BGD Tutorial - Applied Embryology and Teratology

From Embryology

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 2011, 2010 and 2009 (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: Moore, K.L. & Persuad, T.V.N. (2008). *The Developing Human: Clinically Oriented Embryology* (8th ed.). Philadelphia: Saunders. Chapter 20 - Congenital Anatomic Anomalies or Human Birth Defects (http://www.mdconsult.com/books/linkTo?type=bookPage&isbn=978-1-4160-3706-4&eid=4-u1.0-B978-1-4160-3706-4..50023-2)

Human Embryonic Development (week 1 to 8)

Applied Embryology

This recent data summarised below from Australia's mothers and babies 2009[1], 2008[2] and 2007[3]. This data should help you as a clinician and researcher to understand the current trends in reproductive medicine within Australia. Also see recent general population data in Australian Statistics.

- **2009** - 296,791 live births and 2,341 fetal deaths
- **2008** - 294,737 live births and 2,188 fetal deaths
- **2007** - 292,027 live births and 2,177 fetal deaths

Australia's mothers and babies (2009) cover

Mothers

- Average maternal age in 2009 was **30.0** years compared with 29.0 years in 2000.
- Approximately 41.6% of women were having their first baby.
  - Average age for first time mothers was 27.9 in 2009 which was 0.3 years younger than for 2008.
  - Of all first-time mothers, 13.7% were aged 35 years or older in 2009 (2000 - 10.3%)
- ART was used by **3.6%** of women who gave birth. (see also below Assisted Reproduction Technology)
- 97.3% of women who gave birth at 32 weeks or more gestation attended at least one antenatal visit, with 91.9% attending 5 or more (where data was available).
- 0.3% (863) of all women who gave planned home birth.

Smoking during pregnancy

- Smoking while pregnant was reported by 14.5% of all mothers.
  - down from **16.6%** over the previous five years.
- Smoking by 37.0% of teenage mothers.

Preterm birth

- 8.2% of babies were born preterm (before 37 completed weeks of gestation) (2008 - 7.4%).
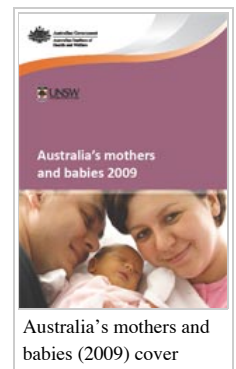- 0.9% post-term (42 weeks gestation or more).

Multiple pregnancy

- The number of multiple births has increased in the last two decades.
- **4,605** multiple pregnancies (1.6% of all mothers) (2008 - 4,634)
  - 4,521 twin pregnancies (2008 - 4,558)
  - 81 triplet pregnancies (2008 - 76)
  - 3 quadruplet pregnancies. ((2008 - 0)

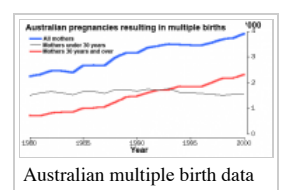Australian multiple birth data

Presentation at birth

- Cephalic (any part (vertex, face or brow) 94.4% (2008 - 94.6%)
- Vertex (crown (vertex) of the fetal head is the presenting part) 94.2%
- Breech presentation (buttocks or feet in labour) 3.9% (2008 - 4.0%)
  - 11,565 women with a breech presentation - 92.2% were singleton and 7.8% were multiple pregnancies.
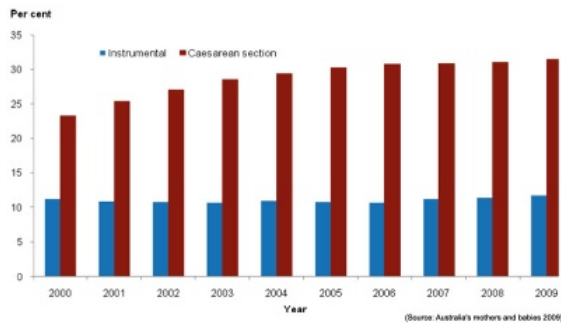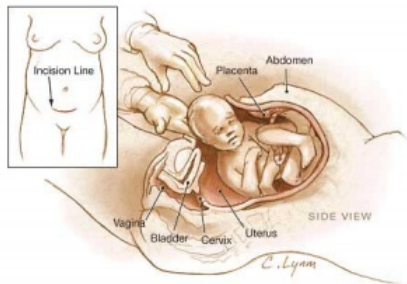
Method of birth

- vaginal birth 201,631 women
- 56.8% had a non-instrumental vaginal birth.
- instrumental vaginal delivery 11.7%

- caesarean sections 92,687
- 31.5% nationally (2000 - 23.3%)

Breech presentation (Galletti, 1770)

Birth caesarean

Caesarean and Instrument Delivery

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
  - Note data is not standard across jurisdictions.

