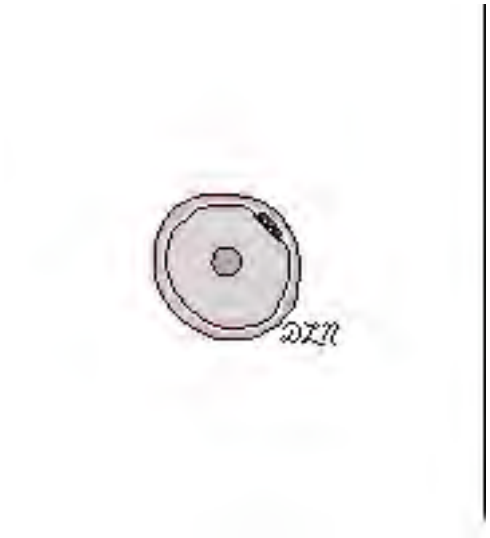
Movie: Development



http://embryology.med.unsw.edu.au/Defect/smoking.htm

Medical Consequences of Smoking in Pregnancy

School of Medical Sciences
The University of New South Wales

Dr Mark Hill

Cell Biology Laboratory

Room G20 Wallace Wurth Building

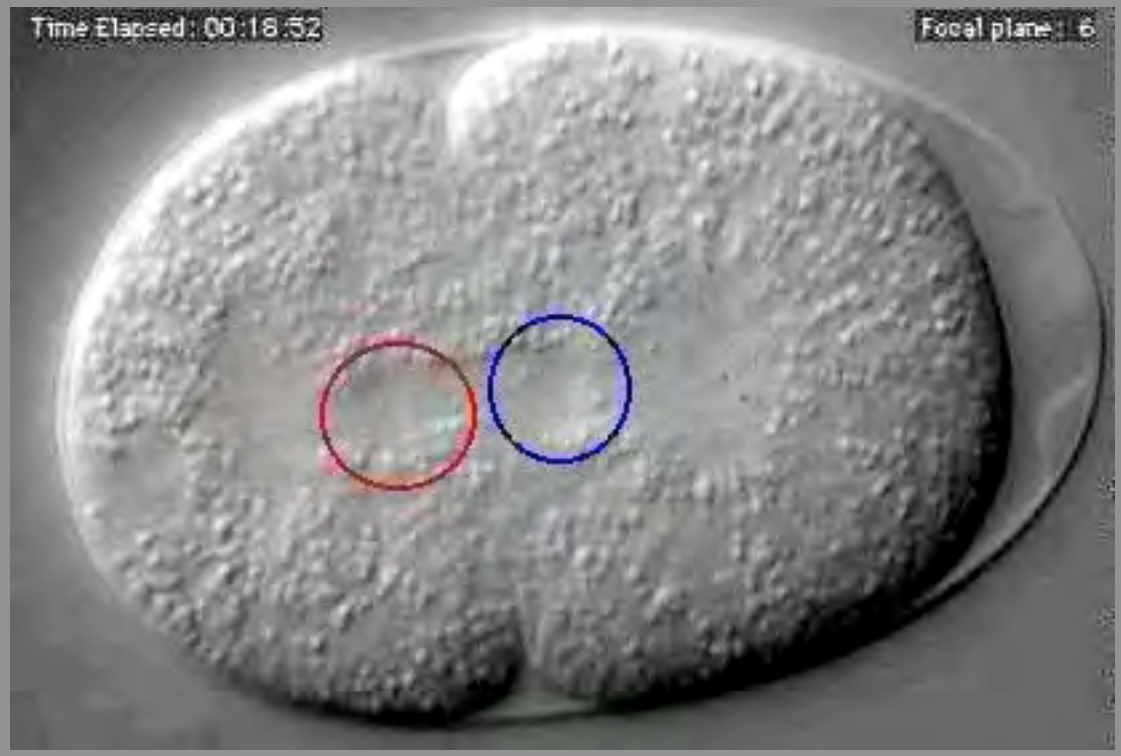
Email: m.hill@unsw.edu.au

UNSW Copyright Notice

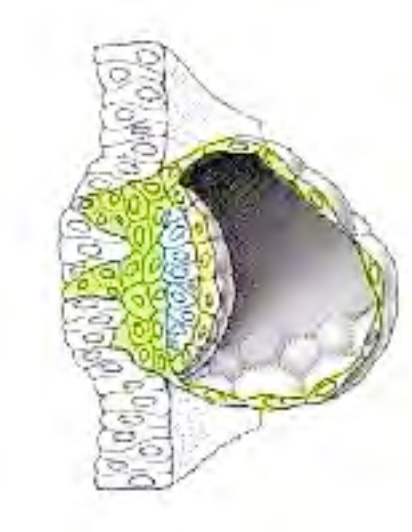
© Dr M. A. Hill, 2005
Cell Biology Laboratory
School of Medical Sciences, Faculty of Medicine
The University of New South Wales, Sydney, Australia

Web: http://embryology.med.unsw.edu.au
Email: m.hill@unsw.edu.au

Early Development

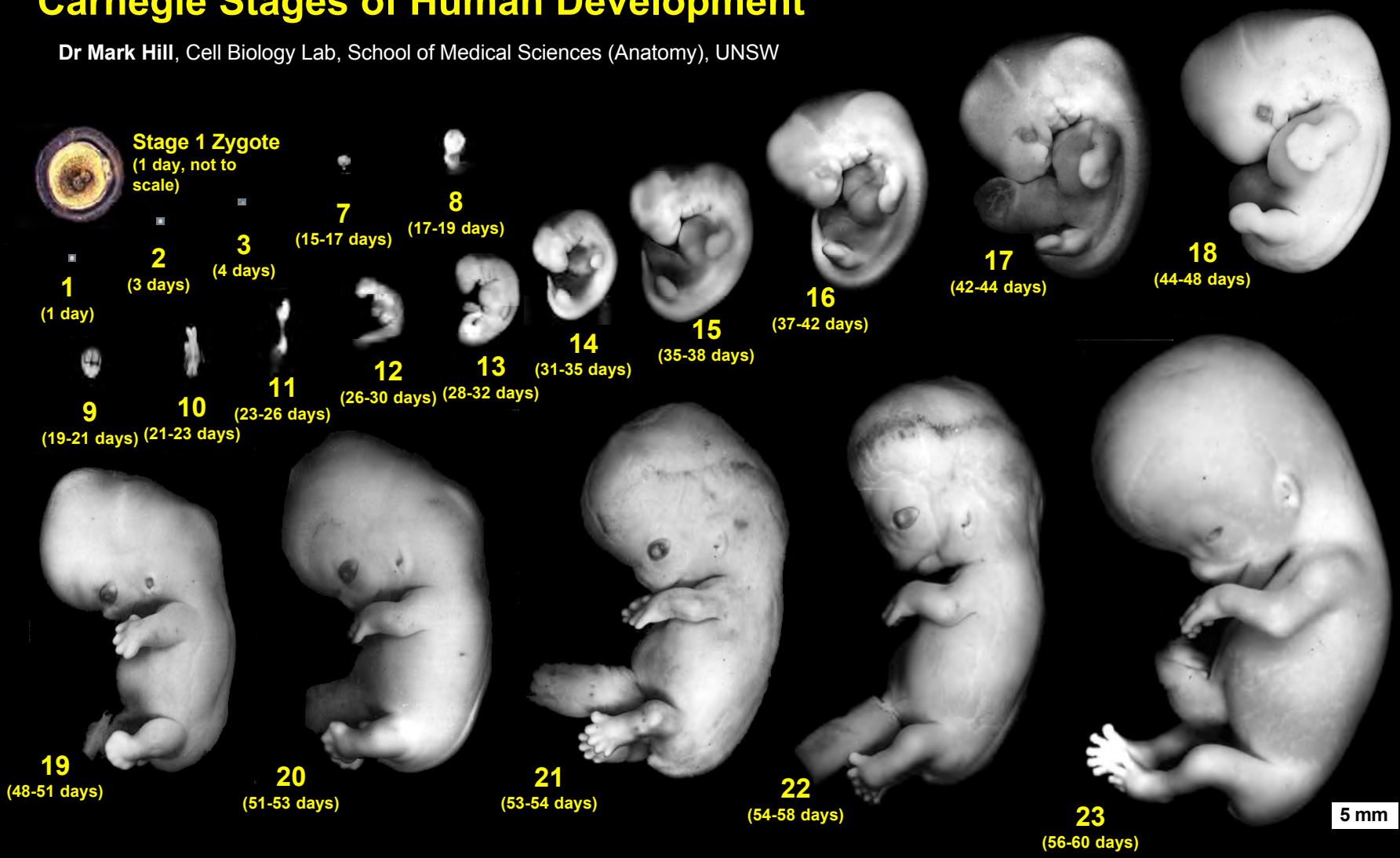


Week 2 - Implantation



Carnegie Stages of Human Development

Dr Mark Hill, Cell Biology Lab, School of Medical Sciences (Anatomy), UNSW



Acknowledgements

Special thanks to Dr S. J. DiMarzo and Prof. Kohei Shiota for allowing reproduction of their research images and material from the Kyoto Collection and Ms B. Hill for image preparation.

