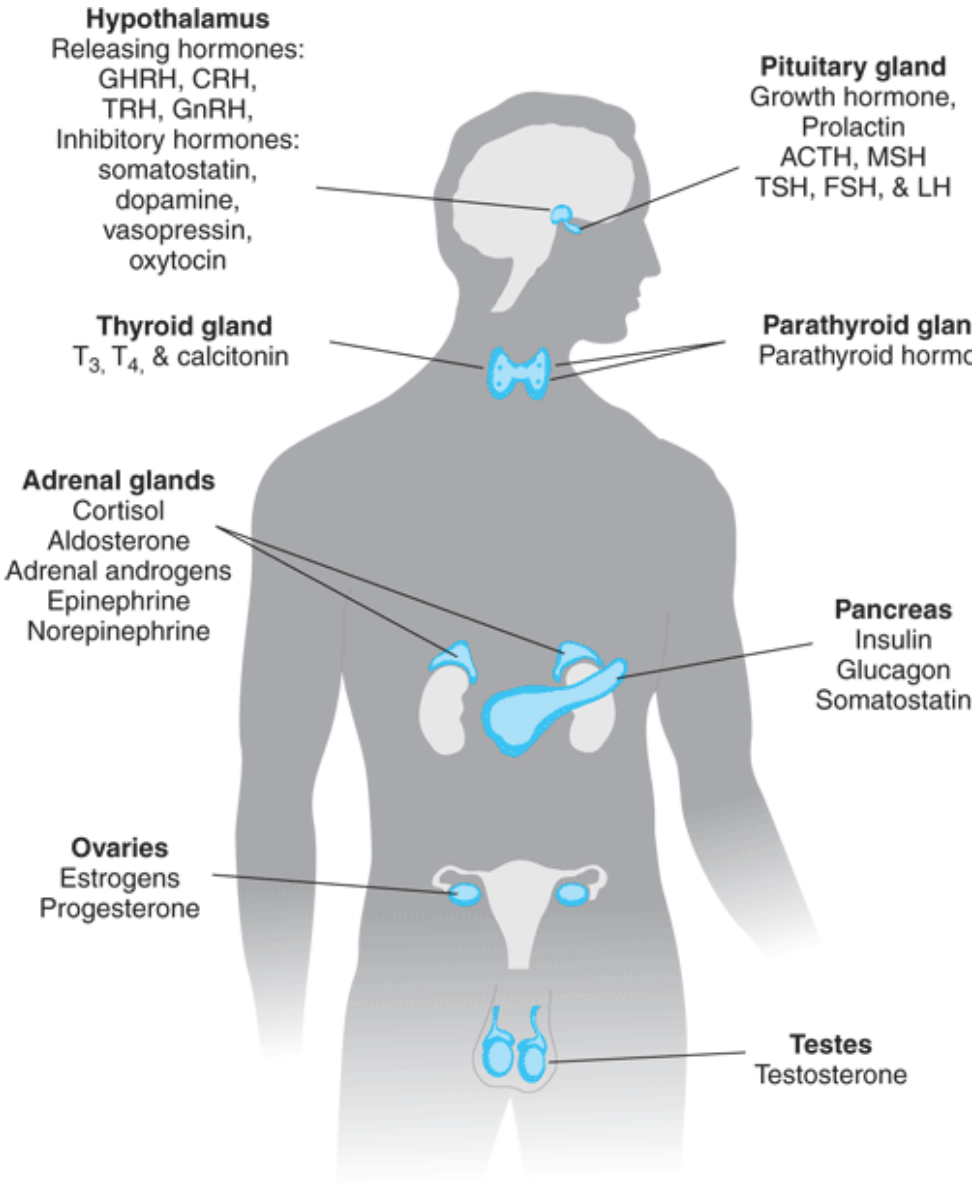
ENDOCRINOLOGY

DISORDERS OF FEMALE AND MALE IMAGE

Kenneth Alonso, MD, FACP



Source: Molina PE: *Endocrine Physiology*, 2nd Edition:
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Fig. 1-1 Accessed 02/01/2010

