BGD Tutorial - Applied Embryology and Teratology

Introduction

This Medicine Phase 2 tutorial introduces the topics of Applied Embryology and Teratology. This one and a half hour presentation uses your existing knowledge of normal human development in an applied clinical manner in relation to our existing knowledge of teratogens. In addition, you should begin considering the variables that will not change and those that will in future medical practice. Due to time limitations, only a brief coverage can be given of any one topic.

Self-Directed Learning boxes on this page will not be discussed within the tutorial. You should also return here and later work through the linked online resources for more detailed descriptions and an understanding of these issues. This current page appears in the lefthand menu under Medicine as **BGD 2 Tutorial**.

Similar content was covered in the previous online tutorials in 2010, 2009 (http://embryology.med.unsw.edu.au/Medicine/BGD2tutorial.htm) and 2008 (http://embryology.med.unsw.edu.au/Medicine/BGD2tutorial.htm) .

Objectives

Applied Embryology: birth statistics, unintended pregnancies, ART, abnormalities statistics, timeline of development, trophoblastic disease, embryonic development, placenta, fetal development, maternal diet, multiple pregnancies.

Teratology: definitions, critical periods, medications, chromosomal abnormalities, environmental factors and infections.

Textbook Reading: Human Embryology, WJ. Larsen; The Developing Human: Clinically Oriented Embryology. Moore & Persaud
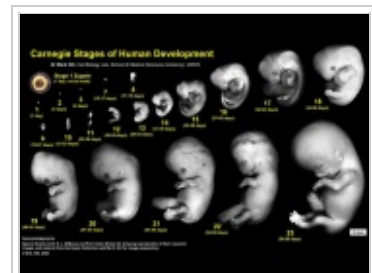

Human Embryonic Development (week 1 to 8)

Applied Embryology

This recent data summarised below from Australia's mothers and babies 2007[1] and 2008[2] is provided to help you as a clinician and researcher understand the current trends in reproductive medicine within Australia. Also see recent general population data in Australian Statistics.

Mothers

Australian Births by Year

- 2007 **289,496** women gave birth to **294,205** babies
- 2008 **292,156** women gave birth to **296,925** babies
  - 2007 increase of 4.3% from 2006, and 14.4% increase since 2004
- fetal death component was *2,177* and **2,188** respectively
- **29.9 years** was the maternal mean age in 2007
  - compared with 28.9 years in 1998 Why is this increasing age important?
- the rate of women aged 15–44 years giving birth in the population decreased slightly between 2007
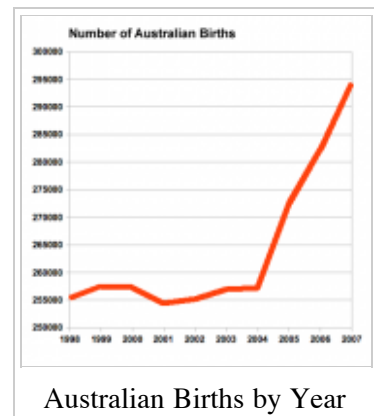
and 2008.
- **41.6%** of mothers had their first baby and 33.5% had their second baby
- **10,883** women were Aboriginal or Torres Strait Islander (3.8% of all women who gave birth)
  - 39.5% of all mothers in the Northern Territory
  - 25.2 years was the average age of these women who gave birth
- **3.1%** women received ART treatment (see also below Assisted Reproduction Technology)

Smoking during pregnancy

- **16.6%** of women smoked during pregnancy (similar proportion over the previous five years)

Preterm birth

- 7.4% of all mothers (less than 37 completed weeks of gestation)
  - 38.8 weeks is the average duration of pregnancy

Multiple pregnancy

- **4,634** multiple pregnancies (1.6% of all mothers) increasing due to the increased use of ART
  - 4,558 twin pregnancies, 76 triplet pregnancies and no quadruplet pregnancies

Australian multiple birth data

Presentation at birth

- 94.6% cephalic (any part vertex, face, or brow of the fetal head)
- 4.0% breech (buttocks or feet)

Method of birth

- **57.9%** vaginal births
  - 11.2% had an instrumental vaginal delivery (forceps or vacuum extraction)
- **30.9%** caesarean section births
  - 21.1% in 1998, 30.8% in 2006, rate recently stable
  - 83.3% of these were repeat caesarean sections

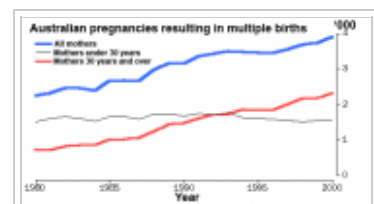## Pre-existing and pregnancy-related medical conditions

- The following conditions were also reported: epilepsy, diabetes mellitus and hypertension, antepartum haemorrhage, gestational diabetes, cord prolapse and retained placenta, pregnancy-induced hypertension, fetal distress in labour and post-partum haemorrhage rates

Breech presentation (Galletti, 1770)

