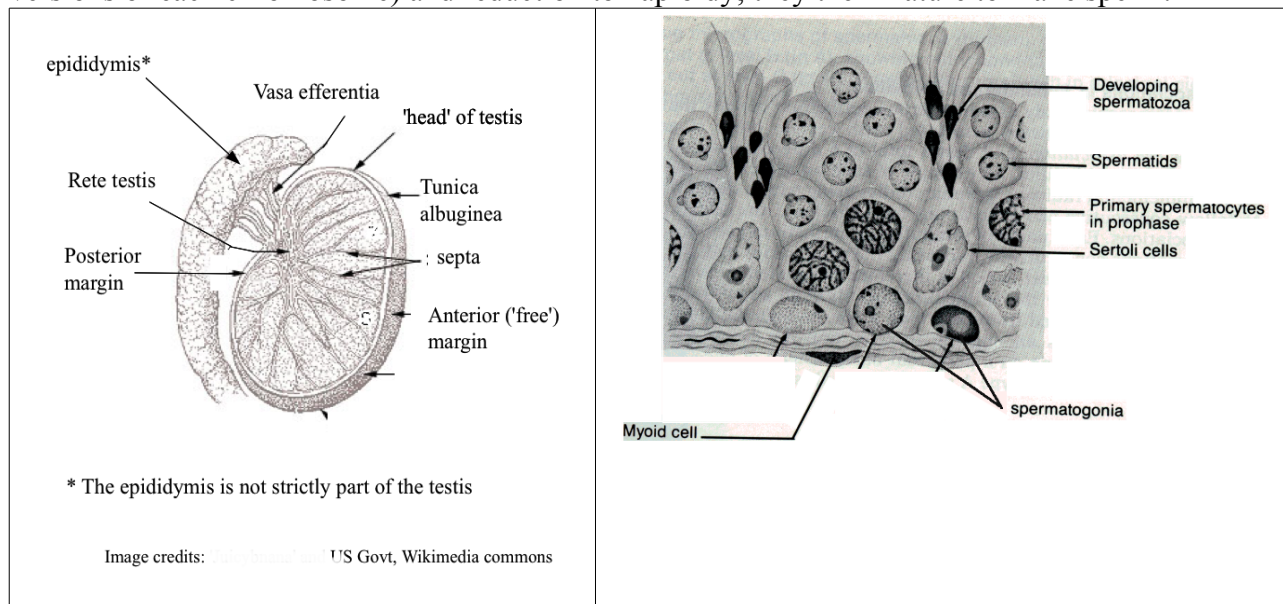# Handout for week 2: Human Embryology and Congenital Abnormalities.

*Important! - This handout is intended to give you the **bare essentials** of the week's material. It is not meant to be a substitute for your taking proper notes.*

Sexual reproduction blends characters of two individuals of the nth generation to make an individual of the $(n+1)^{th}$ generation. Compared to the alternative – asexual cloning – sex has the disadvantage that a tried-and-tested combination of genes (alleles) cannot be passed on unaltered, and also the disadvantage that a partner has to be found (a significant problem in sparse populations of animals). These disadvantages seem to be outweighed by the main advantage – variation between individuals is maintained, which is useful in the face of a changing environment and useful in presenting pathogens with a 'moving target' rather than a set meal. Sexual reproduction requires each parent to contribute just one, haploid, cell to each offspring (massive reduction in complexity that has to be rebuilt again at each generation). The natural instability in a system that starts with each mating type contributing equally results in a divergence between one type that produces large numbers of gametes that contribute nothing much more than DNA and the other that therefore has to provide almost 100% of the other resources, as well as DNA: hence *eggs are expensive and sperm is cheap*. This principle affects the different anatomies and behaviours of males and females.

Gametes are made in specialized organs, gonads. These contain two broad types of cell – germ line (which give rise only to gametes) and somatic cells (which support the process but cannot make gametes directly).

