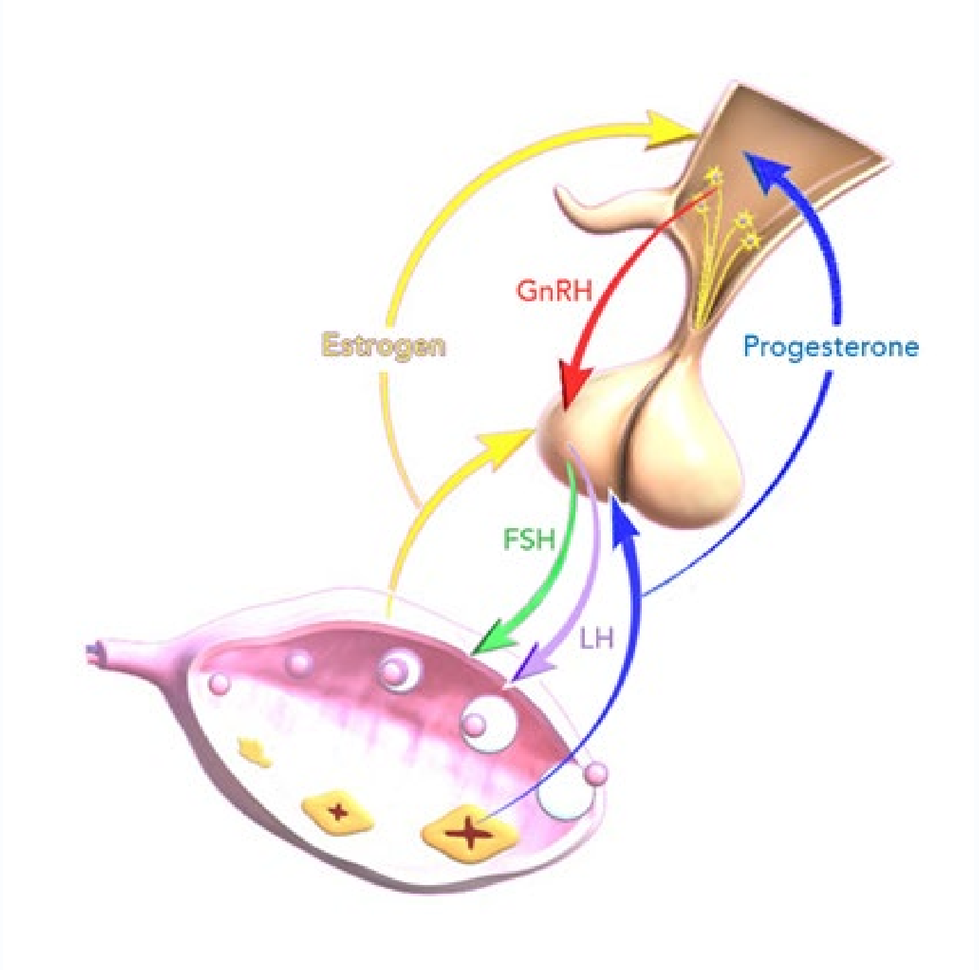
HPO Axis-Part 2
Ovulatory Dysfunction

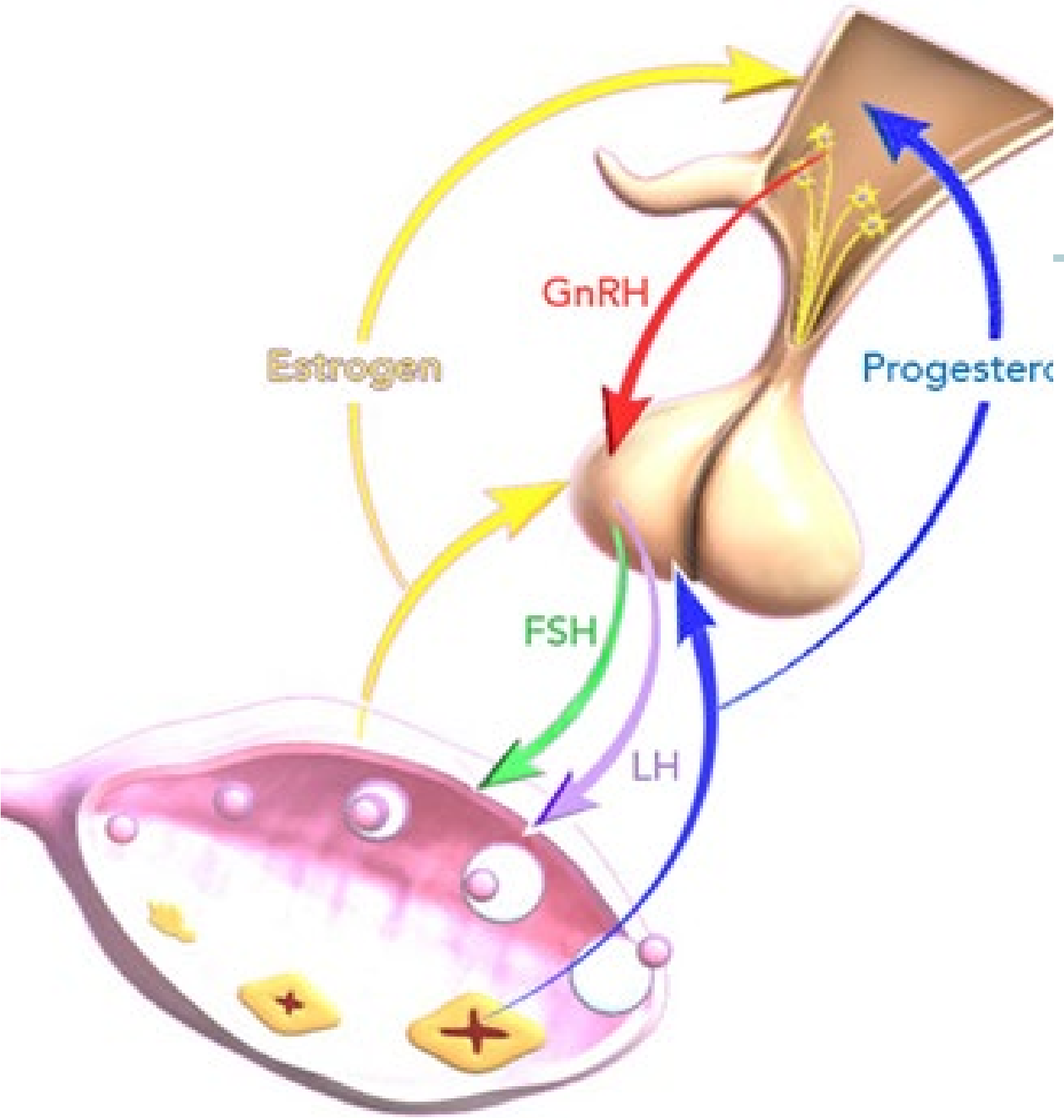
Monica Moore, MSN, RNC



Objectives

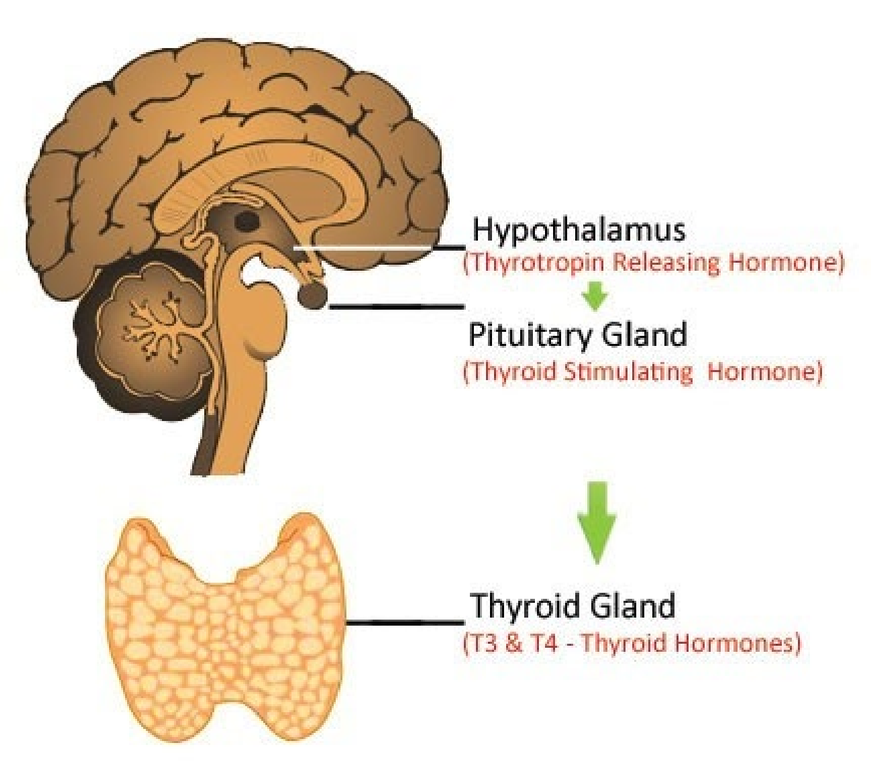
- Identify common causes of ovulatory dysfunction in terms of origin: Hypothalamic, pituitary or ovarian
- Discuss hypogonadism and contrast hyper- vs hypo-gonadotropic cause
- Review the concept of ovarian failure and premature ovarian insufficiency
- Examine the causes of hirsutism and ovulatory dysfunction with special emphasis on PCOS
- Review the workup for amenorrhea

Part 1: Common Types of Ovulatory Dysfunction



Common types of ovulatory dysfunction

- Pituitary
  - Hyperprolactinemia
  - Hypo- or Hyperthyroidism
- Hypothalamic
  - Functional HA
  - Brain tumors or injury
- Ovarian
  - Ovarian Failure (Insufficiency)
    - Incipient or Premature
  - Ovulatory dysfunction with hirsutism



Pituitary causes of ovulatory dysfunction

Image retrieved from http://hypothyroidsymptoms.buygoodreviews.com/www - hypothyroidism.html

Hypothyroidism

- Mild or subclinical hypothyroidism still problematic
  - Associated with impaired fertility and increased risk of miscarriage
  - Only tolerate narrow window (TSH <2.5)
- In early pregnancy, can increase risk of Pre-E, GDM and increase risk of child having lower IQ scores
- Increased metabolism in pregnancy increases thyroid demand
- Hypothyroid most commonly due to autoimmune disease Hashimoto's thyroiditis, but we don't always detect a cause.