Carnegie Stages Online -
http://anatomy.med.unsw.edu.au/cbl/embryo/wwwhuman/Stages/CStages.htm

UNSW Embryology
http://anatomy.med.unsw.edu.au/cbl/embryo/embryo.htm

Teratogen

- Any agent that causes a structural abnormality following fetal exposure during pregnancy
  - Infectious agents
    - rubella, cytomegalovirus, varicella, herpes simplex, syphilis
  - Physical agents
    - ionizing agents, hyperthermia
  - Maternal health factors
    - diabetes, maternal PKU
  - Environmental chemicals
    - organic mercury compounds, PCB, herbicides and solvents
  - Drugs
    - prescription, over- the-counter, recreational

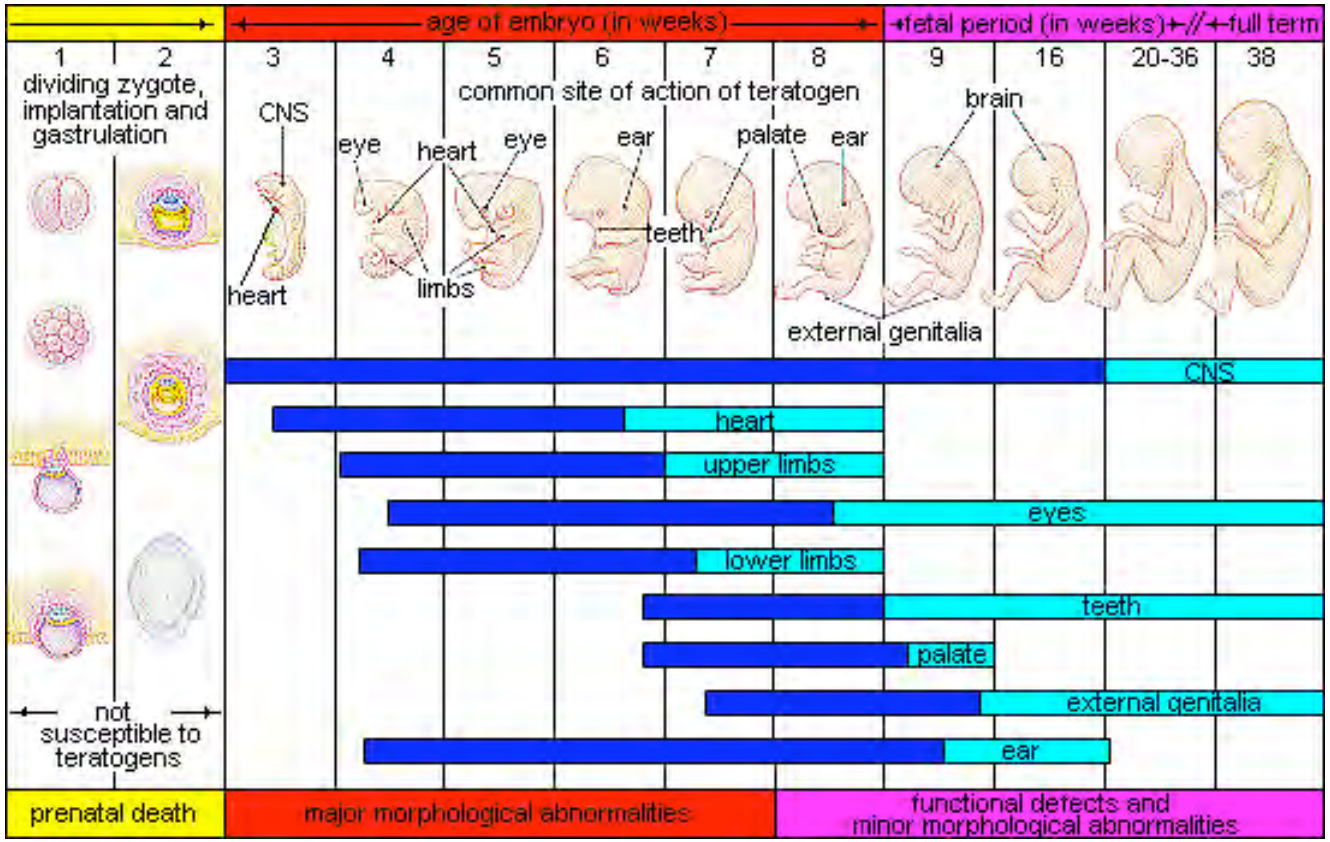
Teratogenic Chemicals

- More suspected teratogens than before
  - increase in synthetic chemical compounds in use
- clinical recognition of subtle malformations as teratogenic effects
  - fetal alcohol syndrome
  - fetal hydantoin syndrome
  - fetal trimethadione syndrome
  - fetal warfarin syndrome
  - smoking associated with low birth weight infants

Teratogenic Effects

- Dose Response
  - greater the dose, the greater the effect
- Time of Exposure
  - certain stages of embryonic and fetal development are more vulnerable

Critical Periods of Human Development



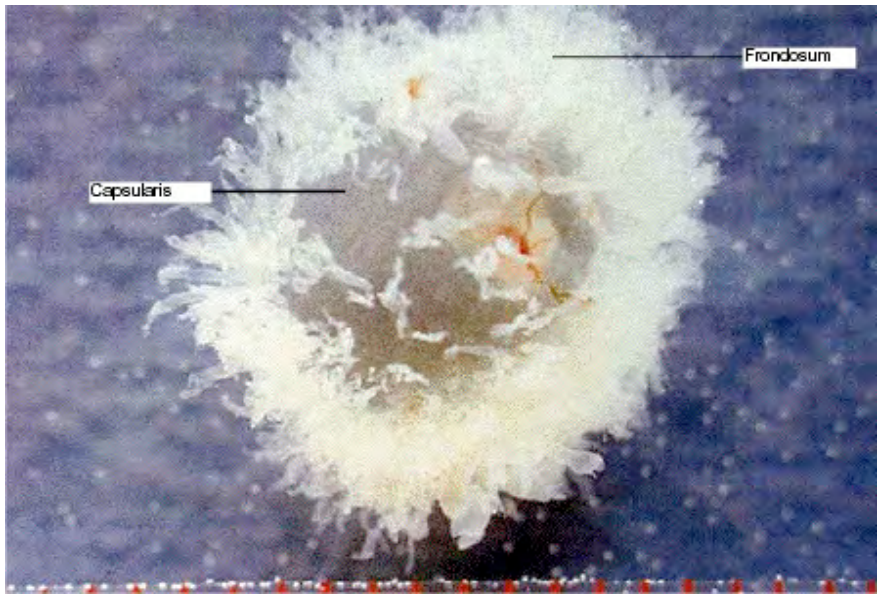
Light blue bars indicate periods when organs are most sensitive to Maternal damage from alcohol, viral infection, smoking, etc.

Adapted from *Human Biology* by Starr and McMillan

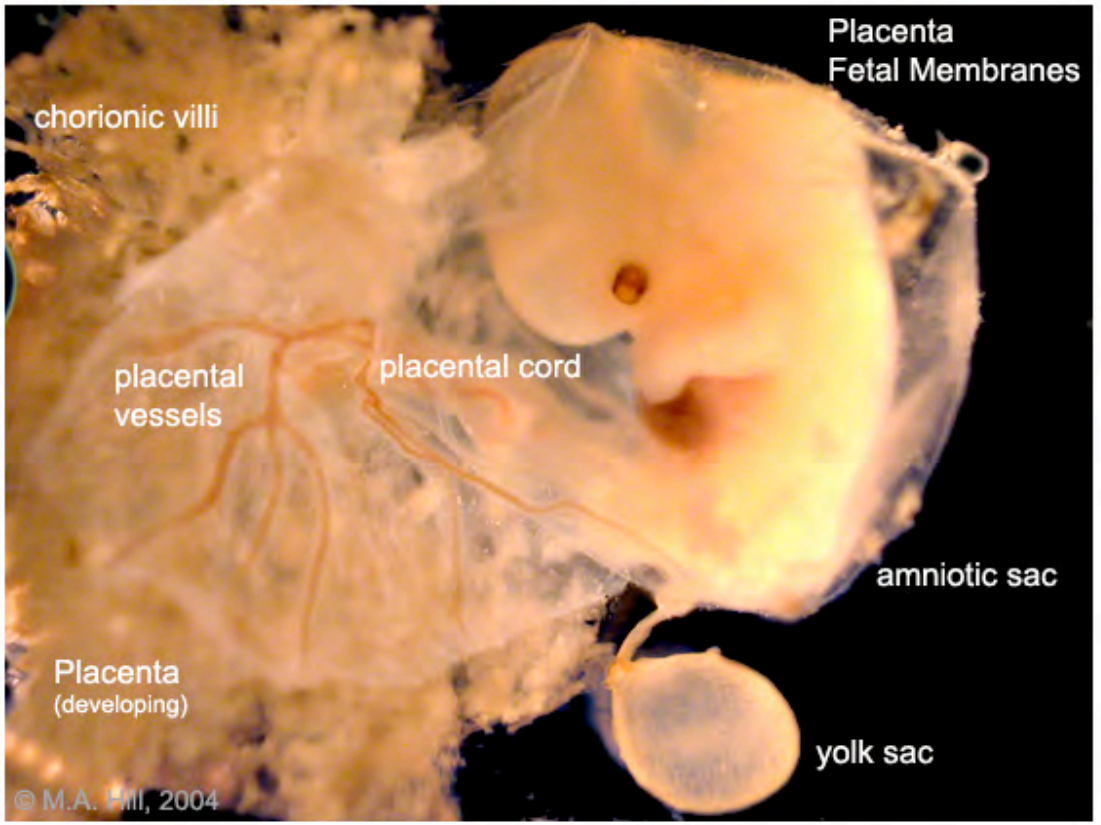
http://www.people.virginia.edu/~rjh9u/hdevsum.html

Chorionic Villi

- cover entire chorionic surface
- become restricted to decidua basalis region
  - Frondosum
  - Capsularis
- Maternal Decidua basalis reaction
  - deposition of glycogen
  - proliferation of blood vessels



