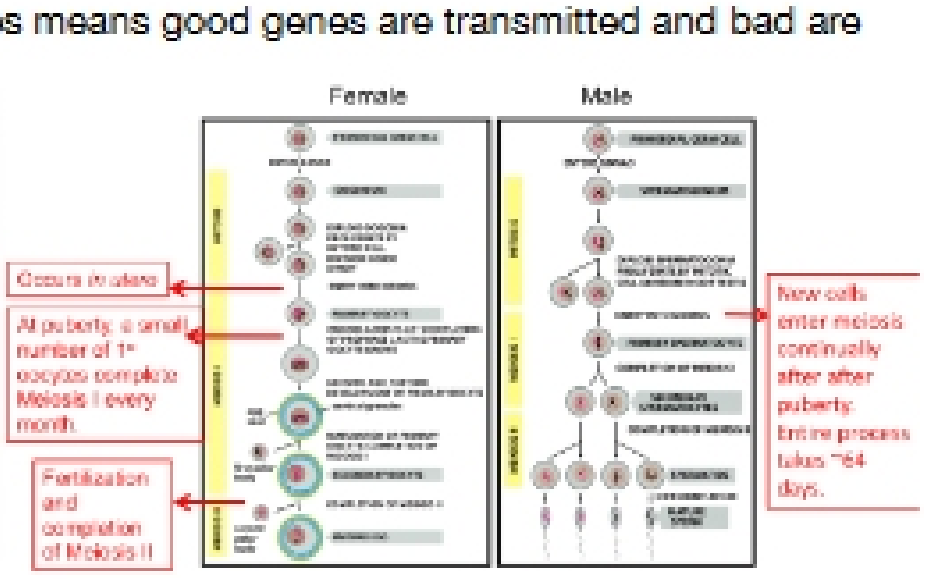
S100: Gametogenesis and Fertilization

Main Ideas

- Sexual reproduction is advantageous evolutionarily because it makes individuals w/novel genetic combinations and provides an efficient way to eliminate harmful mutations.
- Haploid gametes are made by meiosis, where 2 successive cell divisions follow one round of DNA replication.
- Sperm are small, compact cells highly specialized for fertilization of an ovum.
- Spermatogonia only begin to enter meiosis and produce spermatocytes and sperm after puberty.
- Each diploid primary spermatocyte gives ride to 4 mature haploid sperm, takes 64 days.
- Oocytes develop from primordial germ cells that migrate into the developing gonad, where they become oogonia
- After a period of mitotic division, they begin meiosis I and are called primary oocytes
- Primary oocytes stay arrested in prophase I for years, during which they grow, syn. a ZP (zona pellucida), and accumulate ribosomes, mRNAs, tRNAs, and proteins, using nutrients from the surrounding granulosa cells.
- In response to FSH and LH, the oocyte is stimulated to ovulate and completes meiosis I to form a small polar body and a mature oocyte, which proceeds to metaphase of meiosis II.
- The oocyte arrests there till fertilization, which signals the ovum to complete meiosis and begin embryonic development.
- Human fertilization begins when a sperm, which has go thru capacitation in the female genital tract, binds to the ZP
- Binding of the sperm to the ovum induces the sperm to undergo an acrosome rxn, releasing proteases that enable it to penetrate the ZP
- The fusion of the sperm w/the ovum elicits a Ca2+ wave that activate the ovum, which causes the cortical rxn and the development of the zygote.
- Development occurs after the contents of the 2 pronuclei come together and their chromosomes align on the mitotic spindle, which initiates the first mitotic division.