Postnatal length of stay

- 2.0 days non-instrumental vaginal birth
- 3.0 days vacuum extraction delivery
- 4.0 days caesarean section or forceps delivery
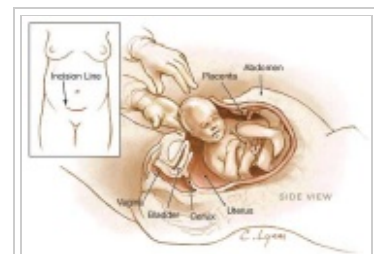

Birth caesarean

Babies

- **292,027** live births and **2,177** fetal deaths
  - stillbirth rate of 7.4 per 1,000 births
- most births occurred in March, August and October
- **105.6** sex ratio (number of male per 100 female liveborn babies)

Gestational age

- **90.9%** term (37–41 weeks gestation)
- **8.1%** were preterm and **33.2 weeks** was the mean gestational age for all preterm births
    - Preterm births were classified groups of 20–27 weeks, 28–31 weeks and 32–36 weeks

Birthweight

- **92.1%** of liveborn babies had a birthweight in the range 2,500–4,499 grams
    - average birthweight was 3,374 grams
- 17,976 (6.2%) low birthweight (weighing less than 2,500 grams) (**6.1%** for 2008)
- 2,956 (1.0%) very low birthweight (weighing less than 1,500 grams)
- 1,288 (0.4%) extremely low birthweight (weighing less than 1,000 grams)

Apgar scores - **1.4%** of liveborn babies had a low Apgar score (between 0 and 6) at 5 minutes (More? Apgar test)

Special care nurseries or neonatal intensive care units - 14.5% of liveborn babies were admitted to an SCN or NICU

Perinatal mortality

- 2,177 fetal deaths (7.4 per 1,000 births)
    - fetal deaths are if the birthweight is at least 400 grams or the gestational age is 20 weeks or more
- 846 neonatal deaths (2.9 per 1,000 live births)
    - neonatal deaths are those occurring in live births up to 28 completed days after birth

- 3,024 Australian perinatal deaths
    - perinatal death includes birthweight of at least 400 grams or, where birthweight is unknown, a gestational age of at least 20 weeks
- 23.5% congenital abnormalities (anomalies)
- 13.8% maternal conditions
- 12.6% unexplained antepartum death

    Self-Directed Learning 1

Special educational need by gestational age (UK data)[3]

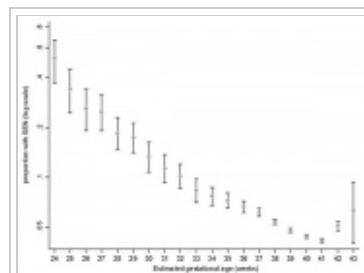Perinatal mortality rate NSW 1992-2002

Unintended Pregnancy

Approximately one-half of pregnancies in the United States (2001) were unintended (Finer 2006, Perspectives on Sexual and Reproductive Health). An earlier 1995 USA National Survey of Family Growth (NSFG) found:
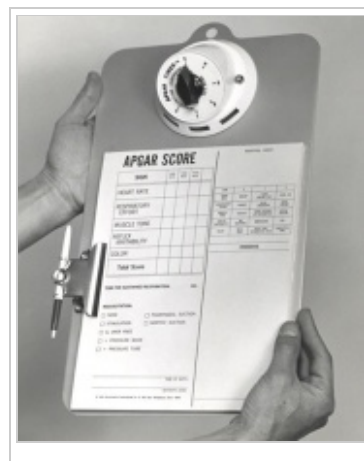
- 49% of pregnancies in the USA (excluding miscarriages)
- 31% of pregnancies resulting in a live birth are unintended

Unintended pregnancy is either mistimed (woman wanted to be pregnant later) or unwanted (did not want to ever be pregnant).
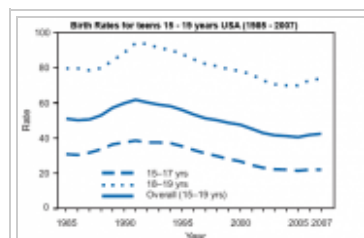
    Self-Directed Learning 2

Teen pregnancy USA

Assisted Reproduction Technology

Assisted Reproduction Technology (ART) is also sometimes also used to identify In vitro fertilization (IVF) but now includes many new techniques. (More? In Vitro Fertilization).


IVF

2007

- **3.1%** women received ART treatment (**3.2%** for 2008)
    - ranging from 1.4% in the Australian Capital Territory to 3.7% in Tasmania
- **34.1 years** was the average age of women who received ART
- 62.7% of mothers who received ART treatment were having their first baby and 37.3% had given birth previously
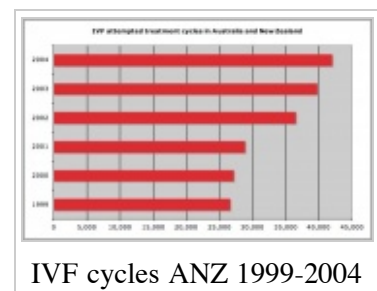
2005

- **51,017 treatment cycles** reported to ANZARD in Australia and New Zealand in 2005.
    - 91.1% were from Australian and 8.9% from New Zealand fertility centres
    - an increase of 13.7% of ART treatment cycles from 2004.
- **35.5** years average age of women (35.2 years in 2002).
- Women aged older than 40 years has increased from 14.3% in 2002 to 15.3% in 2005.

