Reproduction

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Sexual Reproduction

- Gonads, gametes, and zygotes
- Chromosomes
  - 23 pairs
  - autosomes
  - sex chromosomes
    - XX, XY
Barr body

- Females have only one active X chromosome in each cell
- Barr Body=Condensed inactive X chromosomes
- Which chromosome is inactivated in each cell is random
  - Occurs on 16th day of fetal development
  - All cells arising from that cell will inactivate same X
Barr bodies

• Identical twin females may have different patterns of expression

• Random activation of X chromosomes results in genetic mosaics (like calico kittens!)
Formation of ovaries and testes

- Same for both sexes for first 40 days
  - gamete stem cells migrate to gonads from yolk sac
- Testis determining factor & SRY gene
  - male
    - seminiferous tubules develop & spermatogenesis begins in embryo
      - germinal (sperm)
      - non-germinal cells (Sertoli cells)
    - Leydig cells
      - secretion begins 8 weeks post-conception
      - peak 12-14 weeks, then decline
    - scrotum descent near birth
Development of accessory sex organs (male)

- XY
  - SRY gene
    - TDF transcription
      - Testes develop
  - placenta
    - HCG
      - Stimulation of Leydig cells
        - Testosterone
          - Sertoli cells
          - Mullerian inhibitory hormone
            - Mullerian ducts
              - degeneration
            - Internal male development
              - Woolfian ducts

Development of accessory sex organs (female)

XX

No SRY gene

Woolfian ducts

Mullerian ducts

No development

Ovaries
Develop by default
Undifferentiated Primitive Mesonephric Kidney

Wolffian duct
Generates Leydig cells
Differentiates into a male
Epididymis
Testes
Seminal vesicle

Mullerian duct
Generates Absence of Leydig cells
Differentiates into a female
Fallopian tubes
Ovaries
Uterus
Vagina

Urogenital sinus
Disorders of sexual development

- **Hermaphroditism**
  - both ovaries and testes present
  - XX and partial Y
  - These individuals are also mosaic!

Ultrasound of boy with female/male internal sex organs
Disorders of sexual development

- Pseudohermaphroditism
  - female
    - genetically XX
    - external genitalia ambiguous
  - male
    - more complex
    - Y chromosome present
    - genital ducts or external genitalia not completely differentiated along male lines, may be completely female
      - genetic defects of androgen synthesis, defective virilization of embryo, androgen insensitivity syndrome due to mutant androgen receptor
# Abnormal development

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
<th>Gonads</th>
<th>Mullerian duct</th>
<th>Woolfian duct</th>
<th>External genitalia</th>
</tr>
</thead>
<tbody>
<tr>
<td>XY</td>
<td>normal male</td>
<td>testis</td>
<td>regressed</td>
<td>developed</td>
<td>male</td>
</tr>
<tr>
<td>XX</td>
<td>normal female</td>
<td>ovary</td>
<td>developed</td>
<td>regressed</td>
<td>female</td>
</tr>
<tr>
<td>XO</td>
<td>Turner's</td>
<td>no germ cells</td>
<td>developed</td>
<td>regressed</td>
<td>female</td>
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<tr>
<td>XXX</td>
<td>Klinefelter's</td>
<td>Dysgenetic testis</td>
<td>regressed</td>
<td>developed</td>
<td>male</td>
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<tr>
<td>poly-X</td>
<td>female</td>
<td>ovary</td>
<td>developed</td>
<td>regressed</td>
<td>female</td>
</tr>
<tr>
<td>XXXY</td>
<td>male</td>
<td>testis</td>
<td>regressed</td>
<td>developed</td>
<td>male</td>
</tr>
</tbody>
</table>

Turner's syndrome: XO

- Most common sexual abnormality of females (1/2500)
- Four cardinal features
  - Female phenotype
  - Short stature
  - Sexual infantilism
  - Somatic abnormalities
    - Congenital heart disease
    - Hypothyroidism
    - Malformation of kidneys
    - Skeletal abnormalities
Klinefelter's syndrome: XXY

- Frontal Baldness absent
- Tendency to grow fewer chest hairs
- Breast development
- Female-type pubic hair pattern
- Small testicular size
- Poor beard growth
- Narrow shoulders
- Wide hips
- Long legs
Endocrine regulation

- Early development
  - Male = testes secretory in embryo
    - masculinization of embryo
    - inactive at birth
  - Female = ovaries mature in 3rd trimester
    - inactive at birth