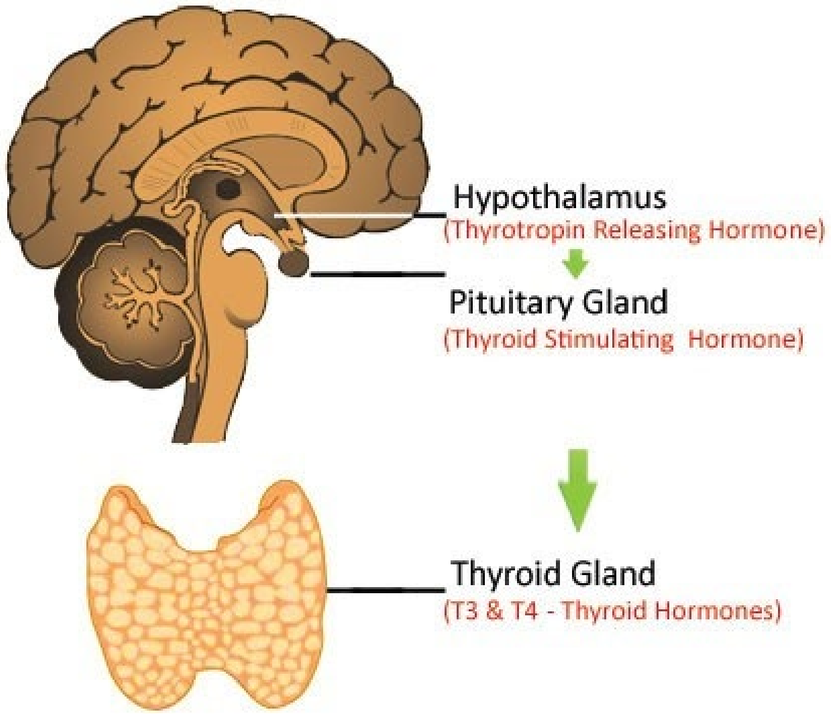


Image retrieved from http://hypothyroidsymptoms.buygoodreviews.com/www - hypothyroidism.html

Hyperprolactinemia

- Causes are many, need to rule out pituitary adenoma if consistently elevated
- Elevated PRL suppresses secretion of GnRH.
  - Only an issue if causes menstrual cycle disruption
  - Can lead to amenorrhea, oligo, galactorrhea and infertility
- Dopamine suppresses pituitary secretion of PRL
  - So, tx'd with dopamine agonist (Dostinex).

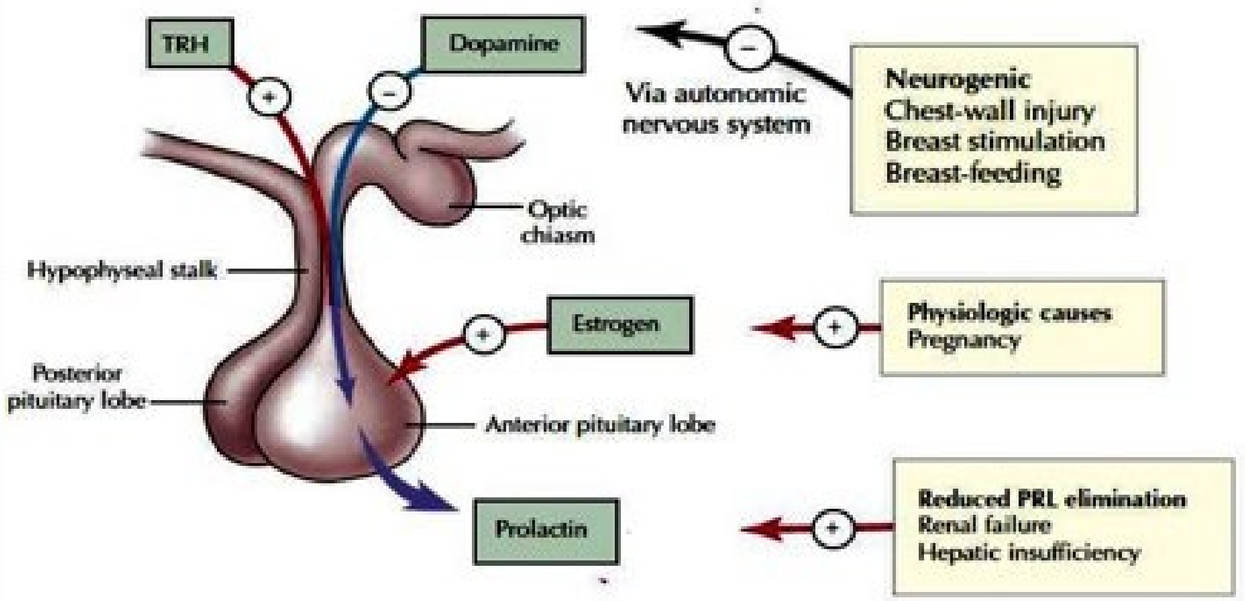


Image retrieved from: https://www.cmaj.ca/content/169/6/575

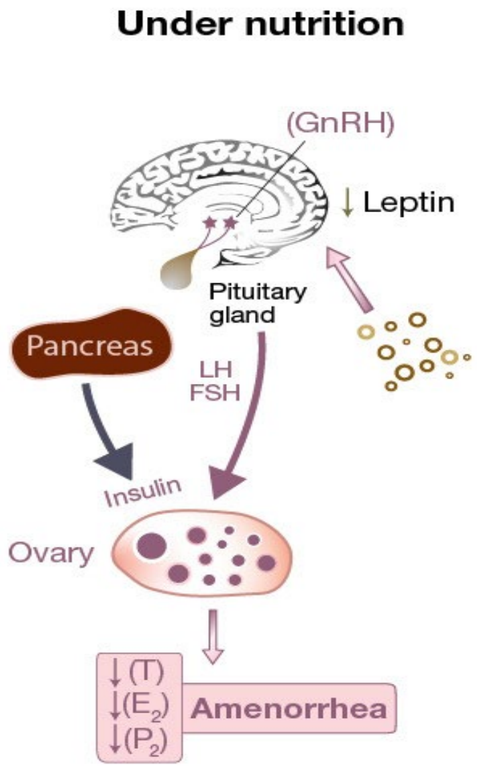
PART 2: HYPOTHALAMIC CAUSES

Hypogonadism

- Diminished functional activity of the gonads (ovaries for women and testes for men)
  - Affects production of hormones and may impair spermatogenesis (in men) or ovulation (in women).
- Congenital or acquired
  - Turner syndrome or Functional HA
  - Hypogonadotropic Hypogonadism (Hypo-Hypo)
  - Impaired secretion of gonadotropins (congenital (Kallman syndrome) or secondary (pituitary tumors, head trauma)
    - FSH and LH <5 IU/L
- Hypergonadotropic Hypogonadism (Hyper-Hypo)
  - Gonadal Failure- FSH>20 IU/L; LH >40 IU/L (due to poor neg feedback)
  - Turner syndrome (45,X) is an example