Hypothalamic control of pituitary hormones

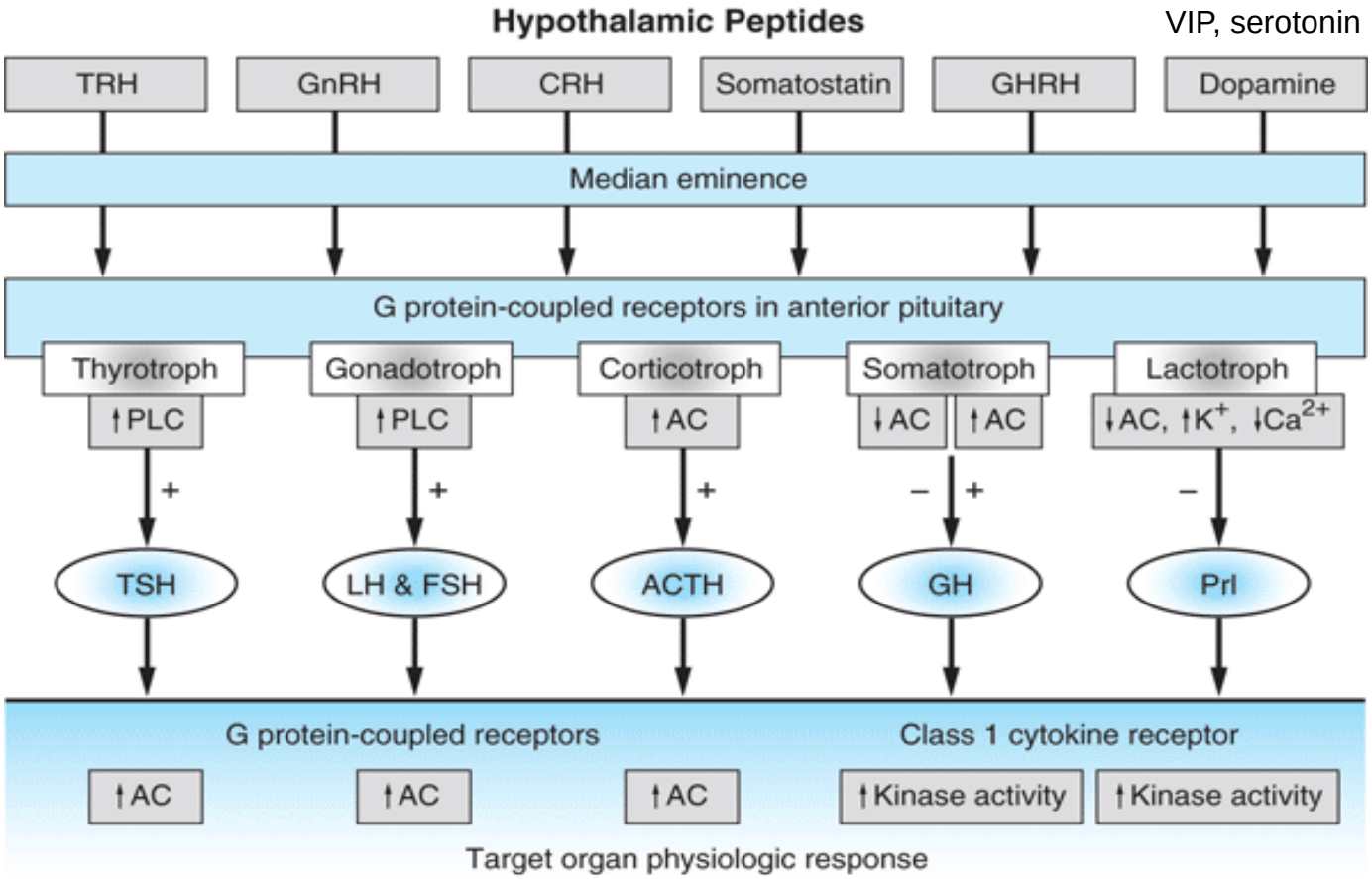


Fig. 3-3 Accessed 02/01/2010

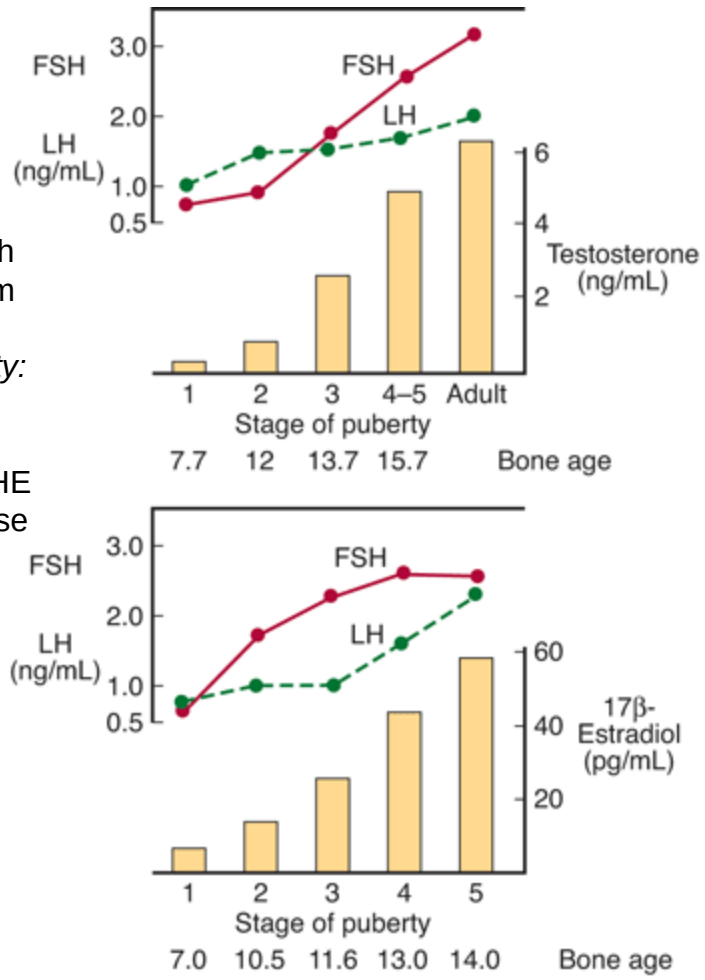
Puberty

- Increased neuronal and hypothalamic expression of a peptide family (kisspeptins) and their receptor (G protein-coupled receptor GPR54), both at 19p3, may trigger gonadotropin releasing hormone production.
- The arcuate nucleus and anteroventral periventricular nucleus are thought to contain the kisspeptin secreting neurons.
- The arcuate nucleus (and medial preoptic area, MPOA) is linked into the olfactory system, through the vomeronasal organ.
- IRF2BPL (14q24.3) inhibits as well as facilitates gonadotropin production.

FEMALE IMAGE

Puberty (girls)

(Modified and reproduced with permission from Berenberg SR (editor): *Puberty: Biologic and Psychosocial Components.* HE Stenfoert Kroese BV, 1975.)



Stage 1 of puberty is preadolescence.
Stage 2 is characterized by breast buds.
Stage 3 is characterized by elevation and enlargement of the breasts.
Stage 4 is characterized by projection of the areolas.
Stage 5 is characterized by adult breasts.

Fig. 25-9
Accessed 02/01/2010

Precocious puberty (girls)

- Hypothyroid state can lead to precocious puberty. Check TSH.
- Elevated estradiol levels suggest liver abnormality (hepatoblastoma) or stromal cell ovarian tumor.
- If virilization, DHEA, free testosterone elevated.
- May see dysgerminoma of the pineal.
- Gonadotropin analogs will suppress endogenous secretion in gonadotropin dependent disease. If independent, tamoxifen.

Ovarian follicle maturation

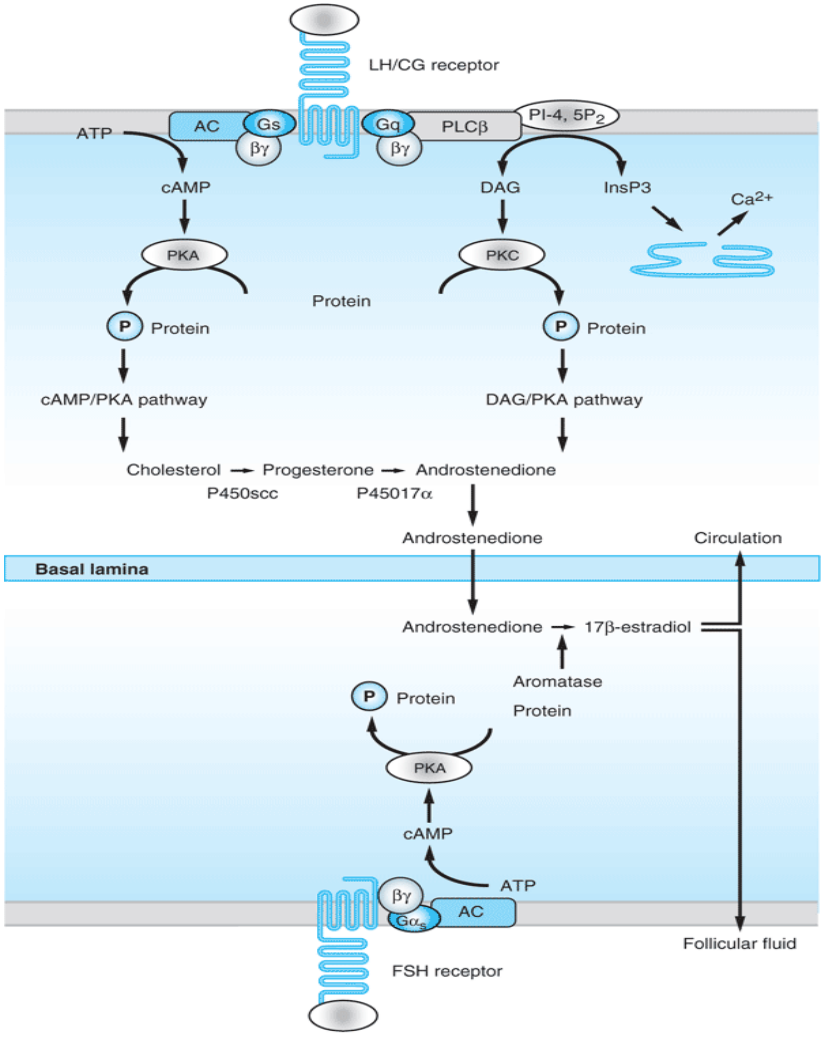
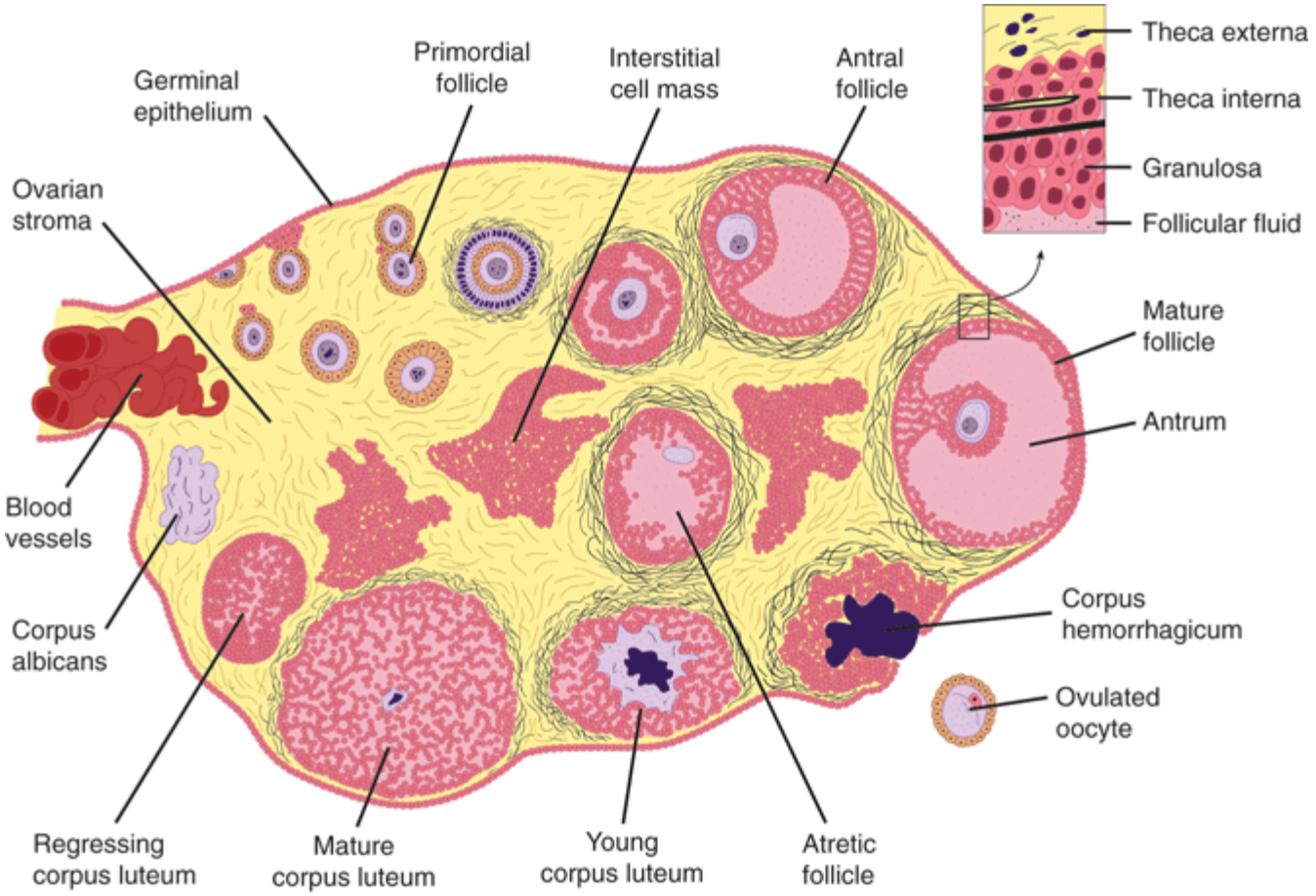