ART types USA 1996
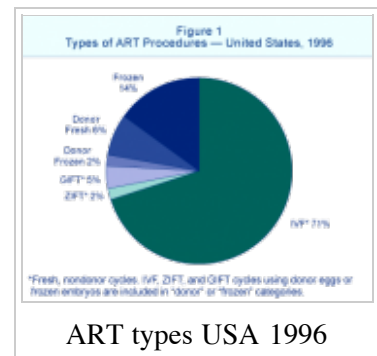
Single Embryo Transfers (SET)

- Significant increase in the number of SET embryos transfer cycles (2002 28.4%, 2005 48.3%)
- increase of SET cycles resulted more singleton deliveries (singleton deliveries 2005 was 85.9%)
- single-embryo transfer babies had better outcomes compared to babies born to women who had a double-embryo transfer (DET).
    - 2005 **3,681 SET babies and 5,589 DET babies.**
- Singletons babies - 96.1% SET, 61.6% DET
- Preterm babies - 11.7% SET, 30.6% DET
- Low birthweight liveborn babies - 8.0% SET, 25.0% DET

IVF cycles ANZ 1999-2004

ART Perinatal mortality rate

- perinatal mortality rate was 14.7 deaths per 1,000 births (2005)
    - 23.8% decrease from 19.3 deaths per 1,000 births in 2004
- Perinatal mortality rate was the lowest among singletons born following SET (7.3 deaths per 1,000 births) in 2005.

(Reference: AIHW National Perinatal Statistics Unit Assisted Reproduction Technology in Australia and New Zealand 2005 (http://www.npsu.unsw.edu.au/NPSUweb.nsf/page/art11))

Self-Directed Learning 3

Early Development Issues

Abnormal Implantation

Ectopic Implantation (Pregnancy) | Ectopic pregnancy ultrasound Flash | Quicktime

Abnormal implantation sites or Ectopic Pregnancy occurs if implantation is in uterine tube or outside the uterus.

Ectopic tubal pregnancy

- sites - external surface of uterus, ovary, bowel, gastrointestinal tract, mesentry, peritoneal wall
- If not spontaneous then, embryo has to be removed surgically

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

Another type of abnormality is when only 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.

Hydatidiform Mole

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.

This topic is also covered in Placenta - Abnormalities

Twinning

- **Twin deliveries and place of birth in NSW 2001-2005**[4] "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.
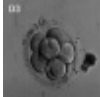
Week	Week 1							Week 2	
Day	0	1	2	3	4	5	6	7 8 9	10 11 12 13 14
Cell Number	1	1	2	16	32	128		bilaminar	
Event	Ovulation	fertilization	First cell division	Morula	Early blastocyst	Late blastocyst / Hatching	Implantation starts	X inactivation	
Monoygotic Twin Type	Diamniotic Dichorionic			Diamniotic Monochorionic				Monoamniotic Monochorionic	Conjoined

Table based upon recent Twinning Review.[5]

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.

Australian abnormalities by System

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).

Abnormality Links: Introduction | Genetic | Environmental | Unknown | Teratogens | Cardiovascular | Coelomic Cavity | Endocrine | Gastrointestinal Tract | Genital | Head | Integumentary | Musculoskeletal | Neural | Neural Crest | Renal | Respiratory | Sensory | Twinning | Fetal Origins Hypothesis

Australian abnormalities by System

Prenatal diagnosis are the clinical tools used to determine both normal and abnormal development. There are a growing number of new diagnostic techniques that are being applied to human embryonic development.

Diagnosis Links: Prenatal Diagnosis | Amniocentesis | Chorionic villus sampling | Alpha-Fetoprotein | Pregnancy-associated plasma protein-A | Fetal Blood Sampling | Ultrasound | Magnetic Resonance Imaging | Computed Tomography | Comparative Genomic Hybridization | Neonatal Diagnosis | Category:Prenatal Diagnosis | Category:Neonatal Diagnosis
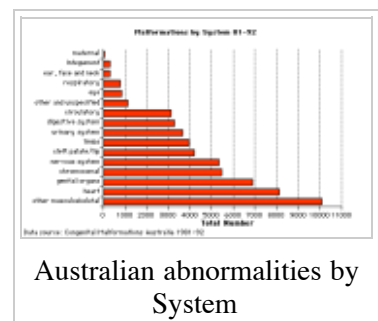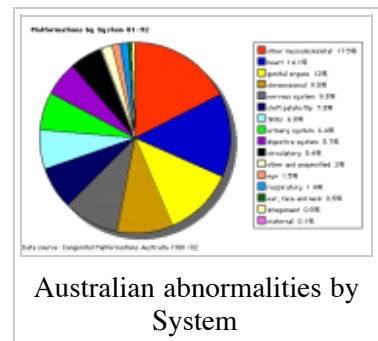
While genetic abnormalities will have well-defined impacts upon development, environmentally derived effects can be harder to define and often variable depending on many different factors (timing, exposure level, and the combination effects with other factors). This combination effect can also be seen between genetic and environmental interacting to give an even broader spectrum of both major and minor abnormalities.

