

Tutorial – Applied Embryology and Teratogenicity

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Introduction

This Phase 2 Medical tutorial introduces the topics of Applied Embryology and Teratology. The one and a half hour presentation has to cover many topics in normal embryo, placenta and fetus development as well as factors leading to abnormal development. Subsequently, only a brief coverage can be given of any one topic. You should come back and look later at the online resources for more detailed descriptions. Some of the concepts of embryonic and fetal development have been covered in your earlier BGD lectures and laboratories (available online).

- What normally occurs in development at specific times?
- How can this be affected by genetic and environmental factors?
- What are the critical periods of development?

Applied Embryology: blastocyst formation, molecular development, trophoblastic disease, embryonic development, placenta, fetal development, folic acid, multiple pregnancies.

Teratology: medications, chromosomal abnormalities, environmental factors, infection.

Online Reading:

UNSW Embryology

<http://embryology.med.unsw.edu.au/>

BGD Tutorial

<http://embryology.med.unsw.edu.au/Medicine/BGD2tutorial.htm>

Embryo Stages

<http://embryology.med.unsw.edu.au/wwwhuman/Stages/Stages.htm>

Abnormal Development

<http://embryology.med.unsw.edu.au/Defect/page1.htm>

Food and Drug Administration (USA)

Evaluating the Risks of Drug Exposure in Human Pregnancies

<http://www.fda.gov/cber/gdlns/rvrpreg.htm>

Office of Children's Health Protection (USA)

Critical Periods in Development

OCHP Paper Series on Children's Health and the Environment (2003)