The testis is organized for very high rates of sperm production. Its internal anatomy consists mainly of many seminiferous tubules with a large total length. The outer layer of each tubule consists of contractile myoid cells. Inside these are germ line stem cells – prospermatogonia – in rapid mitotic division. They maintain their own population and also give rise to large numbers of mitotic spermatogonia connected by cytoplamsic bridges. These cells then each enter meiotic division, which includes crossing over (swapping elements between paternally- and maternally-derived versions of each chromosome) and reduction to haploidy; they then mature to make sperm.

epididymis*
Vasa efferentia
'head' of testis
Rete testis
Tunica albuginea
Posterior margin
: septa
Anterior ('free') margin

* The epididymis is not strictly part of the testis

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Developing spermatozoa
Spermatids
Primary spermatocytes in prophase
Sertoli cells
Myoid cell
spermatogonia

As they do this, developing sperm are 'nursed' by Sertoli cells. The tubules also contain Leydig cells, which make hormones such as testosterone. At your age, sperm production runs at about 10,000 per second. Sperm are matured in the epididymis.

The ovary, in contrast, is organized for the production of very few, very well-provided for gametes: only around 13 per year. Limited mitotic proliferation of the germ line takes place in foetal life, as

does entrance to meiosis (which then stops). Somatic cells cluster round the meiotically-arrested cells to make primordial follciles. Between menarche and menopause, monthly pulses of FSH induce a few follicles to begin to mature: the oocyte enlarges and the granulosa and thecal cells surrounding it multiply and a zona pellucida appears. Eventually the follicle swells with fluid. At a critical stage, it faces a choice between maturing into a Graafian follicle or dying: which it does depends on whether it receives a pulse of LH at the critical time. If it does, it matures and releases its oocyte into the oviduct: the remains of the follicle, the corpus luteum, makes progestrone as long as it lives. The progesterone prepares the uterine lining for implantation: the lininc is lost when the level of progestrone falls, unless embryo-derived hCG takes over, indicating pregnancy.

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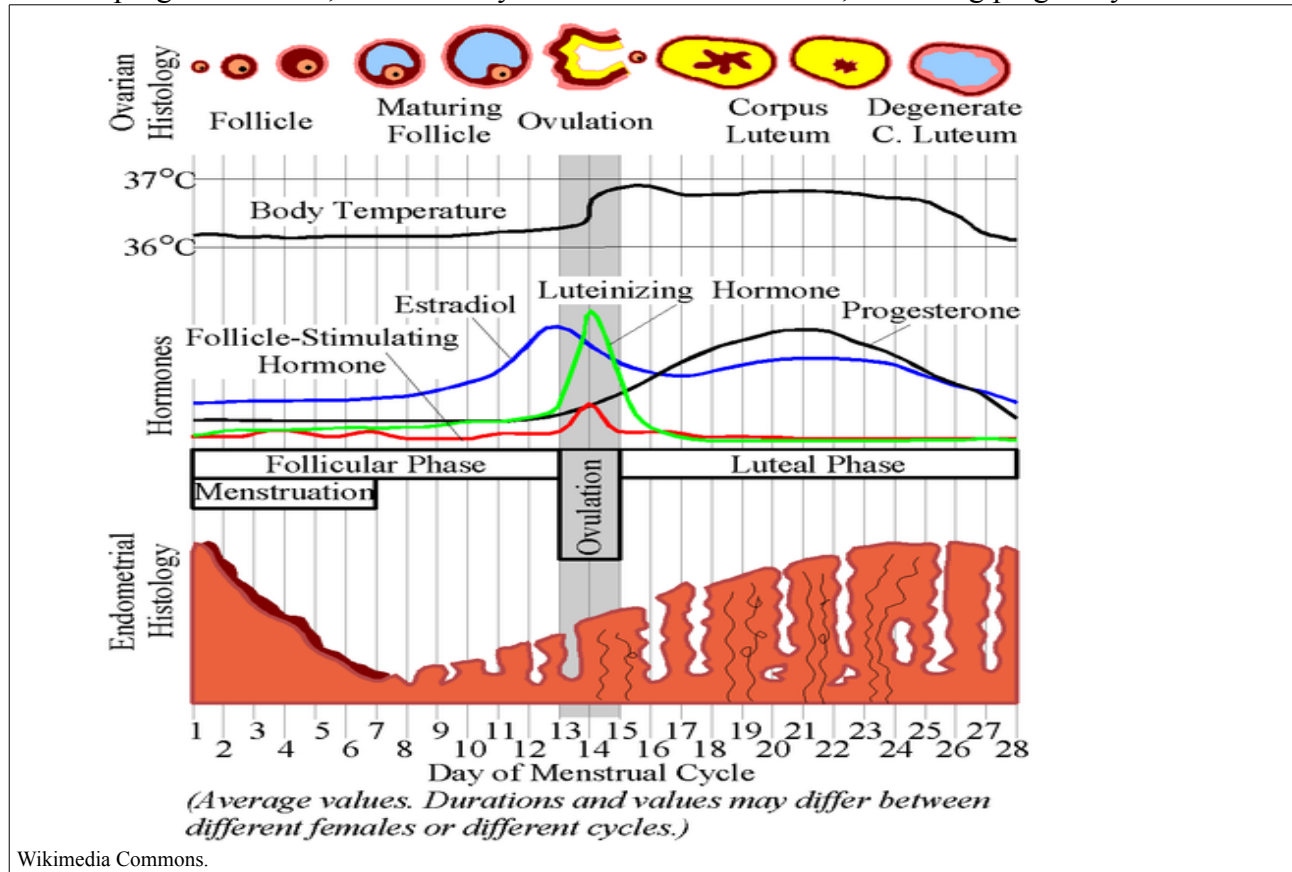
Sperm, once in the female reproductive tract, undergo capacitation and start to swim. They will only make it past the cervix at the right stage of the cycle (cervical mucus changes): whether they swim their way to the oviducts or are moved passively by uterine motion remains controversial. They should meet the oocyte high in the oviduct. Contact with the zona activates the acrosome reaction, which dissolves a hole through which the sperm swim to fuse with the oocyte and deliver their nuclear payload: this also signals the oocyte to become unwelcoming to any more sperm, and at last to finish meiosis. Where this process cannot happen naturally (eg by damage to oviducts or vasa deferentia, low male fertility etc), sperm and oocytes (from superovulation, perhaps from a donor) can be brought together in vitro (ICSI if the sperm are incompetent) and healthy embryos put back in the mother-to-be's uterus.

