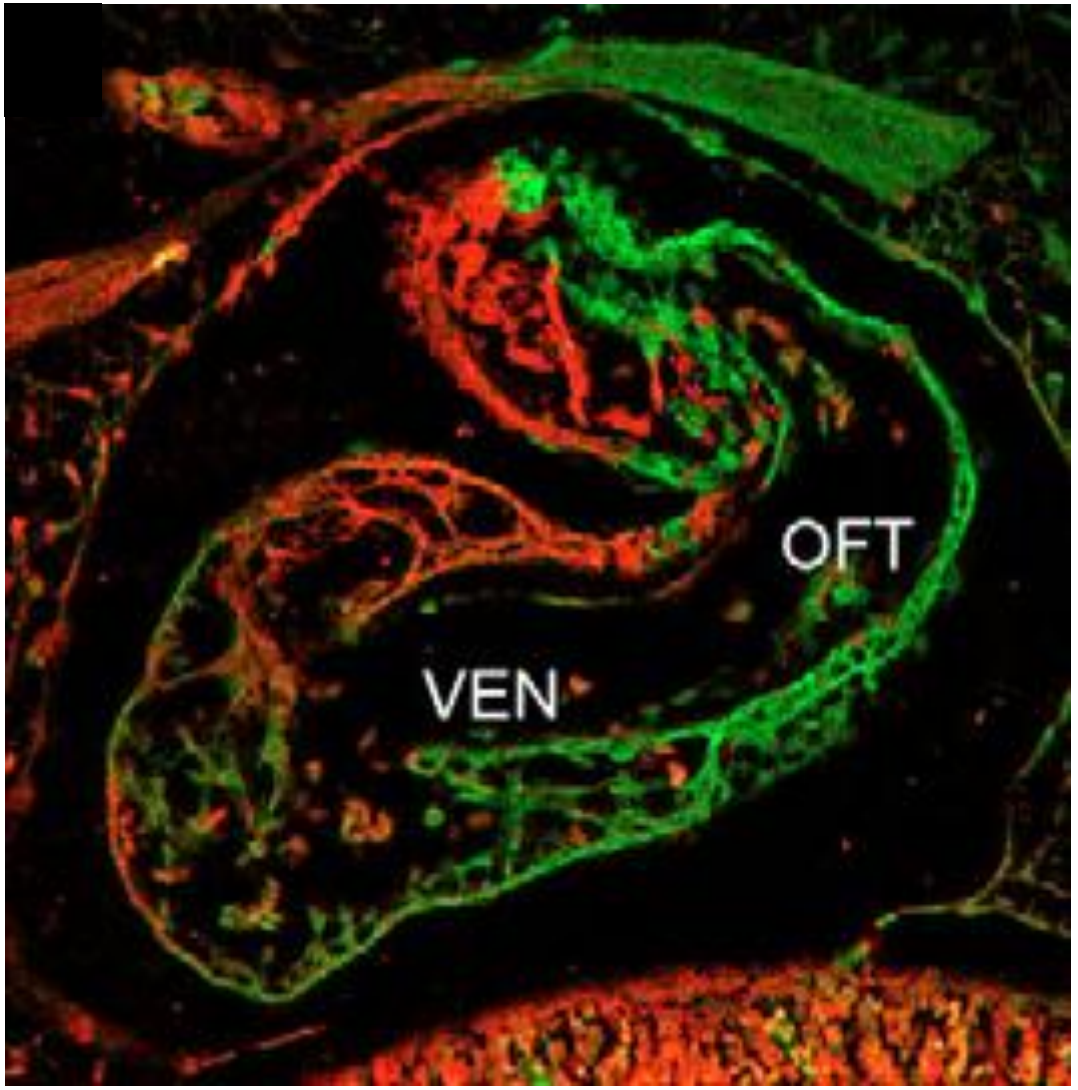






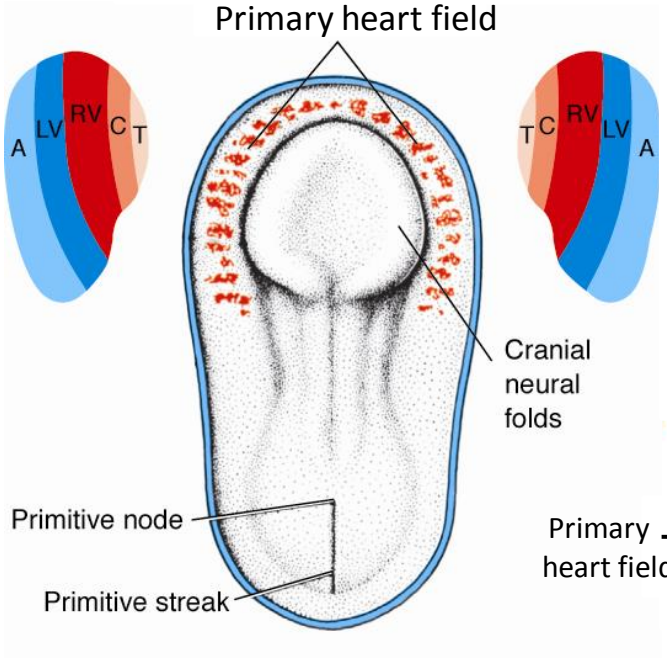
Cells in the primary heart field (PHF) are specified to pattern the heart