Placenta and Membranes



Fetal Membranes

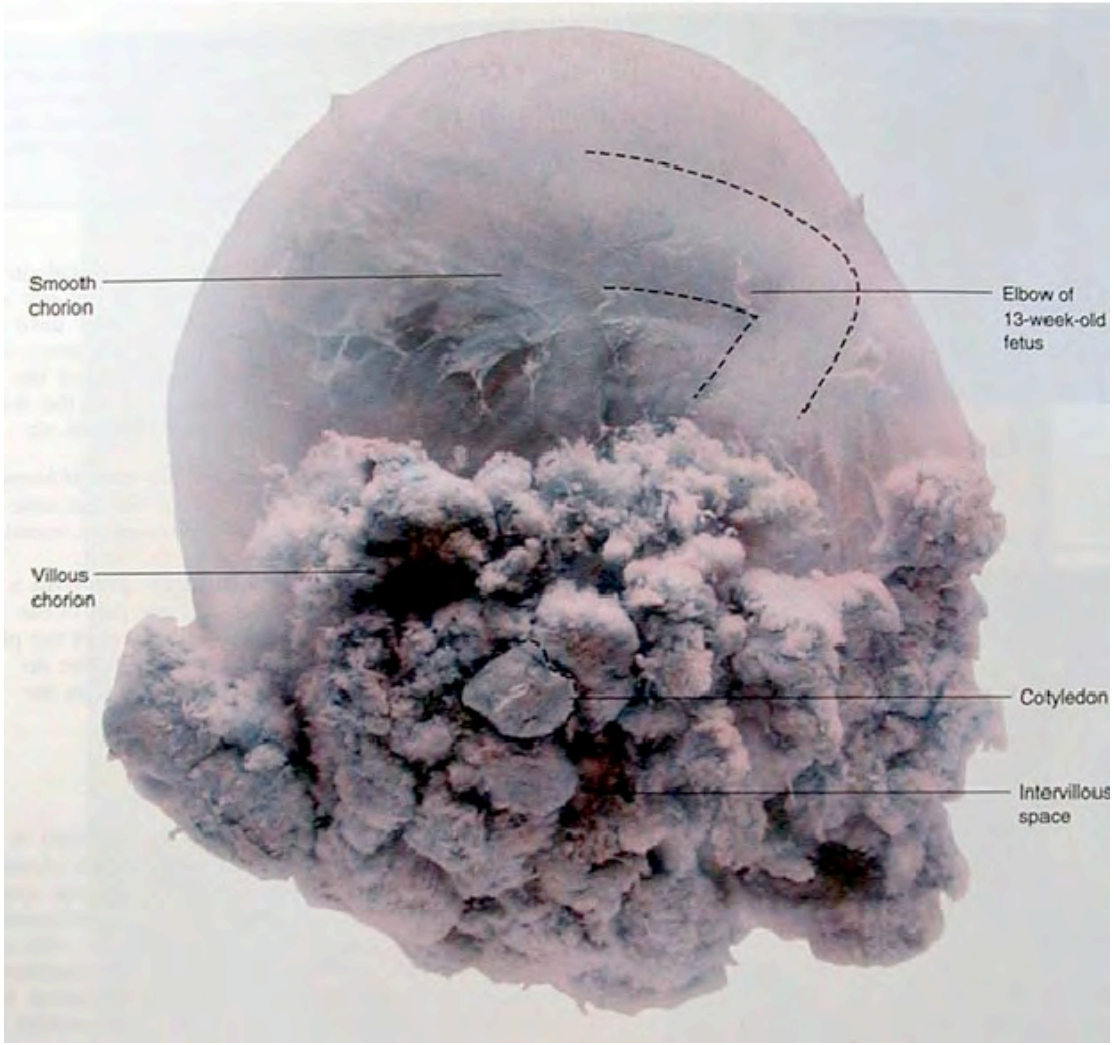
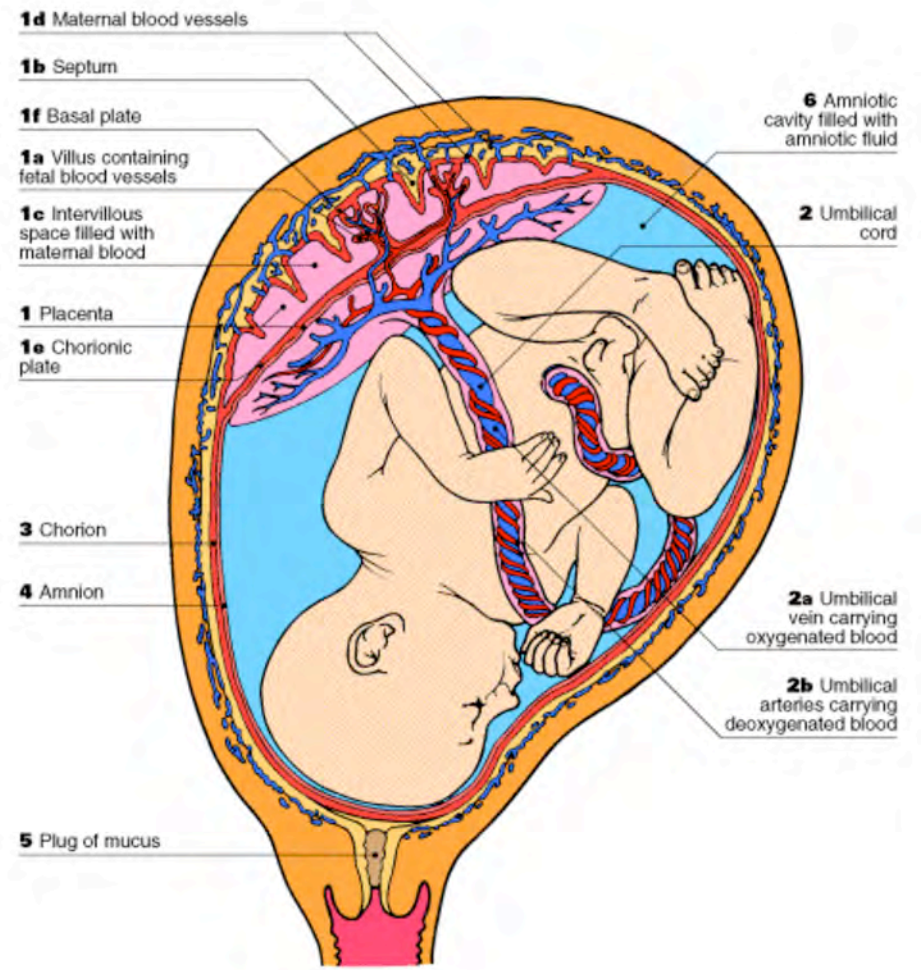