Environmental Links: Introduction | Low Folic Acid | Drugs | Australian Drug Categories | USA Drug Categories | Thalidomide | Herbal Drugs | Illegal Drugs | Fetal Alcohol Syndrome | TORCH Infections | Viral Infection | Parvovirus | Rubella Virus | Polio Virus | Bacterial Infection | Zoonotic Infection | Malaria | Iodine Deficiency | Maternal Diabetes | Maternal Hyperthermia | Chemicals | Heavy Metals | Radiation | Prenatal Diagnosis

Australian Birth Anomalies System

"*The national collation and reporting of birth anomalies data has been suspended in recent years due to concerns about data quality and comparability.*"

- Variability among states and territories in scope of birth anomalies data collections: sources of birth anomalies notifications and definitions and classifications used; method of data collection and available resources.
- Variability among the states and territories in the timing and method of the provision of birth anomalies data to the AIHW National Perinatal Statistics Unit (NPSU) for national collation and reporting.
- New **Australian Birth Anomalies System** should be data for birth anomalies detected up to 1 year of age
    - including data on terminations of pregnancies with birth anomalies and regardless of gestational age (i.e. including less than 20 weeks gestation)
- System will initially be based on data from the states able to detect birth anomalies at least up to 1 year of age (NSW, VIC, WA and SA), further extending the period of detection in the future

The Australian Congenital Anomalies Monitoring System (ACAMS) supersedes the National Congenital Malformations and Birth Defects Data Collection (NCM&BD).

Links: Australian Congenital Anomalies Monitoring System (http://www.npsu.unsw.edu.au/PRERUWeb.nsf/page/CADC) | Congenital Anomalies in Australia 2002-2003 (http://www.preru.unsw.edu.au/PRERUWeb.nsf/page/ba3)

NSW - Congenital Conditions Register

Scheduled congenital conditions (section 2) detected during pregnancy or in infants up to one year of age in NSW are required to be reported under the NSW Public Health Act 1991.

Scheduled congenital conditions include:

1. 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.
2. Chromosomal abnormalities. Examples include Down syndrome and unbalanced translocations.
3. Four medical conditions: cystic fibrosis, phenylketonuria, congenital hypothyroidism and thalassaemia major.

Congenital conditions that are not notifiable include:

1. 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).

2. Birth injuries.
3. Congenital infections which do not result in a structural malformation.
4. Tumours and cysts.
5. Conditions arising from prematurity or asphyxiation.

Links: NSW Health - Congenital Conditions Register - Reporting Requirements 2009 PDF (http://www.health.nsw.gov.au/policies/pd/2009/pdf/PD2009_069.pdf)

Ten most frequently reported birth anomalies

Based upon statistics from the Victorian Perinatal Data Collection Unit in Victoria between 2003-2004.

Hypospadias (More? Development Animation - Genital Male External | Genital Abnormalities - Hypospadia)

Obstructive Defects of the Renal Pelvis (obstructive defects of the renal pelvis, uteropelvic junction obstruction, pelvo-uterero junction obstruction) Term describing a developmental renal abnormality due to partial or complete blockage of the drainage of the kidney pelvis requiring surgical correction. The blockage can also have several causes including: unusual ureter twisting or bending, ureter compression by a blood vessel, malformations of the muscular wall. The blockage leads to an accumulation of urine in the affected region, with several potential effects: nephron damage from compression (hydronephrosis); decreased urine output leading to lack of amniotic fluid (oligohydramnios); respiratory development effects due to the lack of amniotic fluid.

- The most common type of obstruction is at the uteropelvic junction (UPJ), between the junction of the ureter and the kidney.
- Blockage lower as the ureter enters the bladder, the ureterovesicular junction (UVJ), usually involves only one kidney and the back flow enlarges the affected ureter (megaureter).

(More? Renal System - Abnormalities | Renal System Development)