- prepubescent: hormones in male and female same

- puberty
  - increase secretion of tropic hormones triggers increased sex hormone production
Hypothalamus, pituitary, gonads

• Pulsatile secretions of GnRH
• Anterior pituitary: FSH & LH
  - spermatogenesis/oogenesis
  - gonadal hormone secretion
  - maintenance of gonad structure
• Negative feedback inhibition
  - inhibition of GnRH
  - inhibition of tropic hormone stimulated by GnRH
• inhibin
  - secreted by Sertoli cells and ovarian follicles
  - inhibits FSH, not LH
• male vs. female hormones secretion
Onset of puberty

• Increased FSH, then LH
  - two mechanisms
    • increased GnRH due to brain maturation
    • decreased sensitivity of GH to negative feedback effects of sex steroids

• sleep= increased secretions

• secondary sex characteristics accompanied by growth spurt
  - estradiol-17β
  - testosterone

• Effects of body fat and physical activity
Male reproductive system
Male reproductive system

• FSH receptors
  - only on Sertoli cells
  - stimulate spermatogenesis

• LH receptors
  - only on Leydig cells
  - stimulate testosterone production
Control of gonadotropin secretion

• Feedback loop for LH
  - LH stimulates Leydig cells = testosterone
  - long loop of inhibition to anterior pituitary

• receptors in the brain for testosterone
  - conversion to other hormones, estradiol, etc.

• testosterone: secretion and age
  - feedback effects of testosterone & inhibin = relatively constant secretion
  - gradual decline in men over 50
Testicular endocrine production

• **Effects of testosterone**
  - growth of muscle/other structures
  - secondary sex characteristics
  - increased hemoglobin synthesis
  - closure of epiphyseal plate

• **Estradiol**
  - downregulation of Leydig cell function

• **Hormonal interactions**
Spermatogenesis

Primordial germ cell

- Spermatogonium (diploid)
  - Mitotic division
  - Primary spermatocyte (diploid)
    - In prophase of meiosis I
      - First meiotic division
        - Secondary spermatocyte (haploid)
          - Second meiotic division
            - Spermatids (haploid)
              - Sperm cells (haploid)

Sertoli cell

Epididymis

Seminiferous tubule (cross section)

Testis
Role of the Sertoli cells and hormonal control

• Sertoli cells
  - Blood-testis barrier
  - Phagocytosis of cytoplasm
  - Androgen binding protein (ABP)
    • concentrates testosterone in lumen

• Hormonal control
  - FSH initiates spermatogenesis
Male accessory sex organs

- **Pathway**
  - Seminiferous tubules → efferent ductules → rete testis → epididymis → vas deferens → seminal vesicles → ejaculatory duct → prostate → urethra

- **in epididymis**
  - motility
  - resistance to pH and temperature changes
  - increased capability for fertilization
  - storage
Erection, emission, ejaculation

- **Erectile tissue**
  - corpora cavernosa & corpus spongiosum

- **Erection (spinal cord reflex)**
  - parasympathetic nerves
    - vasodilation of arterioles via NO
    - venous obstruction

- **Emission & Ejaculation**
  - sympathetic nerves
    - peristalsis of tubes
    - contractions of seminal vesicles and prostate
    - contraction of muscles at penile base
Vasectomy

I always get a big laugh out of this.

This won't hurt a bit.
Vasectomy
a. Vas identified and clamped with modified towel clamp (Leader) (optional— injection under vas prior to clamp application)

b. Vas injected

c. Small incision made over vas

d. Needle positioned to isolate vas from surrounding fascial investment

e. Vas delivered into incision with Leader vas hook

f. Fascial investment stripped downwards from vas

g. Scrotum elevated to permit tied ends of vas to retract into original position (no skin sutures used)

h. Vas clamped, segment removed, and remaining ends tied
Female reproductive system
Female reproductive system: Development of oocytes

- 5 months gestation
  - 6-7 million oogonia
  - production ceases
- end of gestation
  - inception of meiosis I
  - arrest in prophase I as primary oocytes
  - 2 million remain
- puberty
  - 3-400,000 oocytes remain
Development of oocytes

• Primary follicles
  - primary oocyte surrounded by single, unstimulated layer of granulosa cells

• Secondary follicles
  - several layers of granulosa cells form due to FSH stimulation
  - increase in size with formation of vesicles

