MUNI
MED

Pathophysiology of reproduction – sterility, infertility

Lecture Outline

The Basics
Gametogenesis
Gender determination

Female Reproductive Pathophysiology
Ovarian Cycle
Uterine Cycle
Hormonal control and changes
Disorders

Male Reproductive Pathophysiology

Infertility

The Basics

Gametogenesis

Gametes are produced during Meiosis I & II

Meiosis function

- Production of 4 haploid (n) gametes from each diploid oögonium (2n) or spermatogonium (2n)
- Differences between ♂ (male) and ♀ (female) gamete development
  - ♂
    - continuous development & production of sperm from onset of puberty until….?
    - stem cells are retained
    - Sperm are motile and contain very little cytoplasm
  - ♀
    - the entire complement of dictyate primary oocytes are formed during development with 10-20 continuing development during each ovarian cycle
    - Oocytes are surrounded by follicular cells – forms ovarian follicle
    - stem cells are exhausted
    - oocytes are among the largest cells and are non-motile

The Basics

Gametogenesis

Sperm Production

- During development germ cells are produced
  - Remain quiescent until puberty
    - Actions of hormones from pituitary, sertoli cells and Leydig cells
  - At puberty some spermatogonia will
    - Undergo mitosis continuously
    - Enter into meiosis
      - This ensures a continuous supply of spermatogonia

The Basics

Gametogenesis

Process of sperm production involves three stages

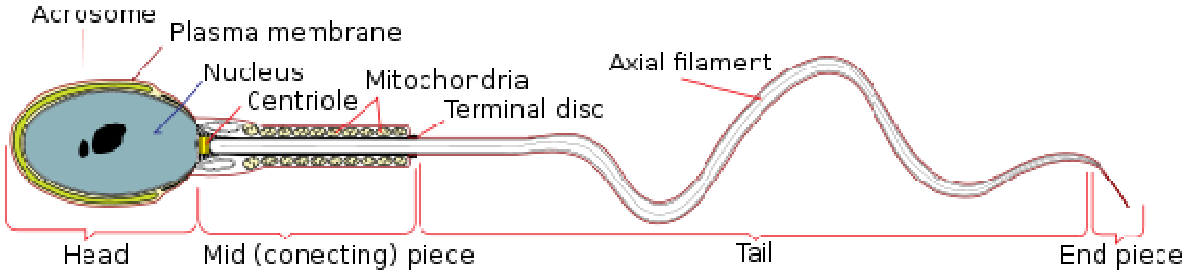
1. Spermatocytogenesis
   produces secondary spermatocytes from spermatogoium
2. Spermatidogenesis
   stage where meiosis I & II occur
   results in spermatid formation
3. Spermiogenesis
   final stage of sperm development
   spermatid becomes a motile spermatozoa during spermiation

The Basics

Gametogenesis

Spermiation

The spermatozoa that are formed are initially unable to move.
The flagella must become motile
Not used however until ejaculated
Prior movement through the male reproductive tract is via peristalsis



The Basics

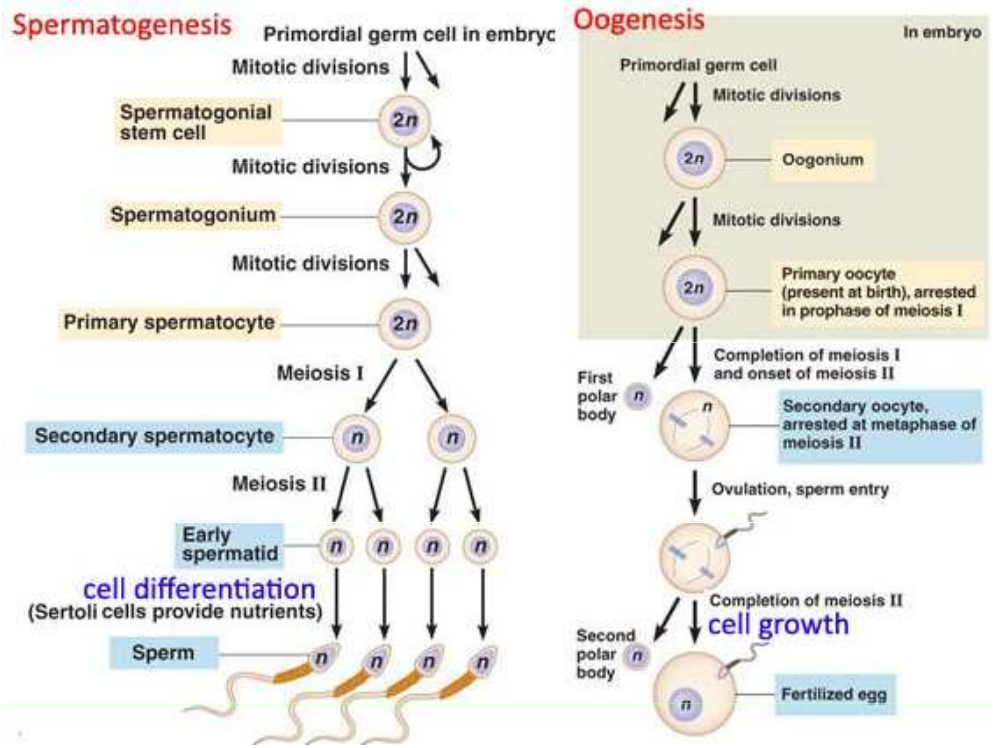
Gametogenesis

Oogenesis

- Results in formation of secondary oocyte which is released during ovulation
  - If no fertilization occurs, meiosis II will not occur.
- Stages of oogenesis
  1. Oocytogenesis
     - Forms oögonia
     - During fetal development starting at week 10 and completing around birth
     - Results in formation of primary oocytes (~1/2 million)
  2. Ootidogenesis
     - Results in the formation of secondary oocytes
     - These are dictyate in prophase I
  3. Formation of ovum (if fertilization occurs)

The Basics

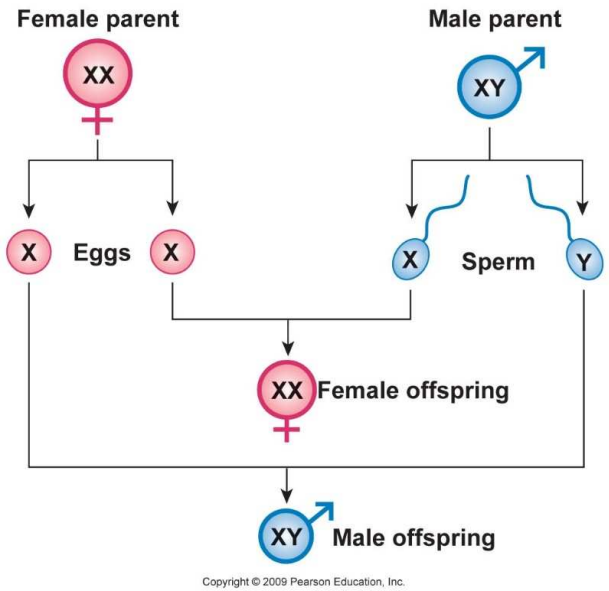
Gametogenesis



The Basics

Gender Determination

Chromosomes determine gender
23 donated by egg (n)
23 donated by sperm (n)
Syngamy
The fusion of gametes to form a zygote
Consists of
- plasmogamy
  - union of cell membranes and cytosol
- Karyogamy
  - union of genetic material
  - Autosomes: 44 or 22 pair
  - Sex chromosomes: 2 or 1 pair
    - XX chromosomes = female
    - XY chromosomes = male



The Basics

Gender Determination

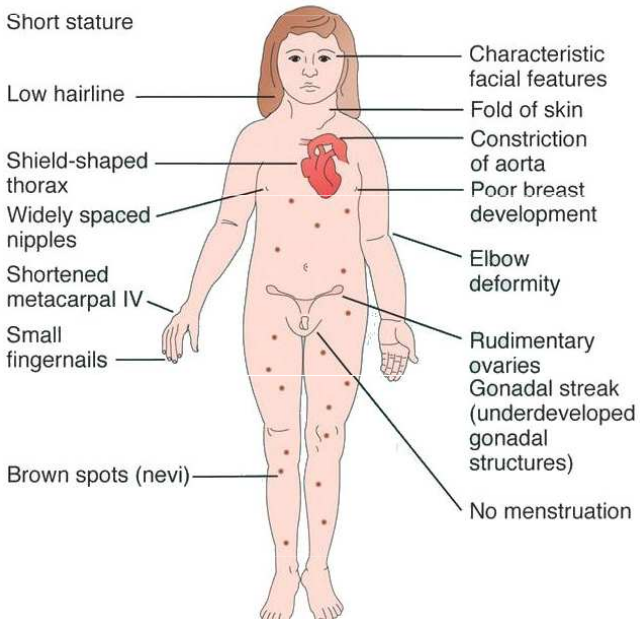
Non-disjunction during meiosis I or II

Monosomy or polyploidy

XO (no Y chromosome, or second X)

Turner's syndrome

Phonotypical female



The Basics

Gender Determination

Non-disjunction during meiosis I or II

Polyploidy

The incomplete separation of homologues during meiosis results in a zygote with too many chromosomes

Regarding the sex chromosomes, it may be

XXY (47 chromosomes total)

Male sex organs; unusually small testes, sterile. Breast enlargement and other feminine body characteristics. Normal intelligence.

XYY

Individuals are somewhat taller than average and often have below normal intelligence. At one time (~1970s), it was thought that these men were likely to be criminally aggressive, but this hypothesis has been disproven over time.

XXYY – male and very rare (48 chromosomes)

XXX (Trisomy X)

Individuals are female normal, undistinguishable except for by karyotype.

The Basics

Gender Determination

The embryo exhibits gender bipotential

Around week seven of fetal development the SRY (ex-determining egion of chromosome) gene becomes activated

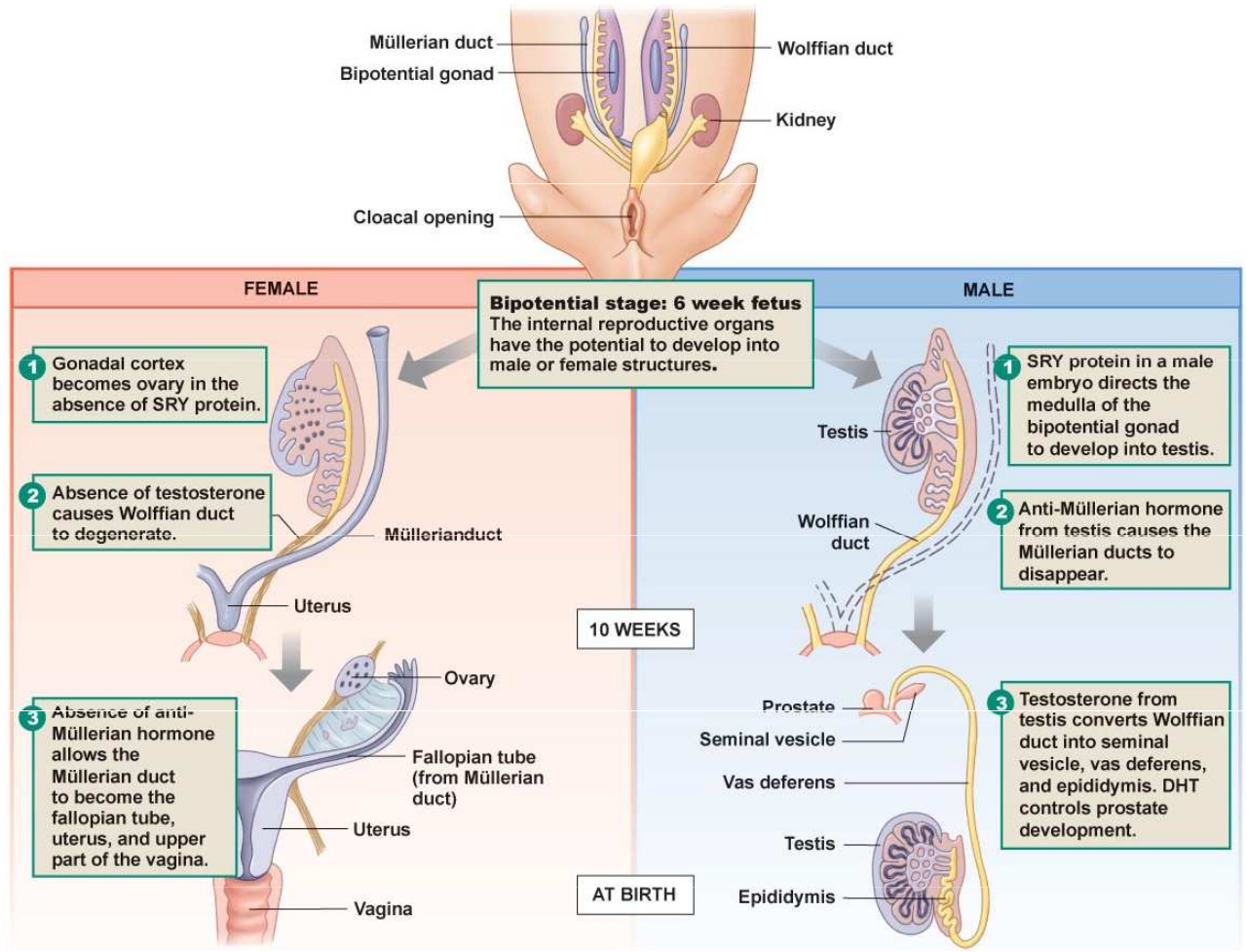
The SRY directs the bipotential gonads

- The absence of this on the X chromosome causes the gonads to develop into ovaries
  - Ovaries then produce further gender biased hormones
- The presence of this gene and its products causes the gonads to descend and develop into testes
  - Testes then produce further gender biased hormones
  - Translocation of the gene to X chromosome results in an XX individual (genotype) but with XY characteristics (phenotype)

