Applied of Embryology in Paediatrics

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DEPT. OF PAEDIATRICS

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EMBRYOLOGY:

- BRANCH OF BIOLOGY THAT STUDIES THE PRENATAL DEVELOPMENT OF GAMATES, FERTILIZATION AND DEVELOPMENT OF EMBRYO AND FETUSES.

FATHER OF EMBRYOLOGY- karl Ernst von Baer

Embryology is a evidence of evolution

PAEDIATRICS:

- Branch of medicine dealing with the health and medical care of infants, children, and adolescents from birth up to the age 18.
- Word meaning “healer of children.”
- Greek words (pais =child,
- iatros=doctor or healer)

Stages of Embryonic development

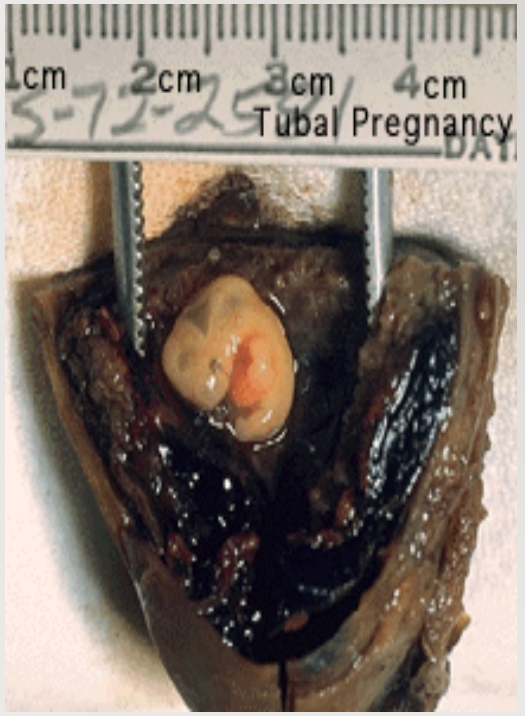
Four stages;

1) **Zygote:** genetic material of the sperm and egg then combine to form a single cell
2) **Germinal** stage of development
3) **Embryonic development-** first 8th week of development. Early stage of human development in which organs are critical body structures are formed.
4) **Foetus** – beginning of 9th week of the embryo

Early Development Issues

ABNORMAL IMPLANTATION:

Ectopic Implantation (Pregnancy)

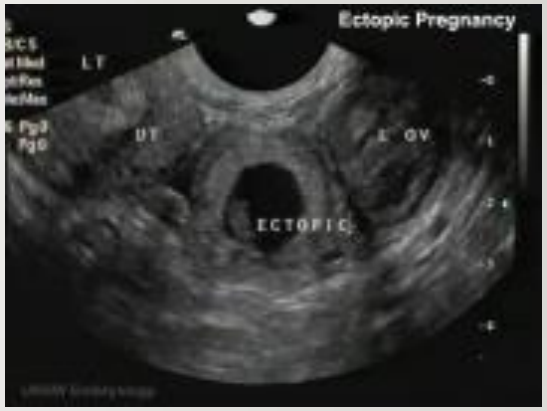


- Abnormal implantation sites or Ectopic Pregnancy occurs if implantation is in uterine tube or outside the uterus.
- sites - external surface of uterus, ovary, bowel, gastrointestinal tract, mesentry, peritoneal wall. If not spontaneous then, embryo has to be removed surgically.

Tubal pregnancy

- **Tubal pregnancy** - 94% of ectopic pregnancies
- If uterine epithelium is damaged

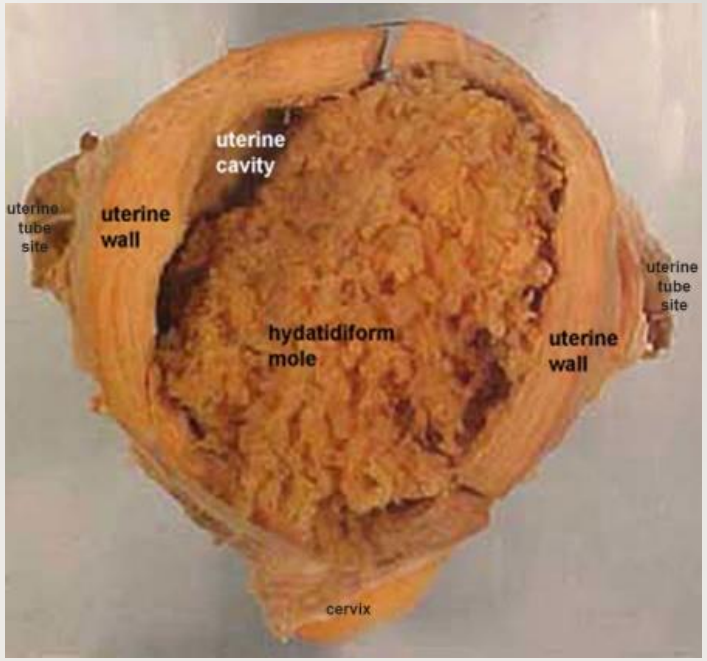
(scarring, pelvic inflammatory disease)



- If zona pellucida is lost too early, allows premature tubal implantation
- Embryo may develop through early stages, can erode through the uterine horn and reattach within the peritoneal cavity

Hydatidiform Mole

- The conceptus trophoblast layers proliferates and not the embryoblast, no embryo develops, this is called a "hydatidiform mole", which is due to the continuing presence of the trophoblastic layer, this abnormal conceptus can also implant in the uterus.



- The trophoblast cells will secrete human chorionic gonadotropin (hCG), as in a normal pregnancy, and may appear maternally and by pregnancy test to be "normal". Prenatal diagnosis by ultrasound analysis demonstrates the absence of a embryo.
- There are several forms of hydatidiform mole: partial mole, complete mole and persistent gestational trophoblastic tumor.