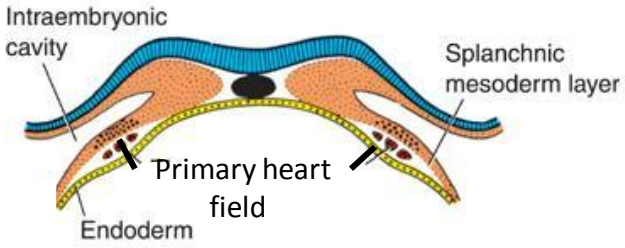


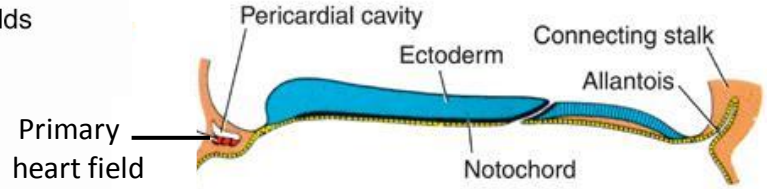


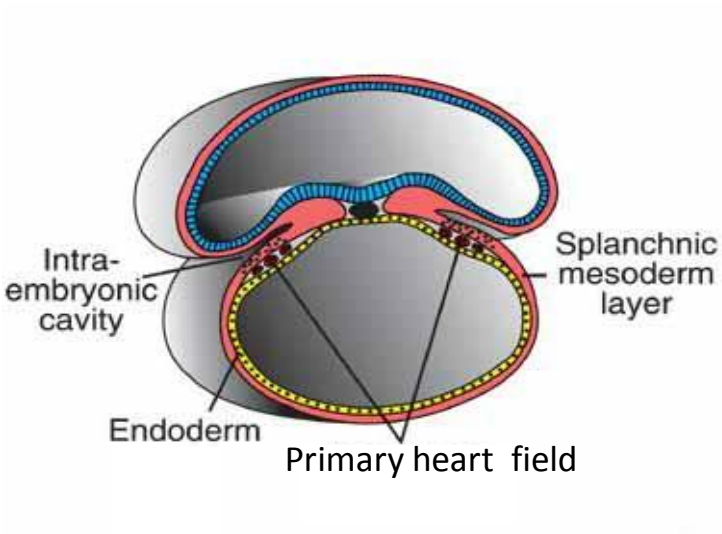
Ramsdell et al., Development 133: 1399, 2006