Fig. 9-2
Accessed
02/01/2010

Secretion of estradiol by the dominant follicle requires cooperation between theca cells, which synthesize androstenedione and testosterone, and granulosa cells of mature follicles, which convert androgens to estradiol and estrone.

In the corpus luteum, granulosa-lutein cells gain vascularity, LH receptors, and the enzymes necessary for progesterone synthesis. The theca-lutein cells remain the source of androstenedione for estradiol production in granulosa-lutein cells

Ovary



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

Menstrual cycle

- Estrogen is produced principally in the ovarian follicle.
- FSH stimulates its production
- Progesterone is produced principally in the corpus luteum of the ovary.
- LH stimulates its production.
- cAMP is the second messenger for gonadotropins.
- LH, FSH best determined on a blood specimen obtained at mid-cycle.
- Biopsy to evaluate secretory state of endometrium best obtained at day 24
- Histologic changes are characteristic of luteal phase

Endometrial cycle

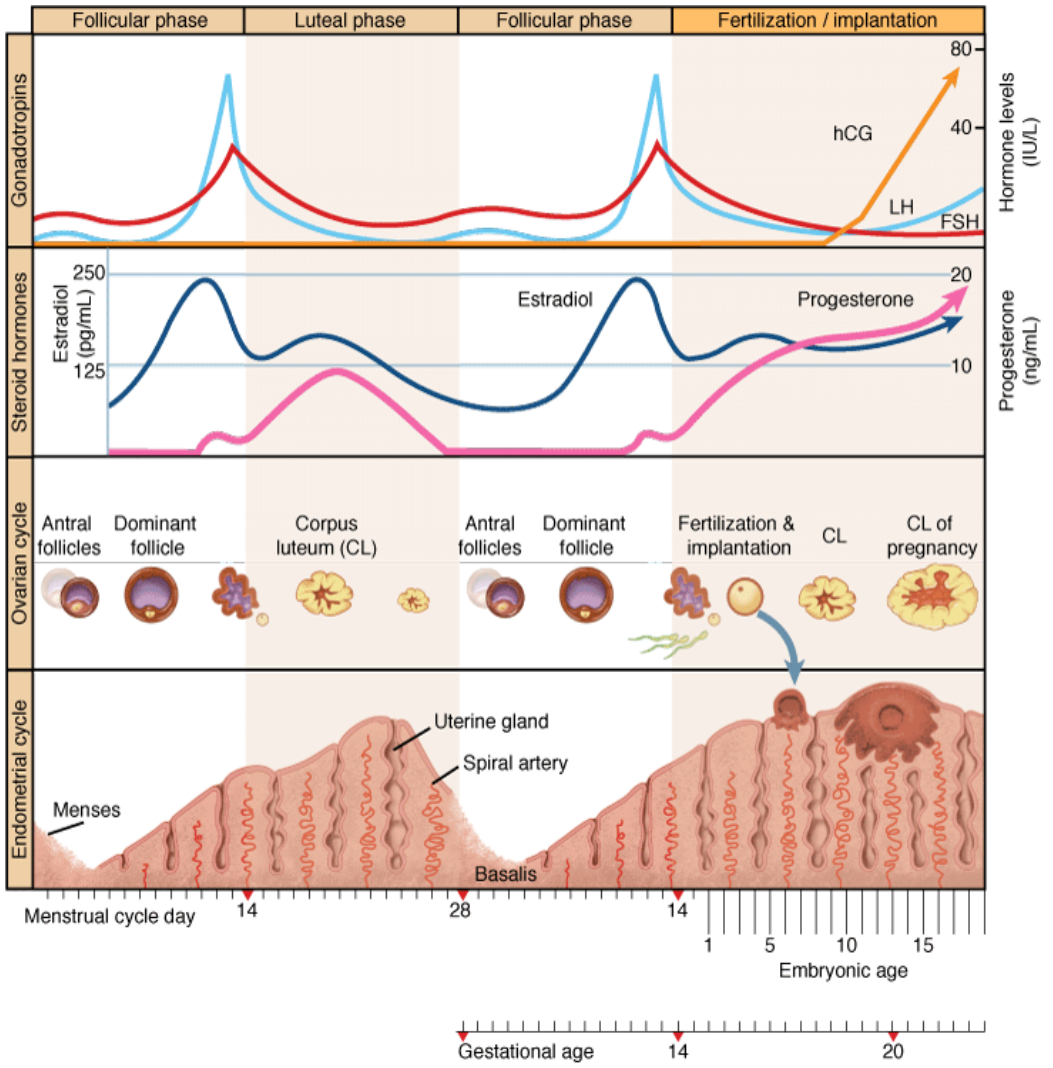


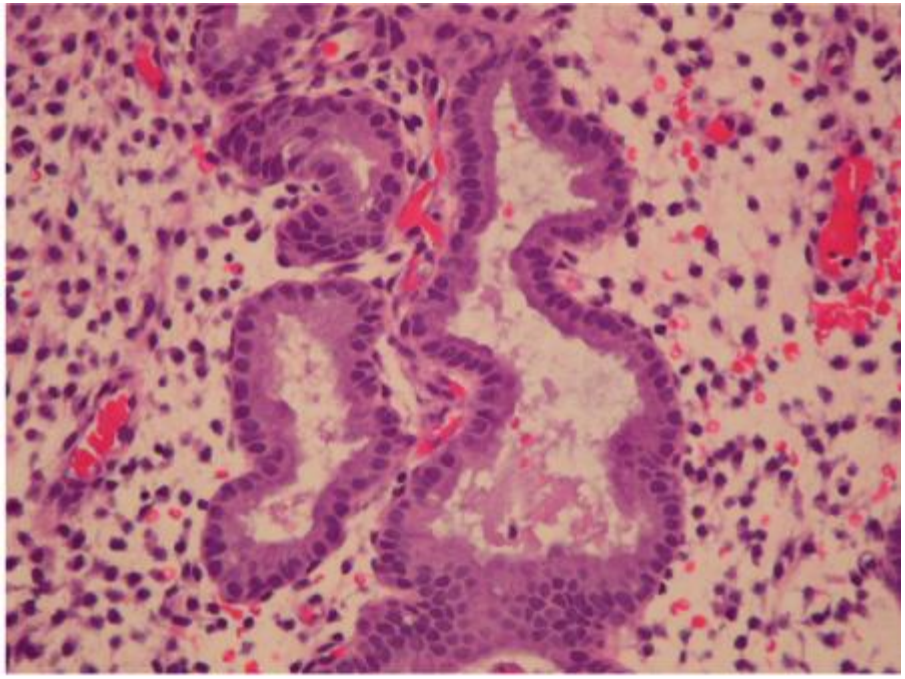
Fig. 3-1 Accessed 02/01/2010.

Fertility

- The LH surge occurs at the midpoint of the menstrual cycle in 30% of women.
- In 60%, it occurs within a 1 day window of the midpoint
- In 95%, it occurs within a 3 day window of the midpoint.
- Spermatozoa are largely viable for only 24 hours (though they may be found for days in the vagina).
- In a woman with a 26-32 day cycle, days 8-19 encompass the period of fertility.