Postnatal length of stay

- median postnatal hospital stay for mothers was 3.0 days
- 2.0 days non-instrumental vaginal birth
- 3.0 days vacuum extraction delivery
- 4.0 days caesarean section or forceps delivery
  - 5.4% caesarean section had a postnatal length of stay of 7+ days

Babies

- 296,791 live births and 2,341 fetal deaths (2008 - 292,027 live births and 2,177 fetal deaths)
  - stillbirth rate of 7.5 per 1,000 births
- most births occurred in October, September and July

- **106** sex ratio, number of male per 100 female liveborn babies. (2008 - 105.6)

Gestational age

- **90.8%** term, 37–41 weeks gestation. (2008 - 90.9%)
- **8.2%** were preterm and **33.1 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
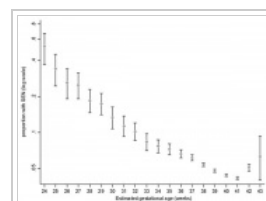
Birthweight

- **92%** of liveborn babies had a birthweight in the range 2,500–4,499 grams
  - average birthweight was 3,374 grams
- 18,347 (6.2%) low birthweight (weighing less than 2,500 grams) (2008 - 6.1%)
- 3,017 (1.0%) very low birthweight (weighing less than 1,500 grams)
- 1,357 (0.5%) extremely low birthweight (weighing less than 1,000 grams)

Apgar scores - **1.5%** of liveborn babies had a low Apgar score (between 0 and 6) at 5 minutes (More? Apgar test)
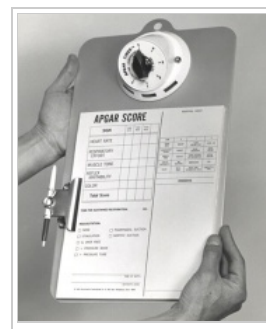
Special care nurseries (SCN) or neonatal intensive care units (NICU) - 14.2% of liveborn babies admitted (2008 - 14.5%)

Special educational need by gestational age (UK data)[4]

Perinatal mortality

- Different definitions in Australia for reporting and registering perinatal deaths.
  - NPDC definition of perinatal deaths to include all fetal and neonatal deaths of at least 400 grams birthweight or at least 20 weeks gestation.
  - ABS definition of a perinatal death includes birthweight of at least 400 grams or, where birthweight is unknown, a gestational age of at least 20 weeks.

- 2,341 fetal deaths, 7.8 per 1,000 births (2008 - 2,177)
- 667 neonatal deaths (3.0 per 1,000 live births) (2008 - 846)
  - neonatal deaths are those occurring in live births up to 28 completed days after birth

- 2,221 Australian perinatal deaths, 70.0% were fetal deaths (2008 - 3,024)

- perinatal death includes birthweight of at least 400 grams or, where birthweight is unknown, a gestational age of at least 20 weeks
- 31.2% congenital abnormalities (anomalies) (2008 - 23.5%)
- 18.9% spontaneous preterm birth

Self-Directed Learning 1

Unintended Pregnancy

Perinatal mortality rate NSW 1992-2002

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

Links: CDC Unintended Pregnancy Prevention (http://www.cdc.gov/reproductivehealth/UnintendedPregnancy/index.htm) | Pregnancy Risk Assessment Monitoring System USA (http://www.cdc.gov/prams/) | The Measurement and Meaning of Unintended Pregnancy (http://www.guttmacher.org/pubs/journals/3509403.html)

Assisted Reproduction Technology

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

The following data from **Assisted reproductive technology in Australia and New Zealand 2009.**[5] 9 Nov 2011 (http://www.aihw.gov.au/media-release-detail/?id=10737420483)

Assisted reproductive technology in Australia and New Zealand 2009

ART treatment cycles

- **70,541** treatment cycles (2005 - 51,017)
- 13,114 live born babies
  - 17.2% of cycles a live delivery (birth of at least one liveborn baby).

single embryo transfer

- increase of single embryo transfer, from 48.3% in 2005 to 69.7% in 2009.
  - reduction of multiple delivery rate from 14.1% in 2005 to 8.2% in 2009.
- average age of women undergoing autologous cycles was 35.8 years

cryopreserved embryos

- 22,472 frozen/thawed embryo transfer cycles.
- 18.3% embryos had been cryopreserved using ultra-rapid method (vitrification).
- 33% blastocyst (day 5–6 embryo) was transferred used vitrified blastocysts.
- 1.7% cleavage embryo (day 2–3 embryo) was transferred.