Image: Larsen, Human Embryology

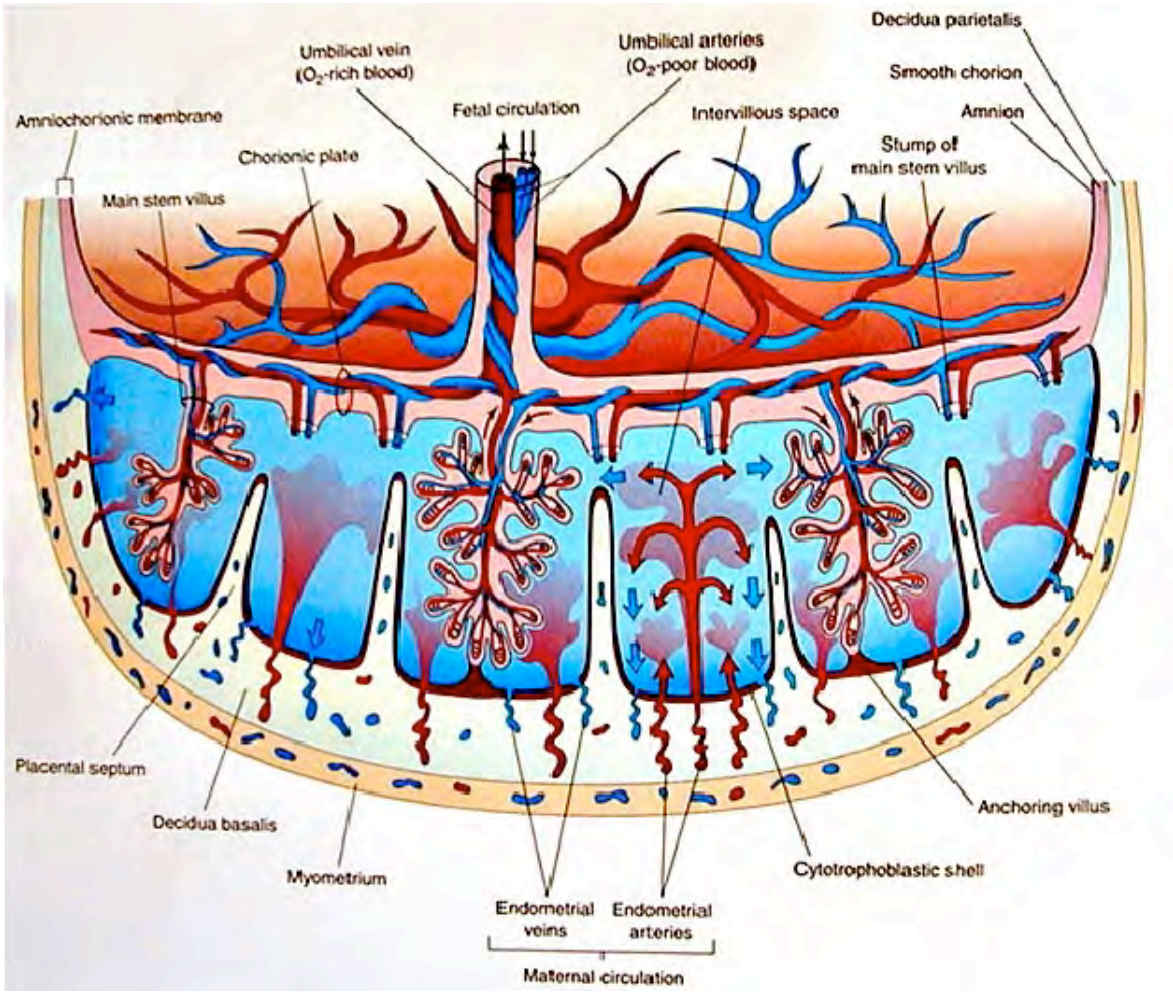
Placenta - Fetal

Section through uterus and membranes to show full-term fetus and placenta



http://www.fofweb.com/Subscription/Science/Science-Detail.asp?SID=1&iPin=H927

Placenta Blood Flow

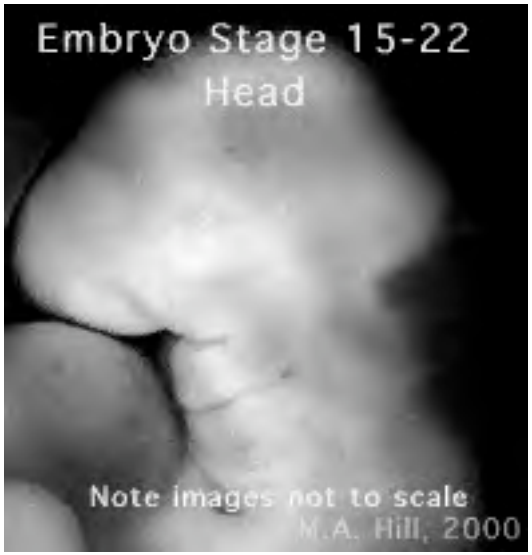


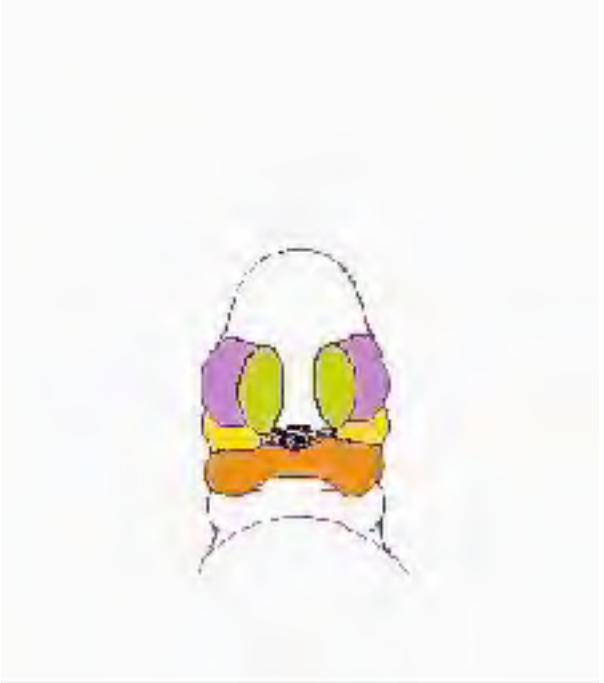
Endocrine Defects

- effects on hormone secretion
  - mediated by pharmacological action of nicotine and by toxins such as thiocyanate
- Smoking affects pituitary, thyroid, adrenal, testicular and ovarian function, calcium metabolism, action of insulin, reduced fertility, development of insulin resistance
- Passive transfer of thiocyanate can disturb thyroid size and function
- maternal smoking increases catecholamine production
  - may contribute too under perfusion of the foetoplacental

European Journal of Endocrinology (2005) 152 491–499

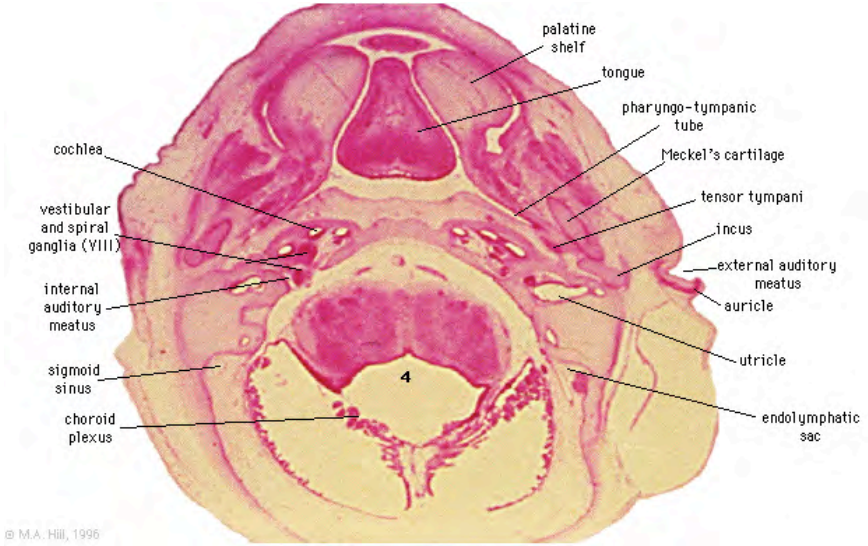
Head Development



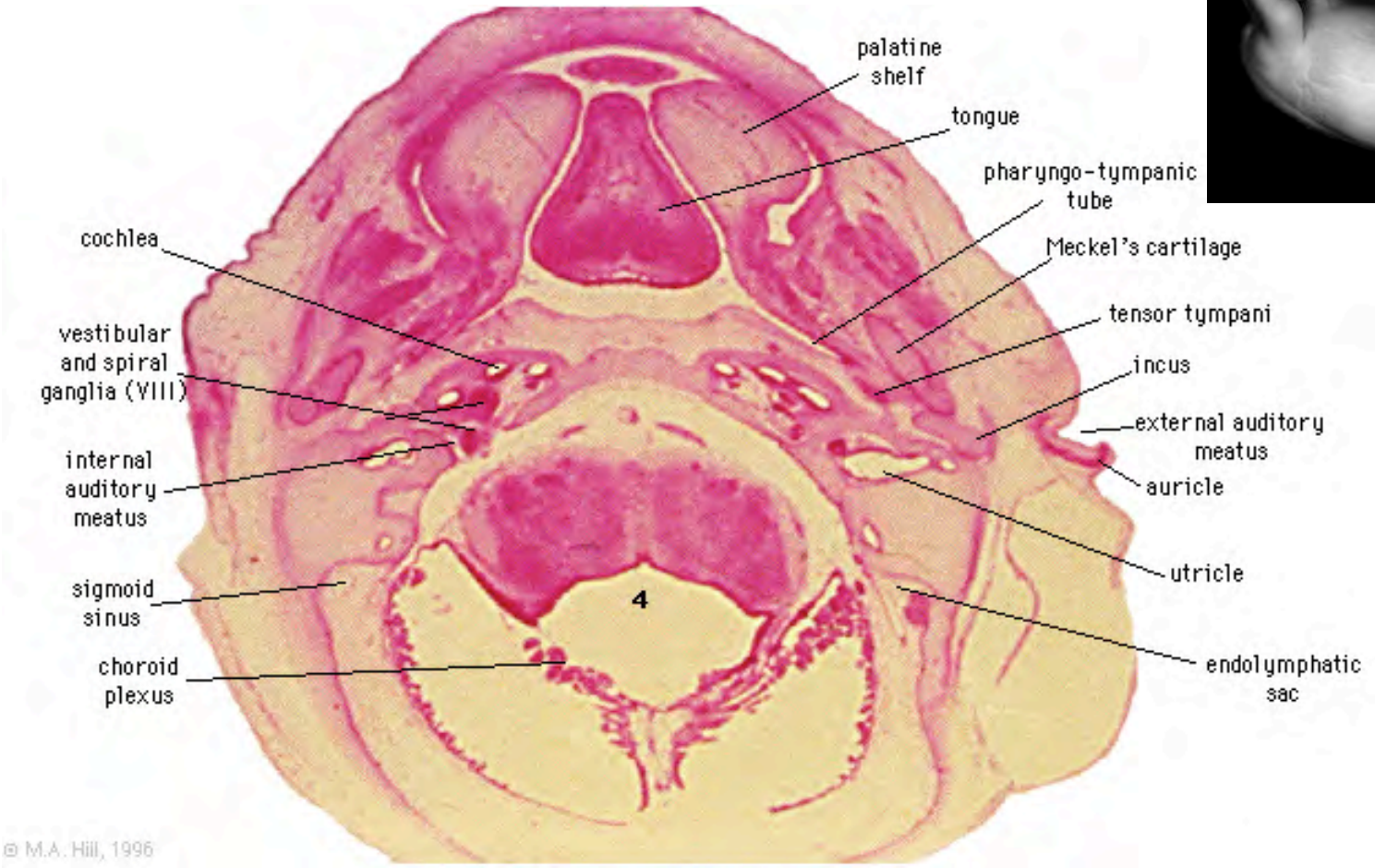


Palate Development

- Palatal development occurs between the 7th and 12th week of gestation
- primary palate (prolabium) premaxilla and cartilaginous septum)
- secondary palate (hard and soft palate)



Stage 22 Embryo



Week 8, 54 - 56 days, 23 - 28 mm

Oral Clefts

- Occur in 82 of 100,000 live births
- Cleft lip (with or without cleft palate)
- Cleft palate
    - Ventura et al.1997, Wyszynski et al. 1997
- increasing risk for cleft lip with or without cleft palate with increasing amount of maternal smoking
- Another study found no dose-effect relationship
  – inconsistency among reports may be explained by an interaction between smoking and genetic factors

Report of the Surgeon General USA (1997)

Oral Clefts (UK)

- Smoking and orofacial clefts: a United Kingdom-based case-control study
  - 190 children born with oral cleft between Sep1, 1997, and Jan31, 2000, and 248 population controls, matched with the cases on sex, date of birth, and region.
  - A positive association between maternal smoking during the first trimester of pregnancy and both cleft lip with or without cleft palate (odds ratio 1.9, 95% confidence interval 1.1 to 3.1) and cleft palate (odds ratio 2.3, 95% confidence interval 1.3 to 4.1)
  - Evidence of a dose-response relationship for both types of cleft. An effect of passive smoking could not be excluded in mothers who did not smoke themselves.