Female fertility

- LH, FSH best determined on a blood specimen obtained at mid-cycle.
- Biopsy to evaluate secretory state of endometrium best obtained at day 24; histologic changes are characteristic of cycle phase.



C

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Fig. 15-24
Accessed 02/01/2010

Primary amenorrhea

- Is there a uterus? [confirm with pelvic ultrasound]
- If there is a uterus, are there secondary sex characteristics?
- What was the age of onset of menses of the mother [and sisters]?
- This may distinguish normal maturation from gonadal or pituitary insufficiency.
- Turner’s or Testicular Feminization changes?
- Pregnant? [always do a pregnancy test]

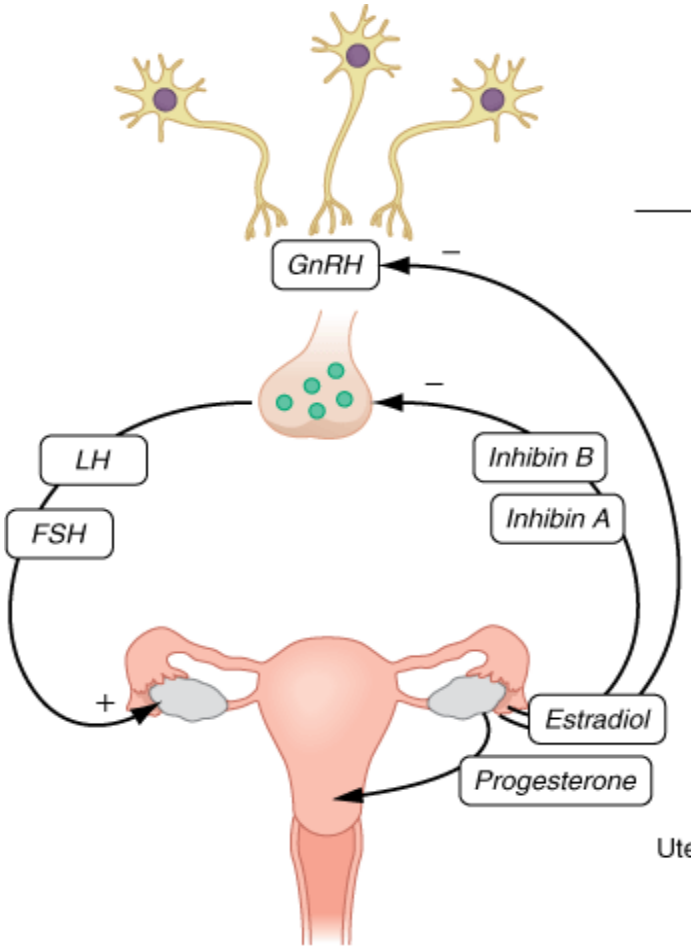
Primary amenorrhea

- Chadwick sign (LR+, 29) and uterine artery pulsation (LR+, 11) are the only clinical signs useful to detect early pregnancy (>7 weeks).
- Must measure β-HCG levels.

Secondary amenorrhea

- Determination of TSH, LH, FSH, and Prolactin are indicated.
- Some prefer to administer a progesterone bolus and wait to see whether menses ensue before determining pituitary hormone levels.
- Low levels of LH and FSH are associated with pituitary disease.
- An elevated Prolactin is compatible with pituitary microadenoma.
- MRI of the sella turcica is indicated.
- Elevated LH and FSH are associated with ovarian failure.

Causes of amenorrhea



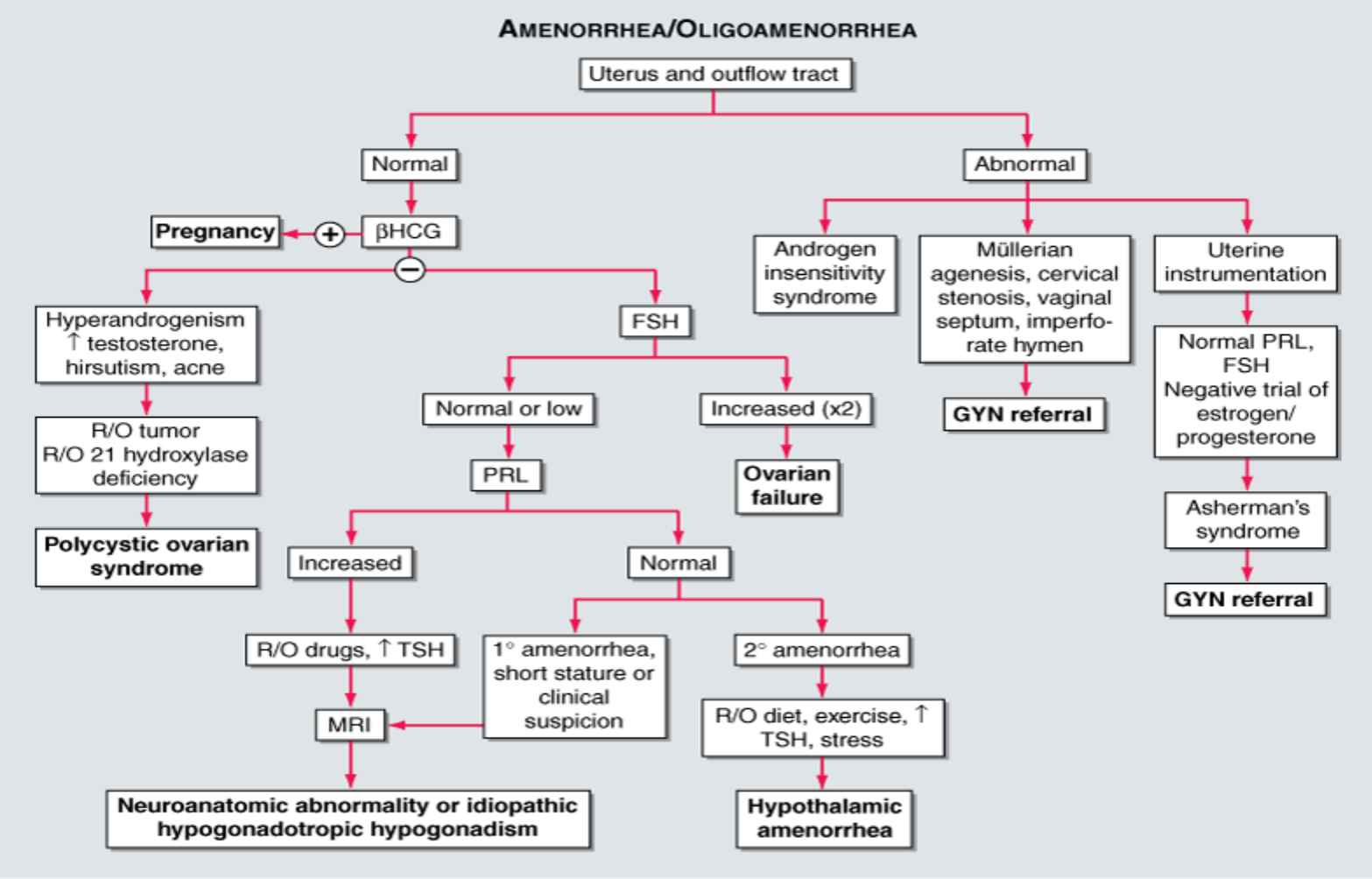
	Primary	Secondary
Hypothalamus	27%	36%
Pituitary	2%	15%
PCOS	7%	30%
Ovary	43%	12%
Uterus/outflow tract	19%	7%