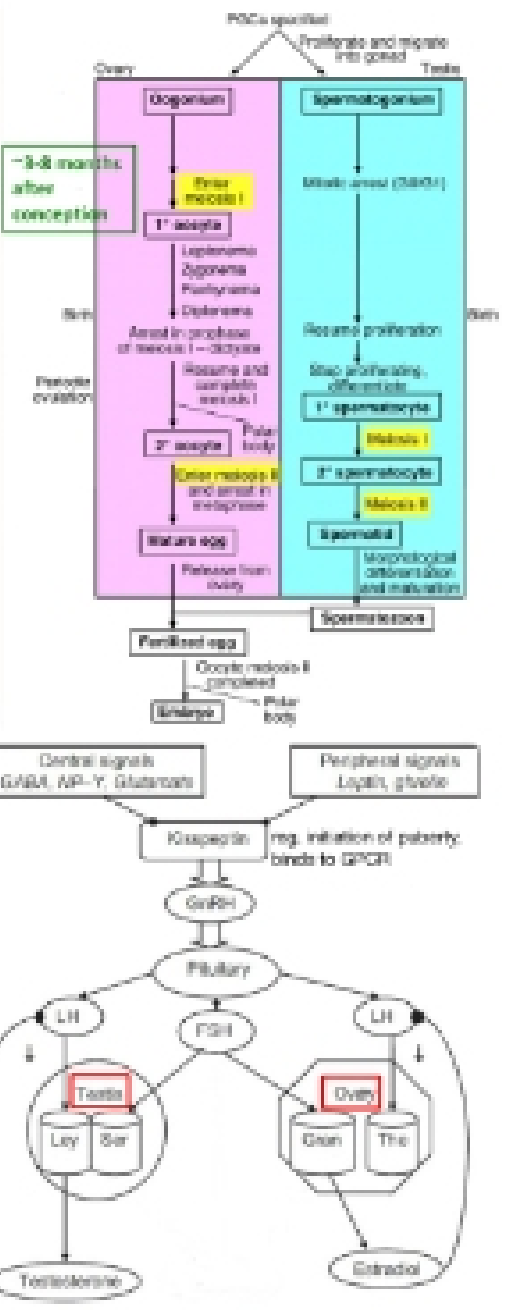
- **Machinery of sexual reproduction is elaborate and many resources spent on it**
  in wild, only fittest and handsomest males get to reproduce
- **Advantages of sexual reproduction**
  - genetic variation
    - novel genetic combos, reshuffling genes helps species survive in an unpredictable envi
  - elimination of deleterious genes
    - stringest selection for fit/handsome males means good genes are transmitted and bad are more efficiently lost
- **Sexual reproduction req. haploid gametes**
  - **Meiosis**: 1 round of DNA syn, 2 successive cell divisions w/chromatid separation
  - Timing, onset, and duration of meiosis= **sexually dimorphic**= diff. for the 2 sexes
  - Females: meiosis I occurs in utero, at pub some complete meiosis I every month, fertilization --> completion of meiosis II
  - Males: new cells enter meiosis continually after puberty, takes 64 days



- **Retinoic Acid (RA) regulates the timing of entry into meiosis I**
  - **RA binds to RAR** (retinoic acid R), a nuclear R
  - in embryonic ovary: high levels of RA --> induce proliferating germ-line cells to enter meiosis at about 11/12 weeks

- in embryonic testis: Sertoli cells make an enzyme (Cyp26b1) that metabolizes RA, after puberty levels of that enzyme decrease --> RA levels can rise and meiosis resumes

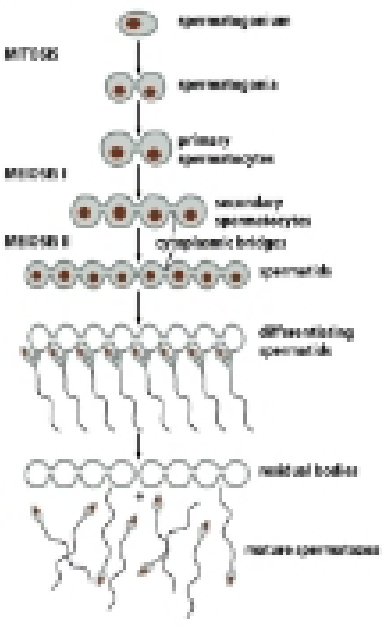
- **Gametes are highly specialized**
  - **Sperm**: small, motile (flagellum), streamlined for efficiency/speed (condensed DNA, no orgs except mitochondia, little cytoplasm), highly competitive envi
  - **Ovum**: large, nonmotile, lots of materials to support embryo growth (proteins, ribosomes, tRNAs, mRNAs, morphogenic factors, protective features), she's the only one!
- **Hypothalamic-Pituitary-Gonadal Axis regulates ovarian and testicular development**
  - **Kisspeptin**= key reg. of puberty onset, binds to a GPCR
  - **GnRH= gonadotropin releasing hormone**, a small peptide released by hypothalamus that signals the release of gonadotropins **FSH (follicle stimulating hormone)** and **LH (luteinizing hormone)** from pituitary