The fertilized oocyte begins development with cleavage to build up cell numbers with no net growth. If the cells lose contact with each other after the first division, each makes an embryo – one cause of monozygotic twinning. The cells, identical at first, switch on an adhesion molecule and clump together hard: some are inside while others have to be on the outside. This changes the fates of the cells and sets up the first internal difference. Outside cells make the trophectoderm, which will make the embryonic placenta, while the inner cell mass stays put in an inflating blastocyst. The layer of it that faces the balstocyst's fluid turns into the hypoblast, some of whose cells spread out under the trophectoderm to make a cavity, the yolk sac. The layer immediately above becomes the

epiblast: this sticks hard to the hypoblast and lets go of the cells above, the opening gap becoming the amniotic cavity.
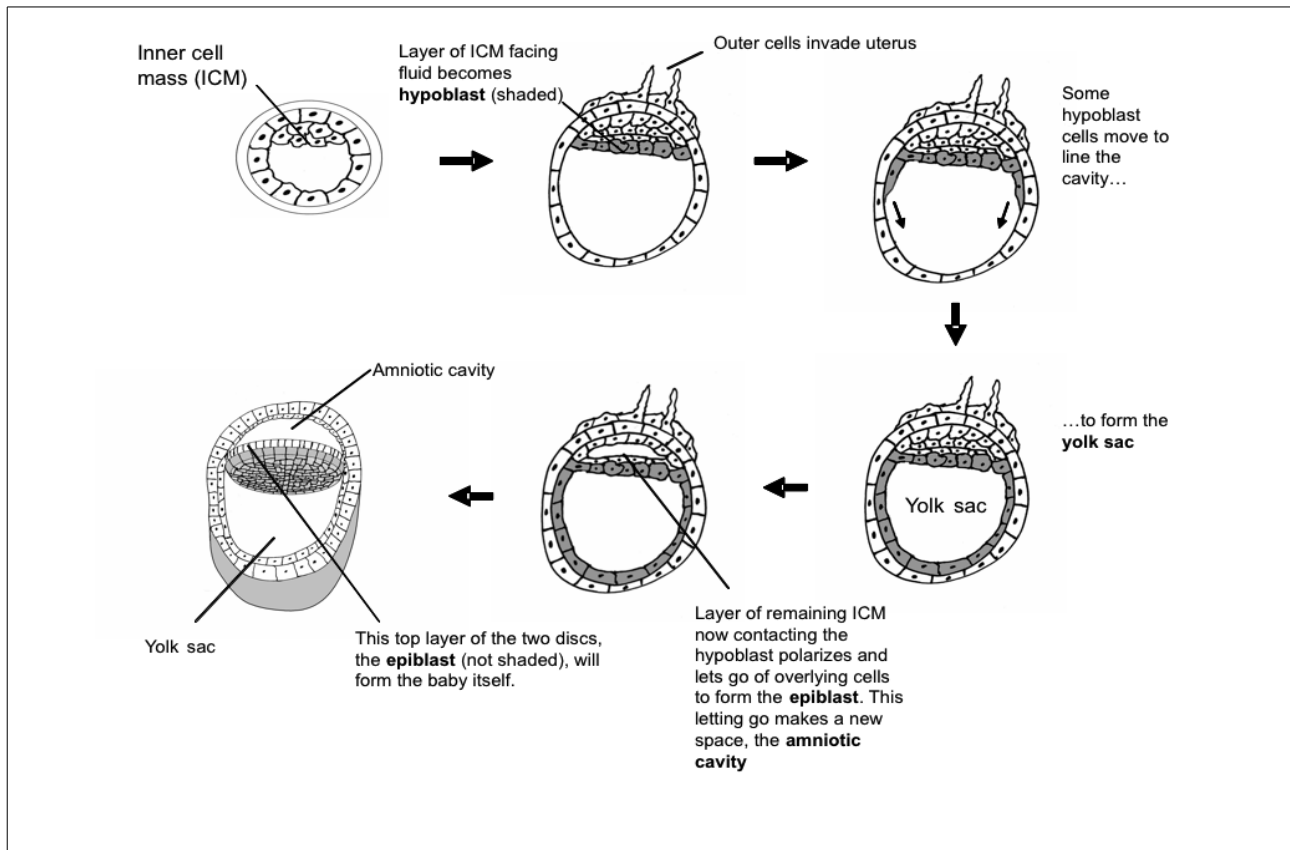
If the ICM splits, each part makes a new individual: these two twins share a trophectoderm layer and therefore a placenta (risk of fetal transfusion syndrome).