http://www.kpbb.org/makalah_ing/Critical%20Periods%20in%20Development.pdf

International Society for the Study of Trophoblastic Diseases

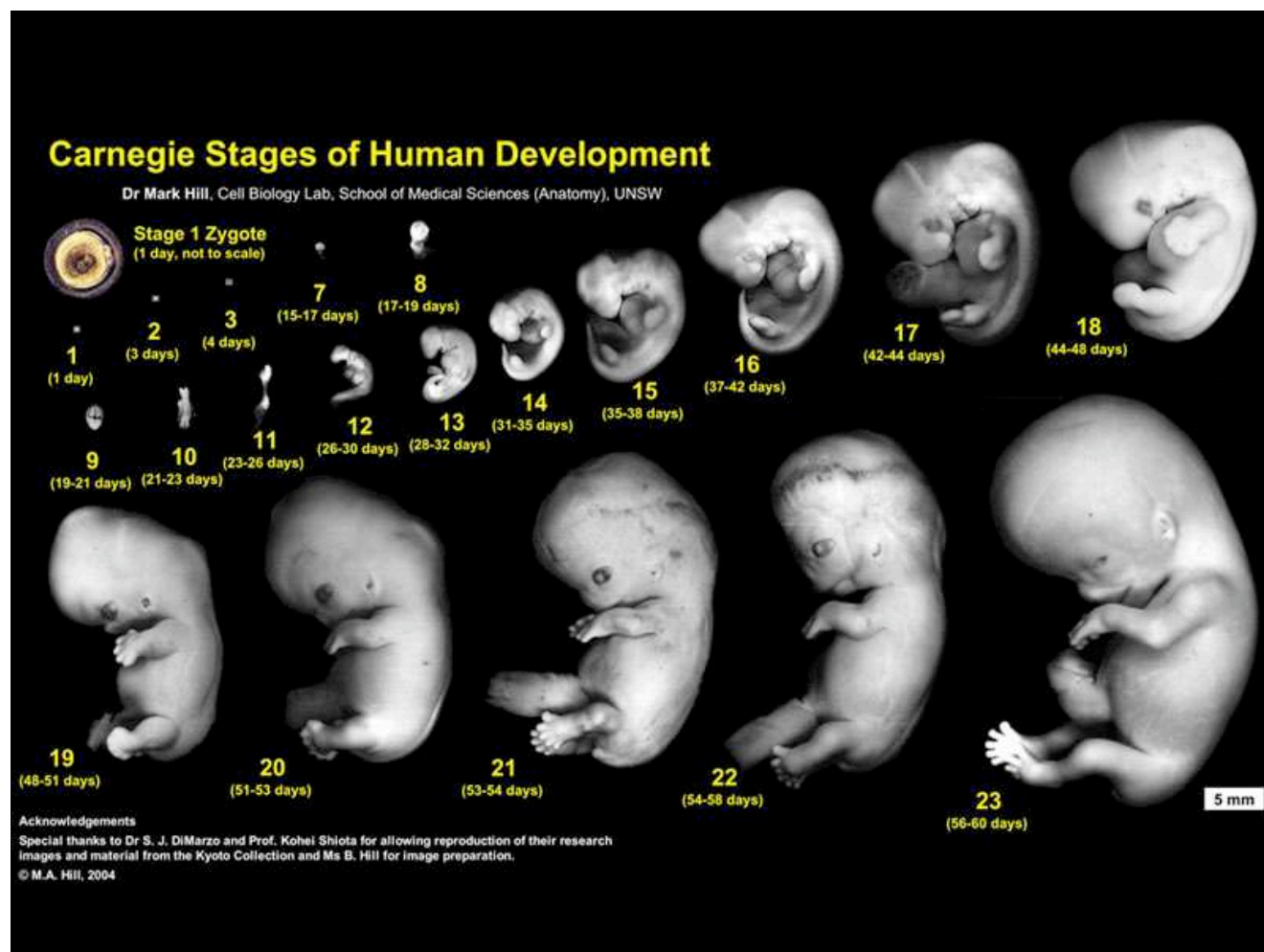
<http://www.isstd.org/intro/index.html>

Congenital malformations, Australia (1997) Hurst T, Shafir E, Lancaster P, & Day P. ISSN 1321 8352; 97pp. <http://www.npsu.unsw.edu.au/cm97.pdf>

Key Textbook Readings:

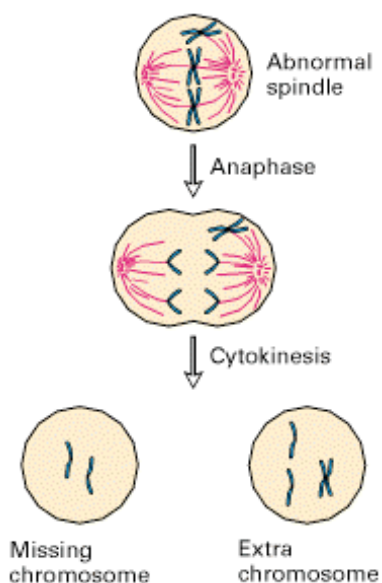
1. Human Embryology, WJ. Larsen
2. The Developing Human: Clinically Oriented Embryology. Moore & Persaud

Embryonic Development



Chromosomal Abnormalities (aneuploidy)

Aneuploidy is a major category of chromosome abnormalities, in which the number is abnormal with the main cause nondisjunction.



Nondisjunction occurs when chromosomes segregate in anaphase before the kinetochore of each sister chromatid has attached to microtubules (red lines) from the opposite spindle poles. As a result, one daughter cell contains two copies of one chromosome, while the other daughter cell lacks that chromosome.