IVF

Links: Assisted Reproductive Technology | In Vitro Fertilization

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.
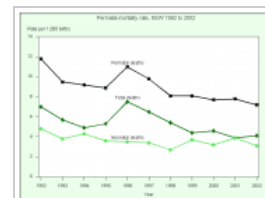
- sites - external surface of uterus, ovary, bowel, gastrointestinal tract, mesentry, peritoneal wall
- If not spontaneous then, embryo has to be removed surgically
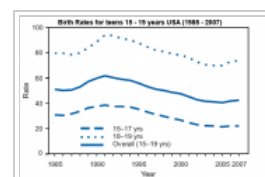
Tubal pregnancy - 94% of ectopic pregnancies

- 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

Ectopic tubal pregnancy

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.
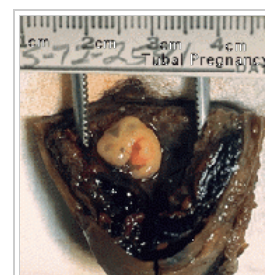
There are several forms of hydatidiform mole: partial mole, complete mole and persistent gestational trophoblastic tumor. Many of these tumours arise from a haploid sperm fertilizing an egg without a female pronucleus (the alternative form, an embryo without sperm contribution, is called parthenogenesis). 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.
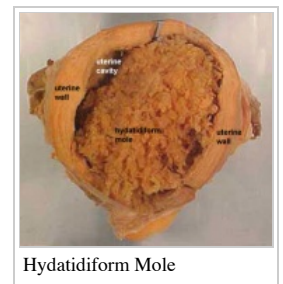
This topic is also covered in Placenta - Abnormalities

Hydatidiform Mole

Twinning

- **Twin deliveries and place of birth in NSW 2001-2005**[6] "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		Diamniotic			Diamniotic				Monoamniotic						
Twin Type		Dichorionic			Monochorionic				Monochorionic		Conjoined				

Table based upon recent Twinning Review.[7]

> Self-Directed Learning 4

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).

Australian abnormalities by System

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

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 | Preimplantation Genetic Screening | Comparative Genomic Hybridization | Neonatal Diagnosis | Category:Prenatal Diagnosis | Category:Neonatal Diagnosis
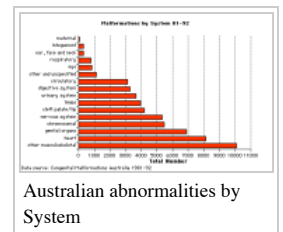

Australian abnormalities by System

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 | Iodine Deficiency | Nutrition | Drugs | Australian Drug Categories | USA Drug Categories | Thalidomide | Herbal Drugs | Illegal Drugs | Fetal Alcohol Syndrome | TORCH Infections | Viral Infection | Bacterial Infection | Zoonotic Infection | Toxoplasmosis | Malaria | Iodine Deficiency | Maternal Diabetes | Maternal Hyperthermia | Biological Toxins | Chemicals | Heavy Metals | Radiation | Prenatal Diagnosis | Neonatal Diagnosis

Bacterial Links: Syphilis | Gonorrhea | Tuberculosis | Listeria | TORCH Infections | Environmental | Category:Bacteria
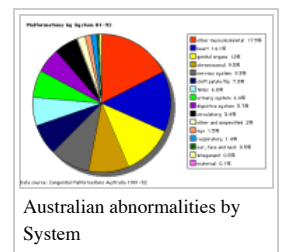
Australian Birth Anomalies System

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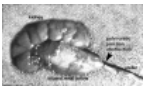
- The most common type of obstruction is at the uteropelvic junction (UPJ), between the junction of the ureter and the kidney.
- Blockage lower as the ureter enters the bladder, the ureterovesicular junction (UVJ), usually involves only one kidney and the back flow enlarges the affected ureter (megaureter).