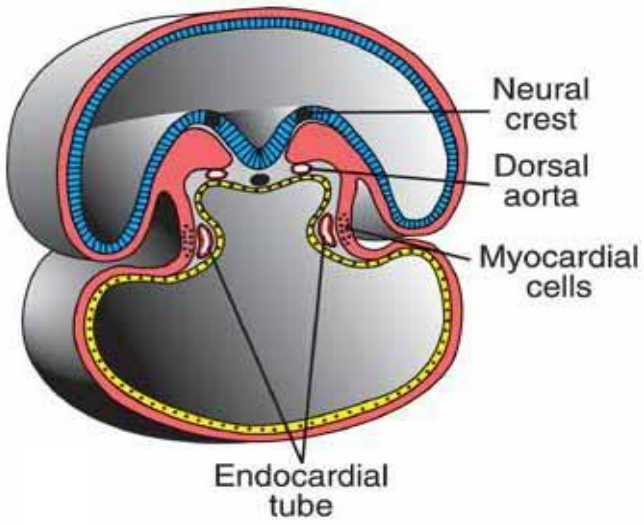
Heart Development late 3rd and early 4th weeks

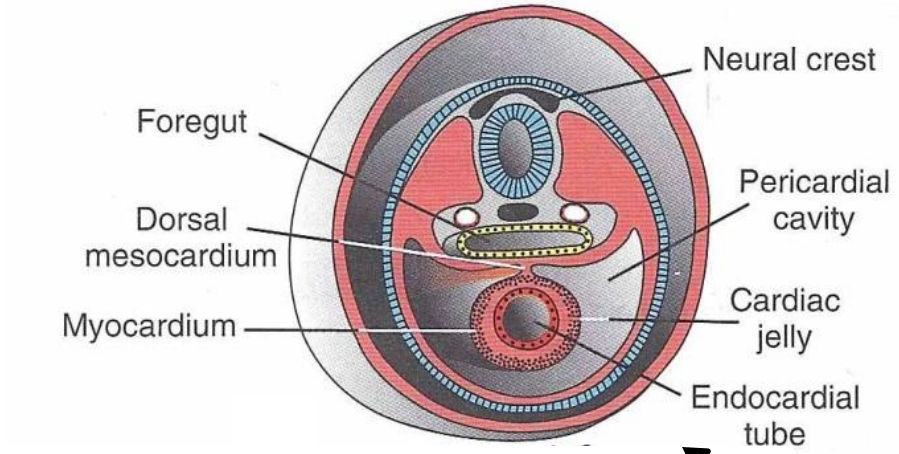


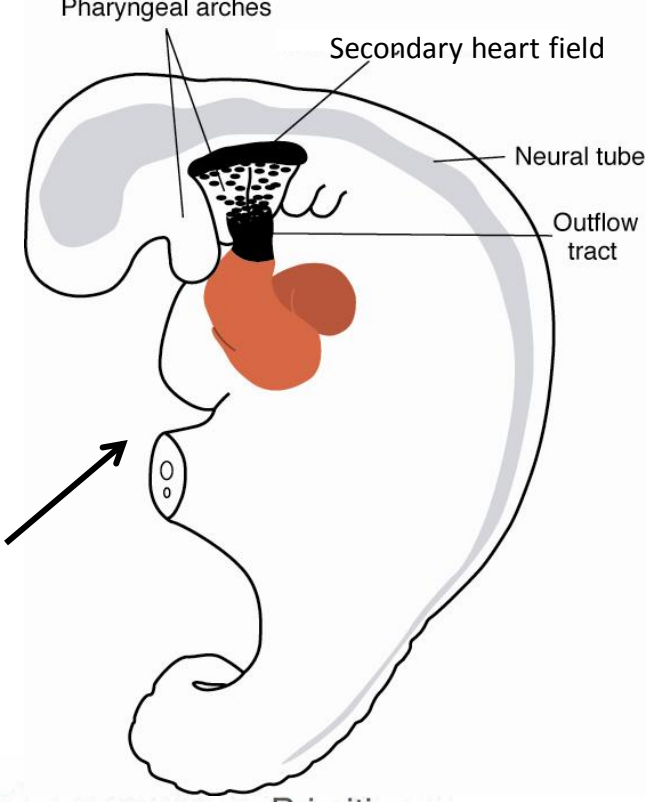