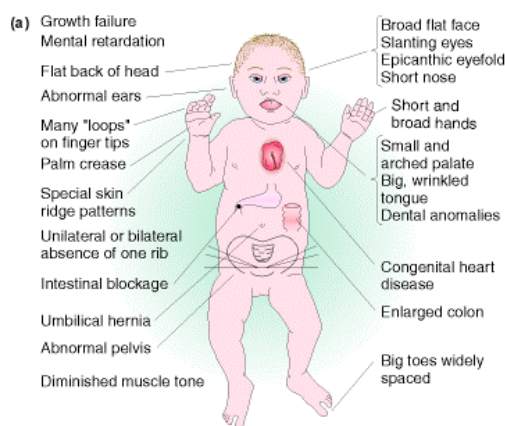
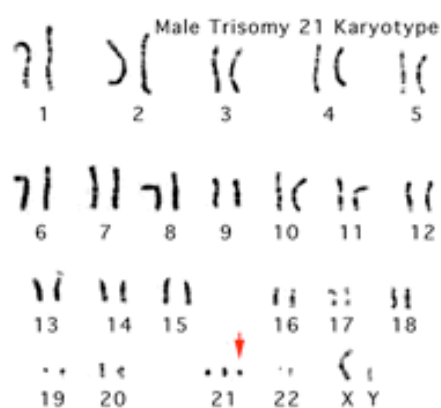
(From: Molecular Cell Biology 4th ed. Lodish, Harvey; Berk, Arnold; Zipursky, S. Lawrence; Matsudaira, Paul; Baltimore, David; Darnell, James E. New York: [W.H. Freeman & Co](#); c1999)

Turner syndrome- a sex-chromosome monosomic complement of 44 autosomes + 1 X produces sterile females, short in stature, web of skin between neck and shoulders. (Aust 1991-97 217 infants)

Klinefelter syndrome - viable trisomics XXY (1 in 1000 male births) males with lanky builds who are mentally retarded and sterile.

Down syndrome - trisomy 21, caused by nondisjunction of chromosome 21 in a parent who is chromosomally normal. Older mothers have elevated risk of having Down syndrome children: mental retardation, (IQ 20 to 50) broad, flat face; eyes with an epicanthic fold; short stature; short hands with a crease across the middle; and a large, wrinkled tongue. Females may be fertile (may produce normal or trisomic progeny). Males have never reproduced. Mean life expectancy is about 17 years, and only 8 percent survive past age 40. (Aust 1991-97 2,358 infants)

(More? <http://embryology.med.unsw.edu.au/Defect/page21.htm>)



Gestational Trophoblastic Disease (Hydatidiform Mole)

Complete mole - chromosomal genetic material from the ovum (egg) is lost, by an unknown process. Fertilization then occurs with one or two sperm and an androgenic (from the male only) conceptus (fertilized egg) is formed. With this conceptus the embryo (fetus, baby) does not develop at all but the placenta does grow but it is abnormal and forms lots of cysts and has no blood vessels. These cysts look like a cluster of grapes and that is why it is called a hydatidiform mole (grape like). A hydatidiform mole miscarries by about 16 to 18 weeks gestational age. Since the diagnosis can be made by ultrasound before that time, it is better for you to have an evacuation of the uterus (D & C) so that there is no undue bleeding and no infection. Human chorionic gonadotropin (hCG) will assist in making the diagnosis.

Partial mole - three sets of chromosomes instead of the usual two and this is called triploidy. The chromosomal (genetic) material from the ovum (egg) is retained and the egg is fertilized by one or two sperm. Since with partial mole there are maternal chromosomes there is a fetus but because of the three sets of chromosomes this fetus is always grossly abnormal and will not survive.