Ventricular Septal Defect (More? Cardiovascular Abnormalities - Ventricular Septal Defect)
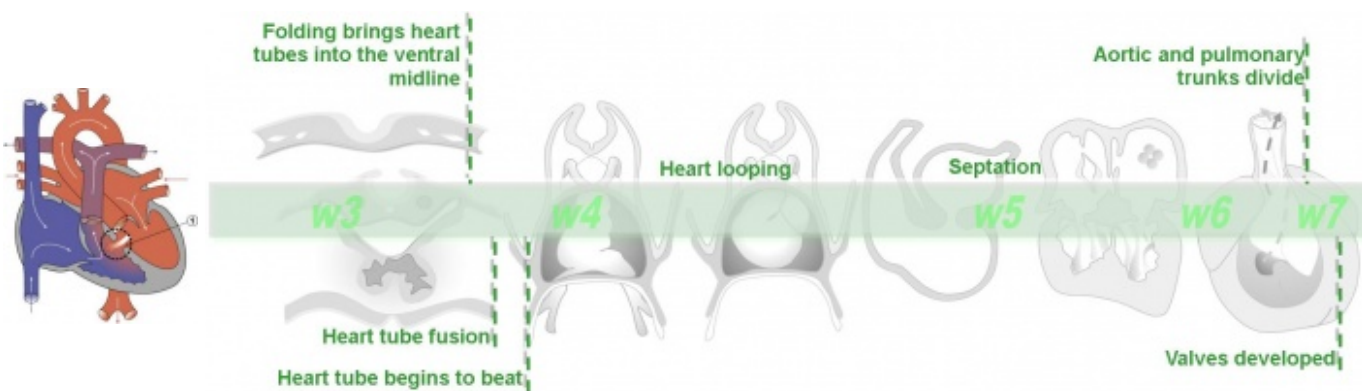
Heart Development Timeline (see Basic Cardiac Embryology)

Congenital Dislocated Hip (More? Musculoskelal Abnormalities - Congenital Dislocation of the Hip (CDH))

(DHH, congenital dislocated hip, congenital hip dislocation, congenital hip dysplasia) Term describes a spectrum of musculoskeletal disorders of hip instability due either to the femoral head being able to move outside the acetabulum (luxation or dislocation), or abnormally within the acetabulum (subluxation or partial dislocation). This includes presentation

 following a normal examination of the hips in the newborn period (Ortolani and Barlow tests). When detected can be managed with splinting (Denis-Browne splint) allows the hip joint to develop normally and does not require surgery. If undetected and left untreated, the hip joint develops abnormally and surgical reduction is required. (More? Musculoskeletal System Development)
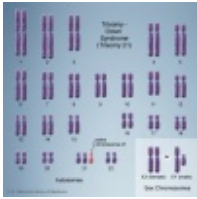
 Trisomy 21 or Down syndrome - (More? Trisomy 21)

 Hydrocephalus (More? Neural Abnormalities - Hydrocephalus | NINDS - Hydrocephalus Fact Sheet (http://www.ninds.nih.gov/disorders/hydrocephalus/detail_hydrocephalus.htm) | Hydrocephalus Support Association (http://www.hydrocephalus.org.au) | USA National Hydrocephalus Foundation (http://nhfonline.org/treatment.php))

 Cleft Palate (More? Development Animation - Palate 1 | Development Animation - Palate 2 | Cleft Palate)
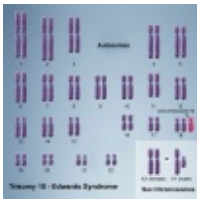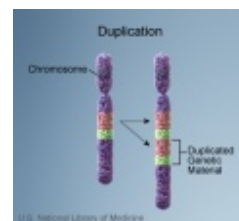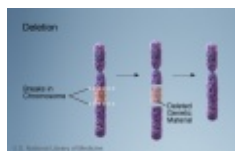
 Trisomy 18 or Edward Syndrome - multiple abnormalities of the heart, diaphragm, lungs, kidneys, ureters and palate 86% discontinued (More? Trisomy 18)
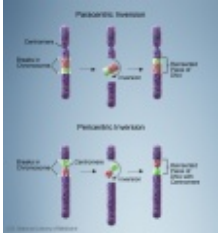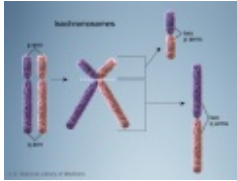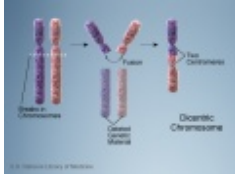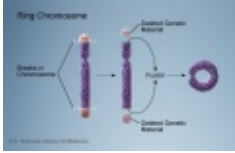
Renal Agenesis/Dysgenesis - reduction in neonatal death and stillbirth since 1993 may be due to the more severe cases being identified in utero and being represented amongst the increased proportion of terminations (approximately 31%). (More? Kidney Abnormalities - Renal Agenesis (http://embryology.med.unsw.edu.au/Notes/urogen2.htm#Renal_Agenesis))

 Cleft Lip and Palate - occur with another defect in 33.7% of cases. (More? Cleft Lip)

Genetic

Chromosome - unbalanced translocation	Chromosome - balanced translocation	Chromosome - deletion	Chromosome - duplication
Chromosome - inversion	Chromosome - isochromosomes	Chromosome dicentric	Chromosome - ring chromosome

Links: Abnormal Development - Genetic

Self-Directed Learning 5

Teratology

Prenatal Screening

How and why do things go wrong in development?

