Chapter 29
Development

Terminology

Pregnancy: All events that occur from fertilization through parturition.
Gestation: Period of time during which development occurs
Conceptus: The organism (conceptus is 1 day old, when 2-weeks pregnant)

Gestation begins from last menstrual period (it's just easier to estimate, it's not entirely accurate), so therefore two weeks pregnant at the time of fertilization. Gestation ends at about 280 days (9 months). Note that conceptus age is always 2 weeks younger than gestational age!

The conceptus is called different things based on where it is in development:

- Pre-embryo: Weeks 1-2, basically fertilization through day 14
- Embryo: Weeks 3-8
- Fetus: Weeks 9-birth
- Infant: After birth

The Trimesters

- The first trimester is for embryological and fetal development. At this time, cellular differentiation produces different tissues, which become organs.
- The second trimester is for development of the fetal organs
- The third trimester is for rapid growth and energy storage. The organs become more functional, especially the heart.

Developmental stages of the 1st trimester

Fertilization (union of oocyte and sperm) usually takes place in the ampulla. Since the oocyte is viable for about 24 hours, intercourse should take place 2 days prior to 1 day after ovulation. Once fertilized, the oocyte gets to change its name…it's now an ovum!

The ovum supplies the zygot everything it needs…organelles, raw materials, genetic programming, chemical messengers…for the first week of development. After that the ovum is fully implanted and able to sponge of mom for the next 8 months and 3 weeks.

Sperm are viable for about 3-6 days, but are at their most viable 24-48 hours. Before a sperm can fertilize an egg, it must go through capacitation…this involves changes in the membrane of the head and increased motility. The first step of capacitation is mediated by chemicals in the vesicular fluid (from the seminal vesicles), and the second step is mediated by the chemical environment of the female reproductive tract.

Sperm undergo a rough journey!

- Millions immediately leak from the vagina
- Millions are destroyed by low pH of the vagina
- Millions don't make it through the cervical canal
- Thousands in the uterus are destroyed by phagocytes

- About half choose the wrong tube (idiot sperm!)
- About 100 make it to the egg
- Dozens are required for penetration

Sperm penetration
The sperm must penetrate the corona radiata and the zona pellucida, then bind to receptors on the oocyte membrane. The first sperm to bind wins!!! This results in the fusion of the sperm and oocyte membranes.

To get through the corona radiata takes the acrosomal enzymes (hyaluronidase) of dozens of sperm. Once through the corona radiata, one sperm (who was smart and saved his acrosome) binds to sperm receptors on the zona pellucida. The reaction of the acromsome penetrates the zona pellucida via acrosin.

Next, the sperm head-membrane fuses with the oocyte membrane and the oocyte is activated! The membrane depolarizes, causing a release of intracellular Ca++, which causes:

- Rapid increase in metabolic rate and protein synthesis…gotta make a baby!
- Oocyte completes meiosis II, and there is a formation of a second polar body.
- The oocyte is now called an ovum
- Zona pellucida hardens, and sperm in the ZP get removed (prevents polyspermy)

At this time the sperm loses his tailpiece (men are always losing something!) and the nucleus swells…this is called the male pronucleus. At the same time, the female nucleus also swells…this is the female pronucleus.

Once the male and female pronuclei are joined by the mitotic spindle, then it is TRUE FERTILIZATION. This combining of chromosomes marks fertilization and we now have a new diploid zygote. This is immediately followed by DNA replication, then the first mitotic division…it now enters pre-embryonic development.

The pre-embryo undergoes mitosis while it is traveling to the endometrium…these are rapid divisions with no time for growth. This results in the formation of blastomere, then morula then blastocyst.

In 36 hours, two blastomeres
Day 3-4, 16-32 cells (morula—this is a solid
ball of cells that enters the uterine cavity)
Day 5-6, 100+, blastocyst (has a big cavity called a blasteocoele). Hatching is when the trophoblast (outer cells) degrade the hard zona pellucida…the blastocyst can now expand in size! The inner cell mass (ICM) will become the embryonic disc.

Cleavage = rapid cell divisions

Implantation
Implantation requires a receptive uterus. In order for the blastocyst to adhere, the stratum functionalis has to be "just right"…the right thickness, the right chemical signals, the right receptors. If not receptive, then the implantation will not occur or may implant lower down (risk for placenta previa.) Implantation starts about 7 days post ovulation, and takes about 3 days to complete and be entirely sealed off by uterine epithelium.

The first thing that happens is the TROPHOBLAST cells proliferate and develop into:

- Cytotrophoblast (which is just the new name for the outer layer now that it has implanted)
- Synctiotrophoblast (this is the outer layer that develops into a multinucleated cellular mass that digests and burrows into the endometrium by secreting digestive enzymes called hyaluronidase.