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

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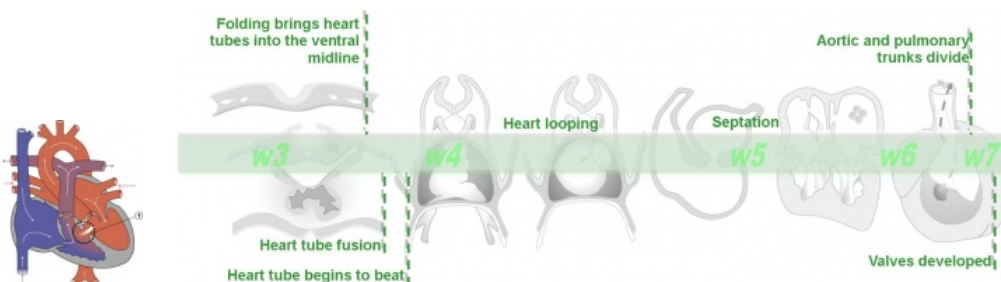
Heart Development Timeline (see Basic Cardiac Embryology)

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)
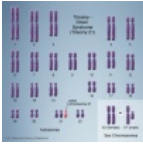

Trisomy 21 or Down syndrome - (More? Trisomy 21)

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)
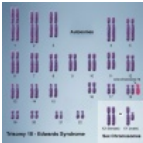

Trisomy 18 or Edward Syndrome - multiple abnormalities of the heart, diaphragm, lungs, kidneys, ureters and palate 86% discontinued (More? Trisomy 18)

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? Renal Abnormalities - Renal Agenesis)
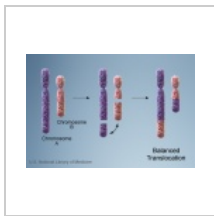

Cleft Lip and Palate - occur with another defect in 33.7% of cases. (More? Cleft Lip)
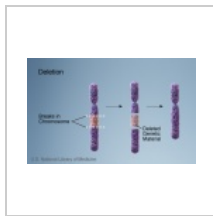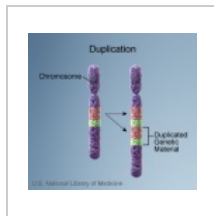
Genetic
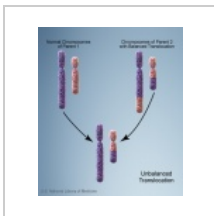
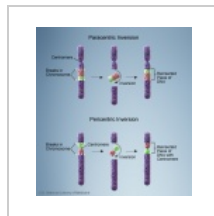

Chromosome - unbalanced translocation

Chromosome - balanced translocation
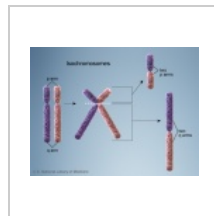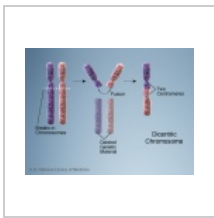
Chromosome - deletion

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.
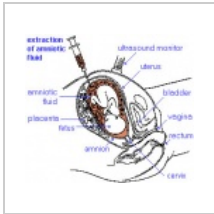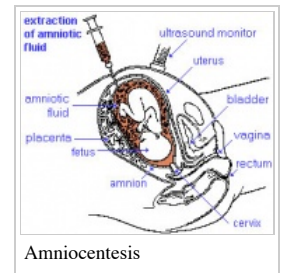

Amniocentesis
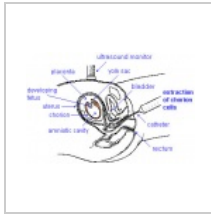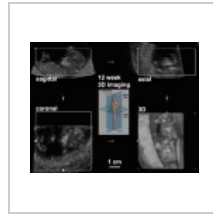
Amniocentesis