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.
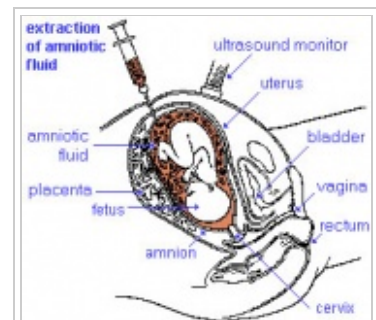
Amniocentesis
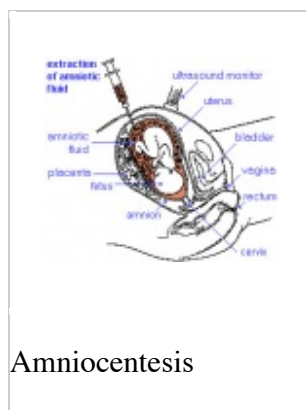
Amniocentesis
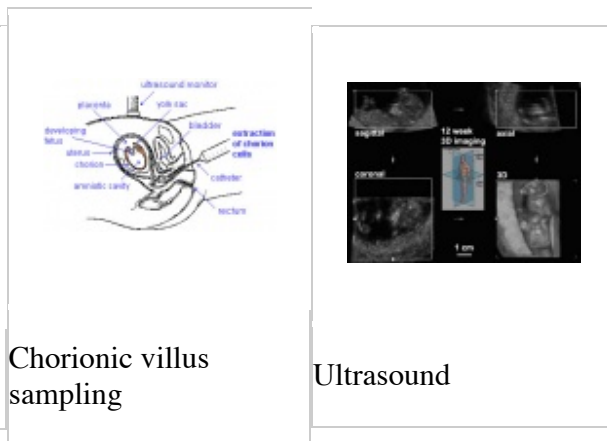
Chorionic villus sampling
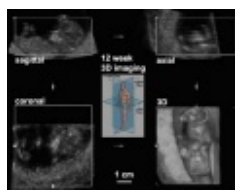
Ultrasound

Diagnosis Links: Prenatal Diagnosis | Amniocentesis | Chorionic villus sampling | Alpha-Fetoprotein | Pregnancy-associated plasma protein-A | Fetal Blood Sampling | Ultrasound | Magnetic Resonance Imaging | Computed Tomography | Comparative Genomic Hybridization | Neonatal Diagnosis | Category:Prenatal Diagnosis | Category:Neonatal Diagnosis

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. (More? [images/hcriticaldev.gif Critical Periods of Development])

- **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.

- **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**.

Links:

Abnormality Links: Introduction | Genetic | Environmental | Unknown | Teratogens | Cardiovascular | Coelomic Cavity | Endocrine | Gastrointestinal Tract | Genital | Head | Integumentary | Musculoskeletal | Neural | Neural Crest | Renal | Respiratory | Sensory | Twinning | Fetal Origins Hypothesis
Environmental Links: Introduction | Low Folic Acid | Drugs | Australian Drug Categories | USA Drug Categories | Thalidomide | Herbal Drugs | Illegal Drugs | Fetal Alcohol Syndrome | TORCH Infections | Viral Infection | Parvovirus | Rubella Virus | Polio Virus | Bacterial Infection | Zoonotic Infection | Malaria | Iodine Deficiency | Maternal Diabetes | Maternal Hyperthermia | Chemicals |

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.

Human critical periods of development

Conceptus   **Embryonic development** (weeks)   **Fetal period** (weeks)