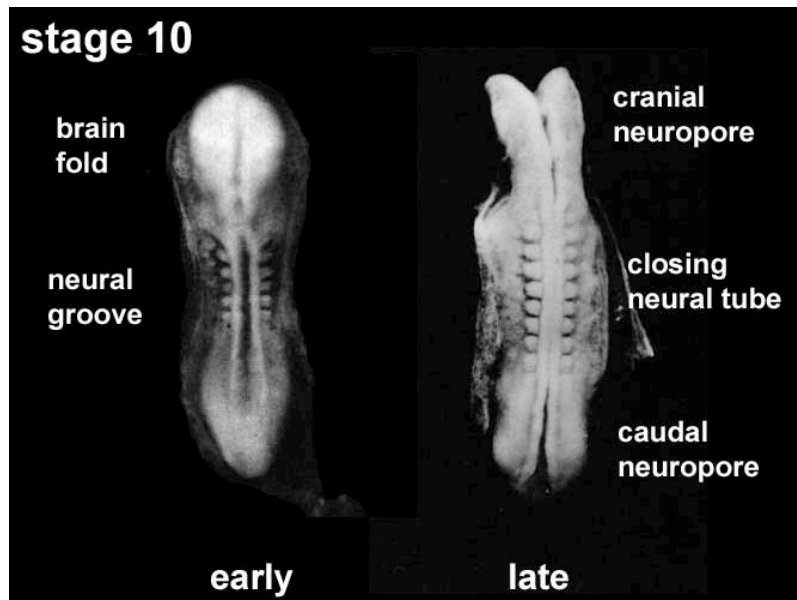
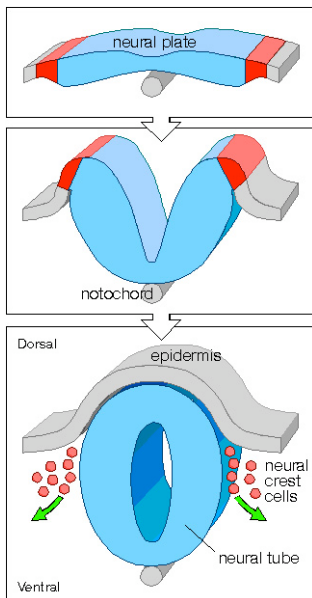
(Text modified from: International Society for the Study of Trophoblastic Diseases)



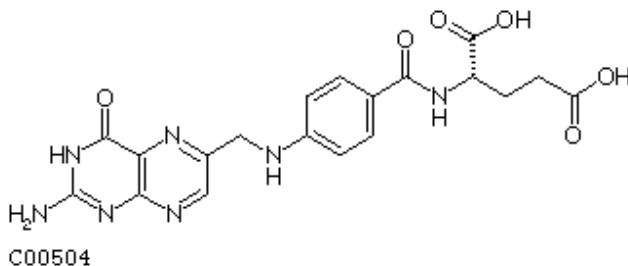
Tumour has a "grape-like" placental appearance without enclosed embryo formation. Like any tumour, unless removed there is a risk of progression.

- Stage I: Tumor confined to uterus (non-metastatic)
- Stage II: Tumor involving pelvic organs and/or vagina
- Stage III: Tumor involving lungs, with or without involving pelvic structures and/or vagina
- Stage IV: Tumor involving distant organs

Folic Acid and Neural Tube Defects



In 2001, the Australian estimated birth prevalence of neural tube defects was 0.5 per 1,000 births (National Perinatal Statistics Unit). Research over the last 20 years has suggested a relationship between maternal diet and the birth of an affected infant, and recent evidence has confirmed that folic acid, a water soluble vitamin, found in many fruits (particularly oranges, berries and bananas), leafy green vegetables, cereals and legumes, may prevent the majority of neural tube defects.



Folate Facts

Approximately one in 500 babies in Australia is born with a neural tube defect (NTD) such as spina bifida. Spina bifida is one of the most common birth defects in the Western world. About 150 babies are born with spina bifida in Australia each year.

Approximately 95 per cent of all NTDs occur with no prior warning or indication that the woman was at risk of having an NTD affected pregnancy.

NTDs, such as spina bifida, occur in the first weeks of pregnancy when the brain and spinal cord are forming.

Spina bifida means "split or divided spine". It is one of the most serious birth defects. The spinal column doesn't close properly and the baby is born with exposed nerves and damaged vertebrae. The effects are permanent. Children with spina bifida can face paralysis, problems with mobility, muscle control, co-ordination and learning.

Seven out of 10 cases (70%) of NTDs such as spina bifida can be prevented by women increasing their intake of folate to 0.5mg/day at least one month before conception and for the first three months of pregnancy.