The centre of the hypoblast generates a special population of cells that stick with each other and migrate to the edge, forming a clump there: this defines one unique point on the edge. The cells signal to the epiblast above. At the opposite side, where these signals are therefore at their weakest, the epiblast cells pile up to make the tail end of the primitive streak, which extends forward to the middle of the disc (which will correspond to the top of the neck): beyond is the future head. Sometimes, two primitive streaks form and two babies result (no separation by membranes: risk of conjoined twinning) and sometimes one streak splits towards two head regions (partial axis duplications – two-headed individuals, rare in humans but common in snakes *etc.*). Once the primitive streak has formed, the epiblast flows towards it, cells diving down to make the endoderm (future gut) and mesoderm. Some endoderm leaves its layer to make the notochord.
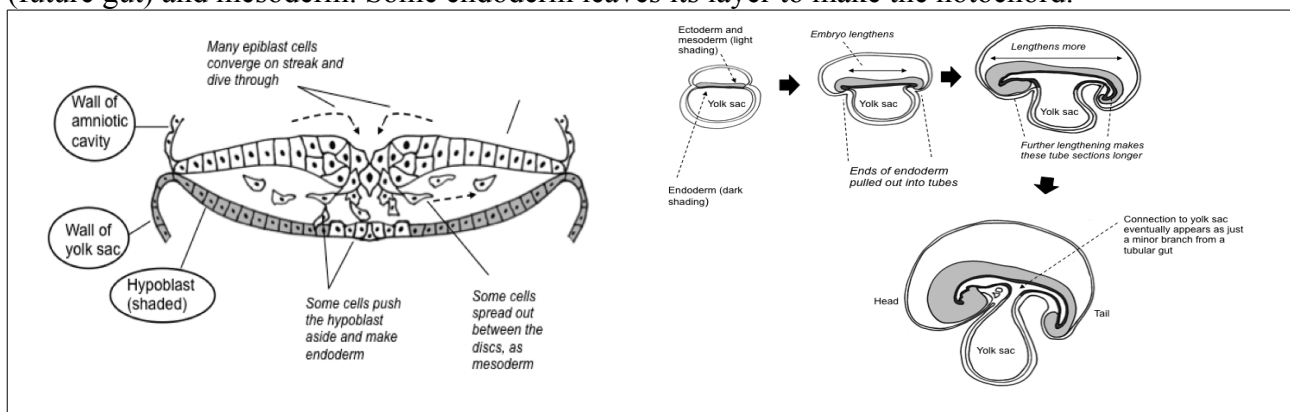
As the embryo elongates, the endoderm layer, initially flat, will be 'pulled out' to make the gut tube.