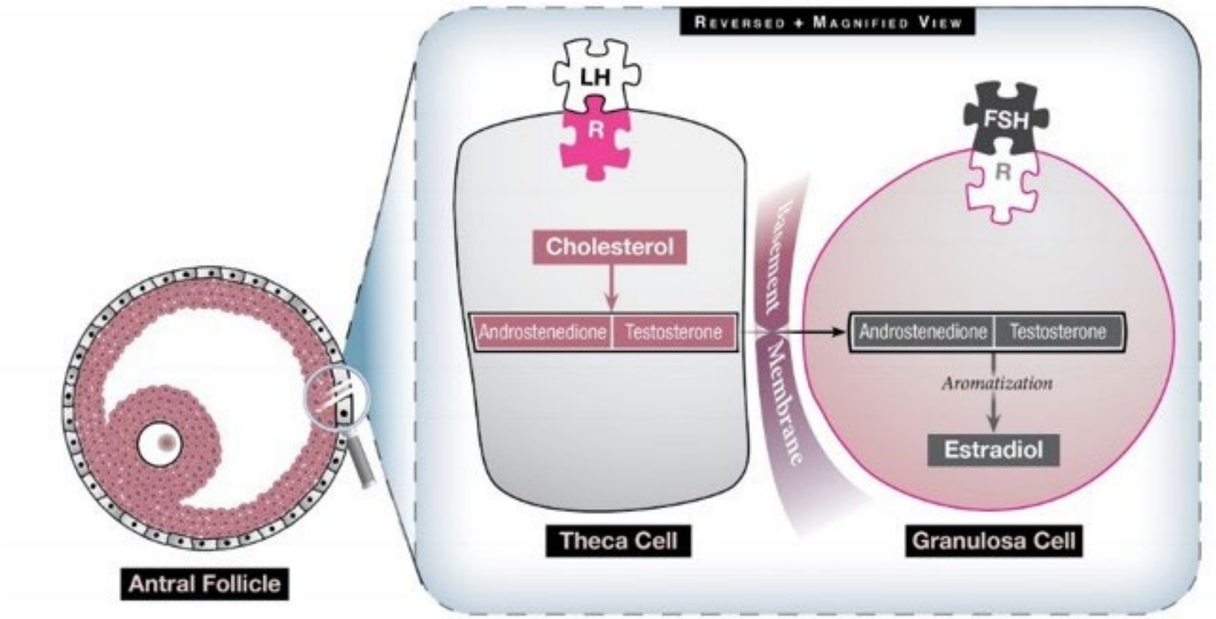
(Functional) Hypothalamic Amenorrhea

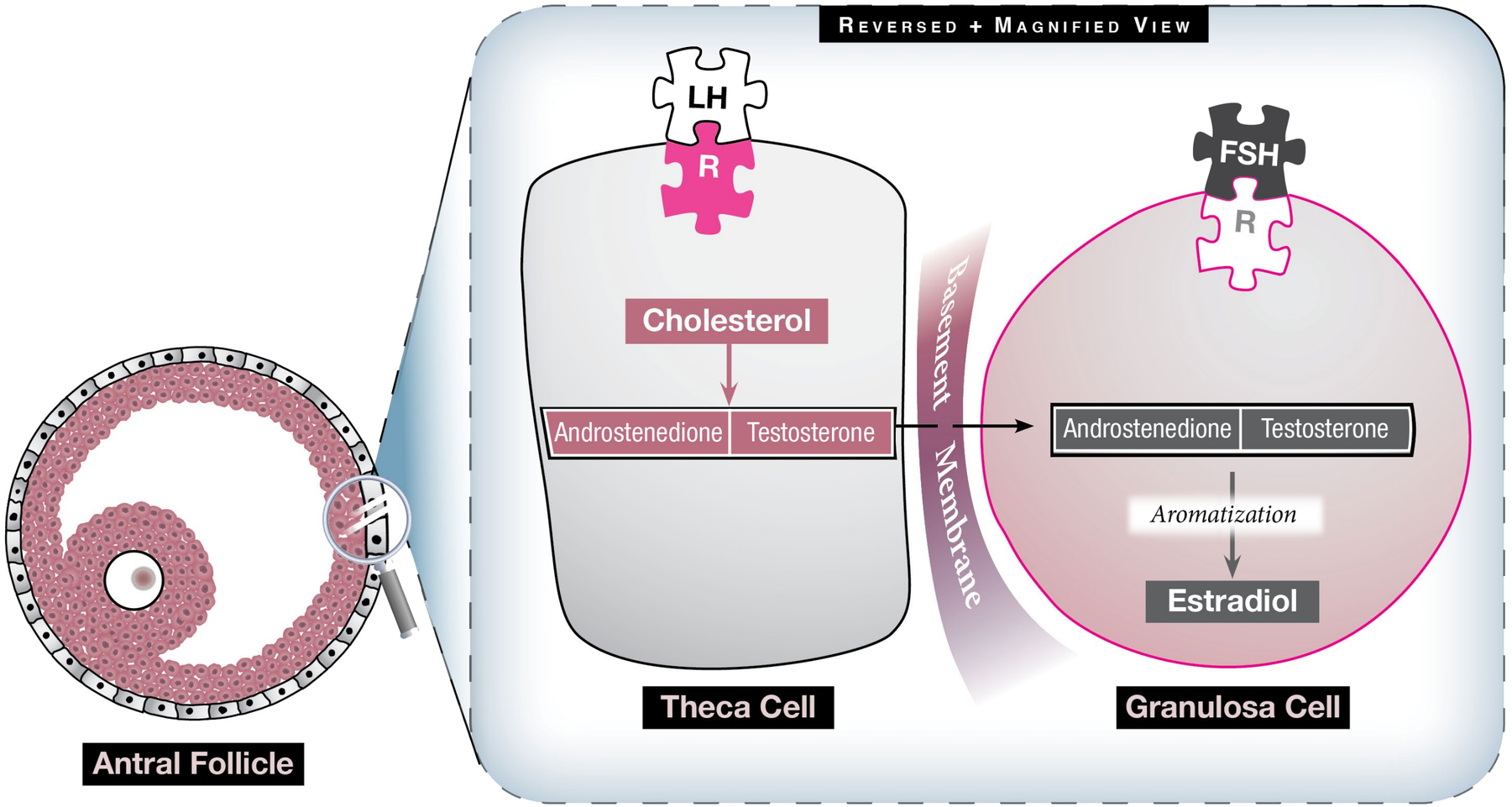
- “Functional“: the ovulatory ovarian dysfunction is reversible with correction of the underlying cause.
- Abnormal pattern of pulsatile GnRH secretion
  - Results in low levels of FSH and LH
- Ovary may have many follicles in resting state.