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 16 | 20-36 | 38 |

Neural

Heart

Upper limbs
Lower limbs
Ear
Eye

Palate

Teeth

External genitalia

Loss   **Major abnormalities**   **Functional and Minor abnormalities**
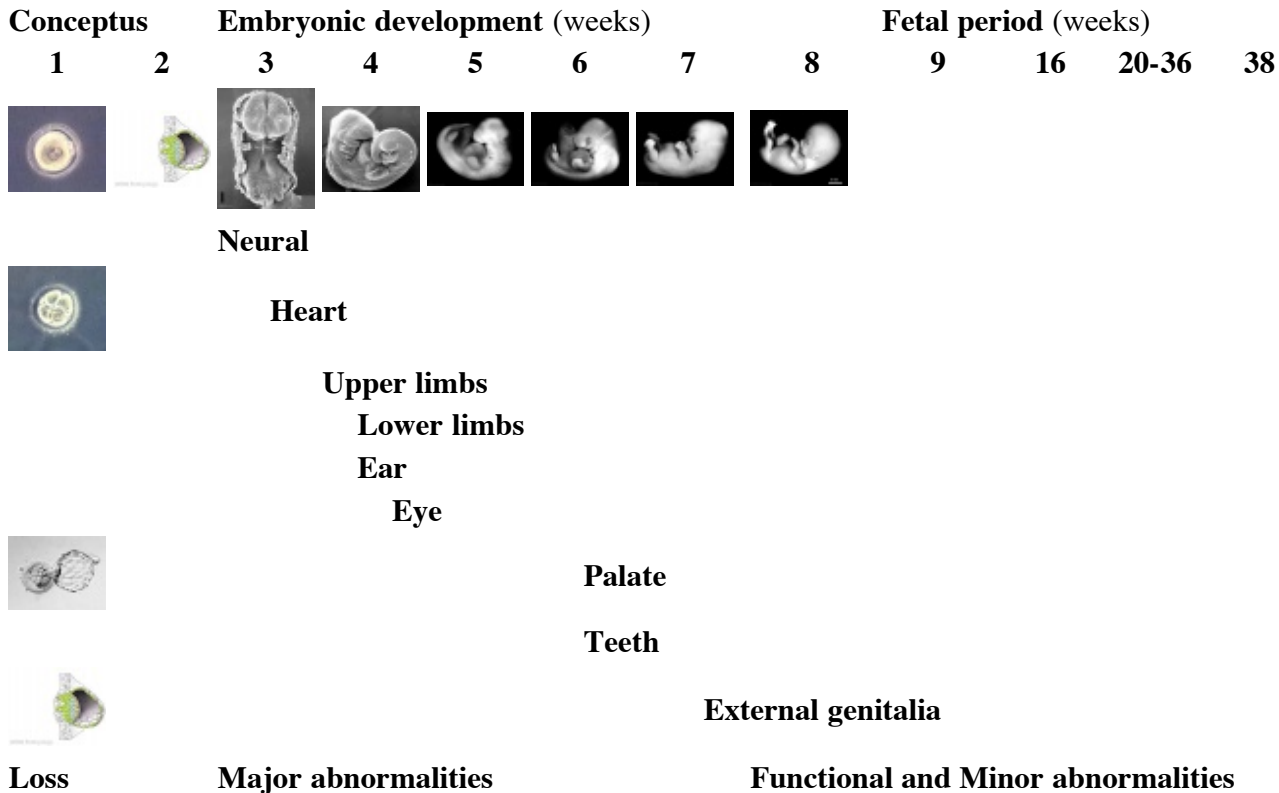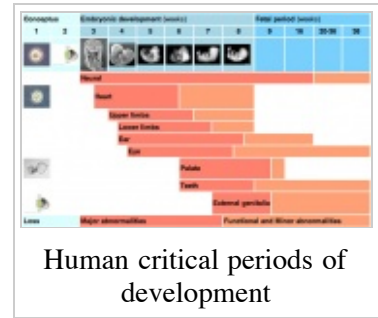
Self-Directed Learning 6

Links: Embryonic Development | Timeline human development | Movie - Human Development annotated cartoon | Human - critical periods

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. In the USA, drugs are classified by the Food and Drug Administration (FDA) into classes (A, B, C, D, and X) to define their safety. (More? Australian Drug Categories)

- **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.

Infant Drug Clearance

The drug clearance data below are only approximate calculated rates for the fetus and infant from NZ Drug Safety in Lactation (http://www.medsafe.govt.nz/Profs/PUarticles/lactation.htm#Infants)

Drug clearance rates

Post-conceptual Age (weeks)	Clearance of Drug (percentage of adults)
24-28	5%
28-34	10%
34-40	33%
40-44	50%
44-68	66%
> 68	100%
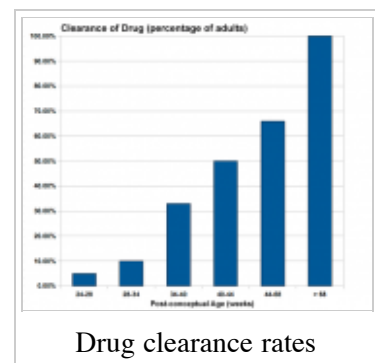
Links: Abnormal Development - Drugs | Australian Fetal Risk Categories | USA FDA Fetal Risk Categories | Therapeutic Goods Authority (http://www.tga.gov.au/) | Australian Drug Evaluation Committee (ADEC) (http://www.tga.gov.au/docs/html/adec/adec.htm) | Prescribing Medicines in Pregnancy (http://www.tga.gov.au/docs/html/medpreg.htm) | Appendix A: Therapeutic goods exempted from pregnancy classification (http://www.tga.gov.au/docs/html/mip/exempt.htm)

Self-Directed Learning 7

References

1. ↑ Laws P & Sullivan EA 2009. **Australia's mothers and babies 2007** AIHW Perinatal statistics series no. 23 (http://www.aihw.gov.au/publications/index.cfm/title/10972) Cat. no. PER 48. Sydney: AIHW National Perinatal Statistics Unit.
2. ↑ Laws P & Sullivan EA 2010 **Australia's mothers and babies 2008** AIHW Perinatal statistics series no. 24 (http://www.aihw.gov.au/publications/index.cfm/title/11813) Cat. no. PER 48. Sydney: AIHW National Perinatal Statistics Unit.
3. ↑ Daniel F MacKay, Gordon C S Smith, Richard Dobbie, Jill P Pell **Gestational age at delivery and special educational need: retrospective cohort study of 407,503 schoolchildren.** PLoS Med.:

2010, 7(6);e1000289 PMID:20543995 | PLoS Medicine
(http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000289)
4. ↑ Charles S Algert, Jonathan M Morris, Jennifer R Bowen, Warwick Giles, Christine L Roberts **Twin deliveries and place of birth in NSW 2001-2005.** Aust N Z J Obstet Gynaecol: 2009, 49(5);461-6 PMID:19780726
5. ↑ Judith G Hall **Twinning.** Lancet: 2003, 362(9385);735-43 PMID:12957099

Links

The following are links to relevant notes pages that cover the key embryology concepts in this tutorial. These pages and their links will provide further detailed information.