Cleft Palate Craniofac J. 2004 Jul;41(4):381-6

Upper Limb Carnegie Stages

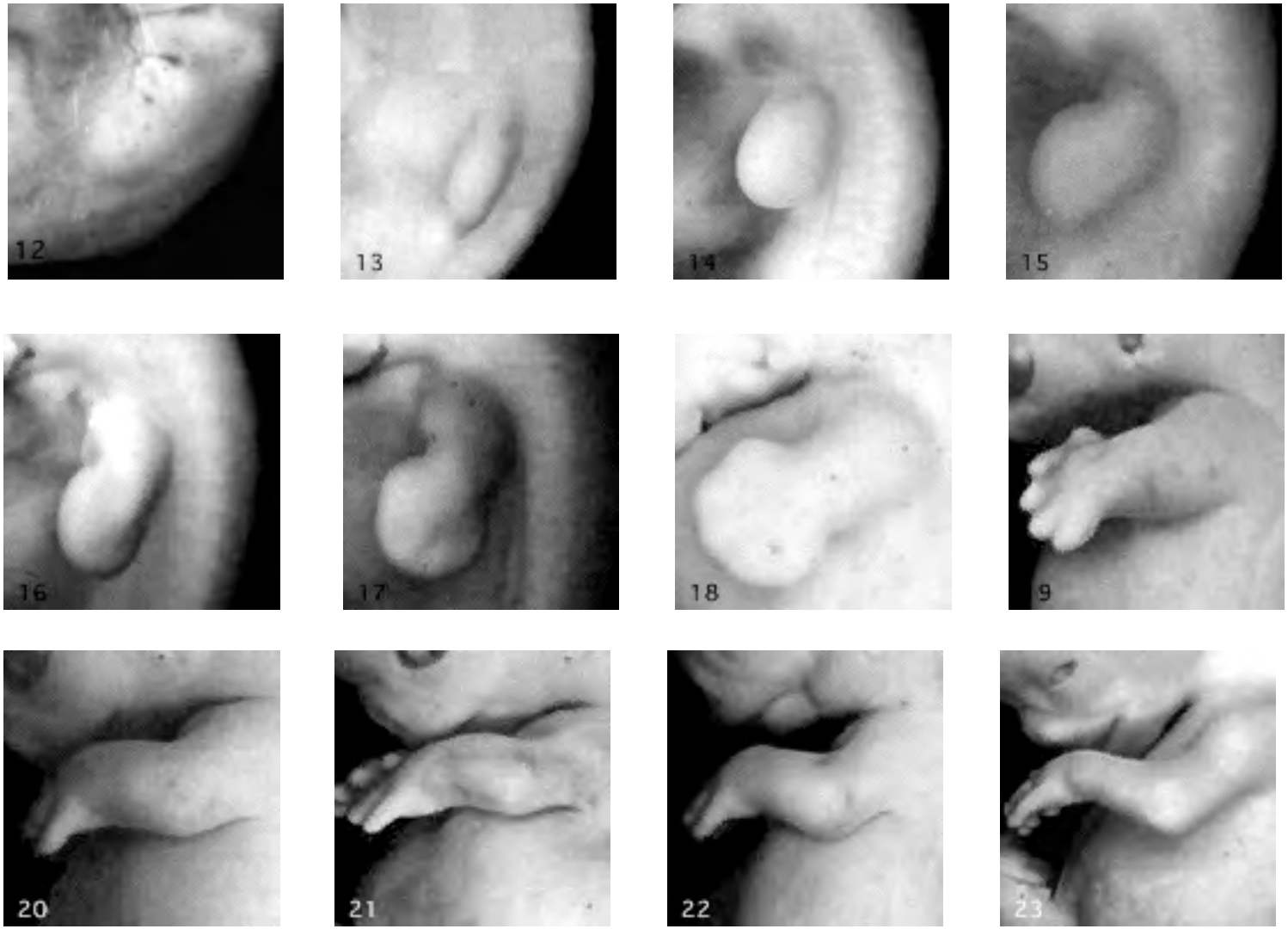
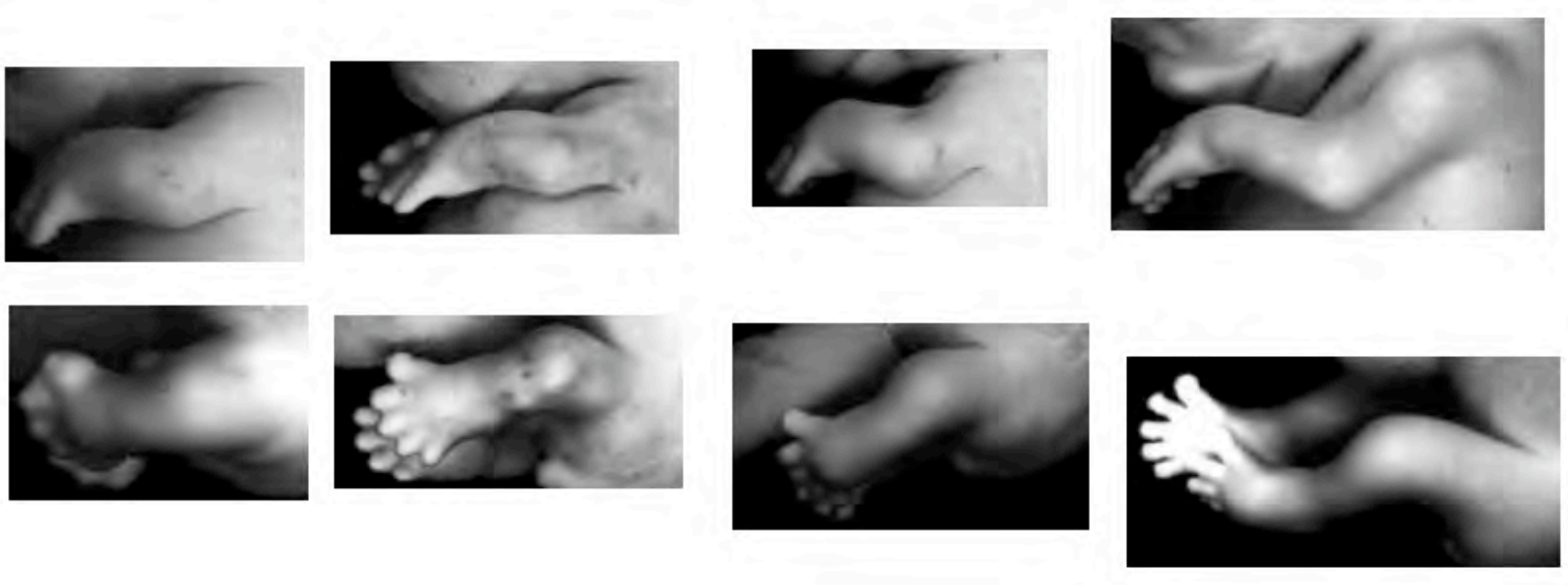


Image: UNSW Embryology

Limb External Appearance



Day 50

Day 56

There are critical stages/times that impact on development of specific systems

Image: UNSW Embryology

Limb Reduction

- Occur in 60 per 100,000 live births (Källén 1997c).
  - Studies have found no effect of maternal smoking on the risk for overall limb reductions (Shiono et al. 1986a; Van den Eeden et al. 1990; McDonald et al. 1992; Wassermann et al. 1996)
  - Swedish infant study found a RR of 1.3 (95 percent CI, 1.1 to 1.5) for any maternal smoking and the risk for limb reduction (Källén 1997c).
- Association between transverse limb reductions and maternal smoking is biologically plausible, because these defects are believed to result from vascular interruption

Report of the Surgeon General USA (1997)

Human Nervous System

Human 25 days

Stage 10: Week 4, 22 - 23 days, 2 - 3.5 mm

CNS Defects

- rate of about 100 per 100,000 live births
- Neural tube defects
  - anencephaly, spina bifida, and encephalocele
  - Several studies show maternal smoking during pregnancy is not related to an increased risk for neural tube defects
    - (Wassermann et al. 1996; Källén 1998)
  - Sweden found a protective effect of smoking for all neural tube defects (Källén 1998)
  - A positive association with microcephaly
    - (Van den Eeden et al. 1990)

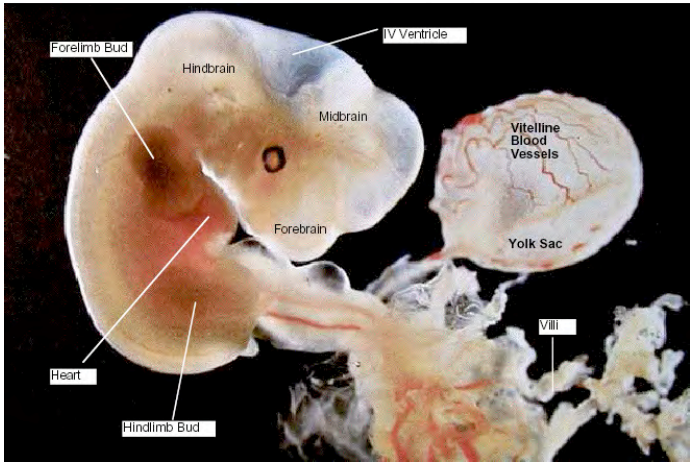
Report of the Surgeon General USA (1997)

Craniosynostosis

- not primarily a CNS defect
  - maternal smoking increased risk for craniosynostosis (Alderman et al. 1994)