The neural tube, future spinal cord and brain, develops by invagination of the ectoderm, driven by local cell shape changes. The valley produced narrows until its edges meet. An exchange of cell neighbours results in the neural tube dropping free into the embryo and the ectoderm closing over behind it. Sometimes this fails (spina bifida / anencephaly). Very rarely, closure of the neural tube can envelop and draw in a twin (ventricular fetus-in-fetu: the more common form of fetus-in-fetu happens with ventral closure in the abdomen).

The mesoderm each side of the neural tube then becomes divided into segments – somites – in a clock-and-wavefront mechanism. The embryo at last actually looks like a first sketch of a little animal. The next stage is internal patterning. Signals (SHH) from the notochord spread to nearby tissues and, depending on how much signal each cell gets, it does a different thing, for example making a motor neuron *vs* an interneuron, or for example making bone *vs* muscle. These cells will make signals of their own, and by these cellular conversations the internal complexity of the embryo pulls itself up 'by its own bootstraps'. Some of this also involves cell migrations, particularly of the neural crest and primordial germ cells.

As the body grows, its parts have to stay in correct proportion. Growth is regulated by Growth Hormone from the pituitary (receptor mutants → Laron syndrome; body-wide so Vitruvian), which is relayed by IGFs. In normal limb growth, the signalling loops that control bone growth in response to these signals have to pass out to the edge of the bone and back, so that the system gets less efficient as the bone gets bigger, limiting maximum size but allowing a delayed bone to catch up with its contralateral counterpart. Mutants that affect this signalling locally cause low limb grown with respect to body (non-Vitruvian) – eg achondroplasia. Limb growth requires the support of very rapid blood vessel growth: thalidomide stops this, and results in phocomelia. Bones seem to lead the setting of body size. Other tissues, such as skin, just follow, probably because of growth in response to tension (also allows skin to stretch over fat, pregnancy, tumours etc).

Sex determination is set primarily by presence/ absence of Y chromosome (SRY gene). This is activated only in somatic cells of the gonad, which then signal to everything else, both germ cells (which enter the body from the yolk sac) and body. It SRY is present, somatic cells make testis, which makes testosterone and AMH to masculinize the body (deletion of M üllerian ducts, which would otherwise make female internal reproductive system, masculine development of external genitalia, of pelvis and of body shape etc). Without these signals, the extragonadal parts of the body will take the female route – seen with complete androgen sensitivity syndrome. Testosterone has to be processed to be 1,25DHT in the tissues before it is very effective in masculinizing the body. People with an Y chromosome but without the enzyme to do this processing look pretty much like girls until puberty: then testosterone levels rise enough that they can masculinize somewhat even without processing, and the 'girl' turns into a young man ('Guevadoces': common in Dominican Republic). There are many other intersex phenotypes, and you should think carefully about the ethics of surgery being imposed on newborns to make them conform to being one sex or another.

This handout began with gametes and has ended with the construction of gonads in the new body and the ability to form new gametes: *a hen is just an egg's way of making a new egg.* This looks like a cycle, but the life cycle is really an illusion. For the chromosomes it is a cycle, but for us, the bodies they make, it is a one-time, one-way journey.

Your job, as medics, will be to make it as good a journey for your fellows as you can: *Vale!*

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