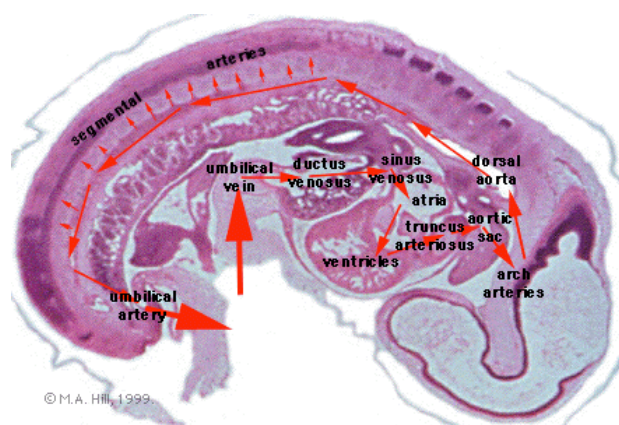
Folate is the natural form of this B group vitamin (tablet form is called folic acid).

Three ways of increasing folate intake: by eating folate rich foods; by including folate fortified foods in the daily diet or by taking a folic acid supplement.

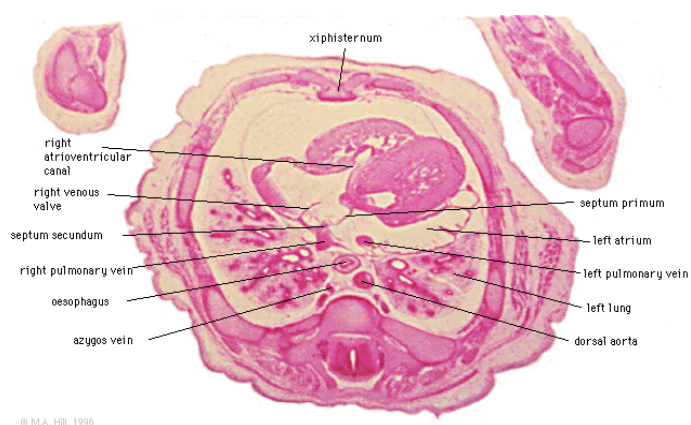
Good sources of folate include green leafy vegetables, fruit (citrus, berries and bananas), legumes and some cereals (more than 20 breakfast cereals now have added folate). The voluntary fortification of several foods with folate has been permitted in Australia since June 1995. Multivitamin supplements contain only very small amounts of folic acid.

(From: NHMRC - Folate Facts, Information sheet on supplementation of folate (folic acid) for women to prevent neural tube defects, such as spina bifida, in babies)

Heart Development



Stage 13/14



Stage 22

The heart forms in mesenchyme (splanchnic) of precordial plate region = cardiogenic region. Growth and folding of the embryo, moves heart ventrally and downward into the anatomical position. By week 3 begins as paired heart tubes, fuse to form single heart tube and then begins to beat (Humans day 22-23). Heart tube connects to blood vessels forming in splanchnic mesoderm and extraembryonic mesoderm.

Timecourse

Week 2 pair of thin-walled tubes

Week 3 tubes fused, truncus arteriosus outflow, heart contracting

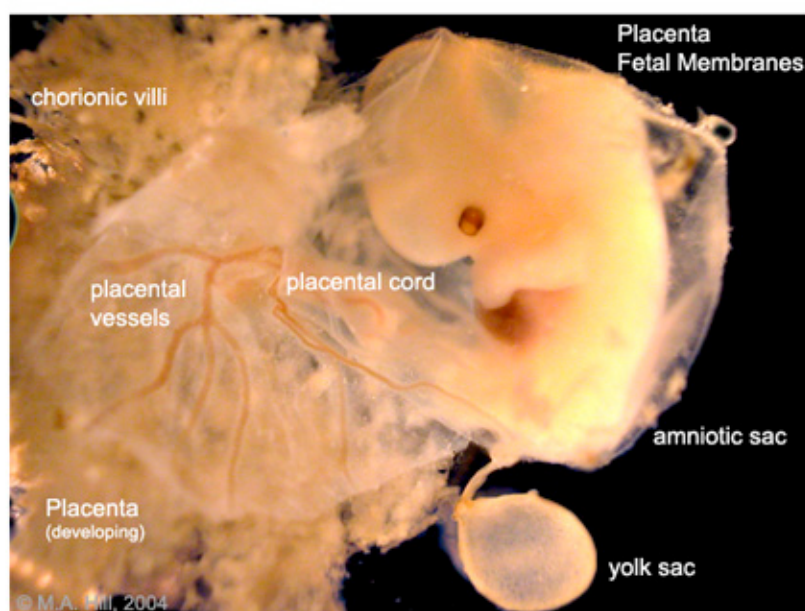
Week 4 heart tube continues to elongate, curving to form S shape