Cardiovascular System

- Heart
  - 4 chambered heart
- Cardiac outflow
  - Transformed aortic arches
  - Pulmonary trunk
- Blood Vessels
  - Systemic, vitelline, placental
  - Vascular bed development in tissues



Heart Malformations

- occur in about 124 of 100,000 live births
  - Ventura et al. 1997) No strong evidence for an association between maternal smoking and risk for cardiac malformation
- Another study that examined the effect of smoking on conotruncal malformations found a higher risk when both parents smoked than when neither parent smoked
    - RR, 1.9; 95 percent CI, 1.2 to 3.1 Wassermann et al. 1996
- No effect was found for maternal smoking only

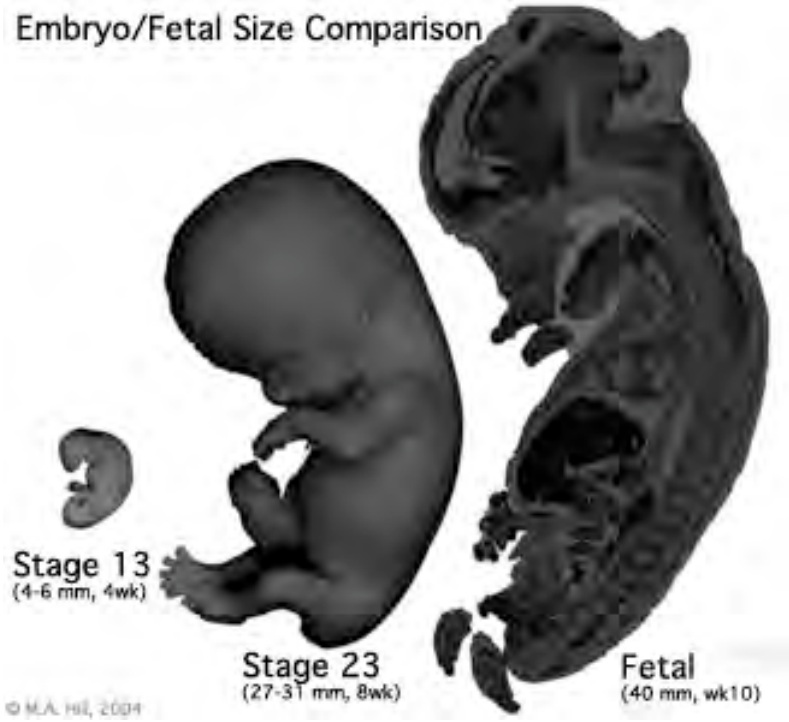
Report of the Surgeon General USA (1997)

End of Week 8 Systems

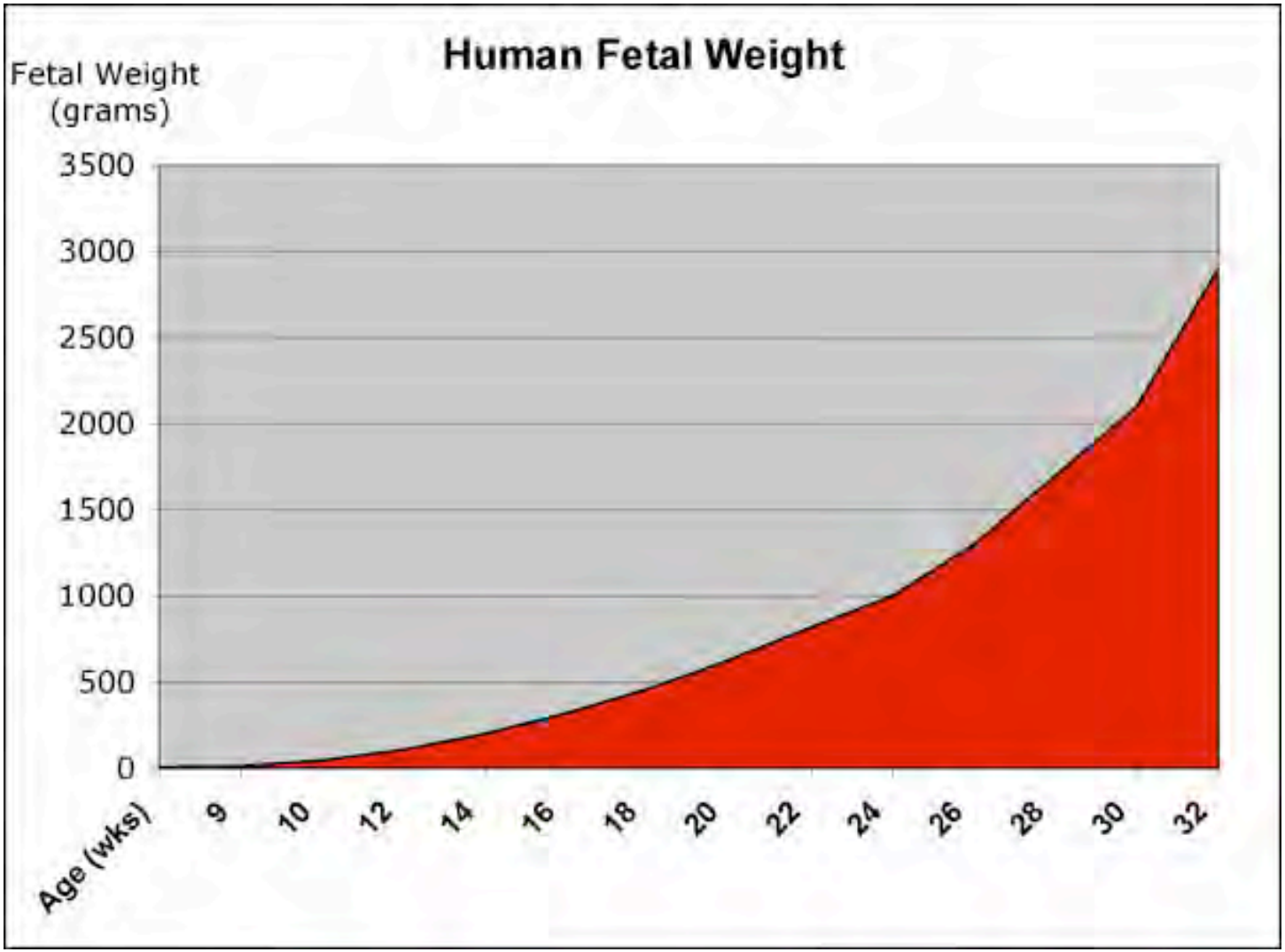
- Nervous
  - CNS, PNS, sensory
- Cardiovascular
  - Heart, blood vessels
- Skeletal
  - Axial, Limbs, Muscle, connective tissue
- Digestive
  - Gastrointestinal tract and associated organs
- Urogenital
  - Kidney, gonad
- Respiratory
  - Upper respiratory tract, lungs

Week 9 - 38 Fetal

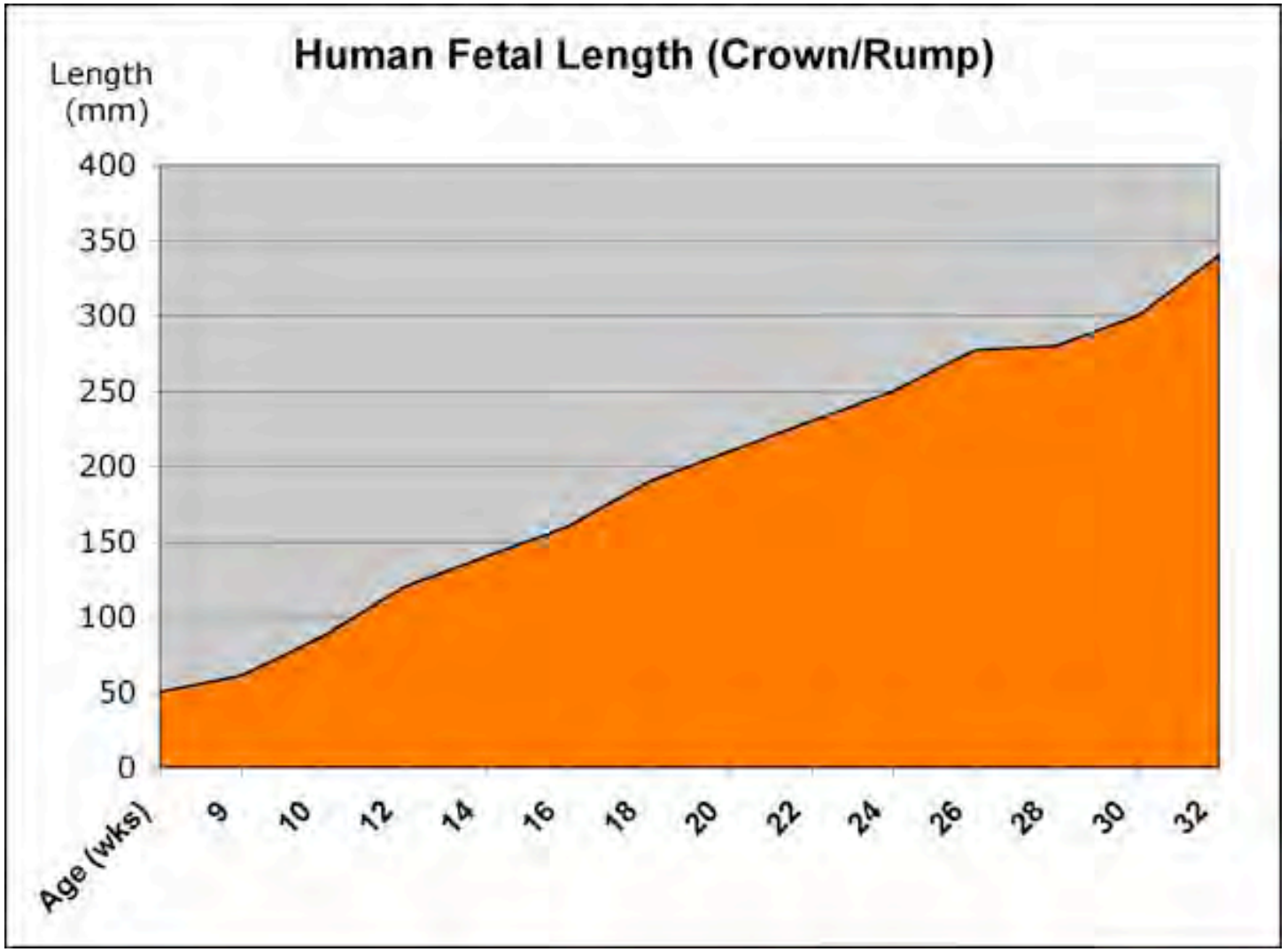
- Rapid body growth
  - Changing relative proportions
    - Head growth slower than body
  - 9-16 weeks most rapid
  - Large body weight gain in final weeks
- Continuing differentiation
  - Of organs formed in embryonic period