- Many of these tumours arise from a haploid sperm fertilizing an egg without a female pronucleus (the alternative form, an embryo without sperm contribution, is called parthenogenesis).
- The tumour has a "grape-like" placental appearance without enclosed embryo formation. Following a first molar pregnancy, there is approximately a 1% risk of a second molar pregnancy.

Twinning

- **Twin deliveries and place of birth in NSW 2001-2005**: "Both infant and maternal morbidity increase from 39 weeks gestation. Delivery of twins before 36 weeks at smaller hospitals (< 500 deliveries per annum) should be avoided. A twin pregnancy where there is a greater or equal to 20% difference in estimated fetal weights should be considered for referral to a tertiary obstetric unit."

Dizygotic Twinning

- Dizygotic twins (fraternal, non-identical) arise from separate fertilization events involving two separate oocyte (egg, ova) and spermatozoa (sperm). Dizygotic twinning can be increased by Assisted Reproductive Technologies (ART) that use double embryo transfer techniques.

Monoygotic Twinning

- Monoygotic twins (identical) produced from a single fertilization event (one fertilised egg and a single spermatazoa, form a single zygote), these twins therefore share the same genetic makeup. Occurs in approximately 3-5 per 1000 pregnancies, more commonly with aged mothers. The later the twinning event, the less common are initially separate placental membranes and finally resulting in conjoined twins.

Abnormal Development

- Embryological development is a robust biological system able to cope with many stresses without long-term consequences. When development does go wrong there are generally 3 major types groups: **Genetic** (inherited), **Environmental** (maternal) derived and **Unknown** (not determined or known) abnormalities. Also often not considered, is that pregnancy itself can also expose abnormalities in the mother (congenital heart disease, diabetes, reproductive disorders) that until the pregnancy had gone undetected.

- Genetic abnormalities in medicine are still mainly about determining a family history and good prenatal/neonatal diagnosis. Realise that there exists in all of us genetic variations and some variations which eventually expand be expressed as a genetic disorder (CAG expansions).

International Classification of Diseases

- The International Classification of Diseases (ICD) World Health Organization's classification used worldwide as the standard diagnostic tool for epidemiology, health management and clinical purposes. This includes the analysis of the general health situation of population groups. It is used to monitor the incidence and prevalence of diseases and other health problems. Within this classification "congenital malformations, deformations and chromosomal abnormalities" are (Q00-Q99) but excludes "inborn errors of metabolism" (E70-E90).

Scheduled congenital conditions include:

- All structural malformations. Examples include spina bifida, microcephaly, transposition of the great vessels, ventricular septal defects, pulmonary agenesis, polycystic lungs, duodenal atresia, exomphalos, hypospadias, cleft lip/palate, microphthalmia, limb reductions, polydactyly, birthmarks greater than 4 cms diameter, cystic hygroma and multisystem syndromes including at least one structural malformation.

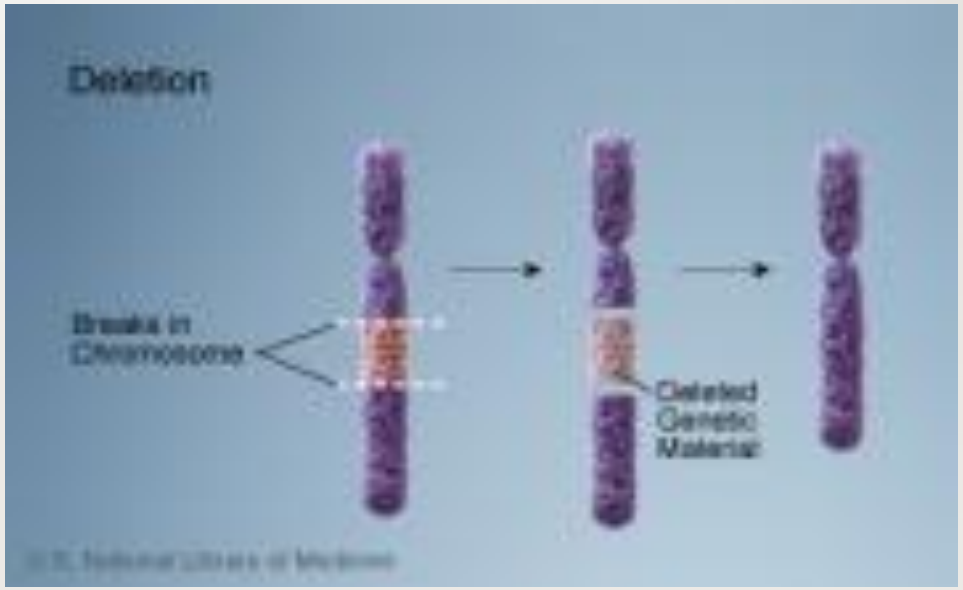
- Chromosomal abnormalities. Examples include Down syndrome and unbalanced translocations.
- Four medical conditions: cystic fibrosis, phenylketonuria, congenital hypothyroidism and thalassaemia major.

Congenital conditions that are not notifiable include:

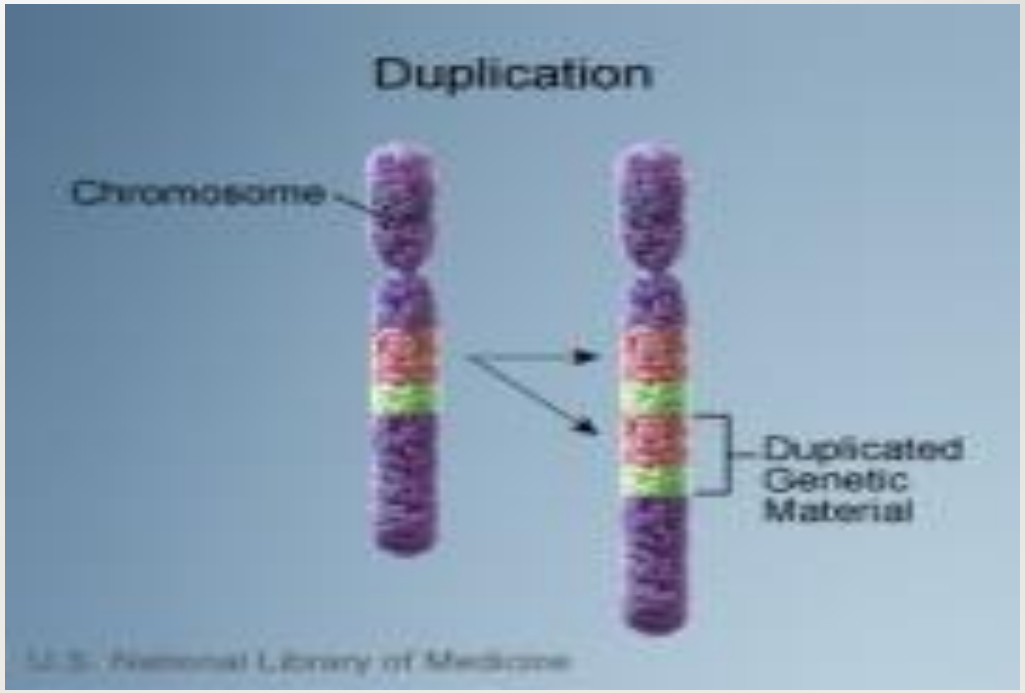
- Minor anomalies occurring in isolation (Examples of minor anomalies include skin tags, deviated nasal septum, tongue tie, benign heart murmurs, clicky non-dislocating hips, sacral dimples, positional talipes, abnormal palmar creases, dysmorphic features).
- Birth injuries.
- Congenital infections which do not result in a structural malformation.
- Tumours and cysts.
- Conditions arising from prematurity or asphyxiation.

Genetic

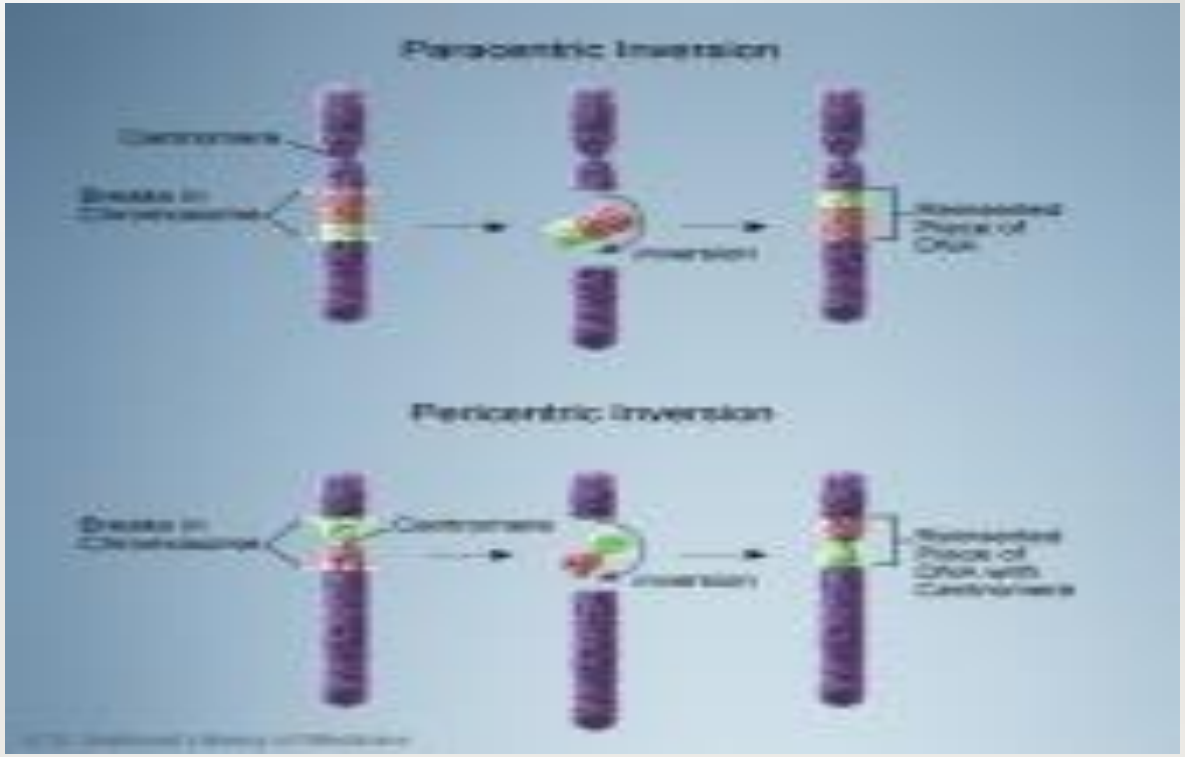
- Chromosome - unbalanced translocation
- Chromosome - balanced translocation