Ovarian Follicles

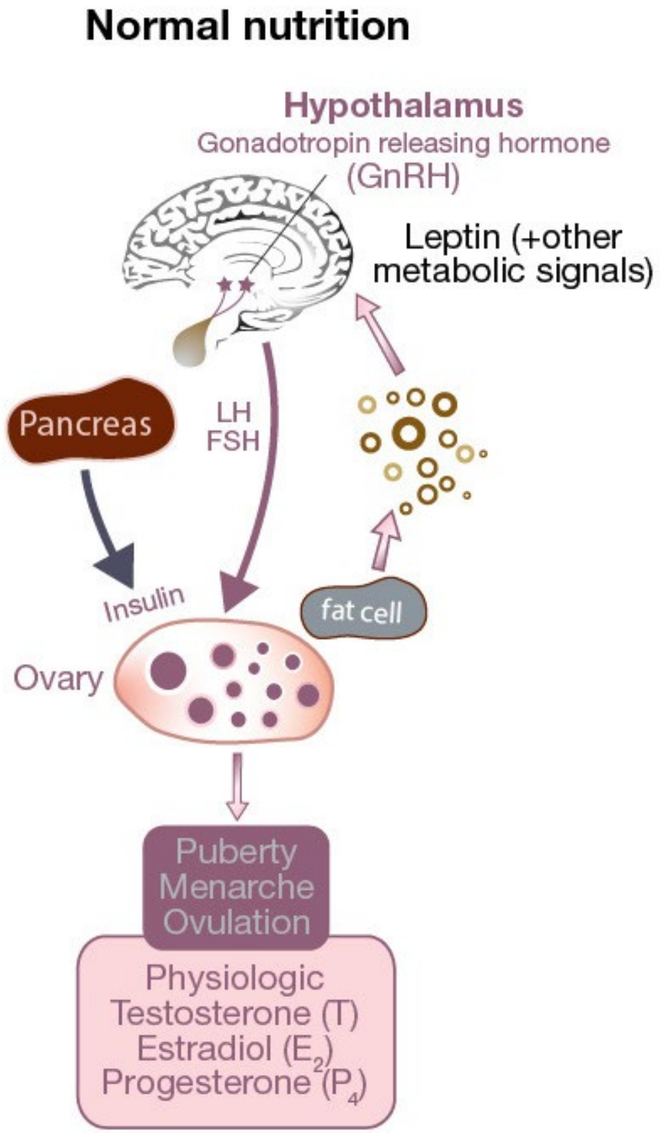
- Each follicle consists of an oocyte surrounded by layers of granulosa and theca cells
- Dominant follicle - acquires the highest concentration of FSH receptors



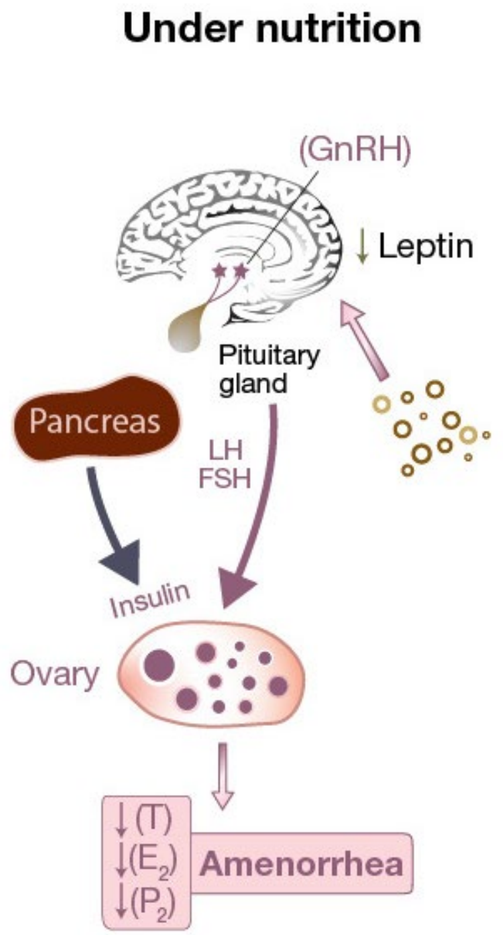

Reversed + Magnified View
LH
R
FSH
R
Cholesterol
Androstenedione
Testosterone
Basement Membrane
Androstenedione
Testosterone
Aromatization
Estradiol
Theca Cell
Granulosa Cell
Antral Follicle