Fig. 51-4
Accessed 02/01/2010

Perimenopause

- Develop menopause in the succeeding three years.
- A family history of early menopause is associated with a positive likelihood ratio (LR+) of 2.0 for early menopause.
- Hot flashes (LR+, 2.1-4.1; LR-, 0.54) and FSH >24 mIu/ml (LR+ 3.1, LR- 0.45) found in symptomatic perimenopausal women.

Diagnostic strategy



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Fig. 51-2 Accessed 02/01/2010

Hirsutism

- Ovarian lesion
- Free Testosterone elevated
- Sex hormone globulin level abnormalities do not affect the determination of free testosterone
- Testosterone immunoassays are inaccurate in women and in children
- Elevated LH and loss of diurnal activity
- LH three times greater than FSH
- Ultrasound to evaluate ovaries (polycystic).

Laboratory diagnosis

- Pitutitary lesion:
- If LH, FSH low, Prolactin normal, is a hypopituitary state.
- If Prolactin elevated, is a pituitary adenoma.
- Galactorrhea noted

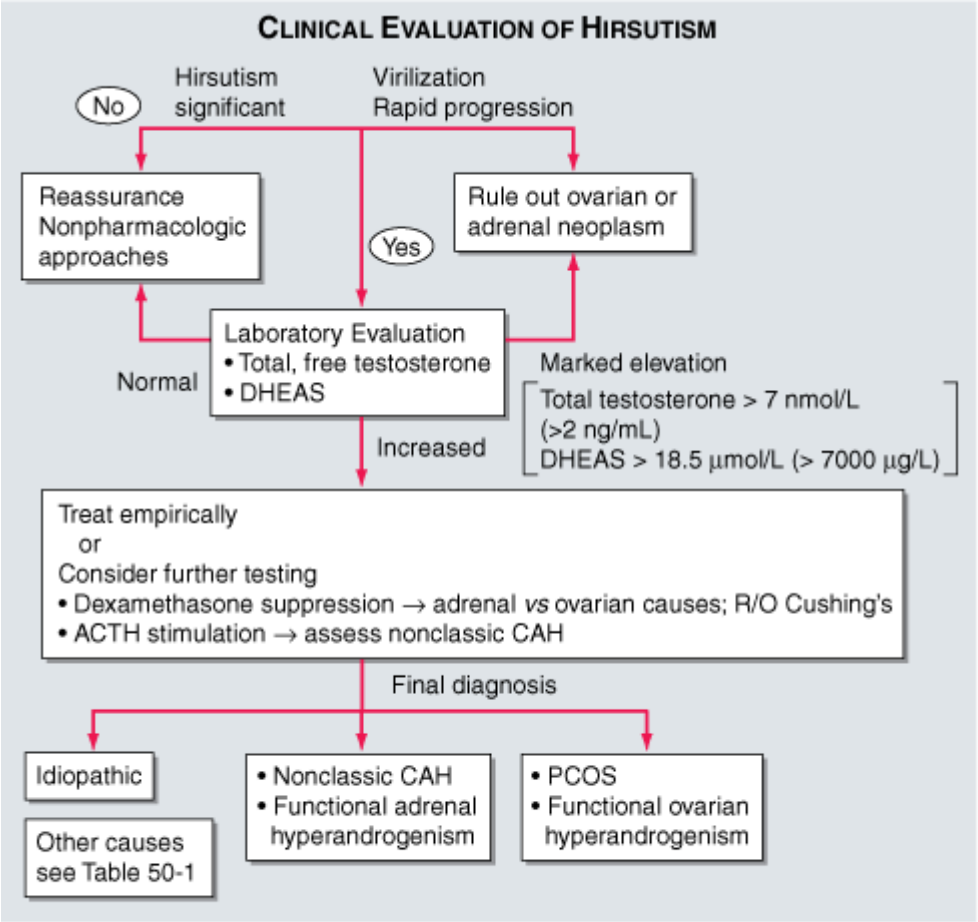
Hirsutism

- Adrenal lesion
- DHEA and DHEA-S a measure of adrenal activity.
- Free testosterone also elevated
- 17OH-P elevated
- If suppresses with 2mg dexamethasone, is hyperplasia
- If does not suppress, is adenoma
- 17OH-P is elevated in 21-β hydroxylase deficiency.

Poly-cystic ovarian syndrome

- Three-fold elevation of endometrial cancer risk as a result of hormonal stimulation.
- May see three-fold elevation of breast cancer risk at menopause.
- Infertility common.
- Oral contraceptives with low levels of progestins (e.g., Tri Cyclen) AND antiandrogens (e.g., spironolactone) are used in women who do not desire pregnancy.
- Metformin reduces insulin resistance.
- Weight loss and dietary modification recommended to reduce cardiovascular risk.

Diagnostic strategy



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Fig. 8-10
Accessed 02/01/2010

Melasma

Source: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ: *Fitzpatrick's Dermatology in General Medicine*, 7th Edition: http://www.accessmedicine.com

Blotchy, brown pigmentation that develops slowly and fades with time.

Overproduction of melanin.

Pregnancy, oral contraceptive use, injected progesterone. Worse with sun exposure.