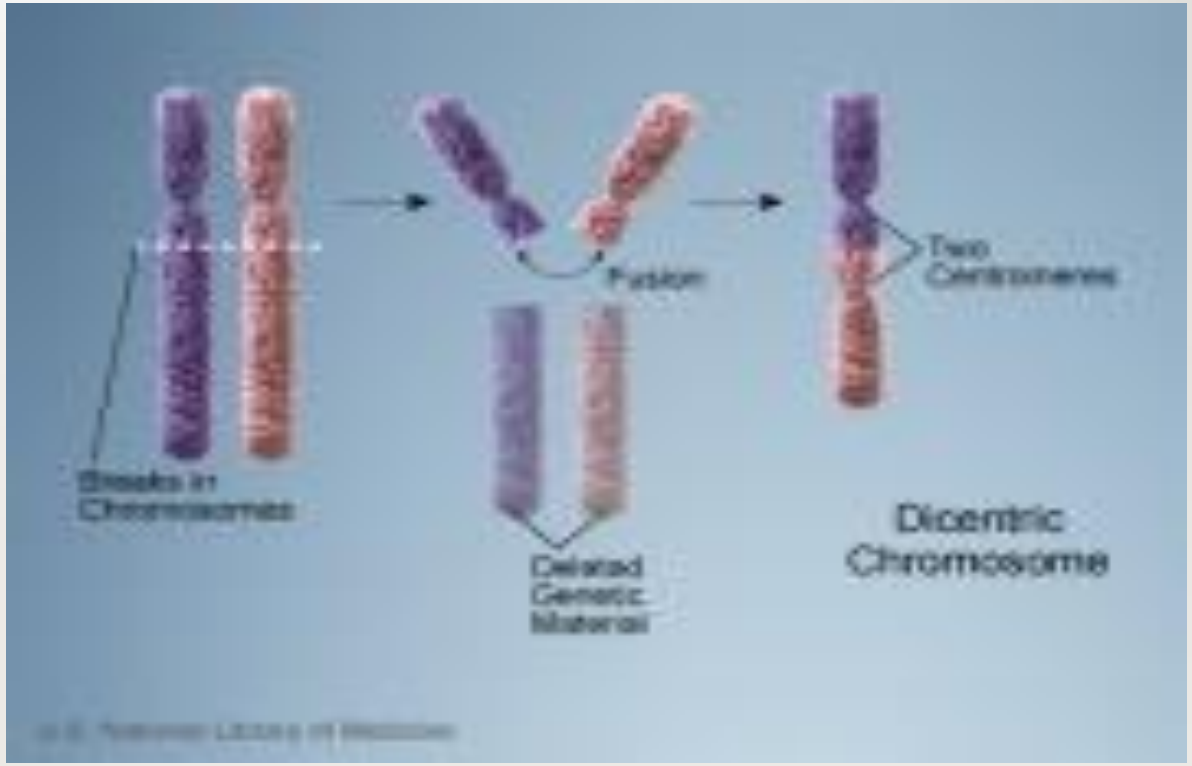
Chromosome - deletion



Chromosome - duplication

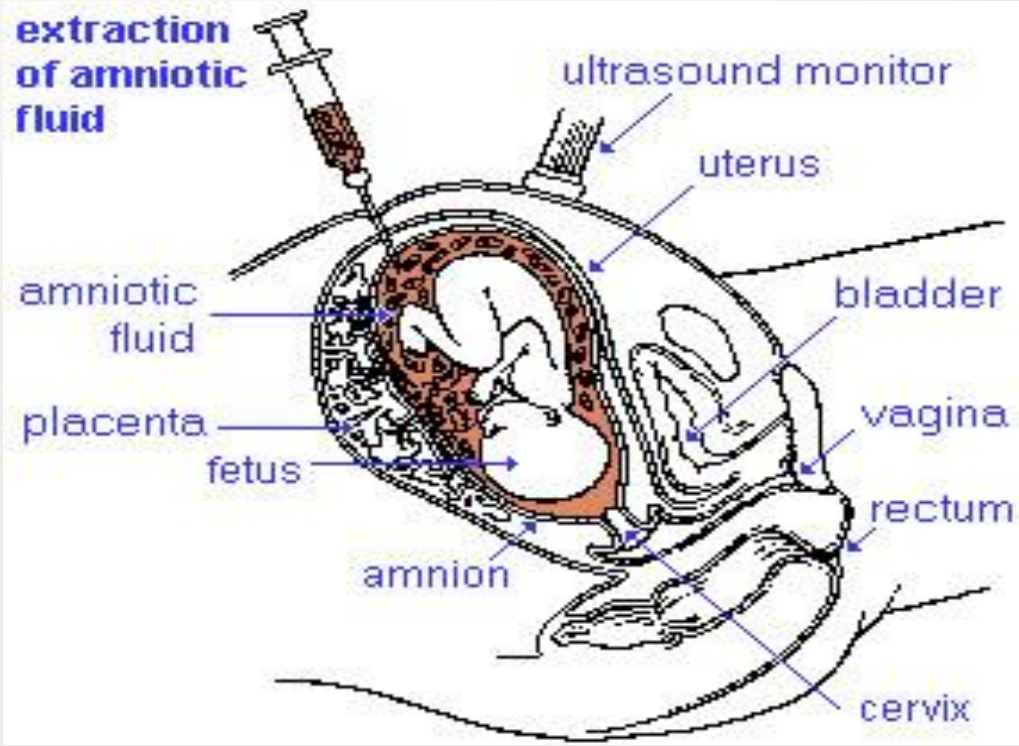


Chromosome - inversion
Chromosome - isochromosomes



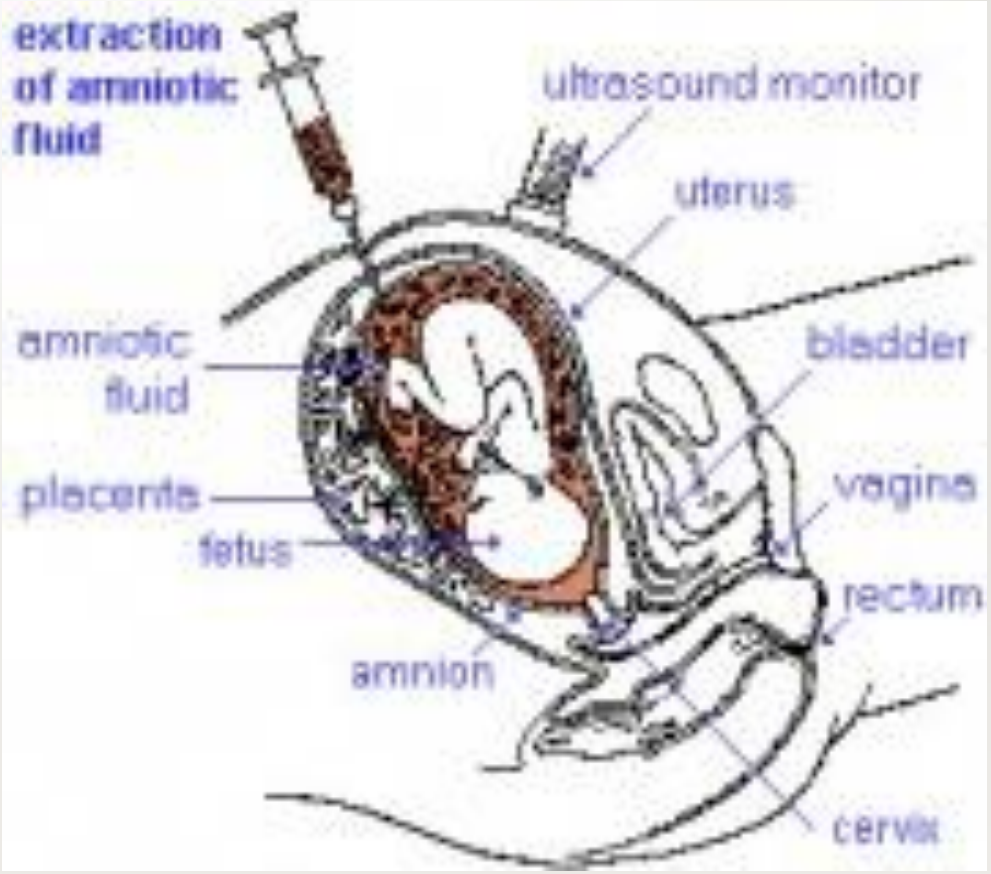
Teratology

Prenatal Screening

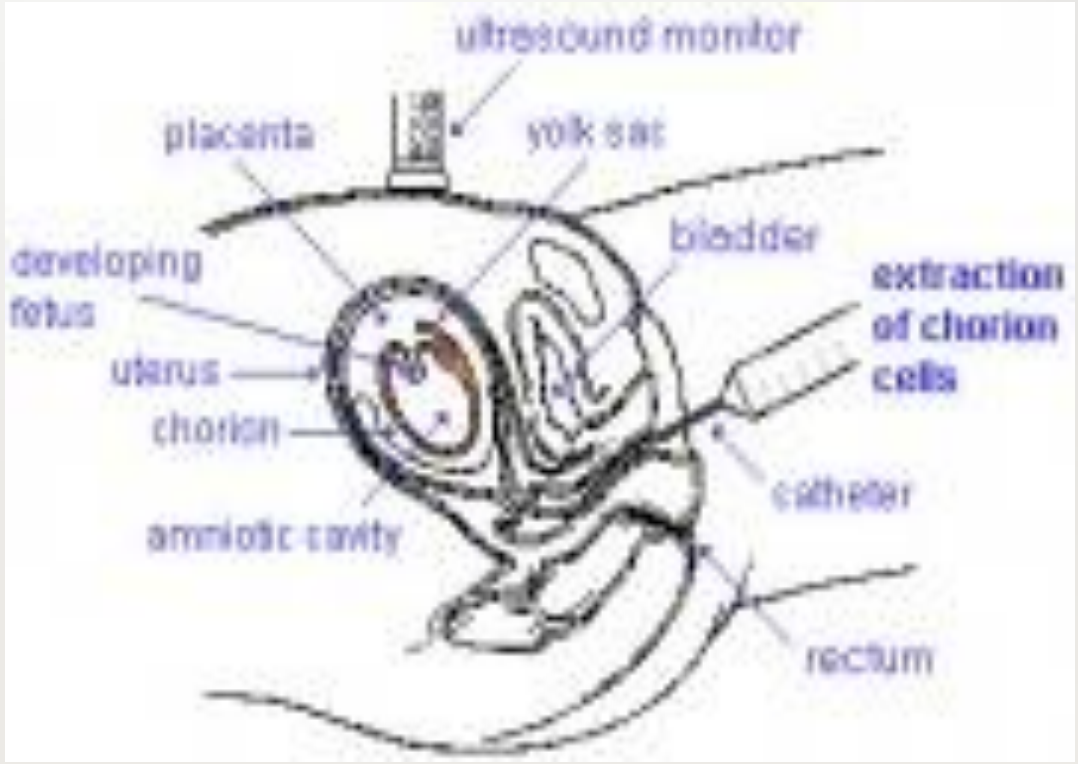


- These notes cover abnormalities that can occur during development often described as congenital defects or birth defects. There are many different ways that developmental abnormalities can occur the 3 major types are **Genetic** (inherited), **Environmental** (maternal) and **Unknown** (not determined) derived abnormalities. The environmental factors that cause or lead to any of these abnormalities are described as Teratogens