The Basics

Gender Determination

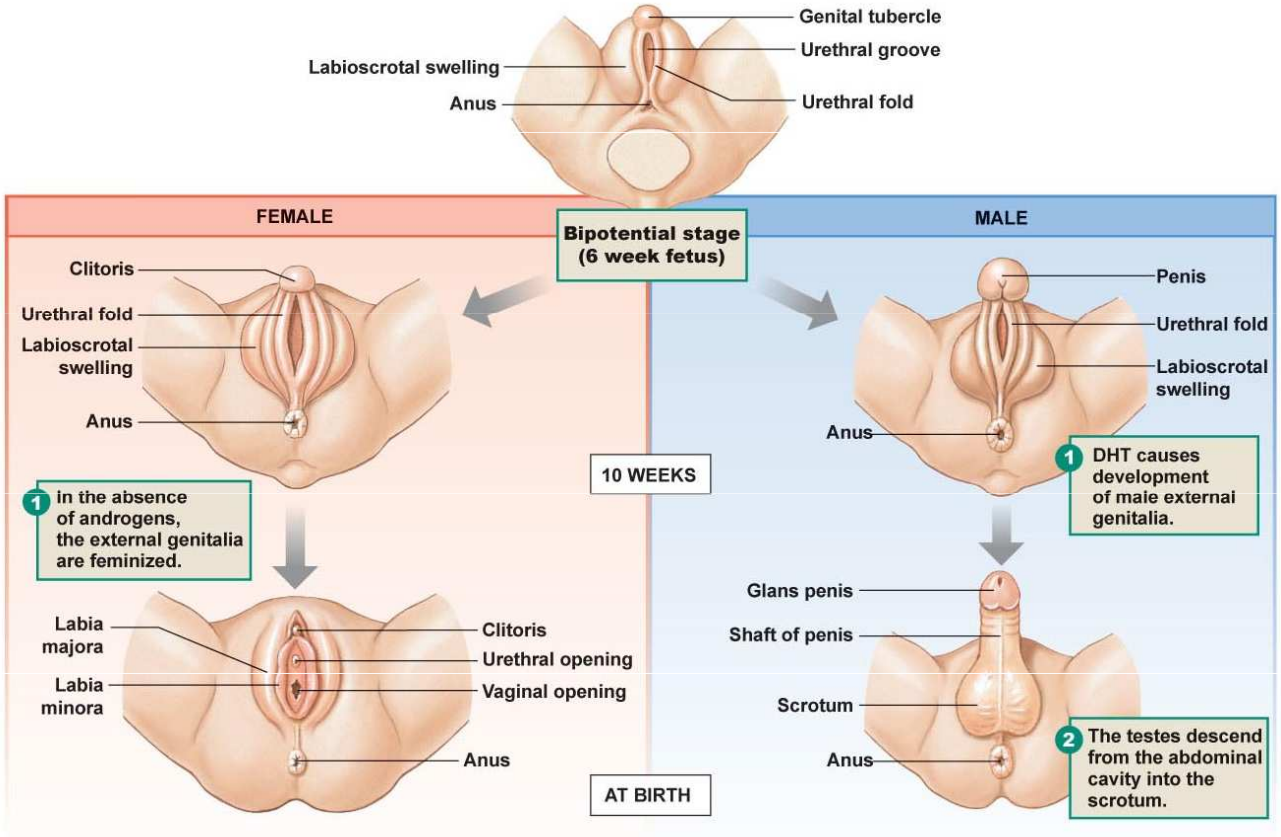
Effects of SRY on sex organ development



The Basics

Gender Determination

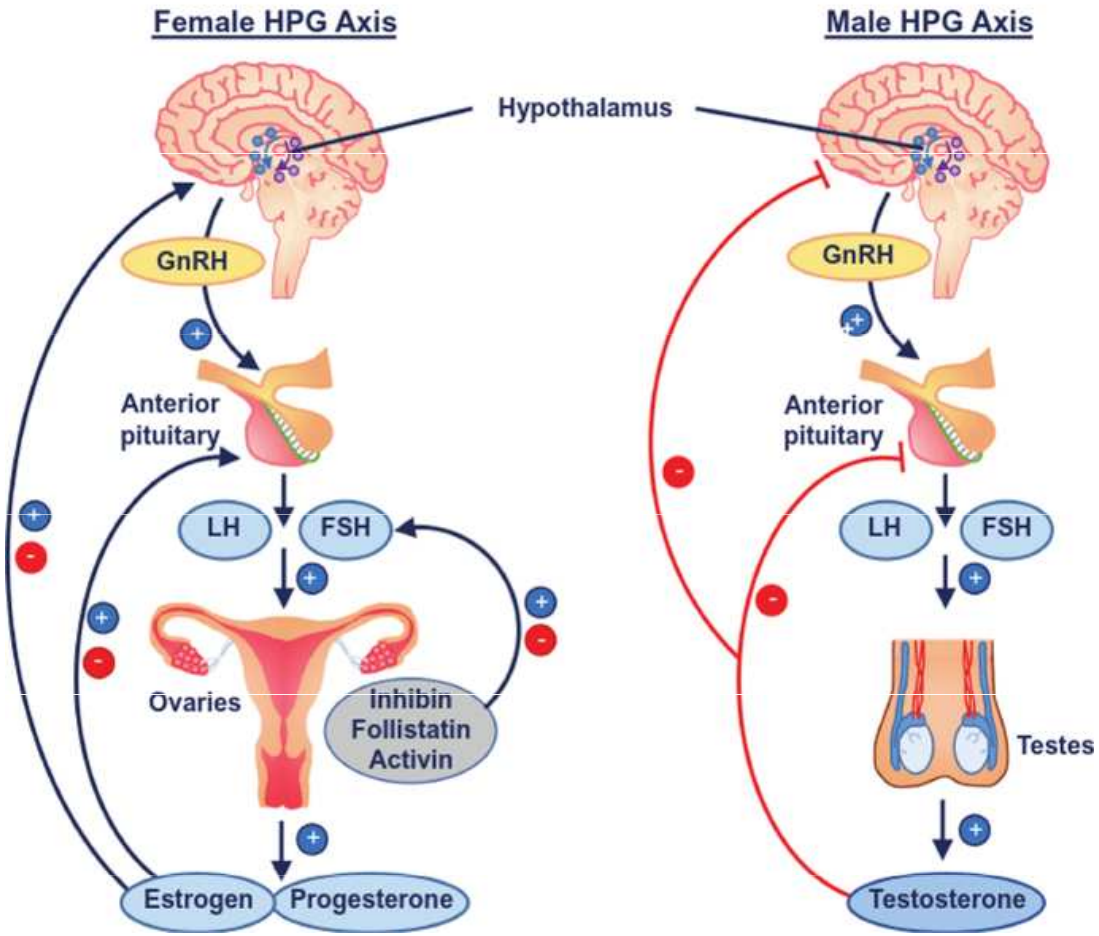
Indirect effects of SRY on male and female genital development

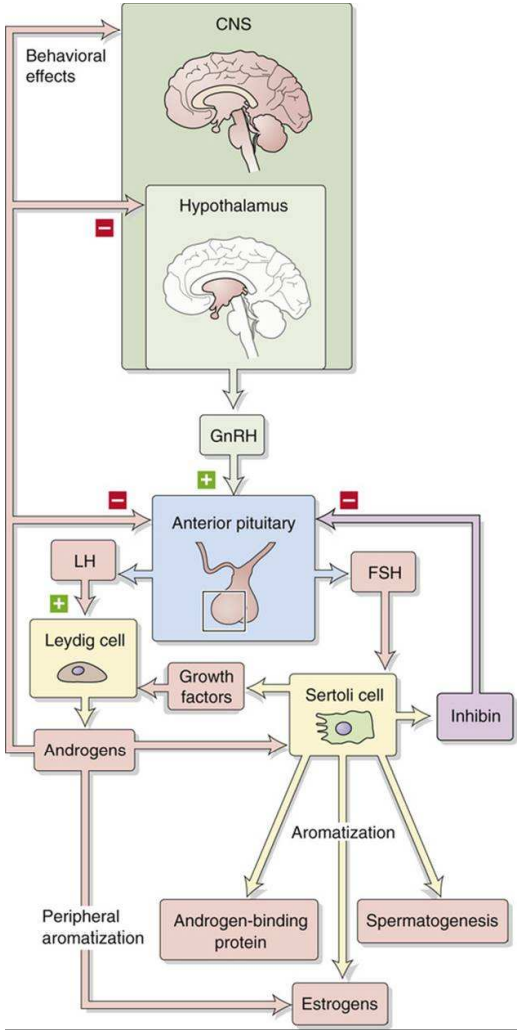


Lecture Outline

The Basics
Gametogenesis
Gender determination
The Pituitary-Gonad Axis
Female Reproductive Physiology
Ovarian Cycle
Uterine Cycle
Hormonal control and changes
Male Reproductive Physiology

The Pituitary-Gonad Axis





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Hormonal controls & changes
Male Reproductive Physiology

Female Reproductive Physiology

Basics

The hypothalamus-pituitary-gonad axis controls the required physiologic changes that occur both in the ovaries and in the uterus of the menstrual cycle.

The Menstrual Cycle

Duration

- Approximately 28 days (ranges 24 – 35 days)
- Starts with the removal of the endometrium & release of FSH by the anterior pituitary

The ovarian cycle

- Development of ovarian follicle
- Production of hormones
- Release of ovum during ovulation

The uterine cycle

- Removal of endometrium from prior uterine cycle
- Preparation for implantation of embryo under the influence of ovarian hormones

Female Reproductive Physiology

The Cycles

Three Phases of the Ovarian Cycle

Follicular phase

Ovulation phase

Luteal phase

Three Phases of the Uterine Cycle

Menses

Proliferative Phase

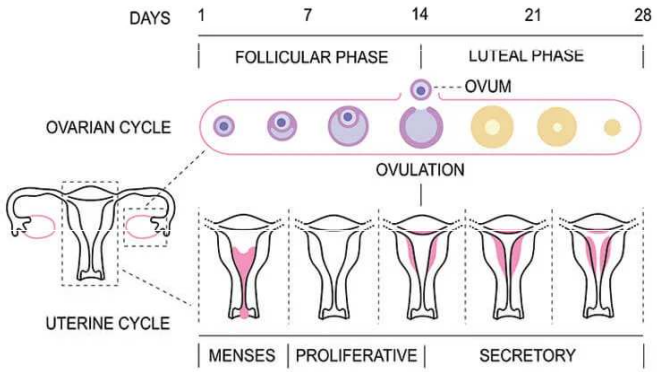
Secretory Phase

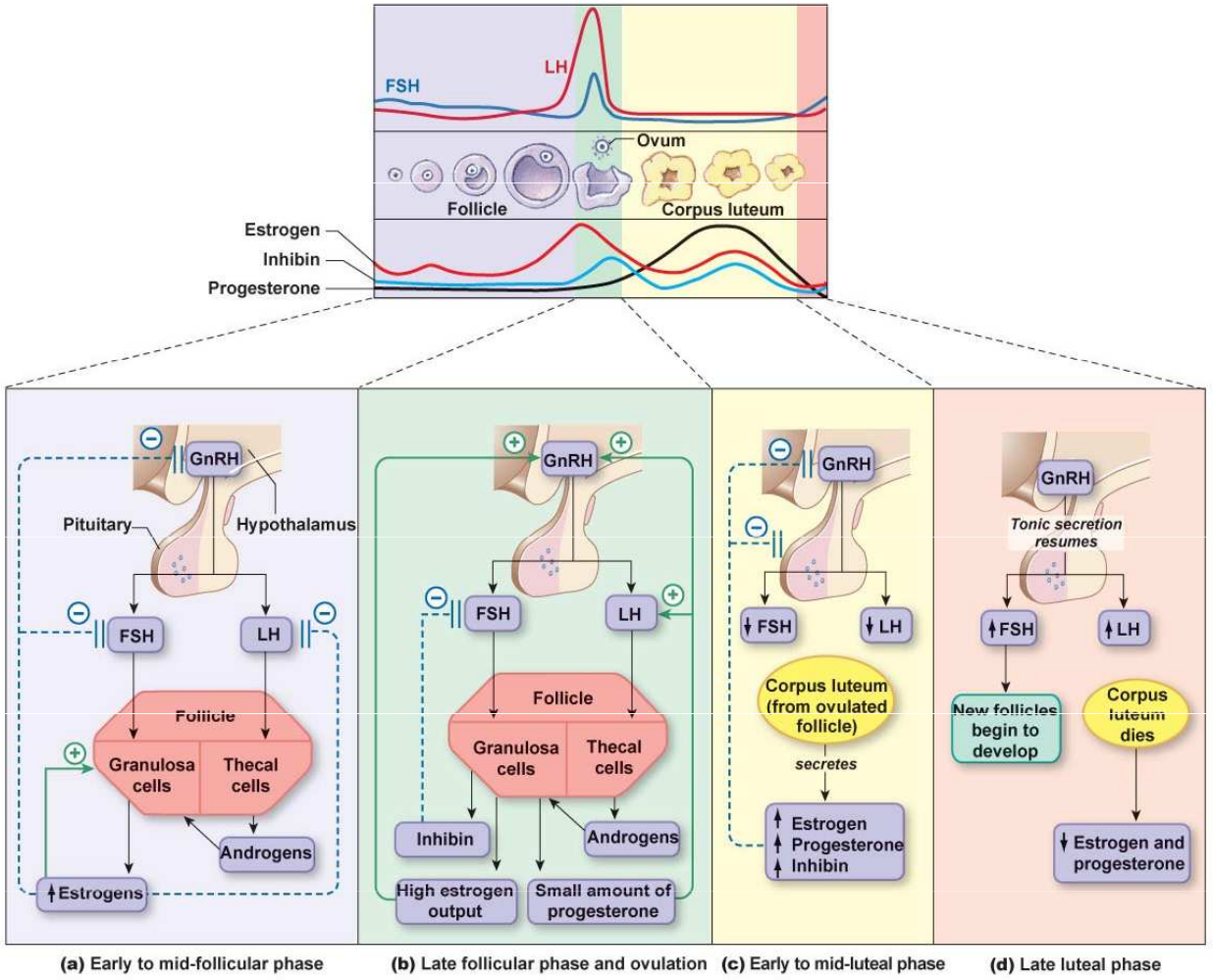
These ovarian and uterine phases are intimately linked together by the production and release of hormones