• Graafian follicle
  - vesicles fuse to form antrum
  - primary oocyte completes meiosis I
  - secondary oocyte remains = arrested in metaphase II
  - some granulosa cells become theca cells and secrete androgens
  - androgens converted to estrogens by granulosa cells (FSH stim)
Structure of the follicle

- Primordial follicle
- Primary follicle
- Secondary follicle
- Graafian follicle

- Zona pellucida
- Granulosa cells
- Theca cells
- Oocyte
- Antrum
Ovulation

• **Definition**: release of oocyte into uterine tube
• atresia
• what is released?
  - Secondary oocyte
  - zona pellucida
  - corona radiata
• What is left behind?
  - Corpus luteum
    • LH stimulation
    • androgens and progesterones secreted
    • Corpus albicans
Ovarian phases

- Follicular phase
- Ovulation
- Luteal phase
Ovarian phases

- **Follicular phase (days 1-13)**
  - initial state
    - lowest hormone levels
    - ovaries have primordial & primary follicles
    - some move forward to form secondary follicles
    - one matures as Graafian follicle
  - FSH stimulation
    - granulosa cells secrete increasing amounts of estradiol
    - FSH receptors on granulosa cells upregulated
    - increased receptor sensitivity = positive feedback loop
      - increased frequency of GnRH pulses produces increased LH
    - upregulation of LH receptors on Graafian follicles
  - Results
    - LH surge which triggers ovulation
Ovarian phases

- **Ovulation (day 14)**
  - LH surge = rupture of Graafian follicle
  - secondary oocyte, zona pellucida, corona radiata expelled

- **Luteal phase (days 15-28)**
  - LH stimulates corpus luteum development
  - mucus thickens and becomes sticky due to progesterone
  - degeneration of corpus luteum at end of luteal phase due to luteolysin (uterine hormone) leads to decreased estrogen and progestone secretion
Uterine phases of menstrual cycle

- Proliferative
- Secretory
- Menstrual
Uterine phases

• Proliferative
  - increased secretion of estradiol leads to stratum functionale proliferation
  - spiral arteries
  - estradiol stimulates upregulation of progesterone receptors on endometrium
Uterine phases

• Secretory
  - development of uterine glands due to increased progesterone
  - preparation for embedding of embryo
    • thickening of endometrium
    • uterine glands engorge with glycogen
    • increased vascularization and sponginess
Uterine phases

• Menstrual
  - decrease in hormone levels
  - spiral arteries constrict
  - cornification of vaginal epithelium
  - thin cervical mucus allows for sperm penetration
Menopause

• **Cause**
  - Loss of GnRH control of cycle (increased amplitude of LH, increased loss of ovarian follicles)

• symptoms due to increased FSH and LH secretions in absence of negative feedback control
  - vasomotor disturbances
  - urogenital atrophy
  - lack of lubrication
  - increased risk of atherosclerosis, CV disease, osteoporosis
Pros and Cons of HRT

- **Pro**
  - Decreased symptoms associated with menopause
  - Decreased risk of osteoporosis
  - Decreased heart disease (has been challenged)

- **Con**
  - with preempro (estrogen + progestin), increased risk of:
    - Heart disease
    - Blood clots
    - Dementia
    - Stroke
    - Breast cancer

The jury is still out.....
Fertilization
Fertilization

- **Ejaculum**
  - 300 million sperm, 100 into fallopian tubes

- **capacitation**
  - requires 7 hours in female vaginal tract

- **fertilization in fallopian tube**
  - penetration of zona pellucida
  - final meiotic division
  - fusion of nuclei results in diploid zygote
    - sperm contributes centrosome (MOC)
    - sperm in female reproductive tract last for 3 days, ovum lasts for one day following ovulation
Cleavage and blastocyst formation

- **Cleavage**
- **Morula**
  - 50-60 hrs
  - ball of 8 cells
- **Blastocyst**
  - implants in 6 days
  - inner cell mass
    - becomes fetus
  - trophoblast cells
    - become placenta

Diagram:
- Ovulation
- Fertilization
- Cleavage
- Morula
  - 2-cell
  - 4-cell
  - 8-cell
- Blastocyst
- Implantation
- Polar bodies
- Sperm & egg nuclei
- 2o oocyte
- 1o oocyte
A word about Stem Cells..