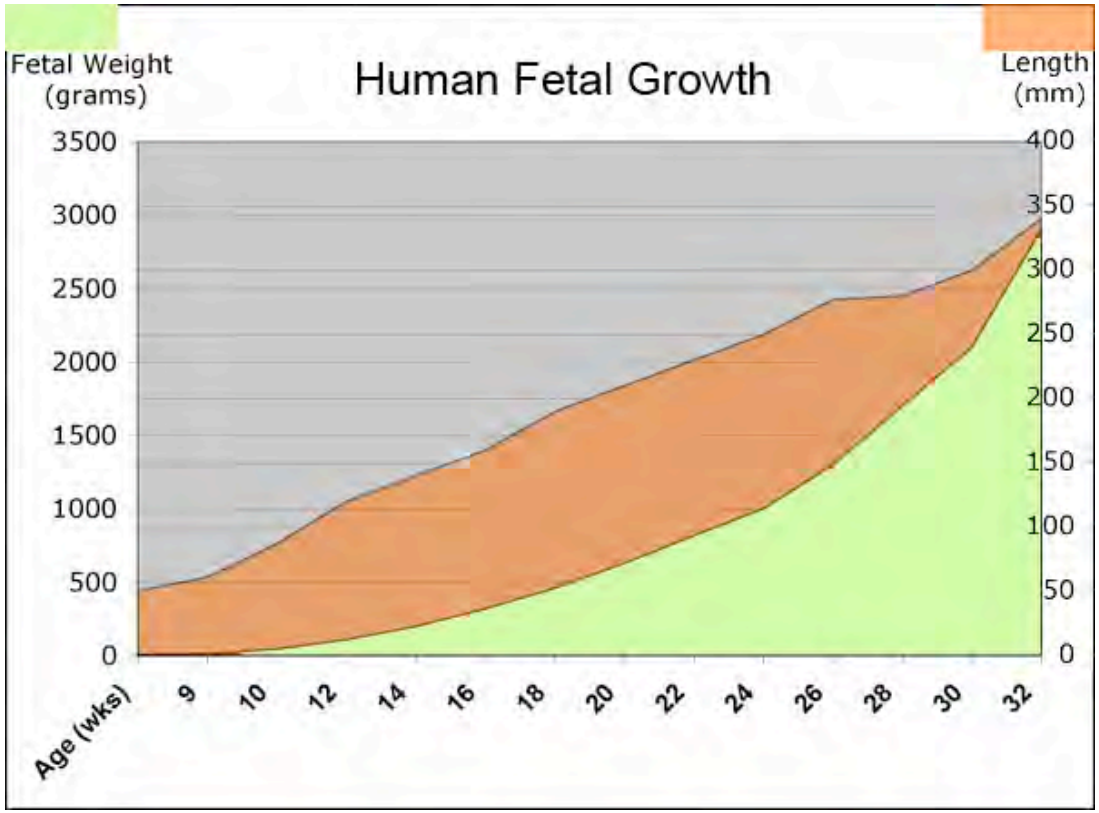
Fetal Weight



Fetal Length



Fetal Growth



Fetal length change is greatest in the middle period (second trimester)
Fetal weight change is greatest in the final weeks of development (third trimester)

Intrauterine Growth Retardation

- UTEROPLACENTAL INSUFFICIENCY (80%)
  - maternal causes deficient supply of nutrients: **smoking**, malnutrition, multiple gestations, anemia, high altitude, maternal vascular disease (more common): severe diabetes
  - primary placental causes: placental infarctions, chronic partial separation, placenta previa
- PRIMARY FETAL CAUSES (20%)
  - decreased intrinsic growth; symmetrical IUGR congenital heart disease, genitourinary anomalies, CNS anomalies, chromsomal abnormalities (trisomy 13, 18, 21), viral infection (rubella, CMV)

intrauterine growth retardation (IUGR)

- < 10th percentile for gestational age
  - not easy to detect before 32-34 weeks
- Incidence
  - 3-7% of all deliveries
  - 12-47% of twin pregnancies
- Complications
  - increased risk for perinatal asphysia, meconium aspiration, electrolyte imbalance from metabolic acidosis, polycythemia
  - 6-8 fold increase for intrapartum and neonatal death

Lies and Statisics…

- Spontaneous abortion, pre-term births, low-weight full-term babies, fetal and infant deaths all occur more frequently among mothers who smoke during pregnancy than among those who do not
  - developmental abnormalities are therefore maternal in origin and not congenital
    - though there are probably genetics involved with a tendency to smoke

Preterm Birth and LBW

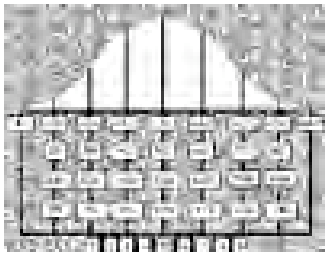
- Preterm birth results in 47% of all neonatal deaths (UK data)
- Also of great concern is that smoking is a suggested causative factor for low infant birth weight (LBW) <2.5kg
- LBW is in turn related to future (postnatal) health by the fetal origins hypothesis

NHMRC Recommendations

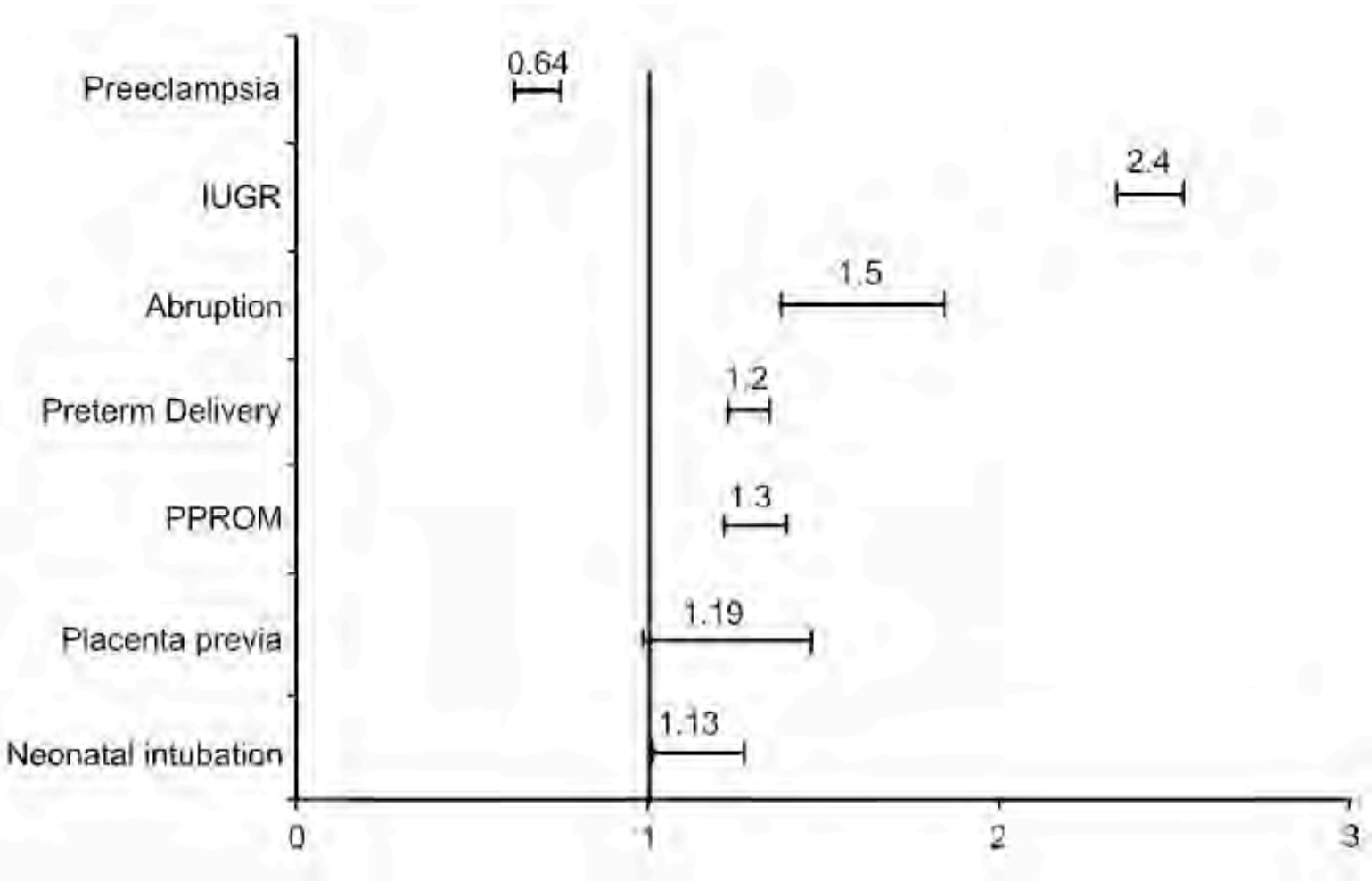
- for neonates be assessed for follow-up care under the following conditions
  - Birthweight less than 1500g or gestational age less than 32 weeks
  - Small-for-gestational-age neonates
  - Perinatal asphyxia
  - Apgar score less than 3 at 5 minutes
  - clinical evidence of neurological dysfunction
  - delay in onset of spontaneous respiration for more than 5 minutes and requiring mechanical ventilation
  - Clinical evidence of central nervous system abnormalities ie., seizures, hypotonia
  - Psychosocial problems eg., infants of drug-addicted or alcoholic mothers.