Female Reproductive Physiology

The Cycles

Hormonal control of the ovarian cycle

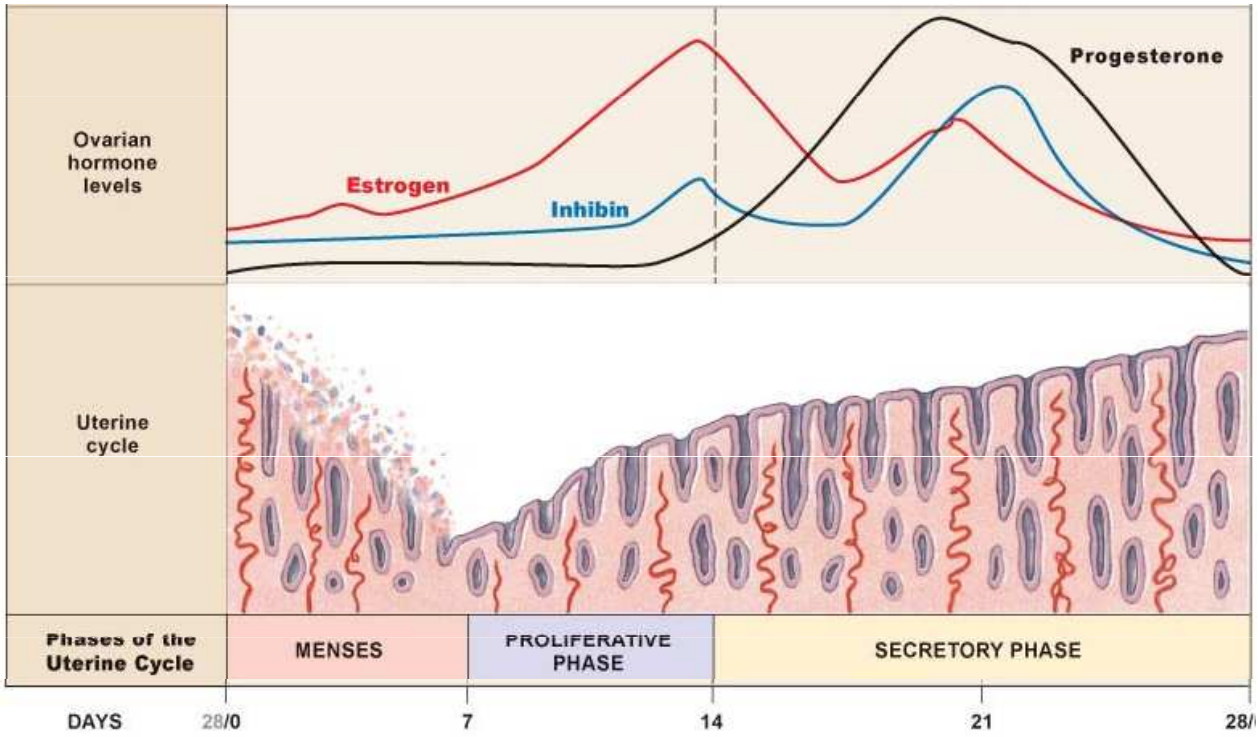




Female Reproductive Physiology

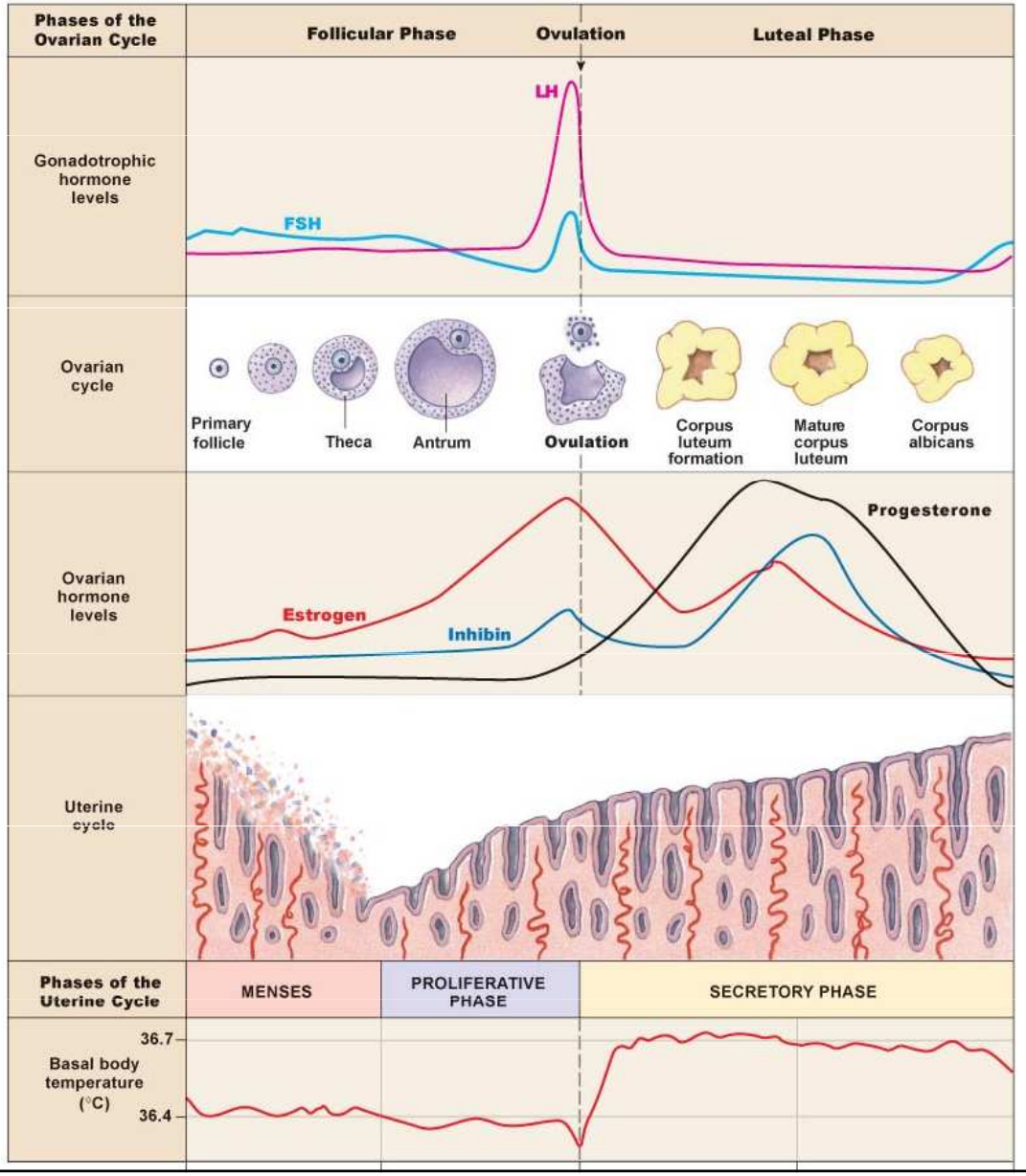
The Cycles

Hormonal control of the uterine cycle



Female Reproductive Physiology

All together



Female Reproductive Physiology

Fertilization Effects

- What happens if fertilization occurs?
- Uterine endometrium is maintained by
  - First the release of progesterone from the corpus lutem, then the release of hCG (human chorionic gonadotropin) which maintains the corpus luteum until the 7th week,
  - From 7th week on, the placenta produces progesterone which continues to maintain the endometrium & the corpus luteum degenerates
    - Placenta also produces estrogen and progesterone which at high levels blocks GnRH
      - Estrogen is also involved in breast development
      - Progesterone is also involved in uterine maintenance and relaxation (prevents premature contractions)
  - Placenta also produces hPL (human placental lactogen)
    - Implicated in breast development and milk production
      - Though determined not the only factor as lack of hPL has no ill effects
    - More important is the role hPL plays in fetal nutrition by altering maternal glucose and fatty acid metabolism

Female Reproductive Physiology

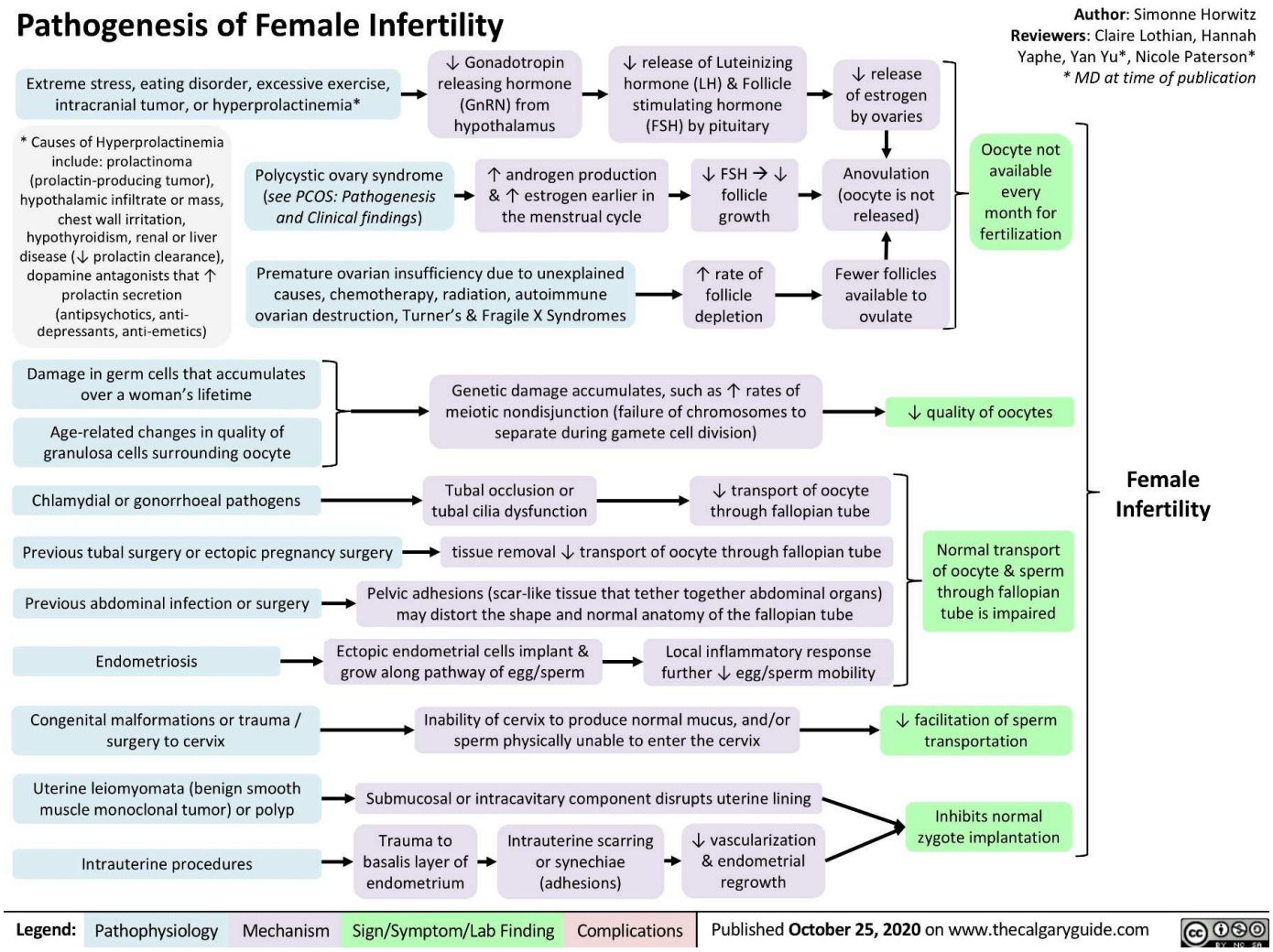
Fertilization Effects

What changes occur to allow parturition?

Increasing levels of corticotropin-releasing hormone (CRH) from the placenta a few weeks prior to delivery

- Early deliveries have been linked to early elevated levels of CRH
- During delivery
  - progesterone levels drop off
  - Oxytocin levels rise
    - Oxytocin receptors on the uterus are upregulated during gestation
  - Inhibin levels increase
    - Relax the cervix and ligaments of the pelvis
    - Allows for increased stretch of the cervix which triggers additional oxytocin which triggers stronger uterine contractions which increase stretch of the cervix which triggers oxytocin which triggers stronger uterine contractions which increases stretch of the cervix which increases oxytocin release which increases uterine contractions which increases stretch on cervix which….

Pathophysiology of female reproduction



Infertility definition

Infertility is defined as the inability of couples to have a baby after one year of regular unprotected intercourse, affecting 10–15 percent of couples. According to the latest WHO statistics, about 50–80 million people worldwide suffer from infertility. Large-scale studies have shown that about half of all cases of infertility occur due to female factors, 20 to 30 percent male factors, and 20 to 30 percent due to common causes of both gender. Recent meta-analysis studies by researchers show that male's factors are present in 20–70 percent of infertility cases.

PATHOLOGICAL PROCESSES, THEIR IMPLICATIONS, AND THERAPEUTIC OPTIONS

A. Folliculogenesis

1. Genetic

Premature ovarian insufficiency (POI) occurs in ~1% of women and is defined as the cessation of menstrual cycles under 40 years of age in the presence of an elevated serum FSH measured on two separate occasions. The causes may be genetic, environmental, infective (subsequent to mumps infection), associated with autoimmune conditions, metabolic [due to biochemical damage in the presence of galactossaemia], and subsequent to cancer therapy or surgery; however, in the majority of cases no cause is determined.

Turner syndrome

Possibly the most common genetic cause of POI is Turner syndrome characterized by the loss of all, or part of an X chromosome, occurring in ~1 in 3,000 female births. Approximately half due to X chromosome monosomy and the majority of the remainder due to mosaicism. This is a condition with several phenotypic features characterized by short stature, cardiac and renal abnormalities, hypothyroidism, webbed-neck, and otological and ophthalmological abnormalities are all common in childhood.

The ovarian insufficiency commonly found in this condition relates to disruption of the *BMP15* gene locus located at Xp11.2, within a critical region related to ovarian failure. Spontaneous puberty occurs in approximately one quarter of girls, more commonly in mosaics; however, premature ovarian failure is universal.