During periods of stress, the HPA axis is activated and inhibits the HPO axis at multiple levels

- When functioning properly, physiologic levels of E, P and T are produced and lead to menstrual cycle regularity

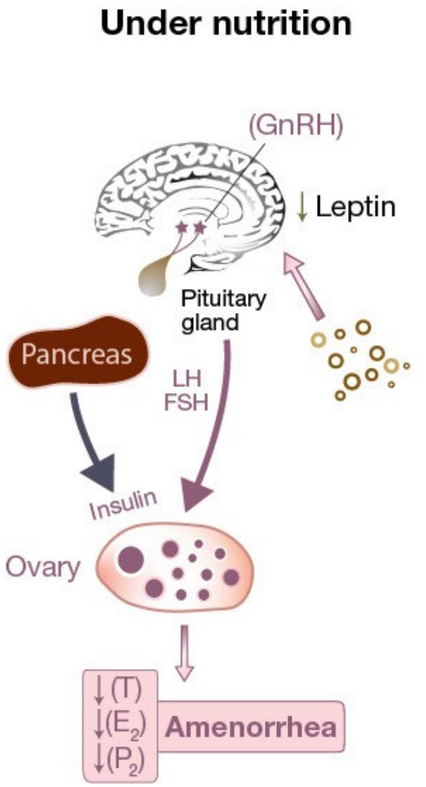


- Undernutrition results in low levels of leptin, skewed GnRH signaling, and low levels of gonadotropins



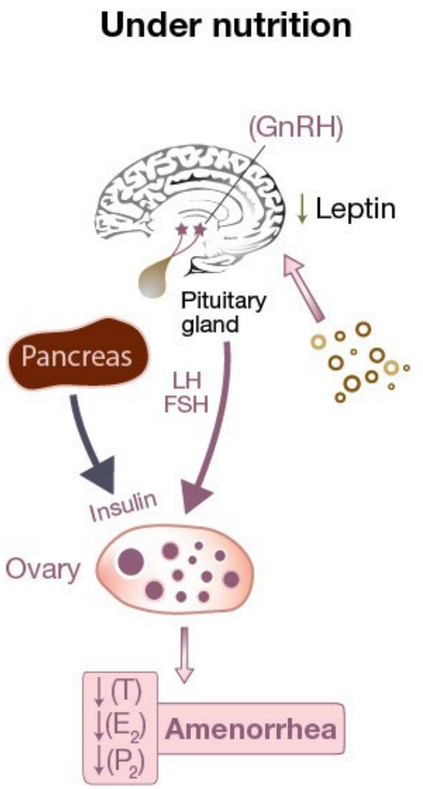
Causes of Functional HA

- Extreme emotional stress
  - Animal studies suggest CRH may inhibit gonadotropin secretion
- Acute weight loss
  - Menstrual function requires that body fat % remain above critical value
  - Secretion of opioids after exercise inhibit GnRH
- Strenuous exercise
  - Particularly those activities associated with low body fat %
- Chronic malnutrition.



‘Treatment’ of Functional HA

- Women with anovulation associated with strenuous exercise or who are underweight have low levels of leptin, LH and estradiol.
- When leptin injected in animal studies* (simulating eating/nutrition), there is an increase in LH and follicular growth.