- Embryonic stem cells are currently obtained by removing the inner mass cells from “extra” products of IVF
- Can also be obtained in cord blood (fewer cells, most with a prescribed lineage)
- Also found in adults (hard to find)
  - Women who have had children = microchimerism (JAMA, April 4, 2007)
  - Collaborative effort has demonstrated that mouse fibroblast cells can be reprogrammed to become stem cells (Cell Stem Cell, July 2007)
Zygote: 30 hours post-fertilization
Implantation and placenta formation

- Trophoblast cells produce HCG
  - maintenance of corpus luteum
  - prevents menstruation
- 10th week
  - decline in HCG
- placenta become secretory
  - 5th-6th week
EPT

- Detects very low levels of HCG in urine
- Can determine pregnancy 1 day after first missed menstrual period
Exchange of molecules

- No mixing of maternal and fetal blood
- Diffusion
  - oxygen & CO₂
  - nutrient molecules & waste products
- high metabolic rate in placenta
  - utilizes 1/3 maternal oxygen & glucose
  - rate of protein synthesis exceeds liver
- barrier
Endocrine functions of the placenta

- **Pituitary-like hormones**
  - **HCG**
    - maintenance of corpus luteum
    - prevents immunological rejection
  - **chorionic somatotropin & growth hormone**
    - glucose sparing due to:
      - lipolysis & increased f/a in plasma
      - decrease of glucose
      - polyuria

- **Steroid hormones**
  - major sex steroid producing gland
  - requires maternal & fetal precursors for hormone synthesis = fetal-placental unit
Labor and partruition

- Uterine contractions
  - oxytocin
  - prostaglandins
- Possible mechanisms
  - induced estrogen levels upregulate oxytocin receptors on myometrium
    - stimulate prostaglandin production
    - increased sensitivity to oxytocin, not increased production
Lactation

- Insulin, cortisol, thyroid hormones
  - growth & development of mammary glands
  - with progesterone
    - development of mammary alveoli
  - with estrogen
    - proliferation of tubules and ducts

- PIH
  - PIH stimulated by high estrogen levels
  - prevents lactation while mammalia are developing during gestation

- prolactin: stimulates production of milk protein
Lactation

• Mechanical stimulus
  - nursing initiates neuroendocrine reflex
    • increased prolactin produced and secreted
    • inhibition of PIH
    • release of PRH
  - milk-ejection reflex
    • nursing stimulates oxytocin release
    • contraction of lactiferous ducts and uterus
Mammary gland development
Advantages of breastfeeding

• Nutritional advantages
• Immune protection
• Uterine contractions facilitate reduction in size
• Emotional advantages
• Simplicity
## Human vs cow’s milk

<table>
<thead>
<tr>
<th>Component</th>
<th>Human milk</th>
<th>Cow’s milk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbohydrates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactose</td>
<td>7.3 g/dl</td>
<td>4.0 g/dl</td>
</tr>
<tr>
<td>Oligosaccharides</td>
<td>1.2 g/dl</td>
<td>0.1 g/dl</td>
</tr>
<tr>
<td><strong>Proteins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casein</td>
<td>0.2 g/dl</td>
<td>2.7 g/dl</td>
</tr>
<tr>
<td>$\alpha$-lactalbumin</td>
<td>0.2 g/dl</td>
<td>0.1 g/dl</td>
</tr>
<tr>
<td>lactoferrin</td>
<td>0.2 g/dl</td>
<td>trace</td>
</tr>
<tr>
<td>Secretory IgA</td>
<td>0.2 g/dl</td>
<td>0.003 g/dl</td>
</tr>
<tr>
<td>$\beta$-lactoglobulin</td>
<td>None</td>
<td>0.36 g/dl</td>
</tr>
</tbody>
</table>

From: http://classes.aces.uiuc.edu/AnSci308/HumanLact.html
# Human vs cow’s milk

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<thead>
<tr>
<th>Component</th>
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<th>Cow’s milk</th>
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</thead>
<tbody>
<tr>
<td><strong>Milk lipids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>4.0%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Phospholipids</td>
<td>0.04%</td>
<td>0.04%</td>
</tr>
<tr>
<td><strong>Minerals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>5.0 mM</td>
<td>15.0 mM</td>
</tr>
<tr>
<td>Potassium</td>
<td>15.0 mM</td>
<td>45.0 mM</td>
</tr>
<tr>
<td>Chloride</td>
<td>15.0 mM</td>
<td>35.0 mM</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.0 mM</td>
<td>30 mM</td>
</tr>
<tr>
<td>Magnesium</td>
<td>1.4 mM</td>
<td>4.0 mM</td>
</tr>
</tbody>
</table>

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