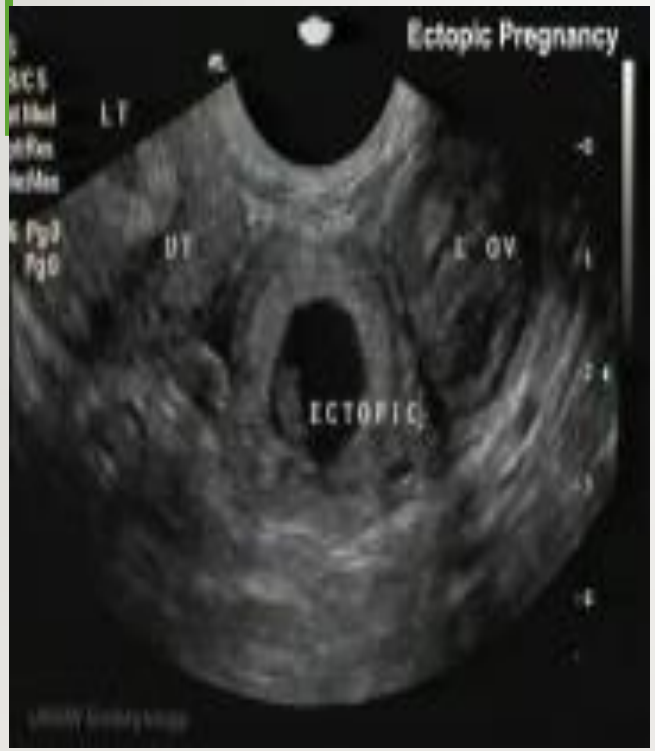
Amniocentesis



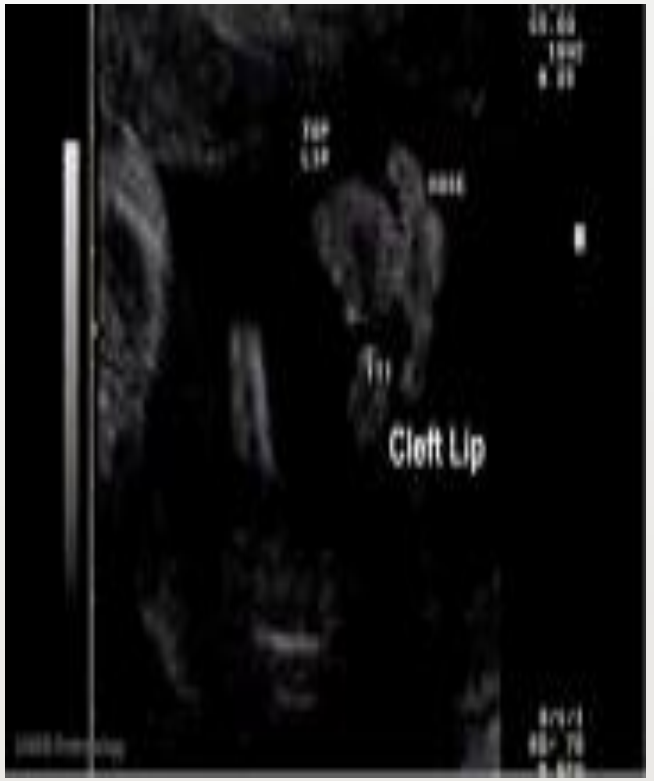
Chorionic villus sampling



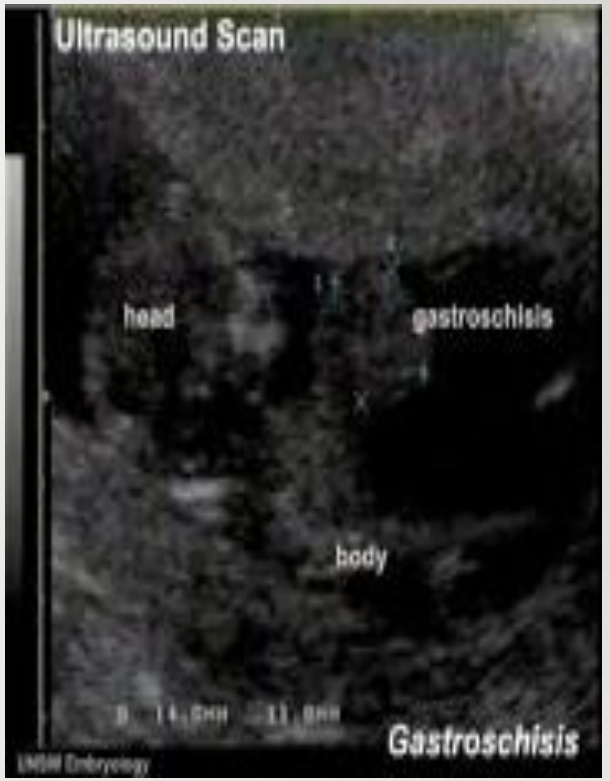
Ultrasound



Ectopic Pregnancy



Cleft Lip 15 Week



Gastroschisis

- Now consider the terms used to describe the different environmental effects that can occur during pregnancy that may influence outcomes.
- **Teratogen** (Greek, *teraton* = monster) any agent that causes a structural abnormality (congenital abnormalities) following fetal exposure during pregnancy. The overall effect depends on dosage and time of exposure.
- **Absolute risk** the rate of occurrence of an abnormal phenotype among individuals exposed to the agent. (e.g. fetal alcohol syndrome)

- **Relative risk** the ratio of the rate of the condition among the exposed and the nonexposed. (e.g. smokers risk of having a low birth weight baby compared to non-smokers) A high relative risk may indicate a low absolute risk if the condition is rare.
- **Mutagen** a chemical or agent that can cause permanent damage to the deoxyribonucleic acid (DNA) in a cell. DNA damage in the human egg or sperm may lead to reduced fertility, spontaneous abortion (miscarriage), birth defects and heritable diseases.

- **Fetotoxicant** is a chemical that adversely affects the developing fetus, resulting in low birth weight, symptoms of poisoning at birth or stillbirth (fetus dies before it is born).
- **Synergism** when the combined effect of exposure to more than one chemical at one time, or to a chemical in combination with other hazards (heat, radiation, infection) results in effects of such exposure to be greater than the sum of the individual effects of each hazard by itself.
- **Toxicogenomics** the interaction between the genome, chemicals in the environment, and disease. Cells exposed to a stress, drug or toxicant respond by altering the pattern of expression of genes within their chromosomes. Based on new genetic and microarray technologies.