B. Ovulation
1. Hypogonadotrophic hypogonadism

Insufficient ovarian stimulation with gonadotrophins LH and FSH results in the condition of hypogonadotrophic hypogonadism (HH), either due to insufficient hypothalamic GnRH stimulation of the pituitary or due to insufficient secretion due to pituitary compromise. After exclusion of excessive exercise, extreme stress, or an eating disorder, and after ensuring pituitary function, other than secretion of LH and FSH, is normal, and pituitary imaging is normal the condition is considered idiopathic HH (IHH). The most common cause of GnRH insufficiency is the failure of migration of the GnRH secretory neurons to the forebrain which may also result in olfactory disorder (Kallman's syndrome); in the absence of olfactory, the condition is described as normosmic IHH.

2. Hyperprolactinemia

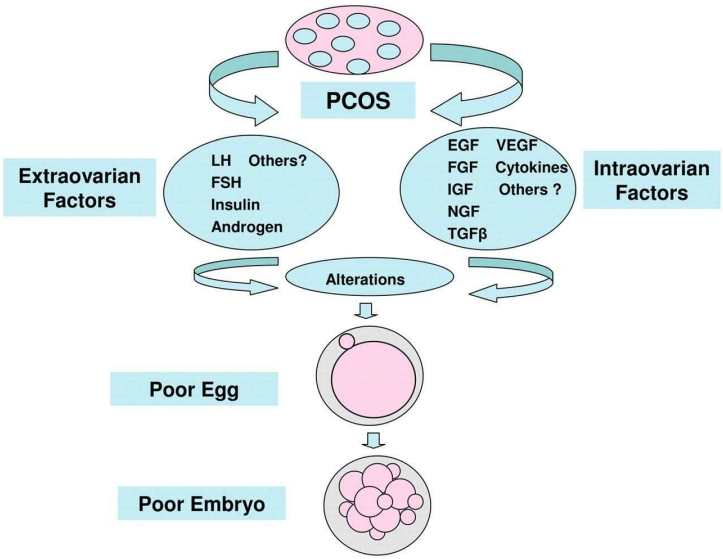
Other central causes of HH can be caused by systemic disease, medication (such as opioids and psychotropic medication), hypothalamic or pituitary compression, or infiltration; however, the most common cause is probably hyperprolactinemia. Hyperprolactinemia may be caused by physiological states such as pregnancy, breastfeeding, stress, exercise, and some medications as well as patients with chronic hypothyroidism. Kidney disease may predispose a patient to hyperprolactinemia due to reduced clearance and altered prolactin metabolism. As prolactin secretion is suppressed by hypothalamic dopamine secretion, interruption or compression of the pituitary stalk by a non-prolactin-secreting pituitary tumor will lead to hyperprolactinemia.

3. Polycystic ovary syndrome

The polycystic ovary syndrome (PCOS) is a collection of signs and symptoms related to ovarian dysfunction, found within a phenotypically heterogeneous group of women. It is classically described by the Rotterdam criteria as a syndrome consisting of two of three criteria related to infrequent or absent ovulation, a morphological description of the ovaries by ultrasound assessment, and hyperandrogenism. Other groups suggest that the excessive androgen secretion is the most significant underlying pathology as this is believed to lead to ovarian dysfunction and the longerterm metabolic consequences these women experience, and they consequently adopt a more stringent definition of PCOS.

PCOS

It is believed that oocyte developmental competence and the embryos resulting from fertilization are altered in women with PCOS, compared with women without PCOS. There are multiple serum and follicular factors that are reportedly altered in women with PCOS that may be responsible for this poor embryonic development and reduced implantation) although it is not clear whether this is associated with an increase in the rate of embryo aneuploidy. Not only is the systemic and follicular environment different in PCOS, the gene expression profile of oocytes derived from women with PCOS are distinctly different.
These genes relate to signal transduction, transcription, RNA and DNA processing, and the regulation of the cell cycle.
Of particular importance in the acquisition of oocyte developmental competence is GDF-9 expression, which is reduced in the oocytes of women with PCOS.



Ovarian hyperstimulation syndrome

OHSS is triggered by the systemic release of inflammatory cytokines, particularly VEGF which leads to endothelial cell damage and increased vascular permeability and the rapid development of ascites, and potentially pleural and pericardial effusion. OHSS is a significant cause of morbidity and in Australia and New Zealand is reported to complicate 0.6% of IVF cycles. Adjuvant therapies that have been demonstrated to significantly reduce the incidence are the use of an GnRH antagonist for pituitary downregulation, particularly with the use of an GnRH agonist trigger, the VEGF receptor blocker cabergoline, and by combing the ovarian stimulation with metformin administration. Other strategies include using low doses of gonadotrophin drugs for stimulation or omitting completely, cancelling the IVF cycle prior to oocyte retrieval, omitting the gonadotrophin drugs for a few days–“coasting” and not proceeding to an embryo transfer (so-called “freeze-all” approach). A further innovation is to use a different stimulation approach called in vitro maturation of oocytes (IVM) where no final trigger for oocyte maturation is administered prior to oocyte retrieval and oocyte maturation is performed in the laboratory with some centers reporting similar pregnancy rates as their standard IVF approach without the risk of OHSS. The evidence for some of the therapeutic interventions employed for women with OHSS is not robust and hence for the prevention of OHSS clinicians are advised to follow guidelines provided by consensus statements after systematic review of the literature.

C. Fallopian Tube Function

1. Disorders of ciliary action
2. Inflammatory disorders: endometriosis and infection
3. Other gynecological conditions

D. Implantation

1. Systemic

It is generally believed that severe systemic illness, such as sepsis or severe renal disease, will prevent embryonic implantation, although infection is an unusual cause of early pregnancy failure. A comprehensive list of all systemic conditions that have been demonstrated to have a significant negative influence on embryonic implantation is difficult to compile; however, conditions such as unstable diabetes, subclinical hypothyroidism, periodontal disease, and uncontrolled celiac disease have been demonstrated to reduce rates of conception, and it is believed that low serum vitamin D and active autoimmune conditions are also associated with a reduced chance of conception, and strategies to control these conditions may improve conception chances. Due to their high prevalence and ease of correction of the abnormality, celiac disease and subclinical hypothyroidism are discussed further.

2. Celiac disease

In a population of women experiencing unexplained infertility or recurrent miscarriage, celiac disease is five times more prevalent than in the general population. A meta-analysis of patients with celiac disease found that the risk of miscarriage is 40% greater with increased risks in the pregnancy for growth restriction and premature delivery, and the effect is tempered if a gluten-free diet is observed.

3. Subclinical hypothyroidism

Overt thyroid disorder must be appropriately managed prior to conception; however, more subtle perturbations in thyroid function are also associated with reproductive disorder. Approximately 1 in 25 women have subclinical hypothyroidism, and thyroid antibodies are present in up to one in eight of women. The presence of thyroid antibodies in a woman with normal thyroid function is believed to be associated with difficulty conceiving, recurrent implantation failure of embryos, and early pregnancy loss, potentially due to an unrecognized thyroid hormone deficiency or due to a potential autoimmune cause. Treatment of subclinical hypothyroidism is believed to potentially improve embryo development and is recommended for women prior to conception; however, whether to treat a woman prior to conception, who is euthyroid in the presence of thyroid antibodies, is contentious.

4. Thrombophilia

It has been unclear whether an inherited thrombophilia leading to microthrombi within the decidua are associated with implantation failure of the embryo as the intervillous spaces are not developed until 10 wk of gestation. Although it is tempting to speculate that perturbations in the clotting system may influence implantation and early embryonic development, for example, factor XII gene expression is increased in endometrial stromal cells during in vitro decidualization, this is believed to lead to an activation of the kallikrein-kininogen-kinin system during the implantation of human embryos.

5. Natural killer cells

There has been substantial interest in the assessment of blood and uterine natural killer cell populations in women with poor embryo implantation. Evidence would appear to suggest that women with unexplained implantation failure may have an abnormal population of natural killer (NK) cells in the blood and in the endometrium in the mid-luteal phase of the menstrual cycle, although strategies to improve the systemic and endometrial environment to facilitate conception have not been proven.

6. Endometrial and myometrial (endometriosis, leiomyomas, hydrosalpines, PCOS, obesity, endometrial polyps)

As evidenced by IVF success rates, embryonic implantation potential is decreased in the presence of endometriosis, leiomyomas, dilated fallopian tubes (hydrosalpines), and PCOS and have been linked to reduced endometrial expression of *HOXA10* and *HOXA11*. In addition, women with endometriosis have reduced expressions of endometrial integrin $\alpha_v\beta_3$ and *LIF*, hypermethylation leading to silencing of the *HOXA10* gene and endometrial progesterone resistance leading to a reduction in the chance of conception which may potentially be improved by surgical intervention or by use of prolonged downregulation with a GnRH analog prior to the initiation of an IVF cycle. Similarly to integrin $\alpha_v\beta_3$ expression normalizing with surgical intervention in the presence of endometriosis, the surgical removal of hydrosalpinges (salpingectomy) will restore the expression of integrin $\alpha_v\beta_3$ and *LIF* improving conception.

7. Embryonic

With the advent of genetic testing of blastomeres from embryos of women undergoing IVF treatment, it has become evident that a significant cause of embryos failing to implant is due to chromosomal rearrangements developing within the embryo as described above. With the ability to perform a low-resolution genome-wide survey of either single blastomeres from a three-day-old embryo or by the study of several cells from the trophectoderm of a five- or six-day-old blastocyst, it has become evident that in addition to the common occurrence of aneuploidy within the embryo, usually arising during meiosis, the embryo is predisposed to segmental chromosomal imbalances which arise during programmed DNA breakage and repair by homologous recombination during prophase I of meiosis. These rearrangements may lead to a failure to develop and implant, but also lead to phenotypic variability and hence ultimately genome evolution [for a detailed description of the origin of chromosomal rearrangement, see Voet et al.]. Hence, in IVF programs the majority of apparently morphologically normal embryos fail to implant as aneuploidy is such a frequent occurrence, occurring more frequently in an older woman, and a woman with a history of failed embryonic implantation.

F. Early Pregnancy Failure

The causes of early pregnancy failure overlap with the causes of embryo implantation failure and hence are not reiterated here. The discussion is limited to a description of possible associations of genetic variations which may influence implantation and predispose to early pregnancy loss.

1. Genetic polymorphisms

Genetic polymorphisms associated with recurrent early pregnancy loss suggest that genes regulating oxidative stress may be involved . Single nucleotide polymorphisms of genes associated with oxygen free radical metabolism, *ABCB1*, *COMT*, *GPX4*, and *OGG1*, have been reported to lead to a doubling of the risk of recurrent miscarriage. In addition, polymorphism of genes that regulate the complement cascade, such as membrane cofactor protein and C4 binding protein, have a putative role in recurrent early pregnancy loss. HLA-G, part of the major histocompatibility complex class I group, has been linked to the success of IVF and is believed to have an immune modulatory role, and potentially lower expression of HLA-G is associated with reduction in embryo implantation and early pregnancy failure.

IV. LIFESTYLE INFLUENCES INFLUENCING OVULATION, FALLOPIAN TUBE FUNCTION, IMPLANTATION, AND MISCARRIAGE

A. Delayed Childbearing

1. Ovulatory frequency

2. Oocyte quality

a) Aneuploidy

b) oocyte mitochondrial function

c) embryo metabolism

d) epigenetic alterations.

3. Fallopian tube function

B. Dietary Restriction and Over-exercise

c. **Stress**

D. Obesity

E. Cigarette Smoking

Stress

Due to central neuronal corticotrophin releasing hormone (CRH) projection to GnRH cells and CRH-induced β-endorphin inhibition of GnRH secretion, stress may exert a modulating effect on subsequent pituitary LH and FSH pulsatility, which may be overcome by modified behavior restoring ovulation. Higher daily reported stress levels in a cohort of normal healthy women were associated with a reduction in serum estradiol, LH, and luteal phase progesterone concentrations as well as a predisposition to anovulation. Furthermore, while it is known that an elevated serum cortisol concentration is related to FHA, women with FHA who resume ovulation have serum cortisol concentrations similar to eumenorrheic women, suggesting that by reducing stress levels by therapeutic interventions normal ovulation may return . The Nurses' Health Study demonstrated that working longer hours (over 40 h/wk) and also lifting heavy loads were associated with increased time to conceive, suggesting a relation to tiredness or stress may impact upon conception.