Applied Embryology

Timeline human development | Fetal Development | Birth | Apgar test | Neonatal Development | Week 2 Abnormalities - Trophoblastic Disease | Placenta Development | Neural Abnormalities | Abnormal Development - Folic Acid and Neural Tube Defects | Week 3 | Cardiovascular Abnormalities | Twinning | Blastocyst | Molecular Development

Teratology Links

Human Abnormal Development | Genetic Abnormalities | Environmental Factors | Drugs | Trisomy 21 (Down Syndrome) | Fetal Alcohol Syndrome | Viral Infection | Rubella Virus | Hyperthermia

Self-Directed Learning

Self-Directed Learning 1 - Australian Statistics
Once you have thought about the Australian statistics, now look at the latest report summary Australia's mothers and babies 2008 and Australian Statistics.

- What are the current trends in Australia?
- What factors may be contributing to these changes?
- Are there any long-term trends in birth statistics?
- What does this mean for future health care provision?

Self-Directed Learning 2 - Pregnancy

- What indications would prompt a woman to take a pregnancy test?
- What test are available and where is test information provided?
- How much do these tests cost?
- When does a doctor become involved and what issues should be discussed?

Self-Directed Learning 3 - Assisted Reproductive Technologies

- Why is this more than "in vitro fertilization"?
- How many different Assisted Reproductive Technologies are available in Australia?
- How has the change from DET to SET impacted on reproductive outcomes?
- What other clinical issues should be considered when discussing ART?
- What preimplantation genetic tests are currently available?

Self-Directed Learning 4 - The First Few Weeks

- After fertilization, when does initial implantation occur?
- Which hormone maintains the initial pregnacy, where is it from and how does it act?
- How would an ectopic pregnancy differ at this stage?
- What additional maternal issues should be considered for multiple pregnancies?

Self-Directed Learning 5 - Abnormal Development

- What are the 3 major forms of abnormal development?
- What are the main chromosomal abnormalities and how do they occur?
- How are congenital abnormalities reported and classified within Australia?

Self-Directed Learning 6 - Prenatal Diagnosis

- What maternal lifestyle issues should be considered for a pregnancy?
- What diagnostic techniques are currently available and in development?
- What can ultrasound normally identify?

Self-Directed Learning 7 - Medications in Pregnancy

- How does drug classification differ between countries?
- Which system(s) do european and asian countries apply for classification?
- How are teratogens identified?
- Why does fetal drug clearance differ from maternal clearance?

External Links

External Links Notice - The dynamic nature of the internet may mean that some of these listed links may no longer function. If the link no longer works search the web with the link text or name.

- **Australia** AIHW National Perinatal Statistics Unit (http://www.preru.unsw.edu.au/PRERUWeb.nsf/page/AIHW%20National%20Perinatal%20Statistics%20Unit) | Victorian Birth Defects Register (VBDR) (http://www.health.vic.gov.au/perinatal/vbdr/index.htm) | Victorian Birth Defects Register brochure (http://www.health.vic.gov.au/perinatal/downloads/vbdr_brochure.pdf)

- **National Perinatal Statistics Unit** Congenital Anomalies Neural tube defects in Australia - An epidemiological report (http://www.preru.unsw.edu.au/PRERUWeb.nsf/page/NeuralTubeDefects) | Congenital Anomalies in Australia 2002-2003 (http://www.preru.unsw.edu.au/PRERUWeb.nsf/page/ba3) | Congenital Anomalies in Australia 1998-2001 (http://www.preru.unsw.edu.au/PRERUWeb.nsf/page/ba2) | Congenital Malformations Australia 1981-1997 (http://www.preru.unsw.edu.au/PRERUWeb.nsf/page/ca4) | Congenital

Malformations Australia 1995 and 1996 (http://www.preru.unsw.edu.au/PRERUWeb.nsf/page/ca3) | Congenital Malformations Australia 1993 and 1994 (http://www.preru.unsw.edu.au/PRERUWeb.nsf/page/ca2) | Congenital Malformations Australia 1981-1992 (http://www.preru.unsw.edu.au/PRERUWeb.nsf/page/ca1)

- **USA** Food and Drug Administration Evaluating the Risks of Drug Exposure in Human Pregnancies (http://www.fda.gov/cber/gdlns/rvrpreg.htm) | Centers for Disease Control and Prevention (CDC, USA) Pregnancy Risk Assessment Monitoring System (PRAMS) (http://www.cdc.gov/prams/) collects state-specific, population-based data on maternal attitudes and experiences before, during, and shortly after pregnancy.
- **Other** Motherisk (Canada) Drugs, chemicals, radiation and herbal products in pregnancy (http://www.motherisk.org/women/drugs.jsp) | International Society for the Study of Trophoblastic Diseases Trophoblastic Diseases (http://www.isstd.org/intro/index.html)

Glossary Links

A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z | Numbers

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