	Male	Female
FSH	Maturation of germ cells - stimulates primary spermatocytes to undergo Meiosis I Also stim. sertoli cell development	Maturation of germ cells - initiates follicular growth Stimulates synthesis of estrogen in granulosa cells
LH	Stimulates synthesis of testosterone by Leydig cells	Simulates synthesis of androgen (precursor to estrogen) in thecal cells Stimulates monthly ovulation

Thecal cells make androgen --> go to granulosa cells --> is converted to estrogen

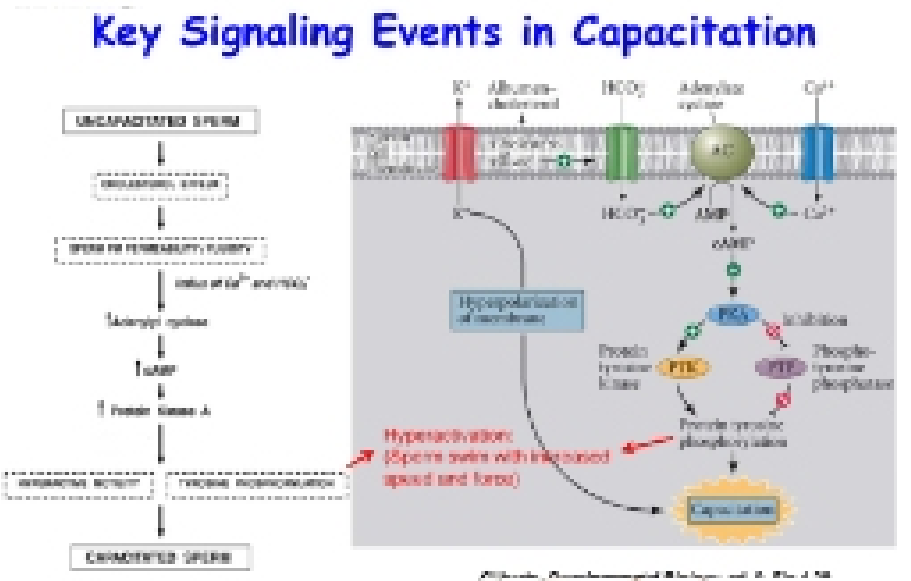
- **Modification of a germ cell to become sperm**
  - **Acrosomal vesicle**: contains hydrolytic enzymes that help sperm penetrate ovum's outer coat
  - DNA tightly condenses by **protamines** and sperm-specific histones
- **Sperm are syn. in seminiferous tubules**
  - **Sertoli cells**: nurse cells for sperm
    - secrete **anti-Mullerian hormone (AMH)** to send developing gonad down male pathway
    - convert testosterone to estradoil to help w/spermatogenesis
    - form the testis-blood barrier
    - after puberty: secrete inhibins and activins (TGFB signaling pathway), reg. FSH secretion
  - **Leydig cells**: interstitial cells
    - make testosterone in response to LH
  - Mature sperm travel to the epididymus, where they're stored and undergo more maturation, not ready to fertilize until they go thru **capacitation**



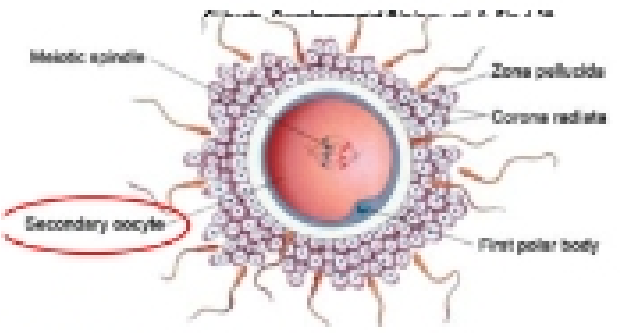
- **Sperm capacitation is req. for fertilization**
  = the set of physio changes that sperm must undergo in the female reproductive tract to become competent to fertilize the ovum
  - prepares sperm for acrosome rxn and allows sperm to become hyperactive
  - happens in ampulla, takes 5-6 hours
  - involves poorly understood mech's in mammals
    - in vitro: req. albumin, Ca^{2+}, HCO_3^-
    - albumin protein from female helps extract Ch from sperm membrane --> increases ability of

membrane to fuse w/acrosome during **acrosome rxn**
- needs to be change in membrane potential where K+ leaves sperm and Ca2+ and HCO3- activate a soluble adenyly cyclase to increase cAMP --> tyrosine P of proteins incl. those needed to hyperactivate sperm and for sperm-ovum fusion