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Male Reproductive Physiology

Basic Functions

Function

Produce, maintain & transport viable spermatozoa

- Testes
- Epididymis
- Ductus deferens
- Accessory glands
  - Prostate
  - Seminal vesicles
  - Bulbourethral glands

Hormone production that

- develops secondary sexual characteristics
- Involved in feedback mechanisms relating to spermatogenesis

Male Reproductive Physiology

Testes

- Site of Sperm production
- Divided into lobules, each with seminiferous tubules.
- Seminiferous tubule functions to
  - Maintain environment for spermatogonia by the basal lamina and the Sertoli cells
    - Sertoli cells separate the lumen from the basal lamina and create a blood-testis barrier
    - Creates three compartments
      - Lumen – low glucose, high K^+ & steroid hormones
      - Basal compartment – the baso-lateral side of the sertoli cells & containing the developing spermatogonia
      - Interstitial fluid space – below the basal lamina and contains the Leydig cells
  - Produce hormones/paracrines
    - From Sertoli cells
    - From Leydig cells

Male Reproductive Physiology

Testis

Sertoli cells

Produce hormones & paracrines involved with control of hypothalamus-pituitary-gonad axis and the testes directly

- Anti-Müllerian Hormone (AMH)
  - Secreted during embryogenesis
  - Prevents development of the Müllerian ducts
- Inhibin & activin
  - Regulate FSH release from anterior pituitary
    - inhibin decreases FSH release
    - activin increases LH function & increases FSH release
- Androgen Binding Protein (ABP)
  - Binds to testosterone and DHT, reduces the loses due to diffusion resulting in an increase in testicular testosterone levels
- Estradiols & Aromatase
  - Support spermatogenesis

Male Reproductive Physiology

Testis

Sertoli cells, cont…

- GDNF (glial derived neurotrophic factor) & ERM transcription factor
  - Maintenance of the stem cell line

Leydig cells

Produce androgens

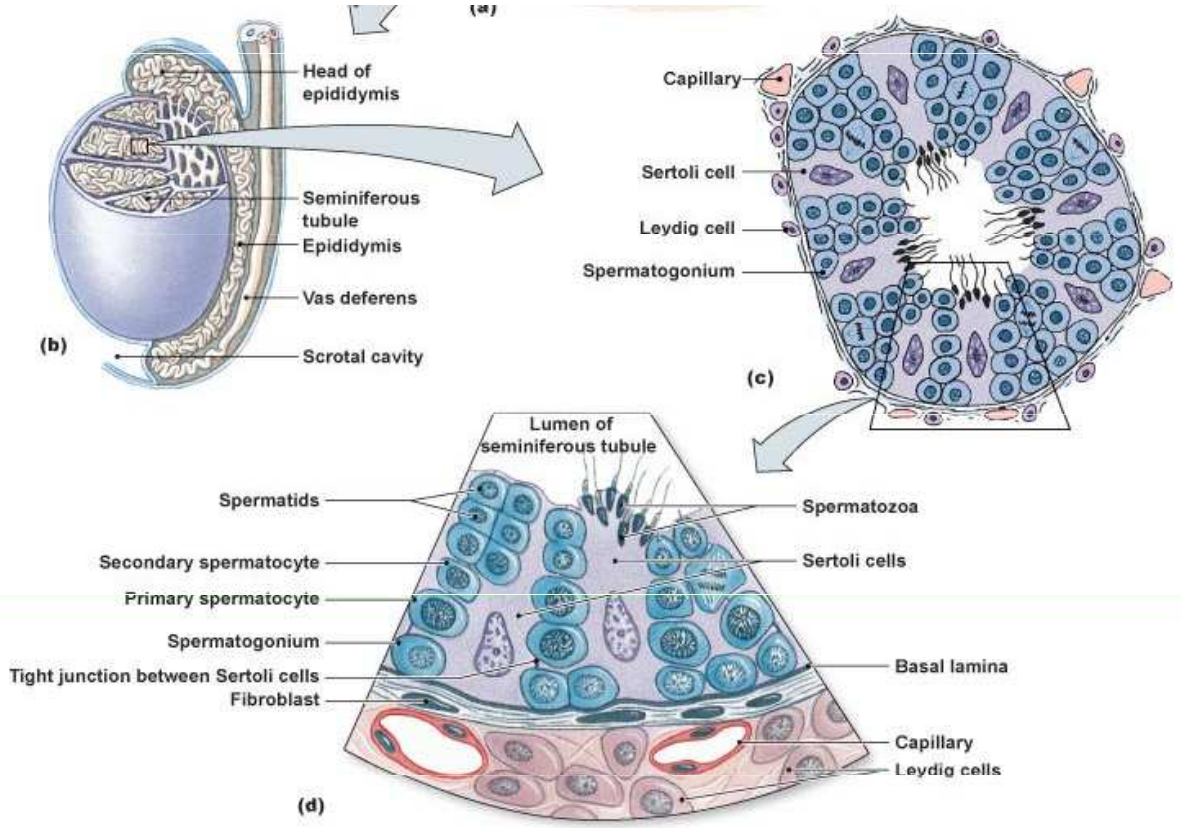
- testosterone, androstenedione and dehydroepiandrosterone (DHEA)
  - Increase spermatogenesis
  - Influence secondary sexual characteristics

Stimulated to produce androgens by luteinizing hormone (LH)

- FSH increases the response to LH by Leydig cells

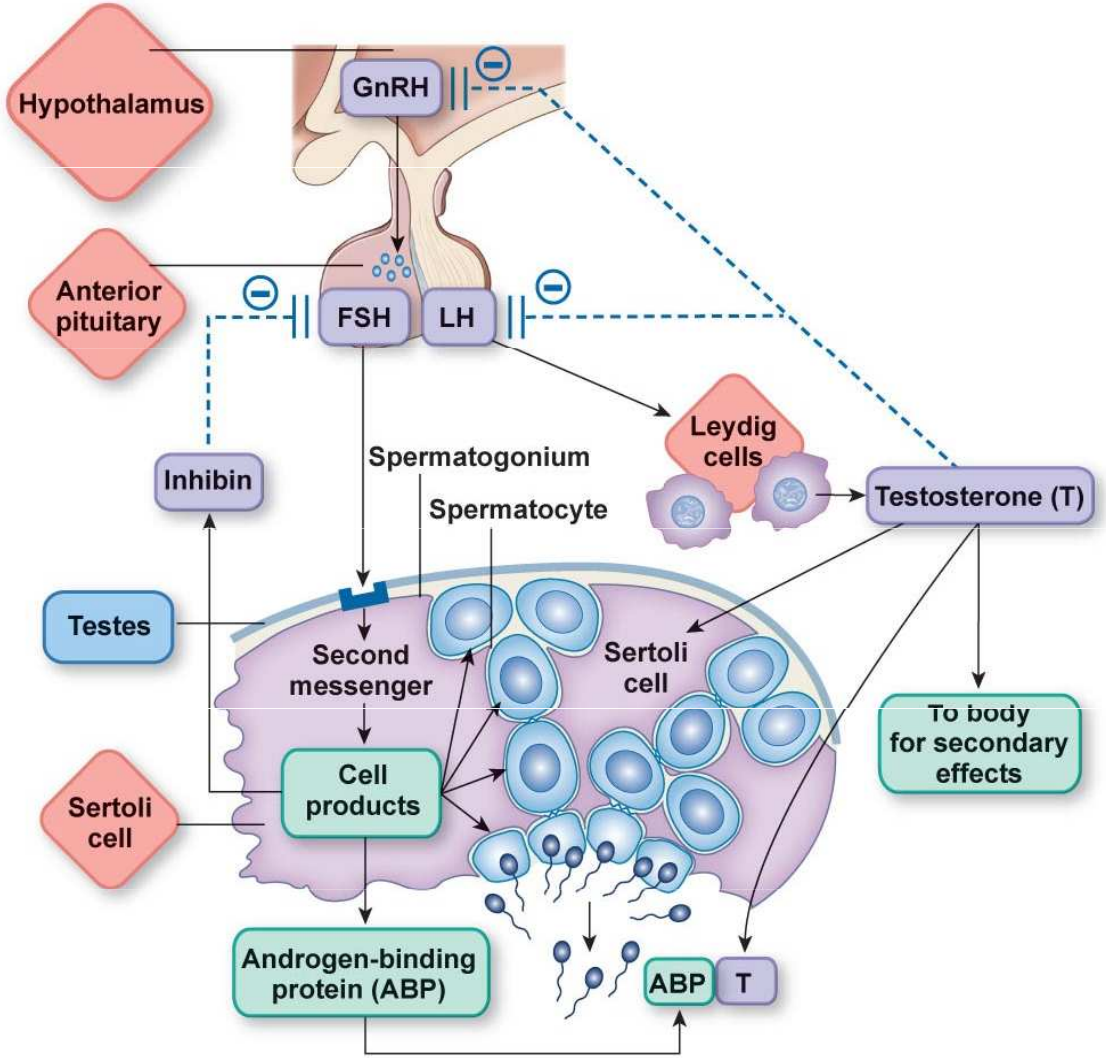
Male Reproductive Phsyiology

Testes



Male Reproductive Physiology
Testes

Spermatogenesis
Hormonal Control
Flow Chart



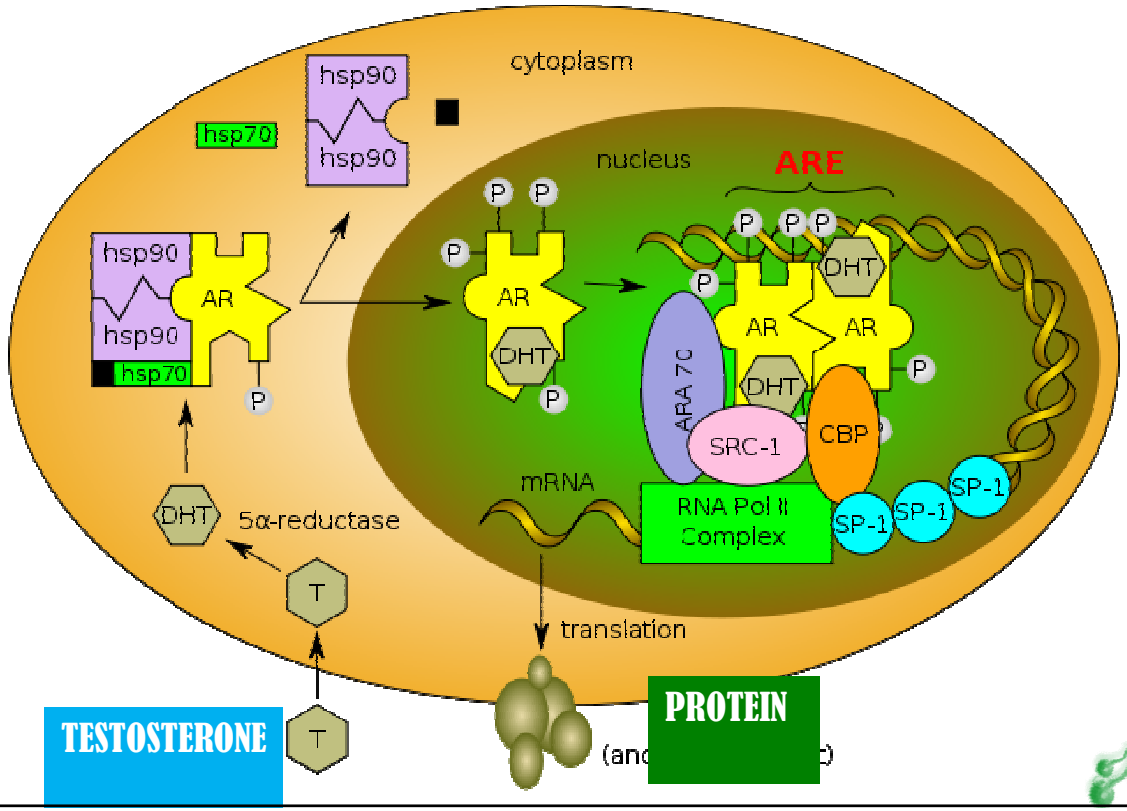
1. ANDROGENS

What does testosterone do ?

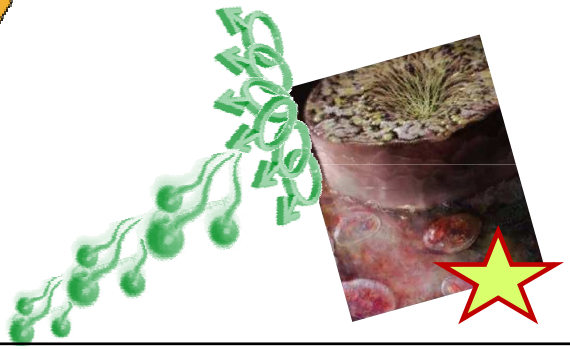
A. It or its DHT metabolite bind to Androgen Receptors [AR]

Like all other steroid hormones they act on;

1. Cytosolic ➔ GENOMIC Action ➔ mediates cell growth & differentation in AR responsive tissues; reproductive, those of 2ndry male sex characters, muscles …

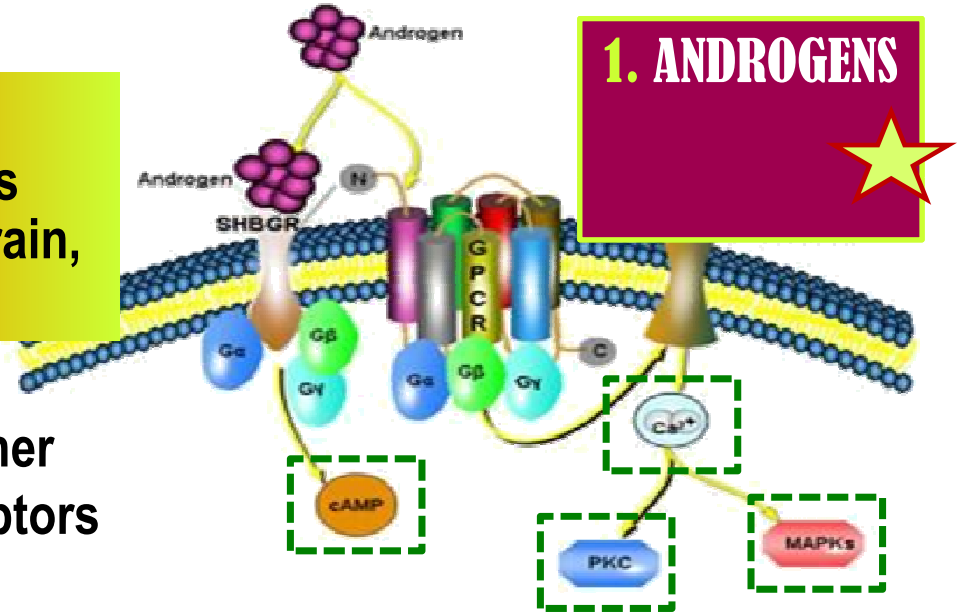


- Binding & Activation
- Nuclear translocation
- Dimerization on SRE
- Gene Transcription
- mRNA Translation
- New Protein Formation