Uterine bleeding

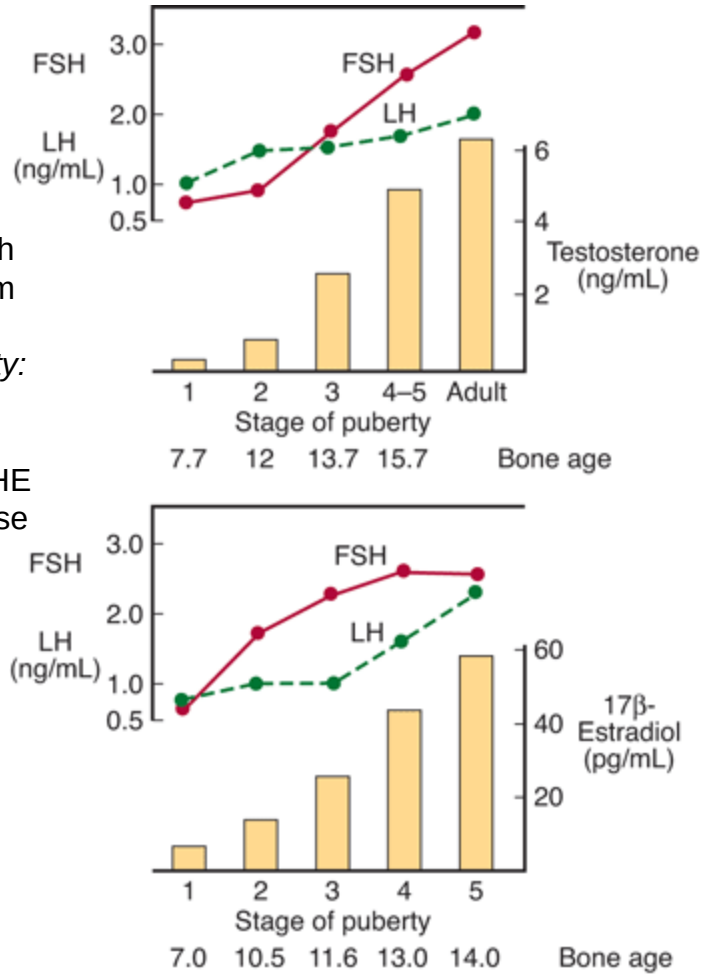
- Is the patient on hormonal medications (or has thyroid disease)?
- Or using an IUD?
- Pregnant or elevated HCG?
- Threatened abortion, ectopic pregnancy, or trophoblastic disease must be considered.
- Dysuria, pelvic tenderness?
- Cervicitis or endometriosis must be considered.
- Cancer?
- Liver disease or coagulation disorders will likely manifest with bleeding at other sites.
- Else, dysfunctional uterine bleeding
- Disordered proliferative endometrium on biopsy.

Dysfunctional uterine bleeding

- Failure of ovulation results in prolonged, excessive endometrial stimulation by estrogens.
- The endometrial glands undergo mild architectural changes, including cystic dilation (persistent proliferative endometrium, disordered proliferative phase).
- Unscheduled breakdown of the stroma may also lead to an irregular ovulatory cycle.
- Manifests clinically as infertility, with either increased bleeding or amenorrhea.

MALE IMAGE

Puberty (boys)



(Modified and reproduced with permission from Berenberg SR (editor): *Puberty: Biologic and Psychosocial Components.* HE Stenfoert Kroese BV, 1975.)

Stage 1 of puberty is preadolescence.
Stage 2 is characterized by beginning enlargement of the testes.
Stage 3 is charactrized by penile enlargement.
Stage 4 is characterized by growth of the glans penis.
Stage 5 is characterized by adult genitalia.

Fig. 25-9
Accessed 02/01/2010

Precocious puberty (boys)

- Testicular enlargement suggests increased LH, FSH secretion.
- Determine HCG as well.
- Consider tumor (pituitary, pineal, testes).
- No testicular enlargement suggests an exogenous or adrenal source.
- Hypothyroid state can lead to precocious puberty. Check TSH.
- Gonadotropin analogs will suppress endogenous secretion in gonadotropin dependent disease.
- If independent, tamoxifen will suppress.

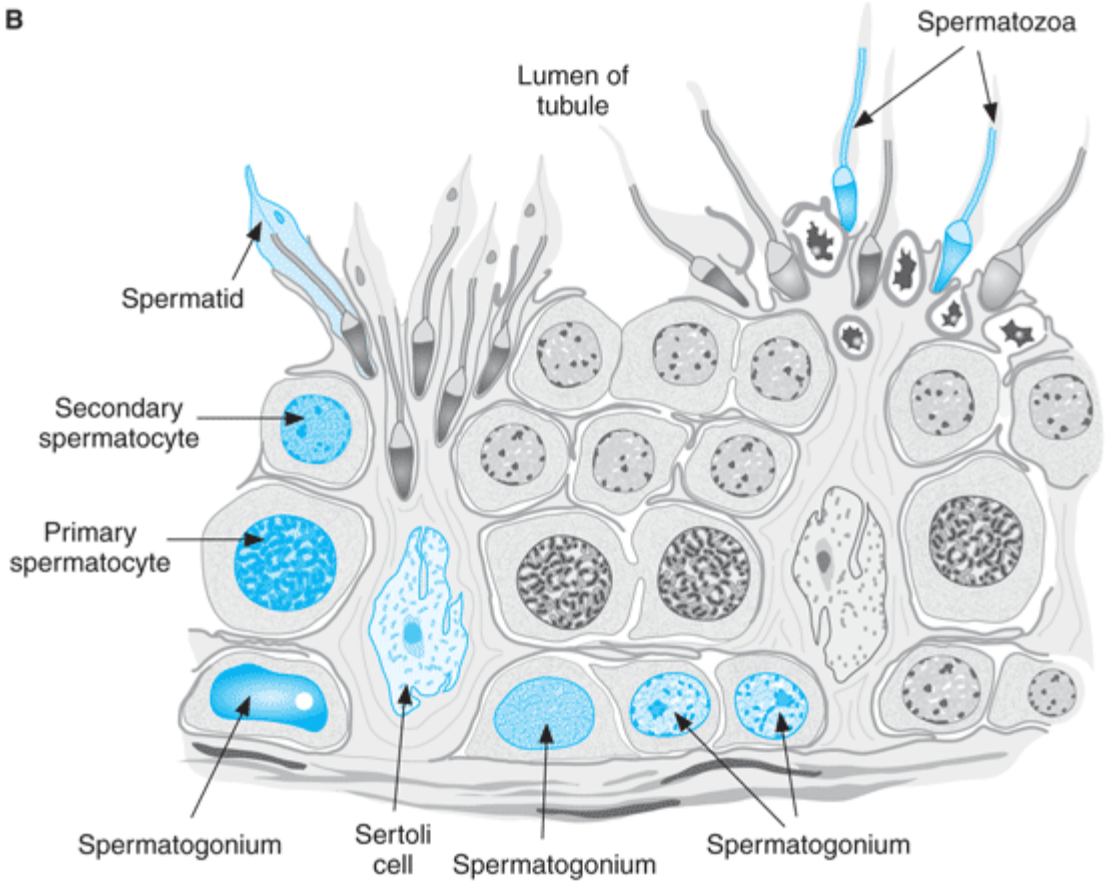
Testosterone

- Testosterone is principally produced in the Leydig cell of the testis.
- LH stimulates its production.
- Testosterone is transported to the Sertoli cell of the testis where it is converted to dihydrotestosterone (DHT)
- FSH stimulates this conversion.
- cAMP is the second messenger for both LH and FSH.
- 17βOH deficiency involves a failure to convert DHEA, androstenedione to testosterone.

Testosterone

- 5α-reductase deficiency involves a failure to convert testosterone to DHT in target organs
- A functional lack of testosterone at birth.
- Increased testosterone synthesis at puberty may be sufficient to masculinize.
- May show ambiguous genitalia.
- No breast tissue.

Spermatogenesis



Source: Molina PE: *Endocrine Physiology*, 2nd Edition:
http://www.accessmedicine.com

Male infertility

- 15% of couples are infertile
- 50% related to male abnormality.
- Is this a male?
- Do Müllerian elements (uterus) persist?
- Ultrasound evaluation
- Testicular feminization?
- Or a 17β hydroxylase or 5α-reductase deficiency
- Or loss of androgen receptors

Male infertility

- 20% azospermic
- 20-30% oligospermic (<1 million/mm^3) or with poor sperm motility.
- If LH, FSH normal with azoospermia, duct obstruction.
- Low semen fructose is noted.