Fetal Origins Hypothesis

- Proposes influences cause permanent changes in embryo/fetus, low birth weight, predisposition to chronic disease in adult life
  - Malnutrition in utero affects brain development
  - "low birth weight" or intrauterine growth restricted (IUGR) babies fare less well on measures of mental development in later life studies
    - Intelligence is a combination of genetic and environmental influences



Pregnancy Complications Related to Smoking



Odds ratios of pregnancy complications that were related to smoking

American Journal of Obstetrics and Gynecology (2005) 192, 1856–63

Smoke and Birth Defects

- Some studies found no association between cigarette smoking during pregnancy and overall risk for birth defects
- Smoking may be modestly related to an increased risk for certain birth defects
  - oral clefts, limb reductions, urogenital or gastrointestinal
- CO and nicotine from cigarette smoke
  - may increase risks for fetal hypoxia and vascular disruption which can cause birth defects
    - Czeizel et al. 1994; Li et al. 1996; Werler 1996

Report of the Surgeon General USA (1997)

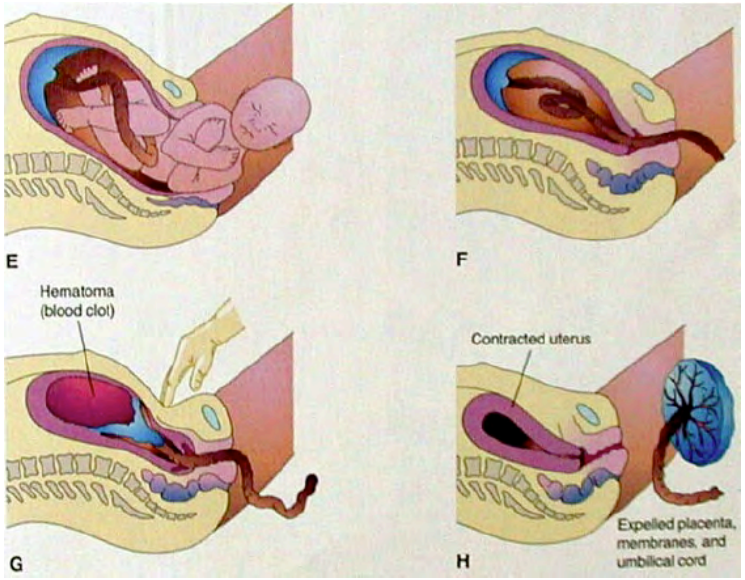
Other Possible Mechanisms

- Cigarette smoke may produce birth defects by
  - toxic metabolites present in the smoke (Li et al. 1996)
  - decreased use of folate (Alderman et al.1994)
  - mutagenic effects (Seidman et al. 1990)

Report of the Surgeon General USA (1997)

Birth

- Complex endocrine regulated
  - Initiated by fetus, uterine muscular development
- Neonatal changes
- Postnatal Development
  - Neural
  - Musculoskeletal
  - Reproductive



Newborn Homoeostasis

- Newborn has to establish
  - lung function
  - circulatory changes
  - thermoregulation
  - endocrine function
  - nutrition
    - gastrointestinal tract function
  - waste
    - kidney function

Nicotine Metabolism

- Neonates have a decreased ability to metabolise nicotine
- 3-4 times longer half-life in newborns exposed to tobacco smoke compared with adults

Report of the Surgeon General

USA (1997) Women and Smoking

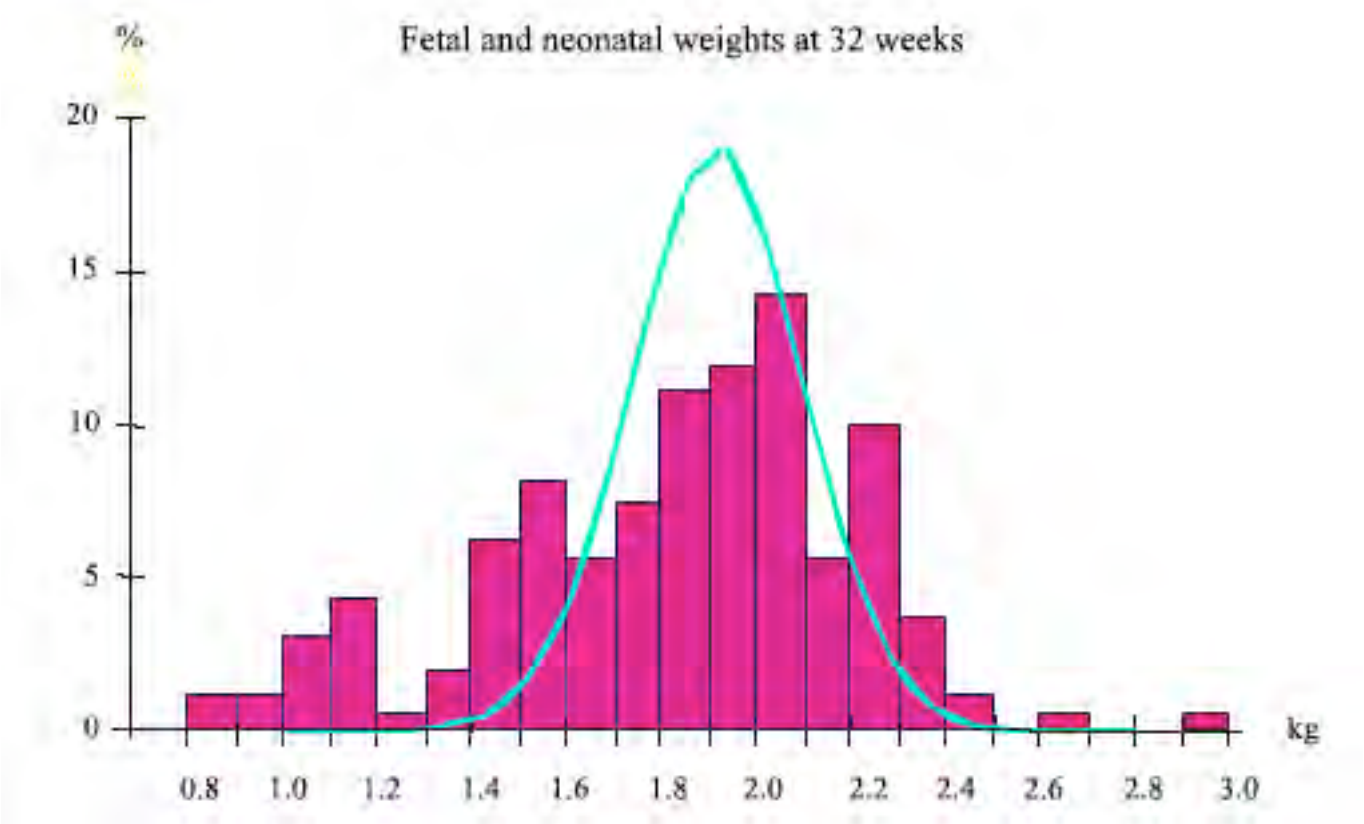
- Chapter 3. Health Consequences of Tobacco
  - "Since 1980, approximately three million U.S. women have died prematurely as a result of a smoking-related disease. In 1997 alone, an estimated 165,000 U.S. women died prematurely of a smoking related disease."

SIDS

- “In the United States, SIDS is the leading cause of death among infants 1 to 12 months of age and affects more than 0.1 percent of live births.
- In many studies, maternal smoking during pregnancy has been associated with SIDS
    - association has persisted after adjustment for covariates such as infant sleeping position, birth weight, and race as well as maternal age, marital status, education, etc.
- However, because smoking during and after pregnancy are highly correlated, it is difficult to separate the effects of these two exposures.”

Report of the Surgeon General USA (1997)

Prematurity and Fetal Growth Restriction



Ultrasound versus birth weight standard at 32 weeks of gestation. The line shows ultrasound weight estimations derived from pregnancies that have proceeded to normal term delivery, according to Hadlock [44]. The curve is characterised by a relatively narrow normal distribution. The histogram shows birth weights of babies born at this same, preterm gestation [11]. The distribution has a lower median, a wider range and negative skewness.

Early Human Development (2005) 81, 43—49

References

- PubMed search 2005 results "smoking and pregnancy" 8247 citations and 920 reviews
  - The effect of parental smoking on lung function and development during infancy.Stocks J, Dezateux C. Respirology. 2003 Sep;8(3):266-85.
  - The effect of maternal smoking during pregnancy on early infant lung function JP Hanrahan, etal. Am Rev Respir Dis. 1992 May;145(5):1129-35.
  - The epidemiology of preterm birth Bibby E, Stewart A. Neuro Endocrinol Lett. 2004 Dec;25 Suppl 1:43-7. Review.
  - Metabolism and disposition kinetics of nicotine Hukkanen J, Jacob P 3rd, Benowitz NL. Pharmacol Rev. 2005 Mar;57(1):79-115. Review.
  - Nicotine metabolism and elimination kinetics in newborns Dempsey D, Jacob P 3rd, Benowitz NL. Clin Pharmacol Ther. 2000 May;67(5):458-65.