1. ANDROGENS

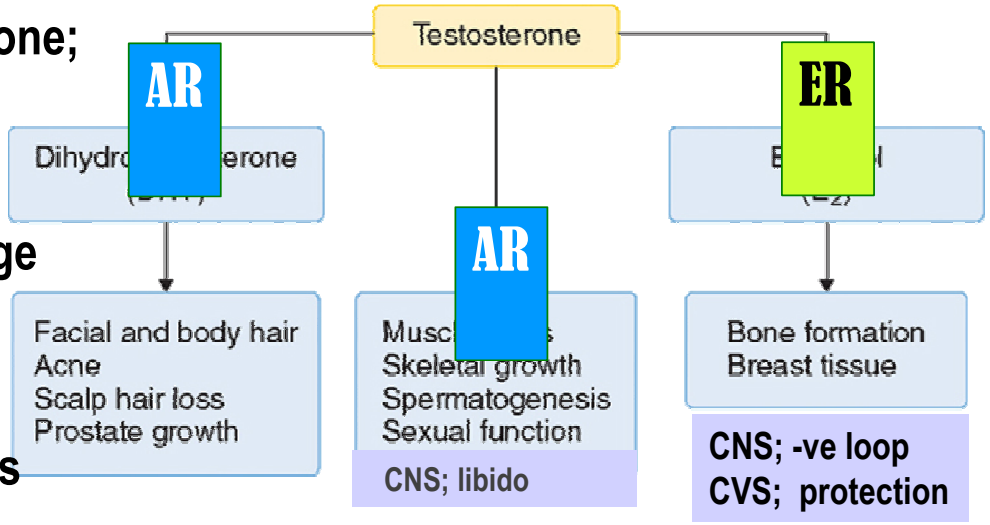
2. Membranous ➔
NON-GENOMIC Action ➔ mediates rapid responses ➔ on some brain, CVS, T cells functions



Like all other steroid receptors

B. It aromatize to estradiol and binds to Estrogen Receptors [ER]

Estradiol rather than testosterone;
1.Responsible for feedback inhibition on hypothalamus (specially –ve LH secretion)
2. Induce maturation of cartilage ➔ leading to closure of epiphyses & conclusion of growth.
3. Some CVS protective actions



1. ANDROGENS

ACTIONS

ACTIONS DIVIDED INTO

- Virilizing effects
  - Gonadotropin regulation
  - Spermatogenesis
  - Sexual dysfunction
  - Sexual restoration and development
- Protein anabolic effects
  - Increased bone density
  - Increased muscle mass
  - Increased red blood cell mass

← Testosterone & Synthetic Androgens

←Anabolic Steroids

Not used in infertility

Male Reproductive Physiology

Accessory Gland Function

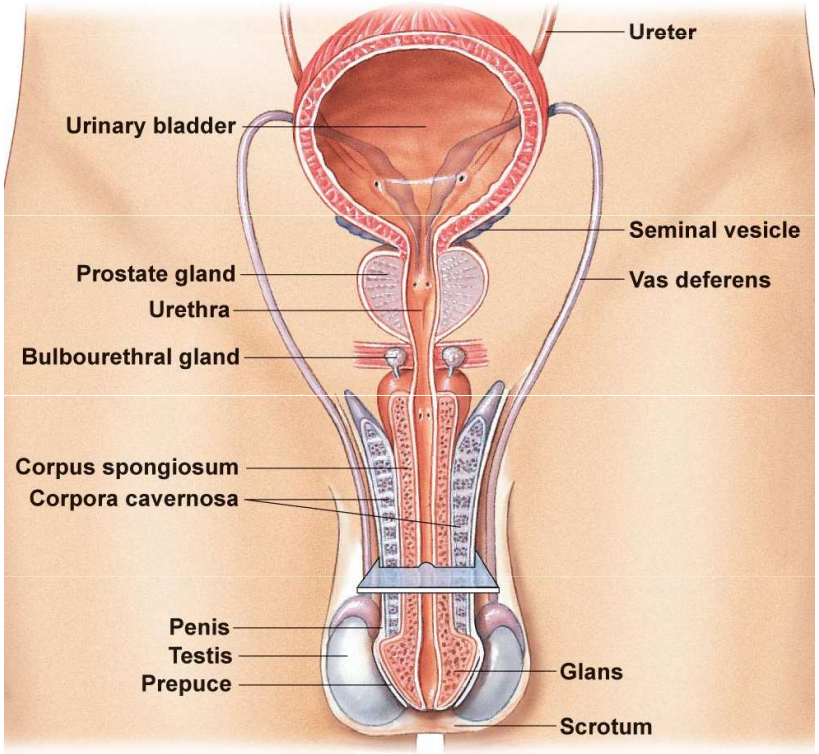
Job of the accessory glands is to

Secrete seminal fluid (99% of semen volume)

- Components of seminal fluid
  - Mucus
  - Water
  - Nutrients
  - Buffers
  - Enzymes
  - Prostaglandins
  - Zinc?

Accessory Glands

- Prostate
- Seminal vesicles
- Bulbourethral glands



Male Reproductive Physiology

Accessory Gland Function

Seminal Fluid Components, Function and Location (source)

From Table 26-3

Mucus	Lubricant	Bulbourethral glands
Water	Provides liquid medium	All accessory glands
Buffers	Neutralize acidic environment of the vagina	Prostate, bulbo-urethral glands
Nutrients	Nourish sperm	
Fructose		Seminal vesicles
Citric acid		Prostate
Vitamin C		Seminal vesicles
Carnitine		Epididymis
Enzymes	Clot semen in vagina, then liquefy the clot	Seminal vesicles and prostate
Zinc	Unknown; possible association with fertility	Unknown
Prostaglandins	Smooth muscle contraction; may aid sperm transport	Seminal vesicles

Male Reproductive Physiology

The sexual response

Remember

Function of the reproductive system is to reproduce

Males contribution is

- Deliver viable sperm into the vagina
- Requires a complex neural reflex – the erection reflex
  - Creates changes in vascular condition within the penile arterioles
    - Initiated by erotic stimuli (visual, auditory, tactile, cerebral)
    - the parasympathetic division of the ANS causes vasodilation of the penile arterioles
    - Erectile tissue fills with blood creating an erection

Male Reproductive Physiology

The sexual response

- Remember
- Function of the reproductive system is to reproduce
- Males contribution is
  - Deliver viable sperm into the vagina
  - Requires a complex neural reflexes
    - Starts with the erection reflex which creates changes in vascular condition within the penile arterioles
      - Initiated by erotic stimuli (visual, auditory, tactile, cerebral) the parasympathetic division of the ANS causes vasodilation of the penile arterioles
      - Erectile tissue fills with blood creating an erection
    - Emission & Ejaculation during climax
      - Emission is the movment of sperm from vas deferens into the urethra adding seminal fluid along the way, this is under sympathetic control
      - Ejaculation is the expulsion of semen due to strong muscular contractions – this is a spinal reflex

Male Reproductive Pathophysiology

The sexual response

Emission & Ejaculation during climax

Emission is the movement of sperm from vas deferens into the urethra adding seminal fluid along the way, this is under sympathetic control

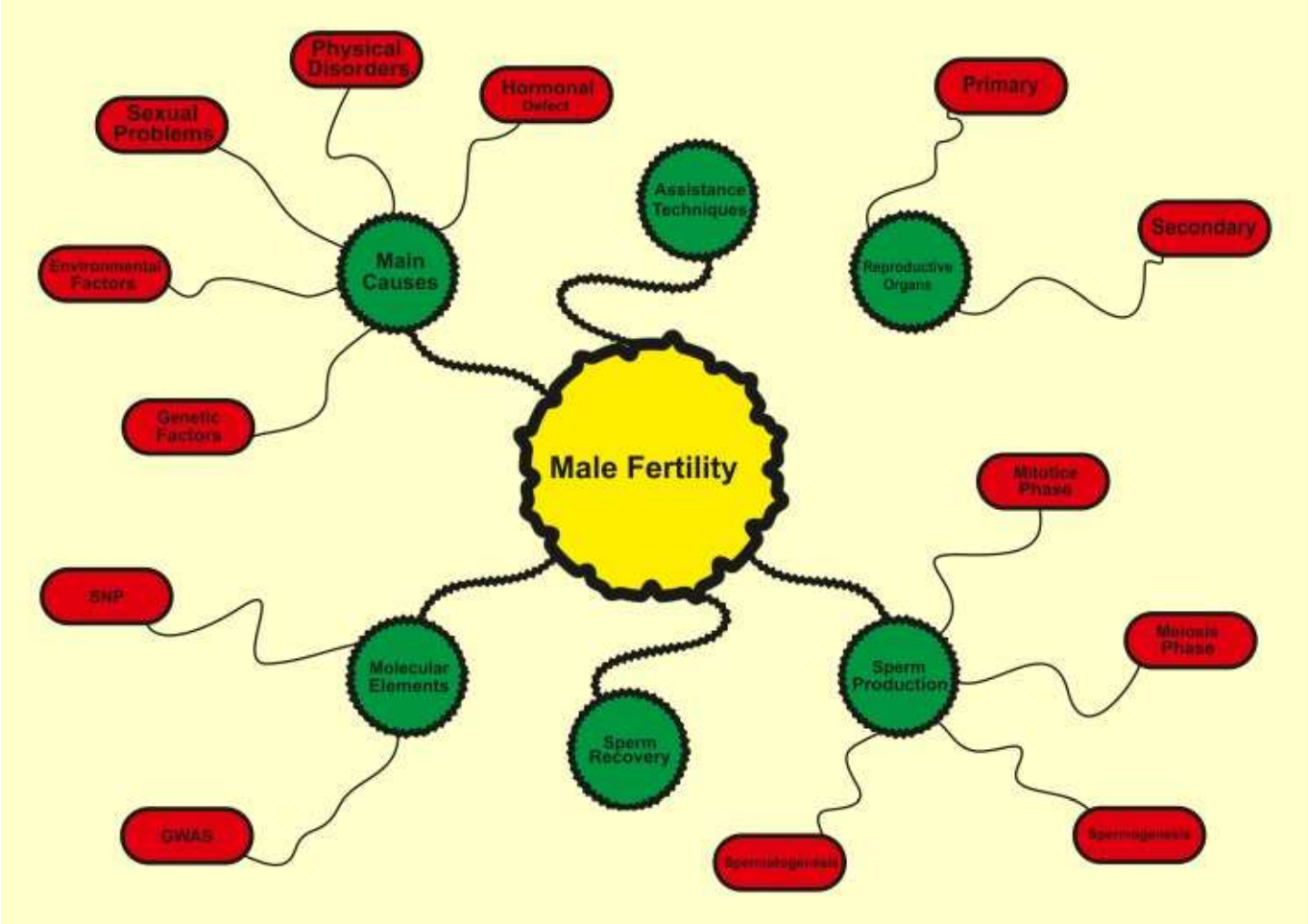
Ejaculation is the expulsion of semen due to strong muscular contractions – this is a spinal reflex

Started with the contraction of the bulbospongiosus muscle

Disorders

Erectile dysfunction (ED)
Premature ejaculation
Prolonged ejaculation / anorgasmic

Male infertility



Male infertility - causes

There are multiple causes for male infertility, which can be broadly classified due to their general underlying etiology. These include endocrine disorders (usually due to hypogonadism) at an estimated 2% to 5%, sperm transport disorders (such as vasectomy) at 5%, primary testicular defects (which includes abnormal sperm parameters without any identifiable cause) at 65% to 80% and idiopathic (where an infertile male has normal sperm and semen parameters) at 10% to 20%. These are broad estimates only as accurate statistics are unavailable due to general underreporting, cultural factors, and regional variations. Patients sent to a tertiary referral center are more likely to have their condition reported, while private patients may never have their data collected.

The causes underlying male infertility are numerous and best categorized by effects at one or more of the following levels: pretesticular, testicular, and posttesticular.

Pretesticular causes of male infertility

Hypothalamic Disease

Gonadotropin Deficiency (Kallmann Syndrome)

Kallmann syndrome (1:30,000) is characterized by central hypogonadism, delayed in puberty, and infertility. Other clinical features include anosmia, small testes and occasionally renal agenesis, bimanual synkinesia, cleft lip, and dental agenesis. When anosmia is not present, the condition is termed idiopathic hypogonadotrophic hypogonadism (IHH). The clinical diagnosis of Kallmann syndrome is confirmed by hormonal assessment revealing low testosterone, low LH, low FSH, and normal prolactin levels. Infertility is treatable with gonadotropin (LH and FSH) replacement over 12–18 months, which induces sperm in the ejaculate in 80% of men. The condition is inherited as a familial disorder in one-third of cases and both X-linked and autosomal inheritance patterns have been described.

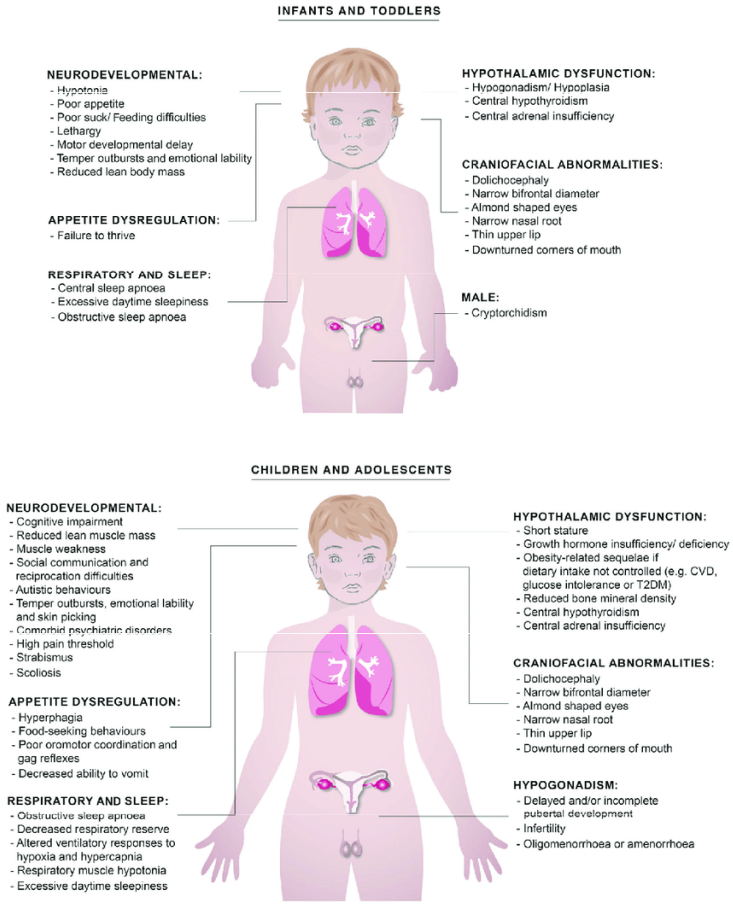
Isolated Gonadotropin Deficiencies

These deficiencies are rare. As the result of a partial LH deficit, there is enough LH to stimulate intratesticular testosterone production and spermatogenesis but insufficient testosterone to promote virilization. The results are a eunuchoid body habitus, variable virilization, and gynecomastia. These men usually have normal size testes, but sperm concentration is low. Plasma FSH levels are normal, but serum LH and testosterone levels are low normal.