  If no vas deferens, consider cystic fibrosis
- Vasectomy reversal does not guarantee fertility

Male infertility

- Y chromosome deletions common (SRY gene encodes for testes determining factor).
- LH normal, FSH elevated.
- Marijuana, anabolic steroid use contribute to infertility
- Testosterone administration has been used as a reversible contraceptive method
- Testicular torsion (abnormally high insertion of tunica vaginalis permits increased flexibility), trauma as possible causes
- If LH, FSH low, Prolactin normal, is a hypopituitary state.
- If Prolactin elevated, is a pituitary adenoma.

Hypogonadism (males)

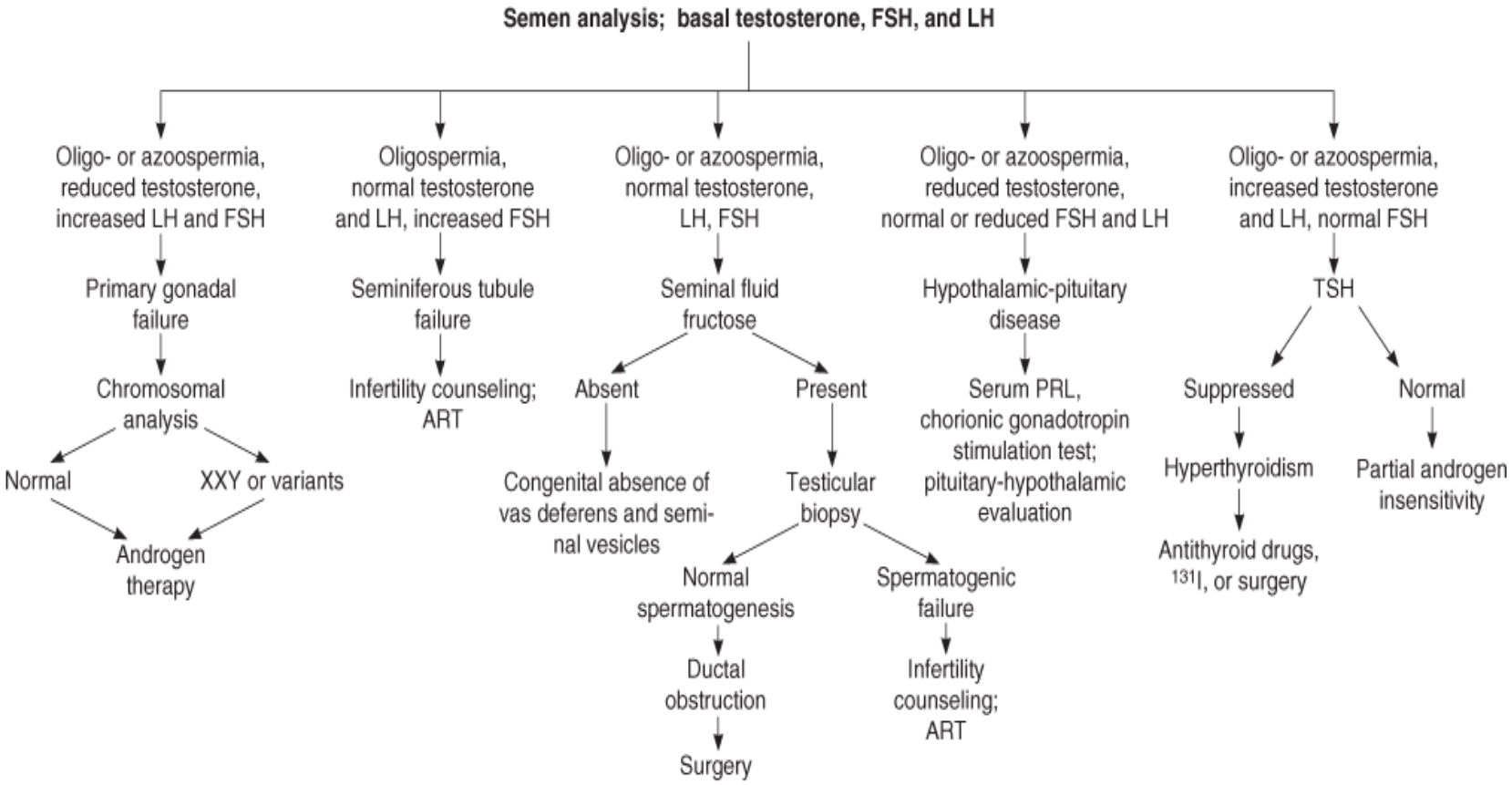
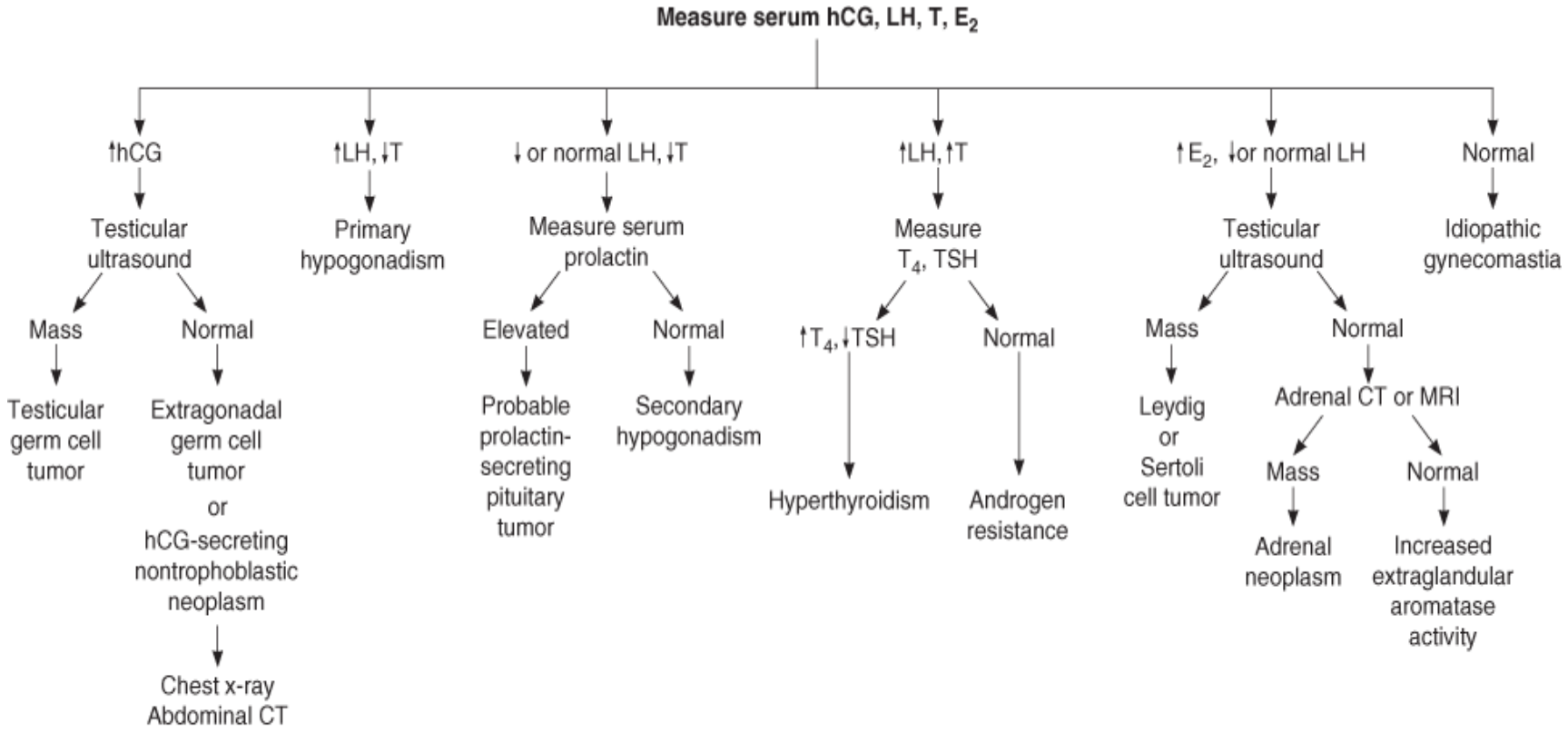