The digestion of the stratum functionalis creates pockets called LACUNAE. The lacunae fill with blood and now the ovum can get nutrients from the maternal blood! Up until now it was only able to get nutrients from the glycogen-rich secretions of the female duct system. So in summary, the blastocyst now gets nutrients from the following sources:

- Uterine gland secretions (glycogen-rich!)
- Digested endometrial cells and glands
- Highly permeable and digestible capillaries

The trophoblasts are also responsible for maintaining the endometrium…recall that we are now approaching the end of the typical ovarian/uterine cycle, so the functionalis would now normally be dying off...but because we're pregnant it has stuck around. Now the trophoblasts now are producing hCG and taking over for LH to maintain the corpus luteum (which normally keeps progesterone and estrogen levels high). This job of the trophoblasts lasts for another three months. After that time the placenta releases hormones to maintain the endometrium. hCG is in detectable amounts about 1 week post fertlization.

Trophoblasts do 2 things:

Develop into endometrium digesting cells

Produce hCG, which takes over for the LH in maintaing the CL (resulting in maintained levels of estrogen and progesterone)

Gastrulation
Gastrulation is the rearrangement of cells to form the 3-layered embryonic disc.

The three layers of the embryonic disc are the body's three primary germ layers. They are developed by day 12!

1. Ectoderm (develops from the superficial layer)
2. Endoderm (new layer!)
3. Mesoderm (develops from the deep layer)

Layers of embryonic disc = germ layers

Extraembryonic membranes
At the time of implantation, the ICM (inner cell mass) is separated from the trophoblast, forming an amniotic cavity. This mass becomes the embryonic disc.

Amnion is a transparent membraneous sac that is filled with amniotic fluid. The function of the amnion is to surround and protect the embryo. The inner layer surrounds every little nook and cranny to prevent adhesion (ex: fingers fused). The fluid provides temperature regulation and buoyancy.

Yolk sac provides early blood cells. Because diffusion (which is what the blastocyst is using now) can't go on forever, we must start building a cardiovascular system right away. The yolk sac also contributes to the formation of the gut and is the source for primordial germ cells…the spermatagonia and oogonia.

Allantois is an extension formed by the yolk sac (sometime between day 9-16). The allantois contributes to the formation of the umbilical cord, and part of the urinary bladder. *FYI…the 3-layer disc is also being formed at this time.*

Chorion is made up of mesoderm of the ICM and trophoblast. It is a vascularized structure that surrounds the embryo and will ultimately become the placenta. It provides exchange of nutrients/wastes between mom's blood and baby's blood.

The chorionic villi contain fetal BVs…there is blood flow by the 3rd week!

The maternal blood and embryonic blood are not in contact. They are separated by trophoblasts and by the basement membrane of the embryonic blood vessels. However, if a substance is lipophlilic it can diffuse thorugh (alcohol, nicotine, THC).

Placentation
The placenta develops from the embryonic chorion and maternal tissues (a part of the endometrium now called the deciduous basalis.)

The placenta is fully fiunctional by the the 3rd month. The functions of the placenta are:
- -nutrition
- -export waste
- -respiratory
- -endocrine

Hormonal functions of the placenta:
Recall that the placenta takes over the secretion of hormones after the corpus luteum has degenerated. High high high levels of estrogen prepare the mammary glands for lactation AND keep the myometrium "quiet"…no contractions! If hCG levels were to fall before the placenta became fully functional, then the corpus luteum would degenerate and not have anyone to take over. The estrogen and progesterone levels would plummet. Since progesterone is the dominant hormone of pregnancy (it maintains the endometrium, preventing spasm of the spiral arteries), if it is not there, then the endometrium cells will spasm causing loss of blood supply then tissue death and spontaneous abortion.

Layers of endometrium surrounding the fetus
At this point, the names of the endometrium layers have changed. The deciduas basalis is the area next to the placenta. The deciduas capilaris is the part that surrounds the baby. The decidula parietalis is the part next to the uterine wall.

The **umbilical cord** is made up of a pair of umbilical arteries which take blood FROM the fetus TO the placenta, and a single umbilical vein which takes blood FROM the placenta TO the fetus.

Sexual differentiation and development
The two gene combinations that determine gender are XX (female) and XY (male). The Y chromosome carries the srY gene. This gene develops the testes! So, in essence ones gender is determined by the presence or the absence of the srY gene. The female system is the default system, so if there is no srY, then ovaries develop.