Week 5 Septation starts, atrial and ventricular

Septation continues, atrial septa remains open, foramen ovale

Week 40 Birth pressure difference closes foramen ovale (fossa ovalis)

Placenta



(More? <http://embryology.med.unsw.edu.au/Notes/placenta.htm>)

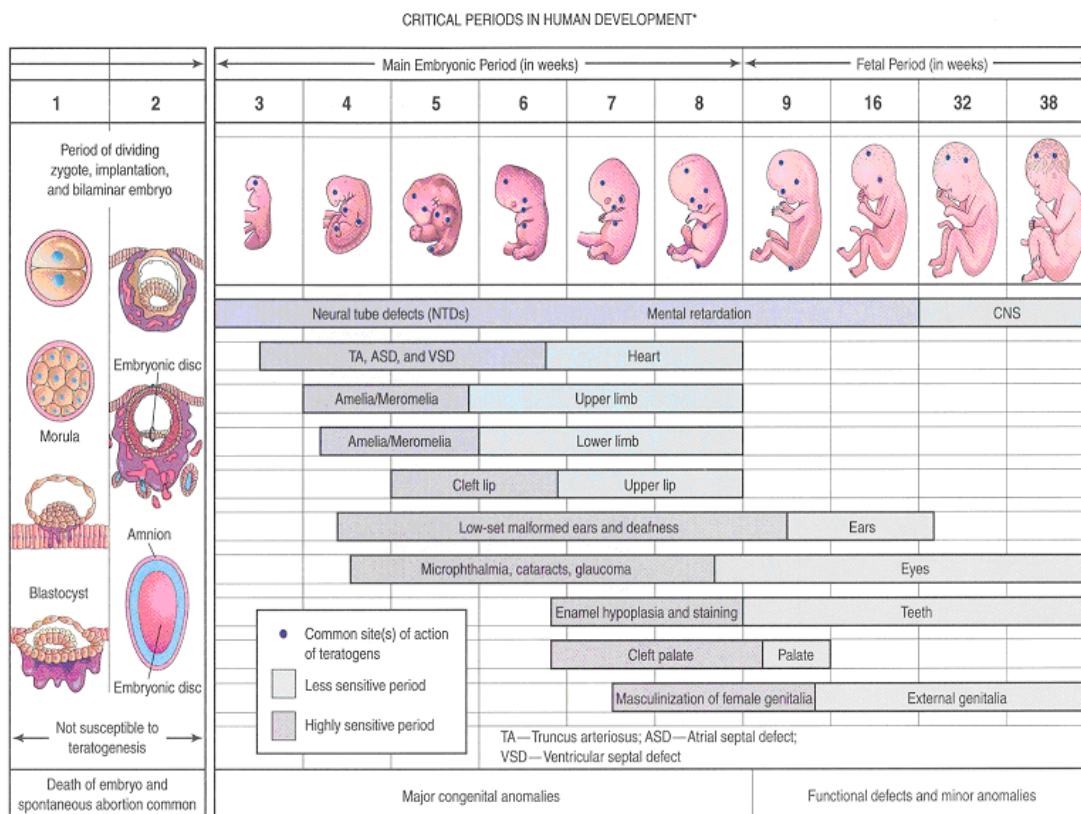
The placenta (Gk. plakuos= flat cake) is a materno-fetal organ which begins developing at implantation of the blastocyst and is delivered with the fetus at birth.