With insufficient FSH production by the pituitary, patients are normally virilized, testicular size is normal, and LH and testosterone levels are normal. FSH levels are uniformly low and do not respond to stimulation with GnRH. Sperm counts range from azoospermia to severely low numbers (oligospermia).

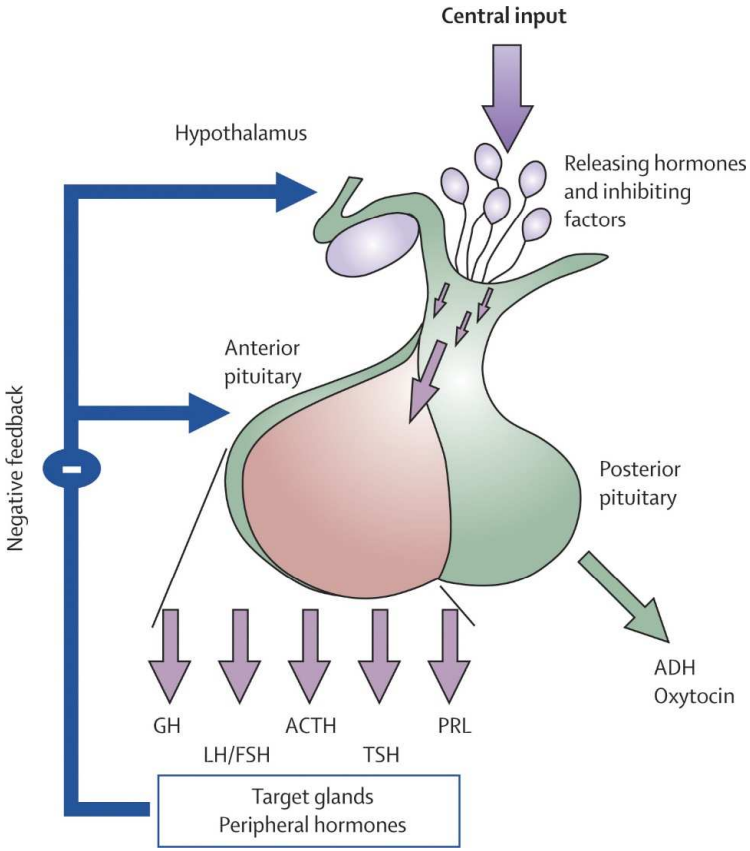
Congenital Hypogonadotrophic Syndromes

Several syndromes may be associated with secondary hypogonadism. Prader–Willi syndrome (1:20,000) is characterized by obesity, mental retardation, small extremities, and hypogonadism and is caused by a deficiency of hypothalamic GnRH. The cause of this condition appears to be a single gene deletion on chromosome 15. Similar to Kallmann syndrome, spermatogenesis can be induced by treatment with FSH and LH. Bardet–Biedl syndrome is an autosomal recessive form of hypogonadotrophic hypogonadism that also results from GnRH deficiency. It is characterized by mental retardation, retinitis pigmentosa, polydactyly, and hypogonadism. The presentation is similar to Kallmann syndrome but includes obesity and may also be treated with gonadotropin administration. Cerebellar ataxia can be associated with hypogonadotrophic hypogonadism. Cerebellar involvement includes abnormalities of speech and gait and these patients can have a eunuchoid appearance with atrophic testes. Hypothalamic–pituitary dysfunction due to pathologic changes in cerebral white matter is thought to underlie infertility.



Pituitary Disease
Pituitary Insufficiency

Pituitary insufficiency may result from tumors, infarcts, surgery, radiation, or infiltrative and granulomatous processes. In sickle cell anemia, pituitary and testicular microinfarcts result from sickling of red blood cells potentially leading to both hypogonadism and spermatogenic failure. Men with **sickle cell anemia** have decreased testosterone and variable LH and FSH levels. **Beta-thalassemia** occurs primarily in patients of Mediterranean or African origin and is caused by mutations in the beta-globulin that leads to abnormal hemoglobin composition and subsequent red cell lysis. Infertility results from the deposition of hemosiderin in the pituitary gland and testes. Similarly, **hemochromatosis** results in iron deposition within the liver, testis, and pituitary and is associated with testicular dysfunction in 80% of cases.



Exogenous or Endogenous Hormones

Estrogens

An excess of sex steroids, either estrogens or androgens, may cause infertility due to an imbalance of the testosterone estrogen ratio, which is normally 10:1. Liver cirrhosis increases endogenous estrogens due to augmented aromatase activity within the diseased liver. Likewise, obesity may be associated with testosterone and estrogen imbalance owing to increased peripheral aromatase activity in adipocytes. Less commonly, adrenocortical tumors, Sertoli cell tumors, and interstitial testis tumors may produce estrogens. Excess estrogens cause spermatogenic failure by decreasing pituitary gonadotropin secretion, thus inducing secondary testis failure.

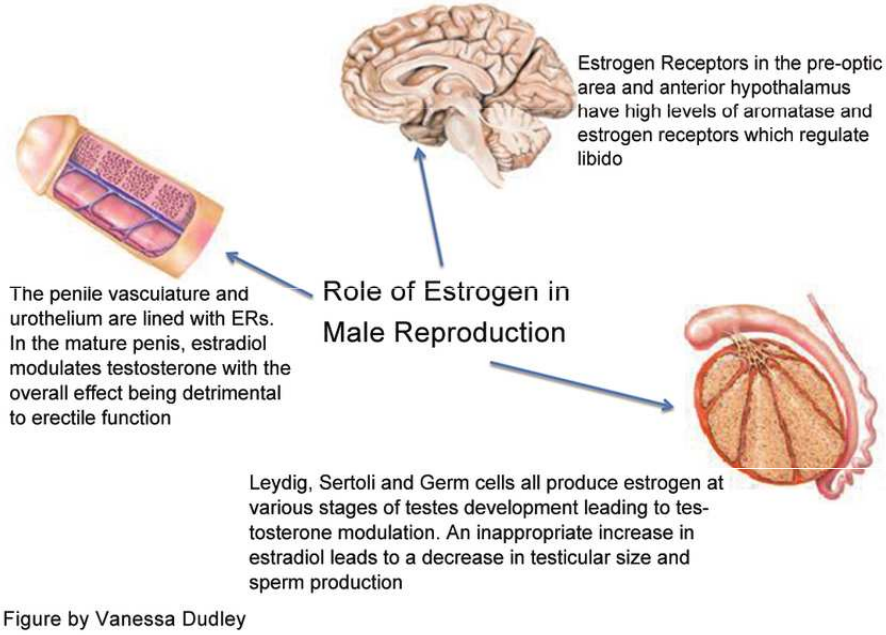
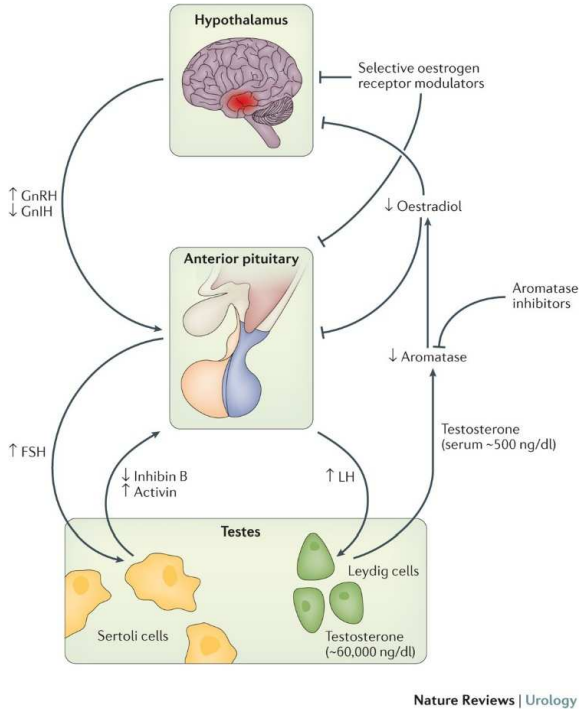


Figure by Vanessa Dudley

Exogenous or Endogenous Hormones

Androgens

An excess of androgens can suppress pituitary gonadotropin secretion and lead to secondary testis failure. The use of exogenous androgenic steroids (anabolic steroids) by as many as 15% of high school athletes, 30% of college athletes, and 70% of professional athletes may result in temporary sterility due to suppression of the normal HPG axis. Treatment includes immediate discontinuation of steroids and reevaluation of semen quality every 3–6 months until spermatogenesis returns. The most common reason for excess endogenous androgens is congenital adrenal hyperplasia caused by 21-hydroxylase deficiency. The resultant absence of cortisol synthesis and excessive adrenocorticotropic hormone production leads to elevated androgenic steroids by the adrenal cortex. High androgen levels in prepubertal boys result in precocious puberty, with premature development of secondary sex characteristics and abnormal enlargement of the phallus. The testes are characteristically small because of central gonadotropin inhibition by androgens. In young girls, virilization occurs with clitoral enlargement. In cases of classic congenital adrenal hyperplasia that presents in childhood, normal sperm counts and fertility have been reported, even without glucocorticoid treatment. This disorder is one of the few intersex conditions associated with potentially normal fertility. Other sources of endogenous androgens include hormonally active adrenocortical tumors or Leydig cell tumors of the testis.



Male infertility

Male infertility contributes to approximately half of all cases of infertility and affects 7% of the male population. For the majority of these men the cause remains unexplained. Despite a clear role for genetic causes in male infertility, there is a distinct lack of diagnostically relevant genes and at least 40% of all cases are classified as idiopathic

Testicular causes

The Testis

Normal male reproduction requires that the testes have both endocrine (steroid production) and exocrine (sperm maturation and excretion) function. Both of these functions are under the control of the HPG axis. Steroidogenesis occurs in the interstitial compartment, where Leydig cells reside. Spermatogenesis occurs in the seminiferous tubules with the support of Sertoli cells.

Endocrine Testis

Testosterone is metabolized into two primary metabolites in target tissues: (1) dihydrotestosterone (DHT) by the enzyme 5-alpha-reductase and (2) estradiol by the enzyme aromatase. DHT is a more potent androgen than testosterone, and in many tissues, the conversion of testosterone to DHT is required for androgen action. While aromatase is present in many tissues, adipocytes play a significant role in the aromatization of testosterone to estradiol. While the mechanisms are still being elucidated, estradiol appears to have a pivotal role in the regulation of the HPG axis.

Exocrine Testis

FSH acts primarily on Sertoli cells within the seminiferous tubules to induce the production of a number of proteins necessary for spermatogenesis, including androgen-binding protein, transferrin, lactate, ceruloplasmin, clusterin, plasminogen activator, prostaglandins, and several growth factors. Through these actions, seminiferous tubule growth is stimulated during development, and sperm production is initiated during puberty and maintained in adulthood.

Common Genetic Causes

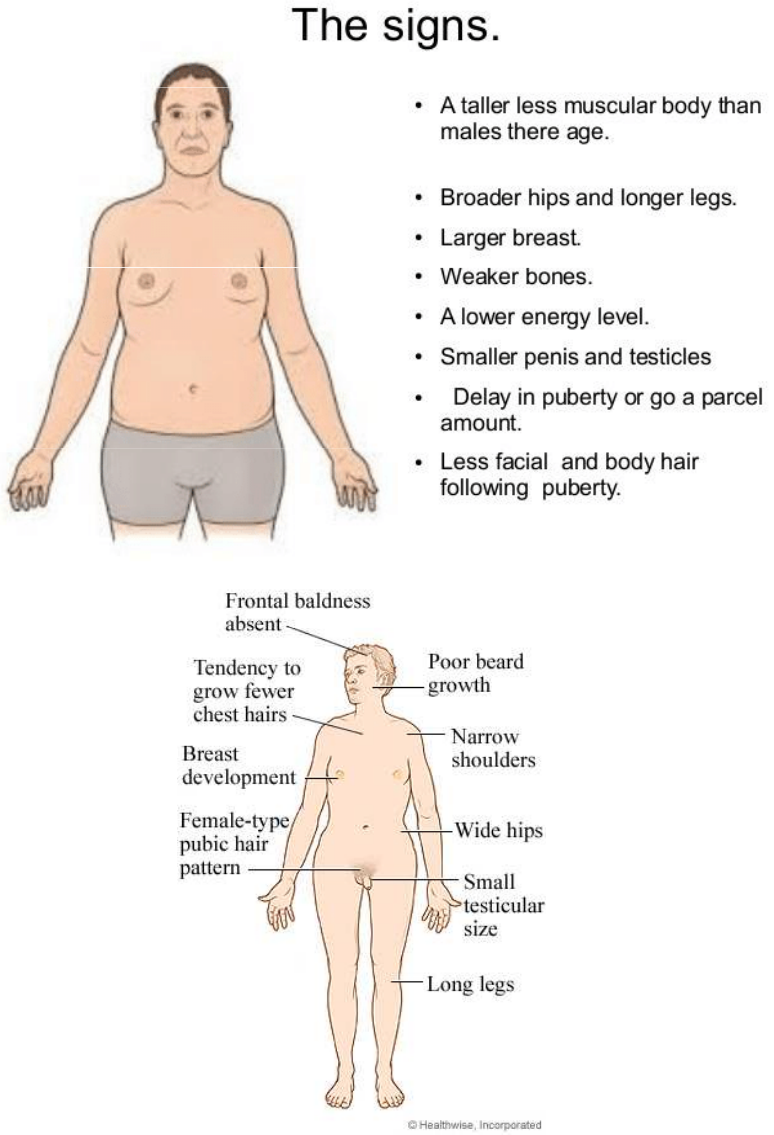
Y Chromosome Microdeletions

Approximately 7% of men with low sperm counts and 13% of men with azoospermia have a structural alteration in the long arm of the Y chromosome (Yq). The testis-determining region genes that control testis differentiation are intact, but there may be gross deletions in other regions that may lead to defective spermatogenesis. The recent explosion in molecular genetics has allowed for sophisticated analysis of the Y chromosome. At present, three gene sites are being investigated as putative AZF (azoospermia factor) candidates: *AZFa*, *b*, and *c*. The most promising site is *AZFc*, which contains the *DAZ* gene region. The gene, of which there are at least six copies in this region, appears to encode a ribonucleic acid (RNA)-binding protein that regulate the meiotic pathway during germ cell production. Homologs of the *DAZ* gene are found in many other animals, including mouse and *Drosophila*. A quantitative polymerase chain reaction–based assay is used to test blood for these deletions. In the future, sperm DNA may also be tested as part of a semen analysis. Since men with these microdeletions can have sperm in the ejaculate, they are likely to pass them on to offspring if ART is used.