Sexual differentation is the PHENOTYPE…the expression of the gene. This comes about because of secretions from the testes. If no testes, then no secretions, then the default is FEMALE!

srY present = testes

srY absent = ovaries

MIS = degeneration of Mullarian duct

Testosterone = male repro tract from Wolfiann duct

DHT = male external genitalia

No MIS = Mullarian ducts develop into female tract by default

No Testosterone = Wolffian degenerates

No Testosterone = female external genitalia by default

Role of Testes
- Testes secrete MIS (Mullarian Inhibiting Substance) from the Sertoli cells.
  - MIS causes degeneration of the default female Mullerian ducts.
- Testes secrete TESTOSTERONE and DHT from interstitial cells.
  - Testosterone develops the male reproductive tract (tubules, ducts, glands) from the Wolffian ducts.
  - DHT develops male external genitalia (penis, scrotum)

Role of Ovaries
- No MIS, so the embryo/fetus develops the female reproductive tract by default. This develops from the Mullarian ducts
- No Testosterone, so the Wolffian ducts degenerate
- No Testosterone, so female external ducts develop by default

Bipotential embryonic tissues
Sexual differentiation begins at week 7, and many analogous tissues are derived from the genital tubercle, urethral folds and groove, labioscrotal swelling.

Descent of the testis involves a migration from the abdominopelvic cavity through the inguinal canal into the scrotum. It is directed by TESTOSTERONE, which causes the contraction of the *gubernaculums testis* (CT cord). The failure of the testis to descend is called cryptorchidism.

Some developmental abnormalities

Testes secrete Testosterone, but not DHT?

- Internal male genitalia and female external genitalia.
- Genotype: Male
- Phenotype: Female

Genetic male (XY) secretes MIS, but not Testosterone?

- MIS means he'll have no Mullarian ducts, but the lack of Testosterone means he'll have no male ducts either. He will also develop female external genitalia by default.
- Genotype: Male
- Phenotype: Female (ductless)

Genetic male (XY) secrets Testosterone, but no MIS?

- Testosterone means he'll have extermal male genitalia and male ducts, but the lack of MIS means he will not break down the Mullarian ducts. So, both duct systems and external male genitalia
- Genotype: Male
- Phenotype: Male

Genetic female (XX) exposed to androgens (no MIS)?

- The lack of MIS means she'll produce the female duct system, but the exposure to androgens means she'll also develop the male duct system. She will have external male genitalia due to the androgen exposure.
- Genotype: Female
- Phenotype: Male

Parturition (childbirth)

At the end of pregnancy, estrogen levels reach their peak (progesterone is also high), and estrogen is important for mammary gland development and is permissive for OT. Another reason estrogen is so important in parturition is that it is antagonistic to progesterone's "quieting effect" on the myometrium. As estrogen levels rise, they increase the excitability of the myometrium toward the end of pregnancy…this causes the Braxton Hicks contractions, which are "false labor" and are irregular and weak.

However, the increased stretching of the uterine wall increases the excitability of the myometrium (which is being suppressed by Progesterone at the same time.) Recall that smooth muscle tends to contract in response to being stretched.

Estrogen is also permissive for OT, increasing the number of OT receptors in the myometrium. This causes OT to enhance contractions of the myometrium.

Estrogen and OT stimulate the secretion of prostaglandins (PGs) from the endometrium, and PGs enhance contractions of the myometrium.

The initiation of TRUE LABOR, which is a positive feedback loop, may have a hormonal trigger. When true labor initiates:

- OT levels are elevated from both maternal and fetal sources.
- PG levels are elevated from both placental and endometrial sources
- CRH levels are elevated from placental and maternal sources

The feedback loop goes like this: OT and PGs enhance uterine contractions, which cause more stretching of the cervix, which causes more secretion of OT from Mom's hypothalamus (neuroendocrine reflex) and more secretion of PGs from the endometrium, which causes more uterine contractions and more cervical stretching for more OT and PG release…etc…

Lactation and Milk Let Down

- Lobes make up mammary gland
- Each cluster = one lobe
- Each lobe has a duct
- Each lobe consists of lobules
- Lobule consists of epithelial cells (secreting cell) and a few myoepithelial cells (work like smooth muscle to squeeze out milk)
- Milk duct is in the lobe
- Lactiferous duct is the one at the nipple

Hormonal control

By the end of pregnancy, estrogen, progesterone and lactogen stimulate the hypothalamus to secrete PRH, which leads to the release of PRL from the adenohypophysis.

PRL stimulates milk production (after initial colostrum…which is antiviral, antibacterial, high in protein and low in fat). Recall that PRL stimulates mammary gland development, while OT stimulates the release of milk. This is because OT targets smooth muscle cells. It is the smooth muscle cells that eject the milk from the nipple in response to suckling.

After birth, the suckling reflex (stretch reflex) is responsible for further milk production (lactation), and milk let down.

The positive feedback loop goes like this:
Suckling of the nipples stimulates mechanoreceptors around the nipple, which send signals to the hypothalamus which secretes PRH and inhibits PIH. The PRH goes to the adenohypophysis where PRL is secreted which causes lactation for the next feeding (always stay full!)

Suckling of the nipples stimulates mechanoreceptors around the nipple, which send signals to the hypothalamus. The hypothalamus secretes OT for enhanced contraction of the myoepithelial cells, causing milk ejection (let down).

OT also helps the uterus shrink back to normal size after birth.

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