Placental Metabolism: synthesizes glycogen, cholesterol, fatty acids, provides nutrient and energy.

Placental Transport: oxygen, carbon dioxide, carbon monoxide water, glucose, vitamins, hormones, mainly steroid not protein, electrolytes, maternal antibodies, waste products, urea, uric acid, bilirubin, drugs and their metabolites (fetal drug addiction), infectious agents (cytomegalovirus, rubella, measles, microorganisms).

Placental Endocrine: Human chorionic gonadotrophin (hCG, like leutenizing hormone, supports corpus luteum), Human chorionic somatomotropin (hCS, or placental lactogen, stimulate mammary development), Human chorionic thyrotropin (hCT), Human chorionic corticotropin (hCACTH), progesterone and estrogens (support maternal endometrium), relaxin.

Critical Periods of Human Development



(From: The Developing Human: Clinically Oriented Embryology (Moore, KL and TVN Persaud, 1998, sixth edition, Philadelphia: W.B. Saunders Company, p. 548, diagram should be printed in colour)

Genetic Abnormalities

Embryos with major genetic abnormalities, that impact on developmental processes, in general fail to develop and are spontaneously aborted. In other embryos, there are several known genetic abnormalities (on the basis of maternal age or family history) that can now be screened for with prenatal testing. Many genetic developmental abnormalities involve only small DNA mutations affecting individual or a few genes, exceptions to this are those that involve abnormal segregation of chromosomes giving an abnormal chromosome complement to the developing embryo. The most common trisomy (the number indicates the affected chromosome) is Down syndrome (or trisomy 21) and then Edwards syndrome (trisomy 18, there is also less commonly trisomy 9, 13, 15). Note that the occurrence of chromosomal abnormalities also increases with increasing maternal age.

There are many pamphlets providing information about prenatal diagnosis (see NSW State Health Publication Checking your baby's health before birth).

Maternal Derived Abnormalities

Relate to lifestyle, environment and nutrition. Some examples of this form of abnormality are the impact of excess alcohol on neural development (fetal alcohol syndrome), viral infection (rubella) at a critical stage of development, inadequate dietary folate intake (neural tube defects), effects of non-prescription drugs (smoking), effects of prescription drugs (drugs, thalidomide limb development), infection (viral infection, Rubella), environment (smoking, chemical, heavy metals) and even maternal endocrine function (thyroid development).

In addition to these obvious maternally-derived abnormalities, there is growing evidence that the interuterine environment has a strong influence on later postnatal health and neurological development.

(More? <http://embryology.med.unsw.edu.au/Defect/maternal.htm>)

Intrauterine Growth Retardation (IUGR) is often related to very low birth weight (VLBW defined as < 1500 grams). It is thought that in addition to genetic effects that programming by the uterine nutritional, oxygenation and endocrine factors may have a role in low birth weight and future health problems.

Fetal Origins Hypothesis

This theory is based on the early statistical analysis of disease/longevity in babies with low birth weights in England by Barker, and was initially called the "Barker Hypothesis" and now called the Fetal Origins Hypothesis.

(More? <http://embryology.med.unsw.edu.au/Defect/page10.htm>)

The Australian NHMRC Recommendations

Recommendations for neonates to be assessed for follow-up care under the following conditions (1988).

(Please note that current guidelines may differ from those listed below)

- Birthweight less than 1500g or gestational age less than 32 weeks
- Small-for-gestational-age neonates
- Perinatal asphyxia
- Apgar score less than 3 at 5 minutes
- clinical evidence of neurological dysfunction
- Delay in onset of spontaneous respiration for more than 5 minutes and requiring mechanical ventilation
- Clinical evidence of central nervous system abnormalities ie., seizures, hypotonia
- Hyperbilirubinaemia of greater than 350umol/l in full term neonates
- Genetic, dysmorphic or metabolic disorders or a family history of serious genetic disorder
- Perinatal or serious neonatal infection including children of mothers who are HIV positive
- Psychosocial problems eg. infants of drug-addicted or alcoholic mothers.