Klinefelter Syndrome

Abnormalities in chromosomal constitution are well-recognized causes of male infertility. In a study of 1263 infertile couples, a 6.2% overall prevalence of chromosomal abnormalities was detected. Among men whose sperm count was <10 million/mL, the prevalence was 11%. In azoospermic men, 21% had significant chromosomal abnormalities. For this reason, cytogenetic analysis (karyotype) of autosomal and sex chromosomal anomalies should be considered ir men with severe oligospermia and azoospermia.

Klinefelter syndrome is the most common chromosomal aneuploidy and a common genetic cause of azoospermia, accounting for up to 14% of cases in some series (overall incidence 1:500 males). The classic triad of findings is small, firm testes; gynecomastia; and azoospermia. Some men may present with delayed sexual maturation, increased height, decreased intelligence, varicosities, obesity, diabetes, leukemia, increased likelihood of extragonadal germ cell tumors, and breast cancer (20-fold higher than in normal men).



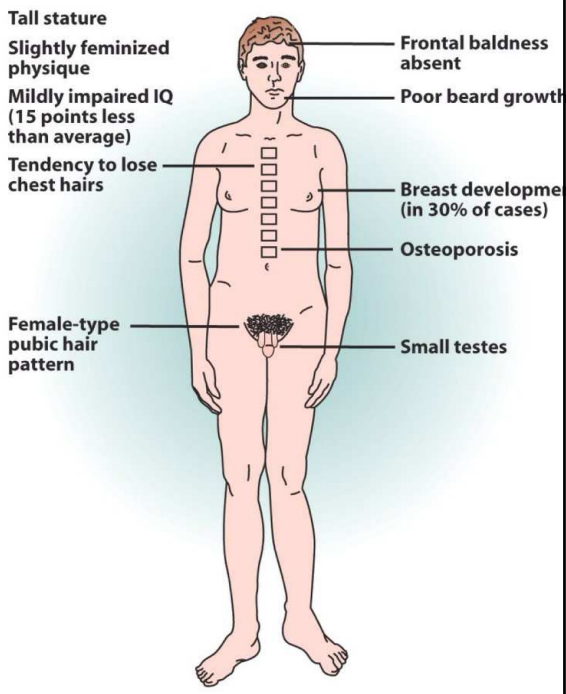
Klinefelter syndrome

Among men with Klinefelter syndrome, 90% have an extra X chromosome (47,XXY) and 10% are mosaic, with a combination of XXY/XY chromosomes. The testes are usually <2 cm in length and always <3.5 cm; biopsies show sclerosis and hyalinization of the seminiferous tubules with normal numbers of Leydig cells. Hormones usually demonstrate decreased testosterone and frankly elevated LH and FSH levels. Serum estradiol levels may also be elevated. With age, testosterone levels decline, and most men will require androgen replacement therapy both for virilization and for normal sexual function. Paternity with this syndrome is rare but more likely in the mosaic or milder form of the disease. Some men will have limited spermatogenesis, whereby sperm may be retrieved from the testicles and used with ICSI to cause pregnancy.

Other Genetic Causes and Syndromes

XX Male Syndrome (De la Chapelle syndrome)

XX male syndrome is a structural and numerical chromosomal condition, a variant of Klinefelter syndrome that presents as gynecomastia at puberty or as azoospermia in adults. Average height is below normal, and hypospadias is common. Male external and internal genitalia are otherwise normal. The prevalence of mental deficiency is not increased. Hormone evaluation shows elevated FSH and LH and low or normal testosterone levels. Testis biopsy reveals absent spermatogenesis with fibrosis and Leydig cell clumping. The most obvious explanation is that sex-determining ratio (SRY), or the testis-determining region, is translocated from the Y to the X chromosome. Thus, testis differentiation is present; however, the genes that control spermatogenesis on the Y chromosome are not similarly translocated, resulting in azoospermia.



Gonadotoxins

Radiation

The effects of radiotherapy on sperm production have been well described. Clifton and Bremner (1983) examined the effects of ionizing irradiation on semen quality and spermatogenesis among a population of healthy prisoners in the 1960s. Before a vasectomy, each of the volunteers was exposed to various levels of radiation and found a distinct dose-dependent, inverse relationship between irradiation and sperm count. Sperm count was significantly reduced at 15 cGy, and azoospermia was temporarily induced at 50 cGy. Persistent azoospermia was induced at 400 cGy, without evidence of recovery for a minimum of 40 weeks. In most subjects, sperm counts rebounded to preirradiation levels with cessation of exposure.

Drugs

Exposure to gonadotropic drugs can result in infertility by various mechanisms. Ketoconazole, spironolactone, and alcohol inhibit testosterone synthesis, whereas cimetidine is an androgen antagonist. Recreational drugs such as marijuana, heroin, and methadone are associated with lower testosterone levels. Certain pesticides, like dibromochloropropane, are likely to have estrogen-like activity. Importantly, the gonadotoxic potential of many pharmaceutical and over-the-counter medications is unknown. Therefore, couples should consider discontinuing and unnecessary medication or supplements prior to their attempt to conceive.

Traumatic injury of testes

Torsion

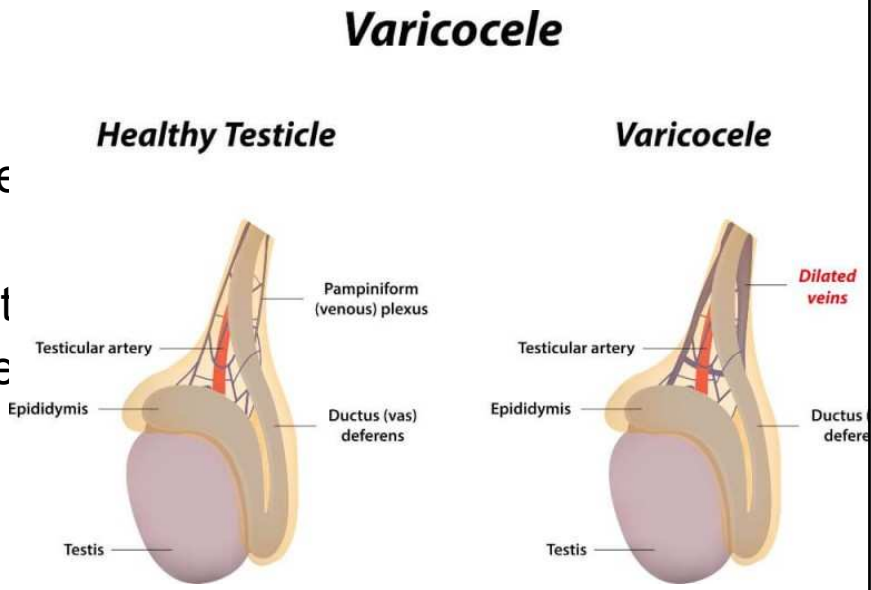
Ischemic injury to the testis secondary to twisting of the testis on the spermatic cord pedicle is common in prepubertal and early postpubertal boys. When diagnosed and corrected surgically within 6 hours of occurrence, the testis can usually be saved. Torsion may result in inoculation of the immune system with testis antigens that may predispose to later immunological infertility. It recognized that the “normal” contralateral mate of a torsed testis could also exhibit histologic abnormalities. It has not been clearly demonstrated whether this is related to the actual torsion or to an underlying abnormality in testes predisposed to torsion.

Trauma

Trauma to the testis can result in infertility. Because of the unique immunologic status of the testis in the body (ie, it is an immunologically privileged site), trauma to the testis can invoke an abnormal immune response in addition to atrophy resulting from injury. Both may contribute to infertility. Trauma to the testis that results in fracture of the testis tunica albuginea should be surgically explored and repaired to minimize exposure of testis tissue to the body.

Varicocele

Varicocele is defined as dilated and incompetent veins within the pampiniform plexus of spermatic cord. Varicocele has been described as the most common surgically correctable cause of male subfertility. This is a disease that develops during puberty when both endocrine and exocrine function of the testicle dramatically increases, along with testicular blood flow. Varicocele is only rarely detected in boys <10 years of age. A left-sided varicocele is found in 15% of healthy young men. In contrast, the incidence of a left varicocele in subfertile men approaches 40%. Bilateral varicoceles are uncommon in healthy men (<10%) but are palpated in up to 20% of subfertile men. In general, varicoceles do not spontaneously regress. An accurate physical examination remains the cornerstone of varicocele diagnosis.



Posttesticular causes of male infertility

Congenital Blockages

Cystic Fibrosis

CF is the most common autosomal recessive genetic disorder in the United States with a carrier frequency of 1:20 among Caucasians. The disease is caused by defective chloride ion transport across cell membranes resulting in fluid and electrolyte abnormalities (abnormal chloride–sweat test). CF typically presents with chronic lung obstruction and pulmonary infections, pancreatic insufficiency, and infertility. More than 95% of men with CF also have congenital bilateral absence of the vas deferens (CBAVD). In addition to the vas, parts of the epididymis, seminal vesicles, and ejaculatory ducts may be atrophic or absent, causing obstruction. Although spermatogenesis is quantitatively normal, recent data suggest that sperm from men with CF may lack the normal capacity to fertilize an egg. Furthermore, some carriers of abnormal CF genes may also have functional sperm defects. CBAVD accounts for 1–2% of infertility cases. On physical examination, no palpable vas deferens is observed on one or both sides. As in CF, the rest of the reproductive tract ducts may also be abnormal and unreconstructable. This disease is related to CF. Even though most of these men demonstrate no symptoms of CF, up to 80% of patients will harbor a detectable CF mutation. In addition, 15% of these men will have renal malformations, most commonly unilateral agenesis.

Idiopathic Epididymal Obstruction

Idiopathic epididymal obstruction is a relatively uncommon condition found in otherwise healthy men. There is recent evidence linking this condition to CF in that one-third of men so obstructed may harbor CF gene mutations.

Adult Polycystic Kidney Disease

Adult polycystic kidney disease is an autosomal dominant disorder associated with numerous cysts of the kidney, liver, spleen, pancreas, epididymis, seminal vesicle, and testis. Disease onset usually occurs in the twenties or thirties with symptoms of abdominal pain, hypertension, and renal failure. Infertility with this disease is usually secondary to obstructing cysts in the epididymis or seminal vesicle.

Acquired blockages

Groin and Hernia Surgery

Groin and hernia surgery can result in inguinal vas deferens obstruction in 1% of cases. There has been concern that Marlex mesh used for hernia repairs may add to perivasal inflammation and increase the likelihood of vassal obstruction.

Bacterial Infections

Bacterial infections (*E. coli* in men age >35 or *Chlamydia trachomatis* in young men) may involve the epididymis, with scarring and obstruction.

Disorders of Sperm Function or Motility

Immotile Cilia Syndromes

Immotile cilia syndromes are a heterogeneous group of disorders (1:20,000 males) in which sperm motility is reduced or absent. The sperm defects are due to abnormalities in the motor apparatus or axoneme of sperm and other ciliated cells. Normally, nine pairs of microtubules are organized around a central microtubule pair within the sperm tail and are connected by dynein arms (ATPase) that regulate microtubule and therefore sperm tail motion. Various defects in the dynein arms cause deficits in ciliary and sperm activity. Kartagener syndrome is a subset of this disorder (1:40,000 males) that presents with the triad of chronic sinusitis, bronchiectasis, and situs inversus. Most immotile cilia cases are diagnosed in childhood with respiratory and sinus difficulties. Cilia present in the retina and ear may also be defective and lead to retinitis pigmentosa and deafness in Usher's syndrome. Men with immotile cilia characteristically have nonmotile but viable sperm in normal numbers. The diagnosis can only be confirmed with electron microscopy of sperm.

Disorders of Sperm Function or Motility

Immunologic Infertility

Autoimmune infertility has been implicated as a cause of infertility in 10% of infertile couples. The testis is an immunologically privileged site, probably owing to the blood–testis barrier, which consists of Sertoli cell tight junctions and locally downregulated cellular immunity. Autoimmune infertility may result from an abnormal exposure to sperm antigens as the result of vasectomy, testis torsion, or biopsy, which then incites a pathologic immune response. Antibodies may disturb sperm transport or disrupt sperm–egg interaction. Many assays are available to detect ASAs, but assays that detect sperm-bound, and not serum, antibodies are the most clinically relevant.

Infections

Various products of activated leukocytes can exist in infected semen. A correlation exists between leukocytes in semen and the generation of superoxide anions, hydrogen peroxide, and hydroxyl radicals (reactive oxygen species), all of which can damage sperm membranes. Sperm are highly susceptible to the effects of oxidative stress because they possess little cytoplasm and therefore little antioxidant activity. Damage to sperm from oxidative stress has been correlated to loss of function and damaged DNA. Although genital tract infection has been linked to infertility in epidemiologic studies, the correlation between individual organisms and infertility is unclear. Uncontrolled studies suggest that pregnancy rates may improve after treatment, but controlled studies do not confirm these findings.

Disorders of Coitus

Impotence

Sexual dysfunction stemming from low libido or impotence is a frequent cause of infertility. The male hormonal evaluation can detect organic reasons for such problems. Most cases of situational impotence, in which the stress of attempting to conceive results in poor erections, are treated with sexual counseling and oral phosphodiesterase inhibitors.

Hypospadias

Anatomic problems like hypospadias can cause inappropriate placement of the seminal coagulum too distant from the cervix and result in infertility.

The next week plan

Pathophysiology of pregnancy
Pathophysiology of birth
Pathophysiology of early post-partum adaptation


WE DO
WHAT?!