- after: sperm can find and bind ovum

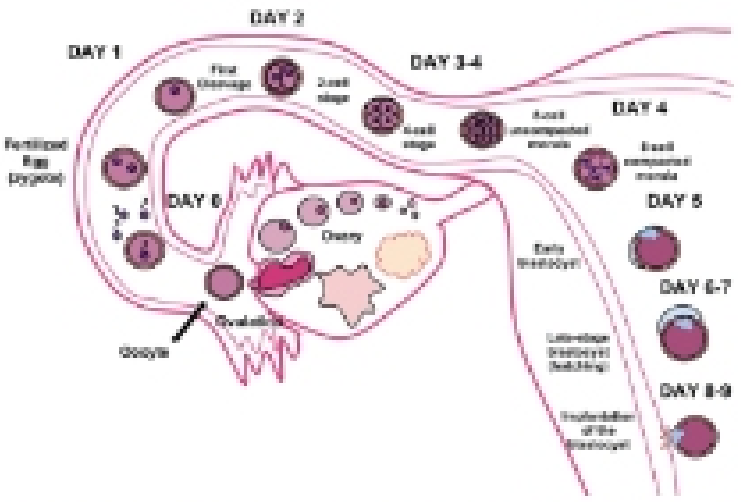


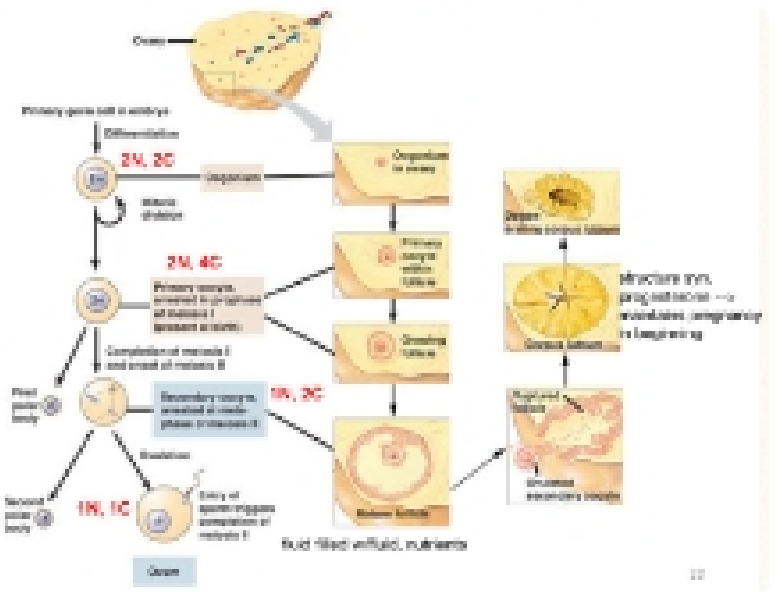
- **Human Oocyte Structure**
  - **Oocyte**: a developing egg/ovum that can't bind sperm or be fertilized
  - **Ovum= egg= mature oocyte**: can bind sperm and be fertilized, second meiotic metaphase
  - **Corona radiata**: layer of cells that provide proteins and nutrients to ovum
  - **Zona pellucida**: a glycoprotein membrane that surrounds the pm of the oocyte and serves as a protective layer, a protein in the ZP (ZP2) is a binding protein for sperm and induces the **acrosome rxn= rxn that occurs in response to sperm-ovum fusion which releases the enzymes from the sperm that can digest the ovum's tough coat**



Oocyte Maturation

• All of the materials necessary for the beginning of growth and development must be stored in the ovum.





- **Maturing Oocyte Prepares for Development that occurs prior implantation**
  - meiotic divisions conserve the cytoplasm because the oocyte doesn't really divide (unlike spermatocytes0
  - most of the growth happens in the primary oocyte (when the cells are bivalent) so there's 2x as much DNA for RNA syn.
  - somes genes (like rRNA genes) become amplified --> can be a burst of protein syn. after fertilization
  - follicle cells (corona radiata cells) link to the occyte thru gap junctions to provide precursors for macromolecular syn.
  - morphogenetic factors that direct the differentiation of cells into certain cell types are stored in the ovum incl. txn factos and paracrine factors --> specify how the cell will divide
- **Arrest in meiosis I req. high levels of cAMP**