Teratogens

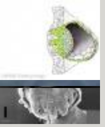
- **Infections**, collectively grouped under the acronym TORCH for Toxoplasmosis, Other organisms (parvovirus, HIV, Epstein-Barr, herpes 6 and 8, varicella, syphilis, enterovirus) , Rubella, Cytomegalovirus and Hepatitis. See also the related topics on **maternal hyperthermia** and bacterial infections. (More? Postnatal Immunisation)

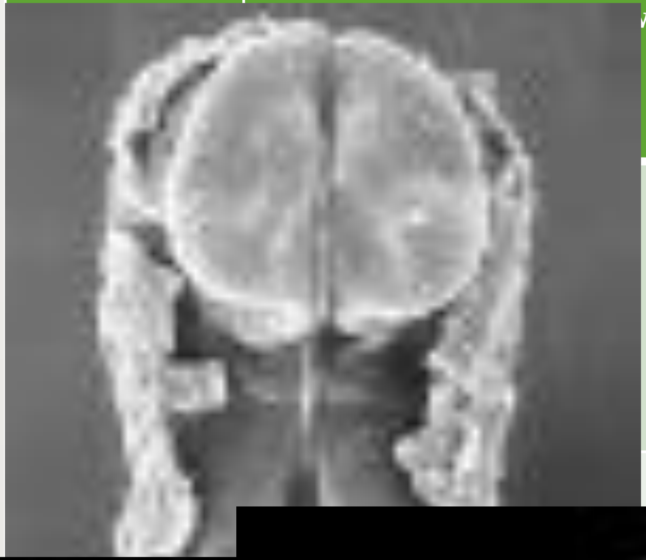
- **Maternal diet** the best characterised is the role of low folic acid and Neural Tube Defects (NTDs) see also abnormal neural development and Neural Tube Defects (NTDs). More recently the focus has been on dietary iodine levels and the role they also play on neural development.
- **Maternal drugs** effects either prescription drugs (therapeutic chemicals/agents, thalidomide limb development), non-prescription drugs (smoking), and illegal drugs (Cannabis/Marijuana, Methamphetamine/Amphetamine, Cocaine, Heroin, Lysergic Acid Diethylamide)

- **Environment** (smoking, chemicals, heavy metals, radiation) and maternal endocrine function (maternal diabetes, thyroid development) and maternal stress.
- **Teratogen synergism**, different environmental effects can act individually or in combination on the same developing system. For example, neural development can be impacted upon by alcohol (fetal alcohol syndrome), viral infection (rubella) and/or inadequate dietry folate intake (neural tube defects). These effects may also not be seen as a direct effect on a system or systems but result in a reduced birth weight and the potential postnatal developmental effects. Consider also this in relation to the increasing support to the **fetal origins hypothesis**.
- Alcohol - In utero alcohol effects on foetal, neonatal and childhood lung disease.

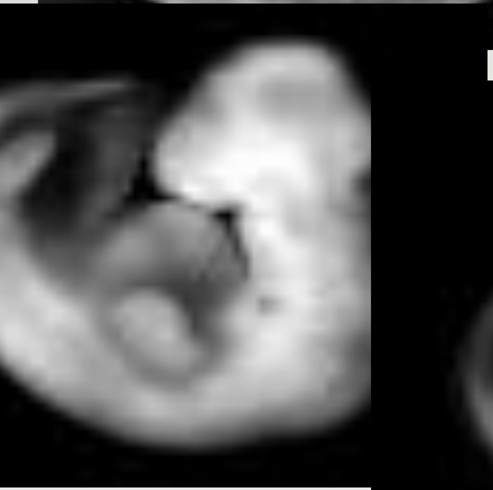
Critical Periods of Development

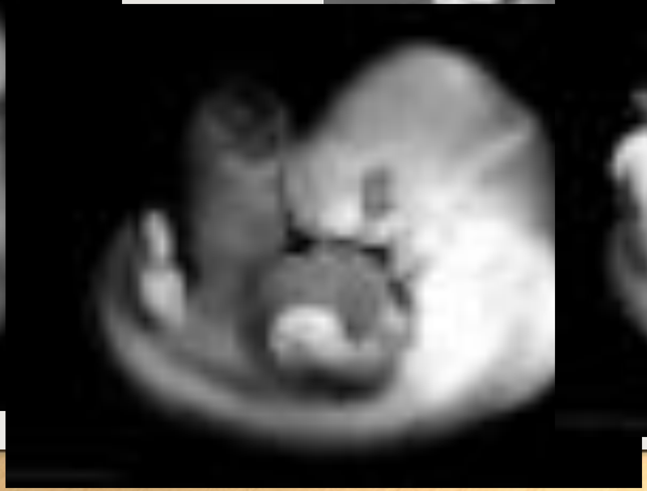
- Human critical periods of development
- Finally, when studying this topic remember the concept of critical periods of development that will affect the overall impact of the above listed factors. This can be extended to the potential differences between prenatal and postnatal effects, for example with infections and outcomes.

