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.

2014 Print Version PDF (10 pages, 670kb)

Similar content was covered in the previous online tutorials in 2014 [link to tutorial], 2012 [link to tutorial], 2014 PDF, 2012 PDF, 2011 PDF and 2010.

What's in the News?

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.

Textbooks


**Neonatal Diagnosis**: APGAR test | Guthrie test | Hearing test | Electrocardiogram (ECG/EKG) | X-ray | Tandem mass spectrometry | Classification of Diseases

**Abnormality Links**: Introduction | Genetic | Environmental | Unknown | Teratogens | Cardiovascular | Coelomic Cavity | Endocrine | Gastrointestinal Tract | Genital | Head | Integumentary | Musculoskeletal | Limb | Neural | Neural Crest | Renal | Respiratory | Placenta | Sensory | Twinning | Developmental Origins of Health and Disease | ICD-10


Links: NLM ID: 101293798 [link to NLM page] | publisher page [link to publisher page] | LUMH [link to LUMH page]

- Chapter 20 – Human Birth Defects
- Appendix: Discussion of Clinically Oriented Problems

**The Developing Human: Clinically Oriented Embryology**
This recent data summarised below from Australia's mothers and babies 2011[1], 2009[2], 2008[3] and 2007[4]. 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.

- **2012** - 312,153 live births and 2,255 fetal deaths
- **2011** - 301,810 live births and 2,220 fetal deaths
- **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

### Mothers

### Babies

### 2013 National core maternity indicators

#### 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).

#### Teen Pregnancy


#### Assisted Reproduction Technology

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

Assisted Reproductive Technology in Australia and New Zealand (2013)[9]

- 71,516 ART treatment cycles reported from Australian and New Zealand clinics in 2013 (66,143 and 5,373 respectively).
- 1.9% increase in Australia and 3.8% increase in New Zealand on 2012.
- 13.7 cycles per 1,000 women of reproductive age (15–44 years) in Australia
- compared with 5.9 cycles per 1,000 women of reproductive age in New Zealand.
- 95.1% autologous cycles (women's own oocytes or embryos)
- 36.6% autologous cycles embryos frozen and thawed.
- 37,192 women who undertook 67,980 autologous fresh and/or thaw cycles in Australia and New Zealand
- 1.8 average fresh and/or thaw cycles per woman were undertaken
- more cycles per woman in Australia (1.9 cycles per woman) than in New Zealand (1.5 cycles per woman).
- Preimplantation Genetic Diagnosis (PGD) was performed in 2,740 cycles (19.4% increase), 4.4% of cycles in which embryos were created or thawed.
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, gastrointestinal tract, mesentery, 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

This is also the most common cause of pregnancy-related deaths in the first trimester. A United Kingdom enquiry into maternal deaths[11], identified ectopic pregnancy as the fourth most common cause of maternal death (73% of early pregnancy deaths).

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

Twinning

- Twin deliveries and place of birth in NSW 2001-2005[12] “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 spermatozooa (sperm). Dizygotic twinning can be increased by Assisted Reproductive Technologies (ART) that use double embryo transfer techniques.

Monozygotic Twinning

Monozygotic twins (identical) produced from a single fertilization event (one fertilised egg and a single spermatozooa, 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.

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<td>Ovulation fertilization</td>
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<td>Morula</td>
<td>Early blastocyst</td>
<td>Hatching</td>
<td>Implantation starts</td>
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<td>Monozygotic Twin Type</td>
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<td>Diamniotic Monochorionic</td>
<td>Monoamniotic Monochorionic</td>
<td>Conjoined</td>
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</table>

Table based upon recent Twinning Review.[13]

Links: Assisted Reproductive Technology  Self-Directed Learning 3
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).

Abnormality Links[Expand]

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.

Prenatal Diagnosis Links[Expand]

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[Expand]

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).

ICD Links: XVII Congenital Malformations | XVI Perinatal Period | Chapter XV Pregnancy Childbirth | Abnormal Development | Reports

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.
- Congenital anomalies are coded using the British Paediatric Association Classification of Diseases (ICD-9-BPA), based on the International Classification of Diseases, 9th Revision (ICD-9).

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

Congenital Anomalies in Australia 2002-2003[Expand]


NSW Data

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, 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 notified 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, normal palm 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 asphyxiating.
Mothers and Babies Report 2010

- preterm birth (less than 37 weeks gestation) was 7.4%.
- rate of low birth weight (less than 2,500 grams) was 6.1%
  - in Aboriginal or Torres Strait Islander babies was 11.2%.
- About 2% of infants are born with congenital conditions each year in NSW.
- In 2004–2010, anomalies of the cardiovascular system were most commonly reported, followed by anomalies of the musculoskeletal system and the genito-urinary system.
- Congenital conditions were more common among premature infants compared to full term infants, and among male infants compared to female infants.
- Rate of congenital conditions increases with increasing maternal age, especially after age 35.
  - However, as most babies are born to mothers aged less than 35 years, the majority of babies with congenital conditions were born to younger mothers.
- Neonatal death was extreme prematurity (41.3%), followed by congenital abnormalities (21.5%).


[Expand] Victoria - 10 most reported birth anomalies

USA Statistics

[Expand] European Statistics

Genetic

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

- **Fetotoxican** 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 independently 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 dietary 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 | Celiac Cavity | Endocrine | Gastrointestinal Tract | Genital | Head | Integumentary | Musculoskeletal | Limb | Neural | Neural Crest | Renal | Respiratory | Placenta | Sensory | Twinning | Developmental Origins of Health and Disease | ICD-10

- **Environmental Links**: Introduction | Low Folic Acid | Iodine Deficiency | Nutrition | Drugs | Australian Drug Categories | USA Drug Categories | Thalidomide | Herbal Drugs | Illegal Drugs | Smoking | Fetal Alcohol Syndrome | TORCH Infections | Viral Infection | Bacterial Infection | Zoonotic Infection | Toxoplasmosis | Malaria | Maternal Diabetes | Maternal Hyperthermia | Maternal Inflammation | Maternal Obesity | Hypoxia | Biological Toxins | Chemicals | Heavy Metals | Radiation | Prenatal Diagnosis | Neonatal Diagnosis | International Classification of Diseases | Fetal Origins Hypothesis

- **Genetic Links**: Introduction | Genetic risk maternal age | Trisomy 21 | Trisomy 18 | Trisomy 13 | Trisomy X | Monosomy | Fragile X | Williams | Alagille | Philadelphia chromosome | Hydatidiform Mole | Prenatal Diagnosis | Neonatal Diagnosis | International Classification of Diseases | 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.

<table>
<thead>
<tr>
<th>Conceptus</th>
<th>Embryonic development (weeks)</th>
<th>Fetal period (weeks)</th>
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<td>20-36</td>
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<td>38</td>
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</tbody>
</table>
Human critical periods of development

Drug clearance rates

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)

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<th>Clearance of Drug (percentage of adults)</th>
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<td>&gt; 68</td>
<td>100%</td>
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Self-Directed Learning 7

References

1. What are the current trends in Australia?
2. What factors may be contributing to these changes?
3. Are there any long-term trends in birth statistics?
4. 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 pregnancy, 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.

- Neonatal Networks
  - Canada Canadian Neonatal Network (http://www.canadianneonatalnetwork.org/portal)
  - USA and Other International Vermont Oxford Network (http://www.vtoxford.org/)
- NSW Poisons Information Centre Poisons Information Centre (http://www.chw.edu.au/poisons)

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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This page was last modified on 13 October 2015, at 13:40.
This page has been accessed 40,074 times.