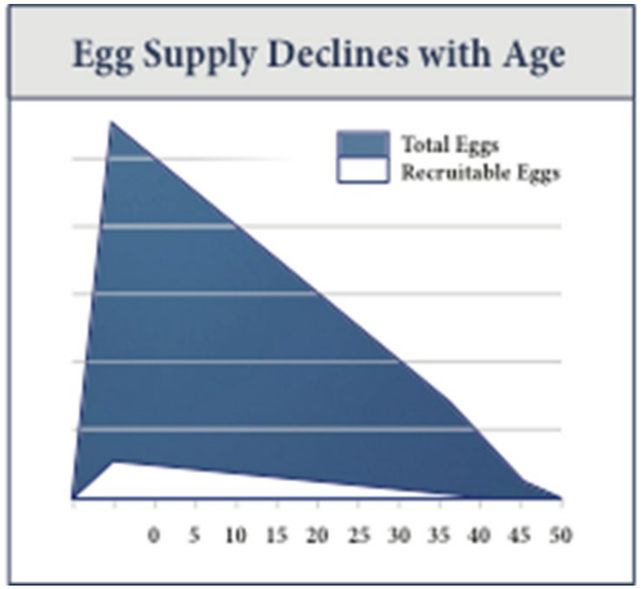


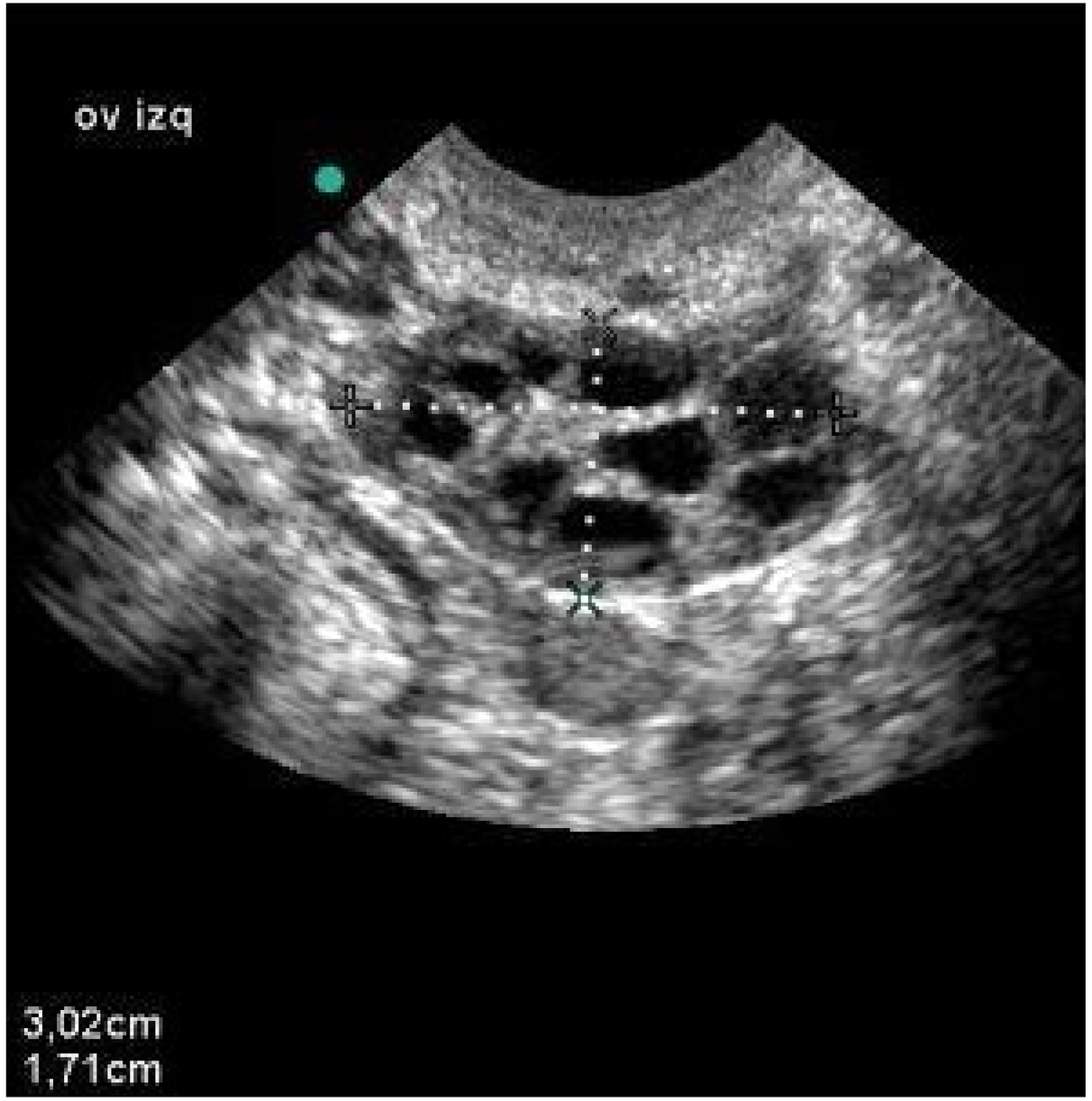
*Welt, et al, 2004.N Engle J Med; 35: 987-997.
Schneider2004. PhysiolBehav; 81:289-317.

Part 3: Ovarian Causes

Premature Ovarian Insufficiency (Failure)

- Few or no follicles remain that are capable of producing estradiol in response to pituitary hormones (in a woman <40 y/o).
- Cause could be idiopathic (90% of the time), but other causes need to be ruled out.
  - Fragile X-Common inherited cause of mental retardation and autism
    - Association between POF and Fragile X mutations
  - Karyotype- (X chromosome deletions and translocations)
- Autoimmune disorders
- Can be caused by chemo/radiation
- May have intermittent ovulation but pregnancy and live birth rates are low (5-10% lifetime preg rate).
  - Donor egg best option.