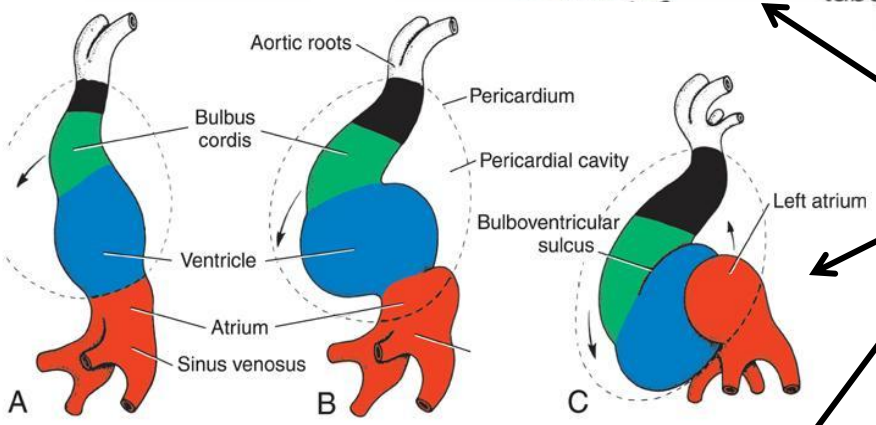




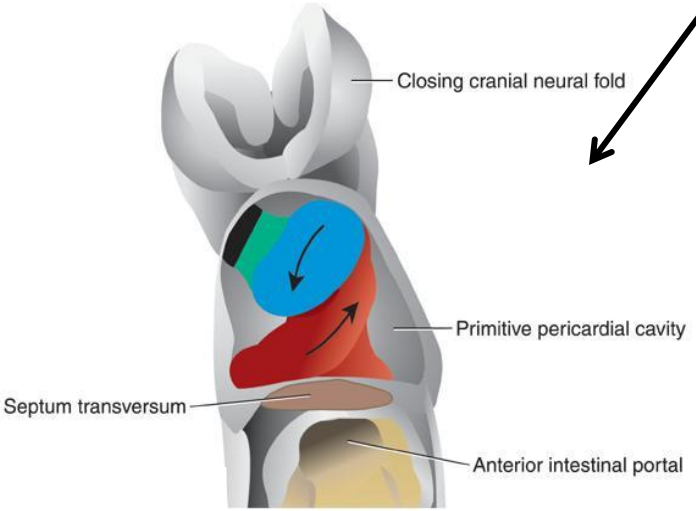


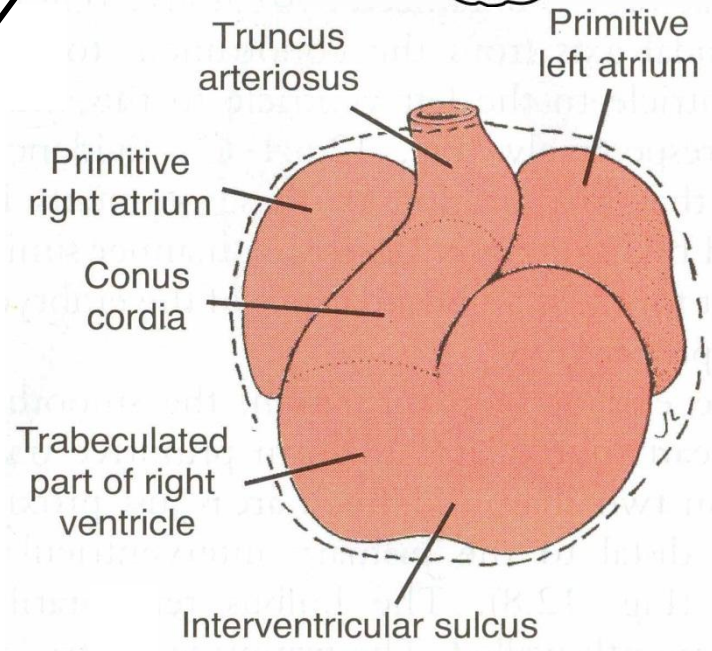






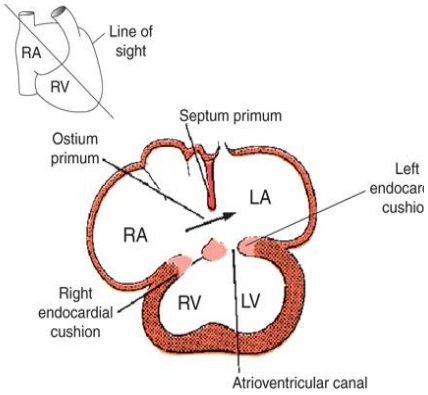
4th week