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 | Preimplantation Genetic Screening | 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**.
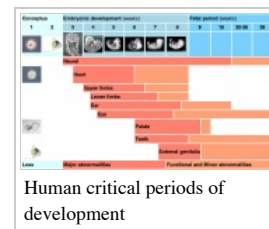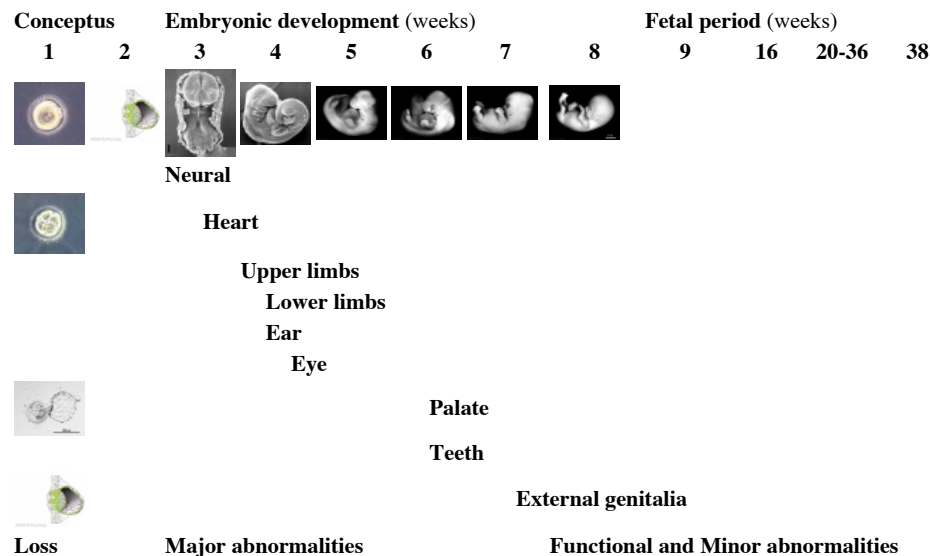
Links:

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 | Iodine Deficiency | Nutrition | Drugs | Australian Drug Categories | USA Drug Categories | Thalidomide | Herbal Drugs | Illegal Drugs | Fetal Alcohol Syndrome | TORCH Infections | Viral Infection | Bacterial Infection | Zoonotic Infection | Toxoplasmosis | Malaria | Iodine Deficiency | Maternal Diabetes | Maternal Hyperthermia | Biological Toxins | Chemicals | Heavy Metals | Radiation | Prenatal Diagnosis | Neonatal Diagnosis
Genetic Links: Introduction | Genetic risk maternal age | Trisomy 21 | Trisomy 18 | Trisomy X | Philadelphia chromosome | Prenatal Diagnosis | Molecular Development - Genetics

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)

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%

Drug clearance rates
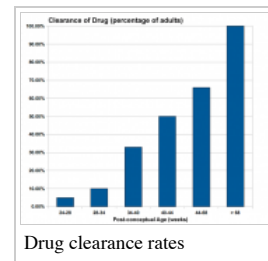
Links: Abnormal Development - Drugs | Australian Fetal Risk Categories | USA FDA Fetal Risk Categories | Therapeutic Goods Authority (http://www.tga.gov.au/) | Australian Drug Evaluation Committee (ADEC) (http://www.tga.gov.au/docs/html/adec/adec.htm) | Prescribing Medicines in Pregnancy (http://www.tga.gov.au/docs/html/medpreg.htm) | Appendix A: Therapeutic goods exempted from pregnancy classification (http://www.tga.gov.au/docs/html/mip/exempt.htm) | NSW Poisons Information Centre (http://www.chw.edu.au/poisons)

Self-Directed Learning 7

References

1. ↑ Li Z, McNally L, Hilder L & Sullivan EA 2011. **Australia's mothers and babies 2009** AIHW Perinatal statistics series no. 25 (http://www.aihw.gov.au/publication-detail/?id=10737420870) Cat. no. PER 52. Sydney: AIHW National Perinatal Epidemiology and 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. ↑ 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.
4. ↑ 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)
5. ↑ Wang YA, Macaldowie A, Hayward I, Chambers GM, & Sullivan EA 2011. **Assisted reproductive technology in Australia and New Zealand 2009.** Assisted reproduction technology series no. 15. Cat. no. PER 51. Canberra: AIHW. Online Summary (http://www.aihw.gov.au/publication-detail/?id=10737420465) | PDF (http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=10737420484&libID=10737420483)
6. ↑ 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
7. ↑ 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 2009 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?
- Do european and asian countries apply the same drug classification system(s)?
- 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.

- **Department of Health and Ageing** The National Maternity Services Plan 2010 (http://www.health.gov.au/internet/main/publishing.nsf/Content/maternityservicesplan) | National Maternity Services Plan: 2010 -2011 Annual Report (http://www.health.gov.au/internet/main/publishing.nsf/Content/349C976EEDDB5EB0CA257862001B3657/$File/NMSP%202011%20Annual%20Report.pdf)

- **Australia** AIHW National Perinatal Statistics Unit (http://www.preru.unsw.edu.au/PRERUWeb.nsf/page/AIHW+National+Perinatal+Epidemiology+and+Statistics+Unit) | 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)

- **Therapeutic Goods Authority** TGA (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)

- **NSW Poisons Information Centre** Poisons Information Centre (http://www.chw.edu.au/poisons)

- **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 | Symbols

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