Fig. 13-6
Accessed 02/01/2010

Gynecomastia

- Excess sex hormone binding globulin.
- May be a result of liver disease.
- Elevated estradiol, T_4 levels.
- However, free testosterone and free estradiol levels may be diminished.
- Leydig cell hyperplasia
- Limited spermatocyte maturation

Gynecomastia



Source: Gardner DG, Shoback D: *Greenspan's Basic and Clinical Endocrinology*, 8th Edition: http://www.accessmedicine.com

Fig. 336-8
Accessed 02/01/2010

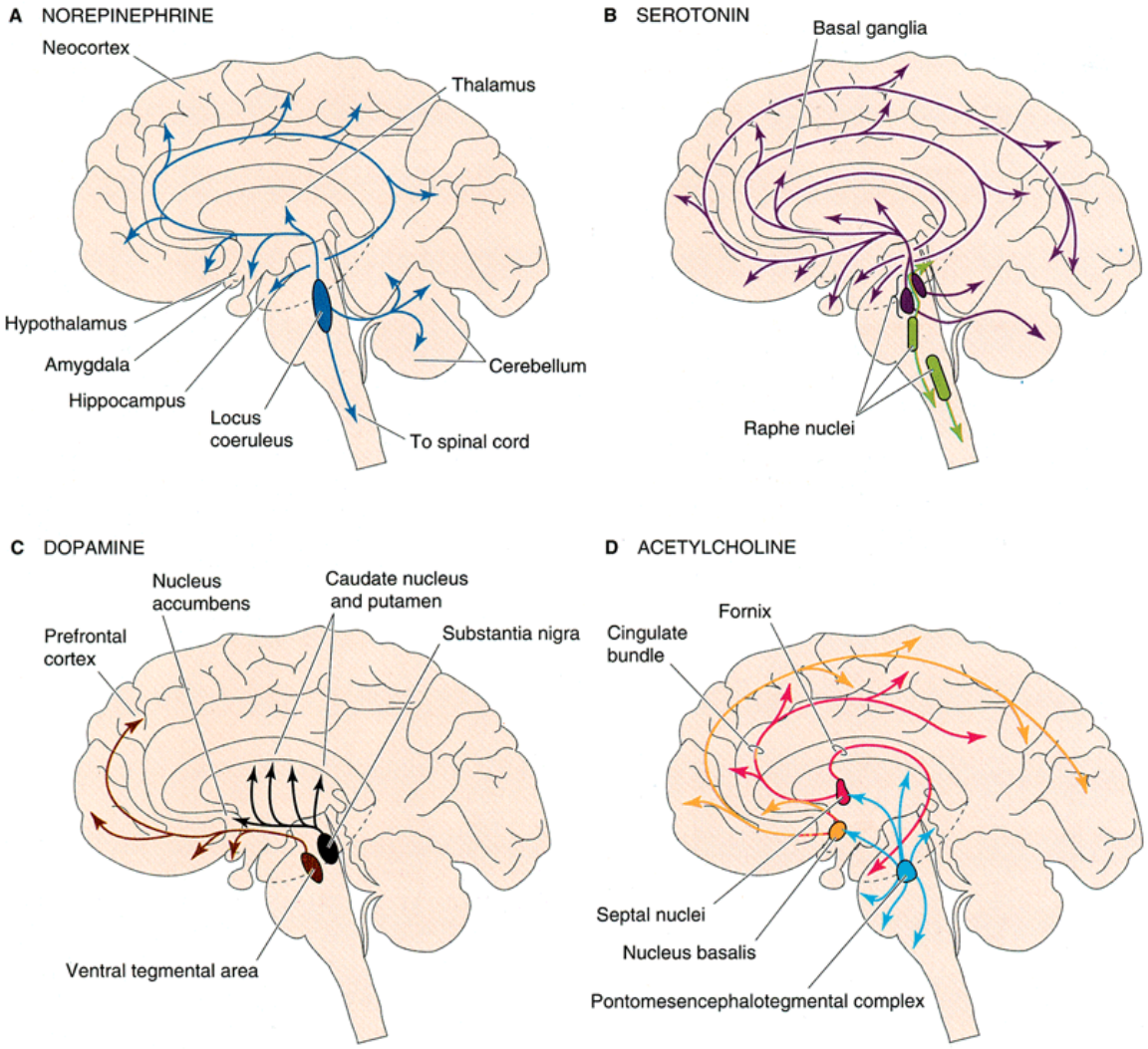
Erectile dysfunction

- Erection is mediated by cholinergic parasympathetic pathways, and nonadrenergic, noncholinergic pathways
- Release nitric oxide and induce vascular smooth-muscle cell relaxation, allowing enhanced blood flow.
- Endothelial cells also release nitrous oxide.
- Sildenafil and congeners enhance erectile function by inhibiting phosphodiesterase type 5
- Maintain high levels of cyclic GMP, depressing levels of intracellular Ca^{2}.

Erectile dysfunction

- Detumescence is mediated by sympathetic pathways that release norepinephrine and stimulate adrenergic pathways
- Leads to contraction of vascular smooth-muscle cells.
- Endothelin, released from endothelial cells, also induces contraction.
- RHO kinase activation via endothelin activity also contributes to detumescence by alteration of calcium signaling.

Neurotransmitters and pathways



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

(Reproduced with permission from Boron WF, Boulpaep EL: *Medical Physiology.* Elsevier, 2005.)

Acetylcholine

- Acetylcholine projections originate principally in the ventral tegmentum and project to the hypothalamus, thalamus, amygdala, hippocampus, basal forebrain, and the pre-frontal cortex.
- Regulate arousal, cognition, and memory, among other functions.
- REM promoting cholinergic pedunculopontine and lateral dorsal tegmental nuclei are counterbalance to the waking serotonergic dorsal raphé and the noradrenergic loci ceruleus nuclei (whose firing is related to state of attention).

Cholinergic cell groups

- Cholinergic cell groups in the basal forebrain include the medial septum, diagonal band, and the nuecleus basalis of Meynert.
- These topographicaly innervate the entire cerebral cortex and hippocampus and amygdala.
- Pontine cholnergic cellgroups innervate the brain stem reticular formation as well as the thalamus.
- The pedunculopointine nucleus is located ventrolaterally near the superior cerebellar peduncle
- Controls firing of glycinergic neurons in the lateral reticulospinal pathway.

Cholinergic cell groups

- The laterodorsal tegmental nucleus is a component of the periacqueductal gray matter just rostral to the locus ceruleus.
- VIP, substance P are neurotransmitters also found in cholinergic ganglia.

Sensory phenomena

- REM sleep is associated with pontogeniculate orbital activity (visual effects) and cortical activation coupled with atonia.
- Serotonin inhibits REM activity.
- Autoscopy (out of body activity) is related to dorsal prefrontal and temporal lobes.
- The ventrolateral periacqueductal gray is the switch between REM and awake states.
- Hypoxia and hypotension turn off locus ceruleus activity, leading to a cholinergic response.
- 85% of vagal efferents are in the neck. May be a protective response of inactivity (healing).