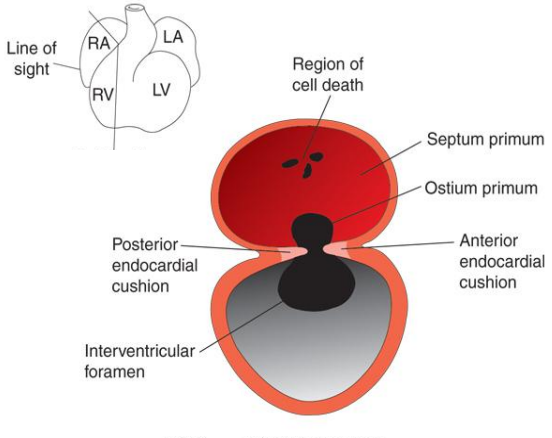




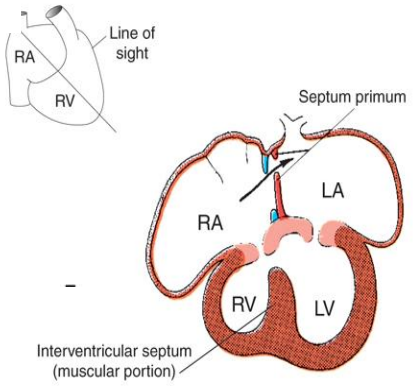
End of 4th week

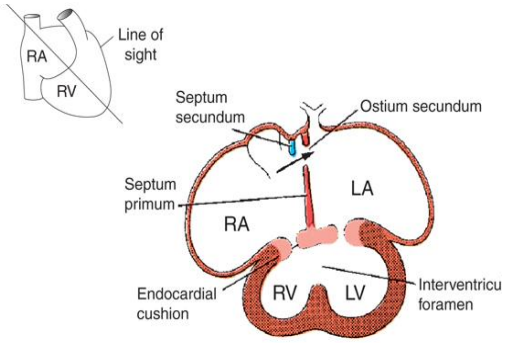
Atrial and Ventricular Septa Formation: 5th and 6th weeks