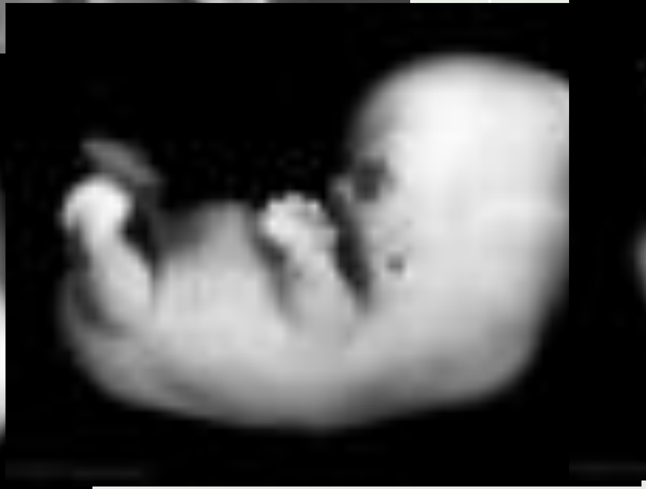


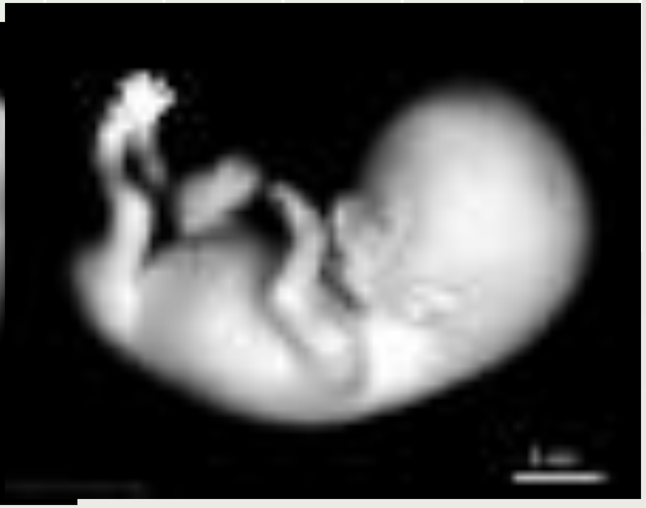


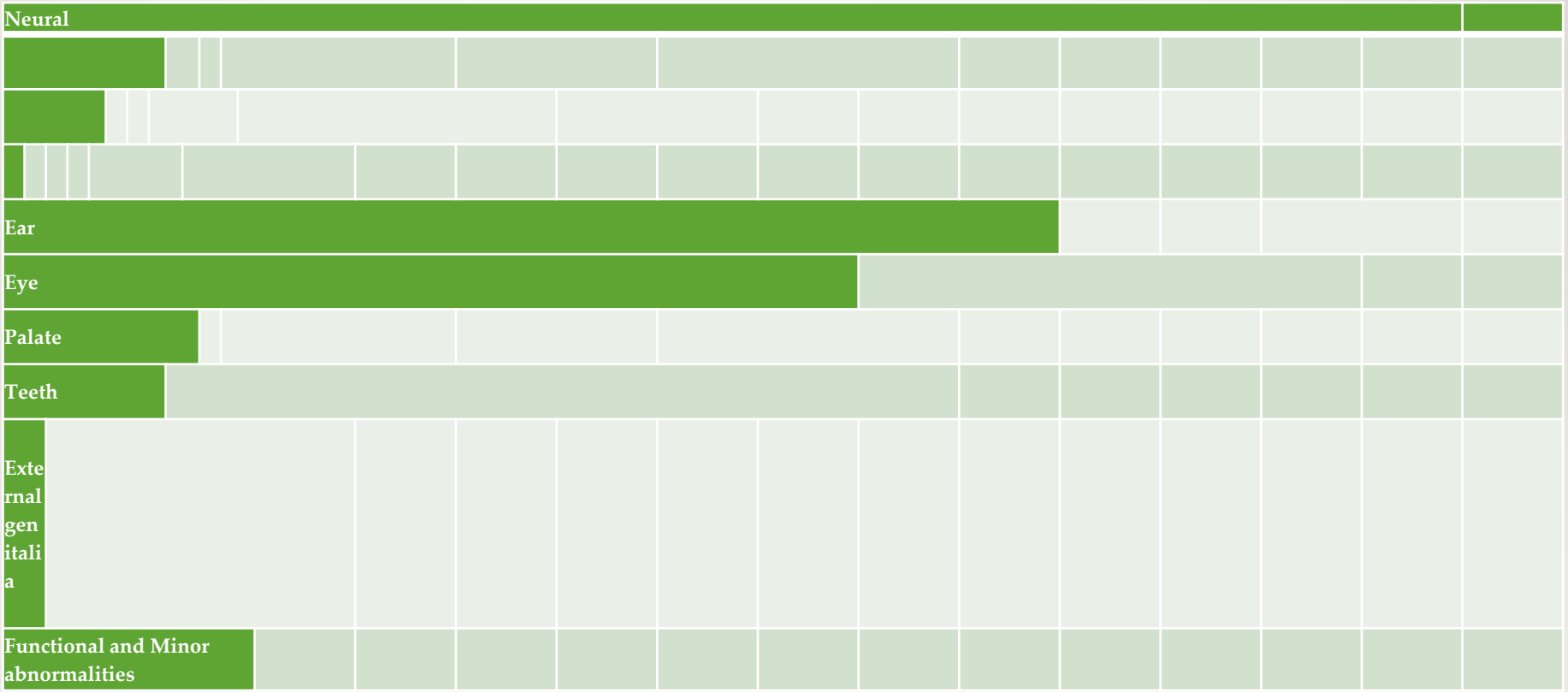
	eeks)						Fetal period (weeks)			
				6	7	8	9	16	20-36	38










Neural
Ear
Eye
Palate
Teeth
External genitalia
Functional and Minor abnormalities

Australian Drug Categories

- Legal drugs are classified, usually by each country's appropriate regulatory body, on the safety of drugs during pregnancy. In Australia, the Therapeutic Goods Authority has classes (A, B1, B2, B3, C, D and X) to define their safety. (More? Australian Drug Categories) In the USA, since 2015 drugs are classified by the Food and Drug Administration (FDA) into new classes to define their safety. The Australian categorisation of medicines for use in pregnancy does not follow a hierarchical structure.
- Human data are lacking or inadequate for drugs in the B1, B2 and B3 categories

- Subcategorisation of the B category is based on animal data
- The allocation of a B category does not imply greater safety than a C category
- Medicines in category D are not absolutely contraindicated during pregnancy (e.g.anticonvulsants)
- **Pregnancy Category A -** Have been taken by a large number of pregnant women and women of childbearing age without an increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.
- .

- **Pregnancy Category B1** - Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage

- **Pregnancy Category B2** - Have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

- **Pregnancy Category B3** - Have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

- **Pregnancy Category C** - Have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

- **Pregnancy Category D** - Have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

- **Pregnancy Category X -** Have such a high risk of causing permanent damage to the fetus that they should NOT be used in pregnancy or when there is a possibility of pregnancy.

Thank you