Pregnancy

Pregnancy:

- Pregnancy in humans lasts about 266 days in humans
    - Only two thirds of humans make it to term
- The time of pregnancy is taken from the last menstrual period
- There are three trimesters
    - The first trimester lasts for the first 12 weeks, this is the period of embryogenesis
        - It is in this time where teratogens can most easily cause malformations
    - The second trimester is from 12 to 24 weeks, there is a huge rapid relative growth of the foetus
    - Growth continues in the third trimester this is where maturation of foetal organs occur
- The first trimester is the embryological period, where the second and third are the foetal periods
- Only 50% of conceptions make it past 20weeks
    - Of the 50% of failed conceptions, 70% are lost as a consequence of early failures

Results of Fertilisation:

- DNA replication in both pronuclei
- Pronuclei fuse to restore diploid number of chromosomes
- After this fusion a zygote is formed and sex is determined
- Cleavage now initiates
    - The first cleavage occurs at 30hours to form two cells
    - The second of 40 hours to form four cells by the 12 to 6 cell stage roughly three days have passed
- When there is a compact ball of cells it is known as a morula
- The cells become polarised which allows them to differentiate to have a certain function

Cleavage:

- The morulla enters the uterus at ~day 4
- The fluid filled space begin to coalesce and form a blastocoele
    - Differentiation of the blastomeres forms the inner cell mass and the surrounding trophoblast

Implantation:

- In some women embryos are unable to hatch
- There is a very narrow window for when implantation can occur
    - Typically it can occur between day 20 and 23 of a 28 day cycle

- The epithelial surface properties of the endometrium must change; there is the appearance of pinopodes which absorb uterine fluid to reduce the volume of the uterine cavity
- There are also changes in the surface charge of the endometrium and loss of glycocalyx
    - Glycocalyx stops inter-cellular communication which helps in implantation
- The appearance of pinopods, change in the surface charge and loss of glycocalyx facilitates apposition of the trophoblast and endometrium
- The endometrium must be primed for implantation by progesterone
    - There is a peak of progesterone and then oestrogen in the luteal phase and then the endometrium will be primed for implantation
- Progesterone dominance causes the endometrium to become secretory and begins decidualsation
- Oestrogen stimulates the growth of the endometrium as well as cytokine release
    - Without cytokine release from the endometrium implantation cannot occur
    - There must be communication between the endometrium and blastocyst
- Normally in the uterus there is an abundance of factors which send inhibitory messages/factors to foreign substances
    - Muc-1 is a glycoprotein complex within glycocalyx on the surface of the epithelial cells
- Stimulatory factors must be turned on
    - Leukaemia inhibitory factor LIF and interleukin-II are both critical cytokines produced by endometrial gland cells and are both critical for implantation
        - They are in the uterine fluid
        - They stimulate the receptivity of the endometrium to the blastocyst
- In women who cannot have embryos implant, uterine flushes often reveal the absence of LIF or IL-II
- Human implantation is very invasive
    - The blastocyst burrows into and becomes covered by the endometrium
    - The trophoblast becomes multinucleated and becomes the syncytiotrophoblast
        - This is crucial for implantation; the syncytiotrophoblast begins to release enzymes which breaks down endometrial cells and maternal blood vessels

Placental Development:

- The placenta is the site of nutrient, gas and waste exchange between mother and foetus
    - It brings maternal and foetal tissues to close proximity, but the two circulations never mix in normal circumstances
- There are two portions to the placenta
    - The foetal portion; villous chorion, and the maternal portion decidua basalis
- Chorionic villi form around the entire blastocyst but will eventually regress on one side and become more complex on the other
    - It is the complex side which will form a definitive placenta
- Humans have a chorioallantoic plancenta
    - Chorio = the trophoblast and extra-embryonic mesoderm
- At the level of the chorion there are invaginations where the foetal blood supplies will go

    - Blood vessels in the allantois proliferate and move into the chorionic villi; which is the begin of the embryonic circulatory system

Decidualisation and the Decidua:

- Differentiation of the endometrium is the decidualsation of stromal cells
    - This controls the extent of the trophoblastic invasion
    - Decidualisation should be as optimal as possible; progesterone is needed for the process
    - Increased in vascular permeability and angiogenesis occurs in decidualisation
- There is also the recruitment of uterine natural killer cells UNK cells
- Once decidualisation occurs the maternal placenta becomes known as the decidua which has three distinct layers
    - The decidua basalis, the decida capsularis and decdiua parietalis are the three layers
    - The mature functioning placenta is composed of villous chorion and decidua basalis
        - Villous chorion is the foetal side whilst the decidua basalis is the maternal side

Functions of the Placenta:

- Immune functions; manage the maternal response to the foetus
    - When this process goes wrong it results in spontaneous abortion
- Exchange; waste and nutrient exchange between the foetus and mother
- Endocrine properties signals to the mother to allow her to adapt to the pregnancy; physiological adaptations which are important for foetal growth and development

Placental Development:

- The placenta structure is in place early on (3 to 4 weeks) but it does not receive maternal blood until 10 to 12 weeks (toward the end of the first trimester)
    - For the first third of pregnancy the placenta is non-functional; the embryo develops in a reduced oxygen environment
- Oxygen can be dangerous to a developing embryo; to its organogenesis due to the creation of reactive oxygen species ROS
    - Oxygen is required for metabolism but as a bi-product of this ROS are created
    - ROS can be removed via the action of antioxidants, however the accumulation of ROS will cause damage to DNA, proteins and lipids
        - The removal of ROS in inefficient at this stage of development so it is thought that the low oxygen environment is an adaptive feature to protect the developing embryo
        - Blood flow is limited to the placenta by the extra-villous trophoblast plugs/cells
- The extra-villous trophoblast plugs plug the spiral (maternal arteries)
    - The spiral formation also limits blood flow

- At the 10th week the spiral arteries straighten and the extra-villous trophoblast plugs disperse allowing blood flow into the inter-villous space so that the maternal and foetal circulations are in direct apposition
- In an optimal placenta it is desirable to have a slow flow of blood on the maternal side to allow for better exchange
- Histiotrophic nutrition
    - First 10weeks, low oxygen concentration, embryogenesis, nutrients from cells
- Haemotrophic nutrition
    - 10 to 38 weeks, increased efficiency of O_2 transmission and CO_2 removal, rapid growth of the foetus as well as maturation

The Placenta:

- The human placenta is the only organ with a definite lifespan before becoming redundant
- The human placenta is discoid shaped
- It is chorioallantoic
- It is haemochorial; there is a cellular barrier between the two circulations

Placental Transport:

- Simple diffusion of O_2, CO_2 and cortisol
- Facilitated diffusion of glucose
- Active transport of amino acids and calcium
- Receptor mediated endocytosis; immunoglobulins and leptin
- Simple diffusion of oxygen and carbon dioxide across the placental barrier is easy; there are more villi later in pregnancy which increases surface area drastically allowing better simple diffusion
    - The distance of diffusion also shortens later in pregnancy
- Facilitated diffusion of glucose is dependent of the presence and availability of transport molecules
    - GLUTs are glucose transporters
    - As maternal blood glucose goes up so goes up so does foetal glucose to a point but at a certain point the transporters becomes saturated and foetal glucose tapers off

Placental Endocrine Function:

- Major placental endocrine signals
    - hCG; human chorionic gonadotropin is only present during pregnancy
    - Progesterone, oestrogon, hCS and corticotrophic releasing hormone CRH
- If implantation occurs hCG will maintain the corpus luteum which secretes progesterone
    - The corpus luteum will continue to secrete progesterone until the plancta is mature
        - Oestrogen levels are also maintained
- There is a correspondence between the progression of pregnancy and the secretion of oestrogen and progesterone
- The placenta secretes progesterone but it does not express 17alpha-hydroxylase

    - The foetal adrenal has a specialised zone which produces large amounts of androgen which can be aromatised by the placenta to create oestrogen; at birth the foetal zone of the adrenal will regress

Maternal Constraint:

- Maternal constraint shown by embryo transfer
    - When a normal embryo is transferred into a dwarf pig, the result is a relatively smaller foetus (had it progressed in the normal mother)
    - Alternatively if a dwarf embryo is transferred into a normal mother it will be relatively larger
- Foetal growth is limited by maternal constraint
    - The placenta's size is limited by the mother's uterus
- Genetic potential is constraint
    - The maternal strategy is to constrain foetal growth so that she can survive and better conserve her resources to spread among her offspring
- Maternal constraint is controlled by
    - The size of the uterus and abdomen
    - Placental weight and blood flow
    - The unequal influence of paternal and maternal genomes

The Haig Hypothesis:

- Maternal strategy is to constrain foetal growth so that she can survive and better spread her resources among offspring
- The paternal strategy is to maximise in utero growth of his offspring at the expense of the mother
    - The offspring can then out compete other offspring sired by different males to maximise his reproductive success
- IGF2 is a growth factor which acts in a similar way to insulin
    - IGF2 is abundantly expressed in the placenta; without IGF2, foetal growth and placental development is severely inhibited
        - Increase IGF2 results in a larger placenta which allows for better transfer of material across it which ultimately results in better foetal development/growth
- It is in the interest of the mother to not express IGF2 and the father to express it
    - So due to epigenetics the maternal allele is silenced and the paternal allele expressed
    - This process is mediated by genomic imprinting; DNA changes during gametogenesis affects gene expression

Hormone Control of Foetal Growth:

- Maternal hormones include:
    - Thyroxine; stimulatory particularly in neural tissue
    - Glucocorticoids have an inhibitory action on foetal growth, the foetus is protected from this with the placental-foetal glucocorticoid barrier (goes into detail later)
- Placental hormones
    - Placental peptide include IGF2 and hCS
        - The foetus also produces IGF2 which goes to the placenta to promote foetal growth via better nutrient and waste exchange
    - Oestrogen and prosteron have unclear effects
- Foetal hormones include IGF1 and its associated binding proteins, insulin; which is highly stimulatory, thyroxine which also has a stimulatory effect and growth hormone which actually is relatively unimportant

Inadequate Foetal Growth:

- Small for gestational age
    - Even if some babies are born small, they may be born at the appropriate size for gestational age
    - However some babies will experience intrauterine growth retardation/restriction resulting in SGA
- Low birth weights are defined as being less than 2500g and very low birth weights are defined as being less than 1500g
- Generally speaking a baby less than the 10^{th} percentile will be SGA
- Within SGA there are subcategories
    - Symmetrical SGAs account for roughly 60% of all SGA births
        - This can be a result of ethnicity, maternal size, toxins, poor nutrition and infections
    - Asymmetrical SGAs account for the other 40%
        - Brain development may occur normally whilst the body doesn't grow properly, such cases are observed in conditions such as preeclampsia

Consequences of Inadequate Foetal Growth:

- Increased perinatal morbidity and mortality
    - Health issues resulting from it
- Increased incidence of disease in adult life which ties to the Barker hypothesis
    - The Barker hypothesis suggests that the foetus is programmed in utero such that if it experiences foetal growth restrictions, it will signal that it will be born into adverse environmental conditions
        - This results in the baby being born with a predisposition for cardiovascular disease, diabetes and hypertension in adult life, all as a result of inadequate foetal growth

Causes for Inadequate Foetal Growth:

- Poor nutrition; maternal over and under nutrition can both reduce foetal growth
- Disease pathologies
- Maternal smoking and alcohol consumption
- Stress; psychological stress and physiological stress

Maternal under nutrition:

- Maternal under nutrition effects depend on the timing of pregnancy
    - The effect will only be seen if under nutrition is severe
- Under nutrition in the third trimester will result in IUGR, whereas if it is isolated in to the first trimester the effects will be less detrimental
    - If it is isolated to the first trimester, the baby will be born with a normal birth weight, but it may still be predisposed to adult diseases

Organ Maturation:

- The organs: lungs, liver, gut and kidneys mature rapidly near term to adapt to life ex utero
- Preterm babies can have severe consequences particularly respiratory distress syndrome
- Glucocorticoids is a key signal for the maturation of organs; it signals a change from the proliferation/growth of organs to their maturation
    - Glucocorticoid can be administered in babies who have the risk of preterm birth to help their organs mature, however excess glucocorticoid may cause IUGR
    - Excess amount of glucocorticoid are prevented from entering the placenta by the placental glucocorticoid barrier