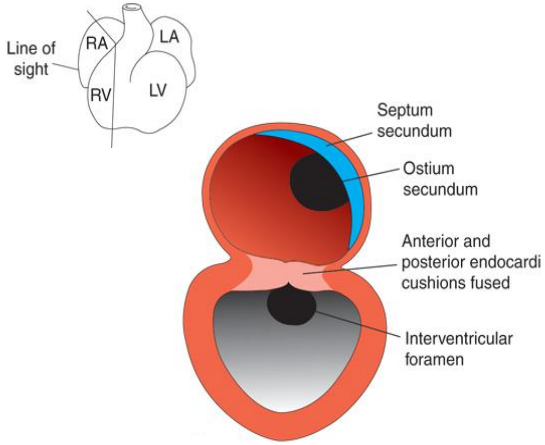


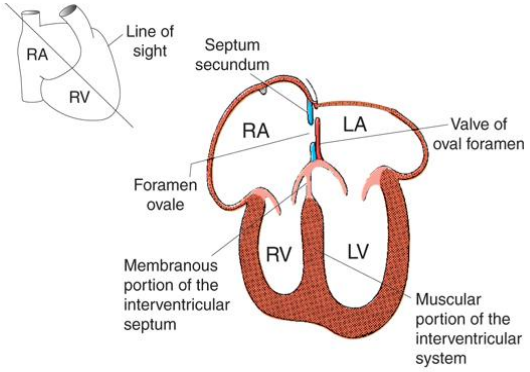


Cut



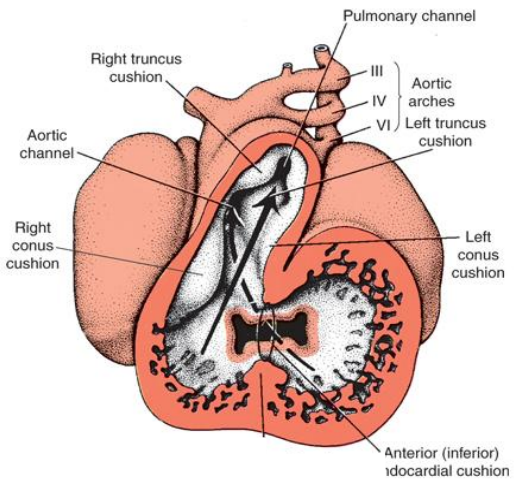


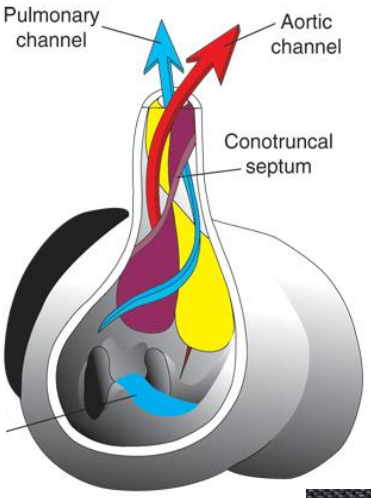


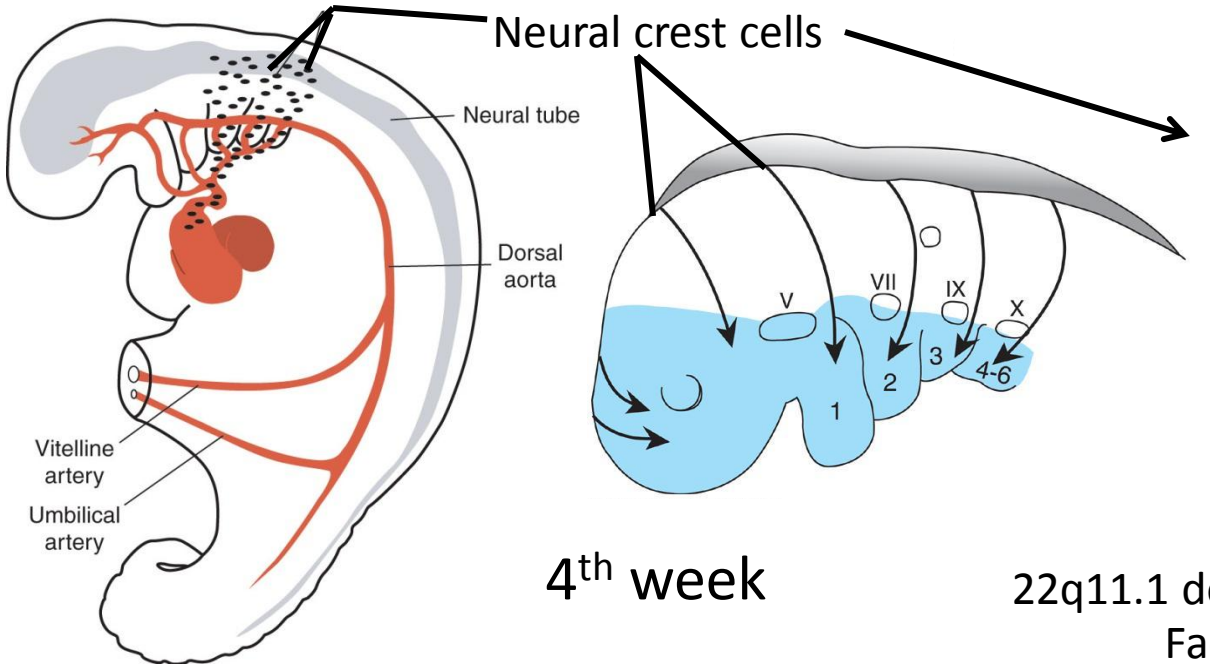


Septum formation in the outflow tract: 4th to 8th weeks

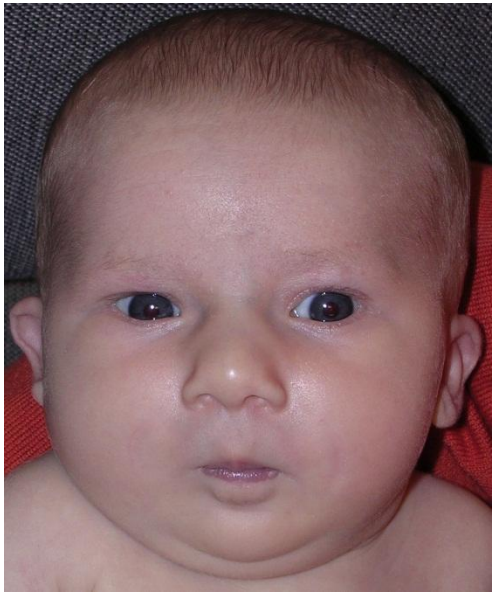
Fusion occurs in the 6th-8th weeks







4th week



22q11.1 deletion (Di George) syndrome
Face and heart defects

Congenital Heart Defects Are Heterogeneous in Origin & Occur during the (3rd-7th weeks)

Target Tissue	Cell Process	Normal Effect	Birth Defect
Cardiac Progenitor cells (Primary Heart Field [PHF])	Laterality & patterning (Week 3)	Specification of the outflow tract ventricles & atria	DORV, TGA, l -TGA, ASD, VSD, atrial isomerism, ventricular inversion, dextrocardia & common truncus arteriosus
Heart tube	Extracellular matrix (Weeks 3&4)	Looping	Dextrocardia
Atrioventricular endocardial cushions	Cell proliferation & migration (Week 5)	Division of the AV canal; Formation of the AV valves; Formation of the membranous IVS	VSDs, ASDs, mitral insufficiency, tricuspid atresia, positioning & leaflet defects
Secondary heart field (SHF)	cell proliferation, migration & viability (Week 4)	Lengthening, positioning and division of the outflow tract	Tetralogy of Fallot, pulmonary stenosis & atresia, TGA, DORV
Outflow tract (Conotruncus)	Neural crest cell proliferation, migration & viability (Weeks 4-7)	Formation of the conotruncal endocardial cushions	Common truncus arteriosus

When it comes to development, timing is everything!

- The embryonic period (3rd to 8th weeks) is the most sensitive time for causing structural birth defects
- The fetal period (9th week to birth) is not very sensitive to teratogen induced birth defects, although some organs remain at risk, especially the brain
- Some organs will be susceptible for long periods (the heart), others for shorter periods (the forelimb)
- Not every organ will have the same sensitivity to a given concentration of a teratogen, but primordial cells and stages will be more susceptible than later stages (primordial heart and neural crest cells)
- Multiple organs may be “hit” at the same time, sometimes resulting in the characteristics of a syndrome

Why is Preconception care the way to prevent birth defects?

See Below!