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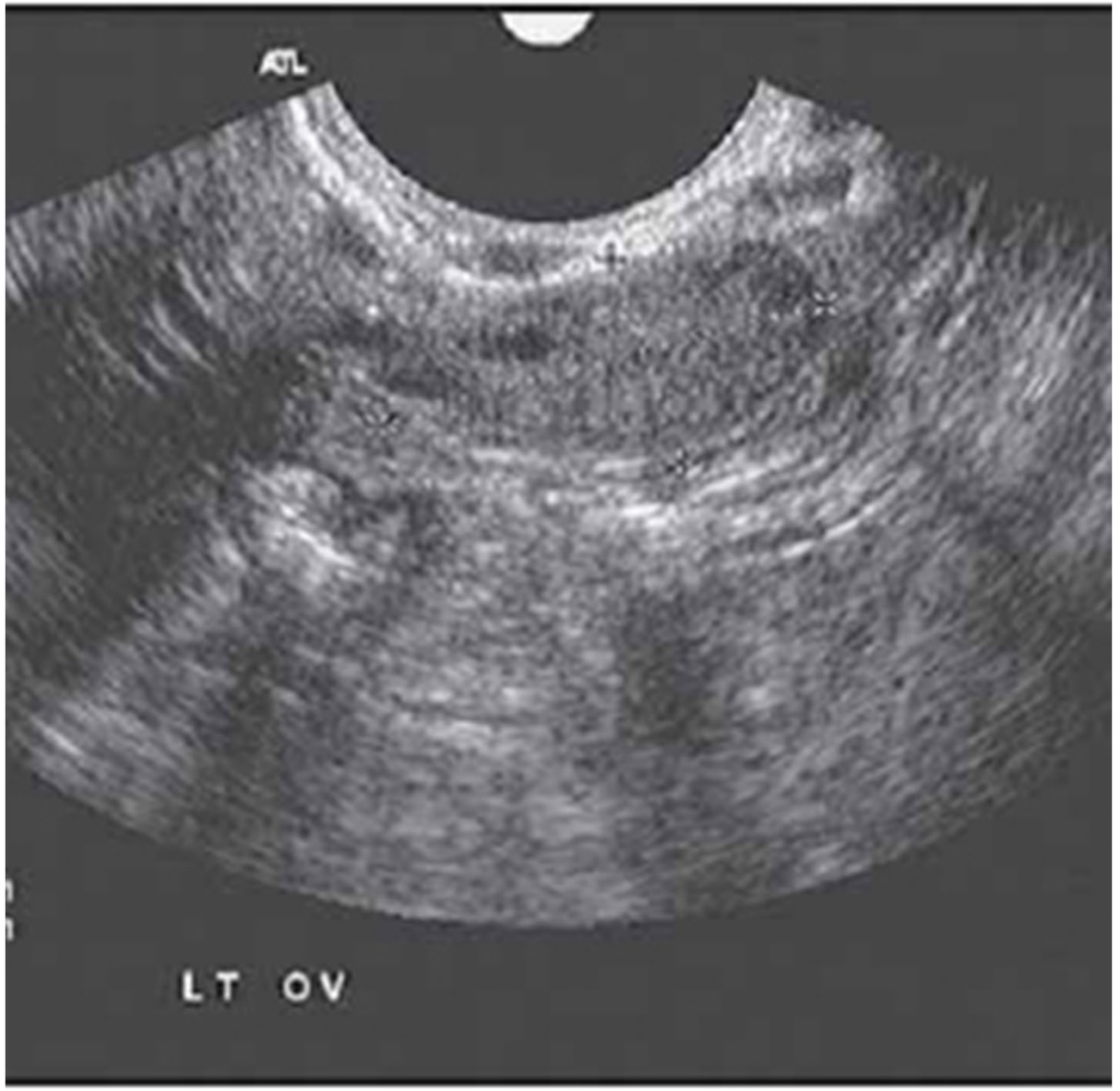
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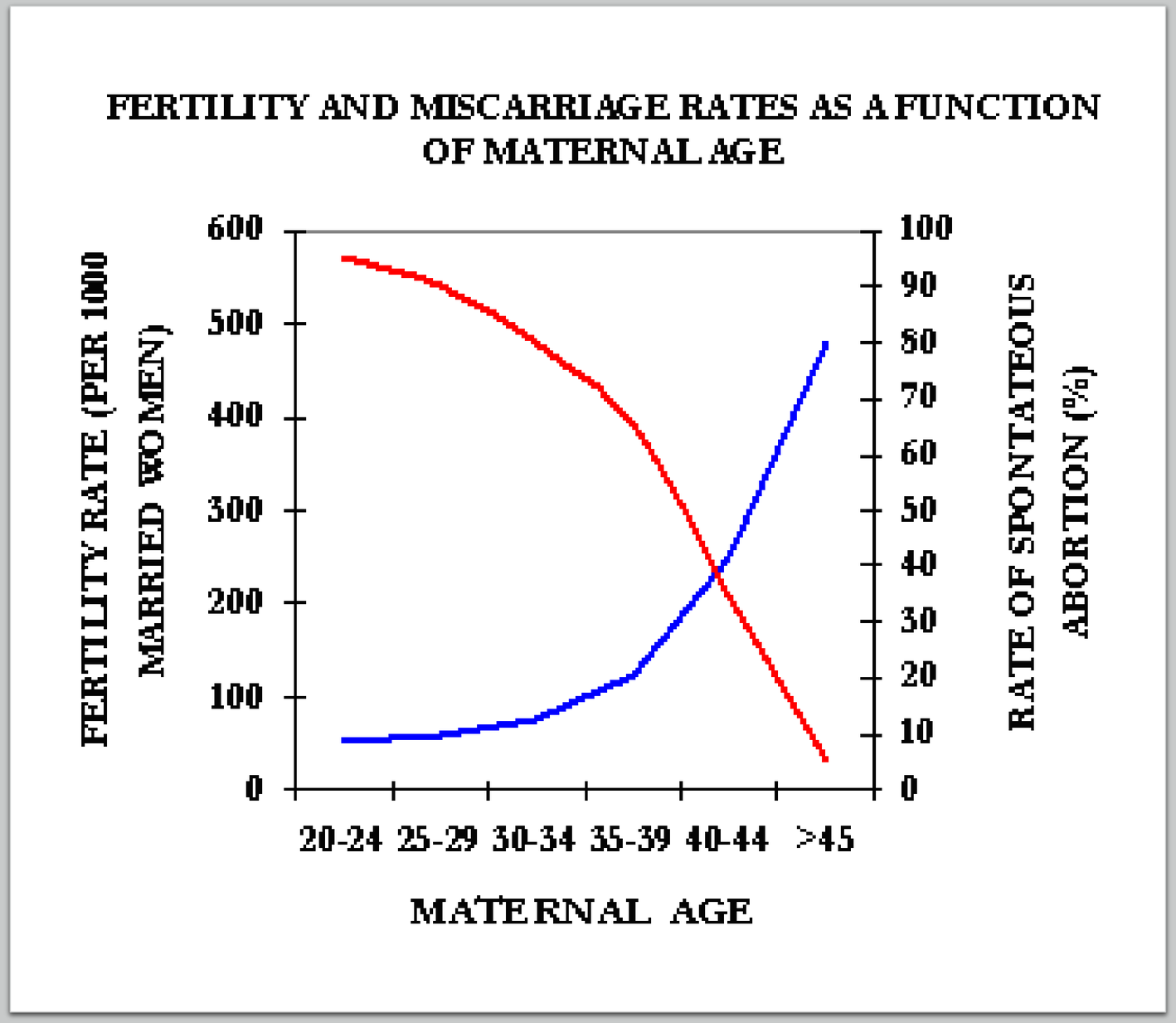


Image retrieved from NEJM (2004) 351(19): 1927-9. DOI: 10.1056/NEJMp048087.

Hirsutism and Ovulatory Dysfunction

Causes of Hirsutism and Ovulatory Dysfunction

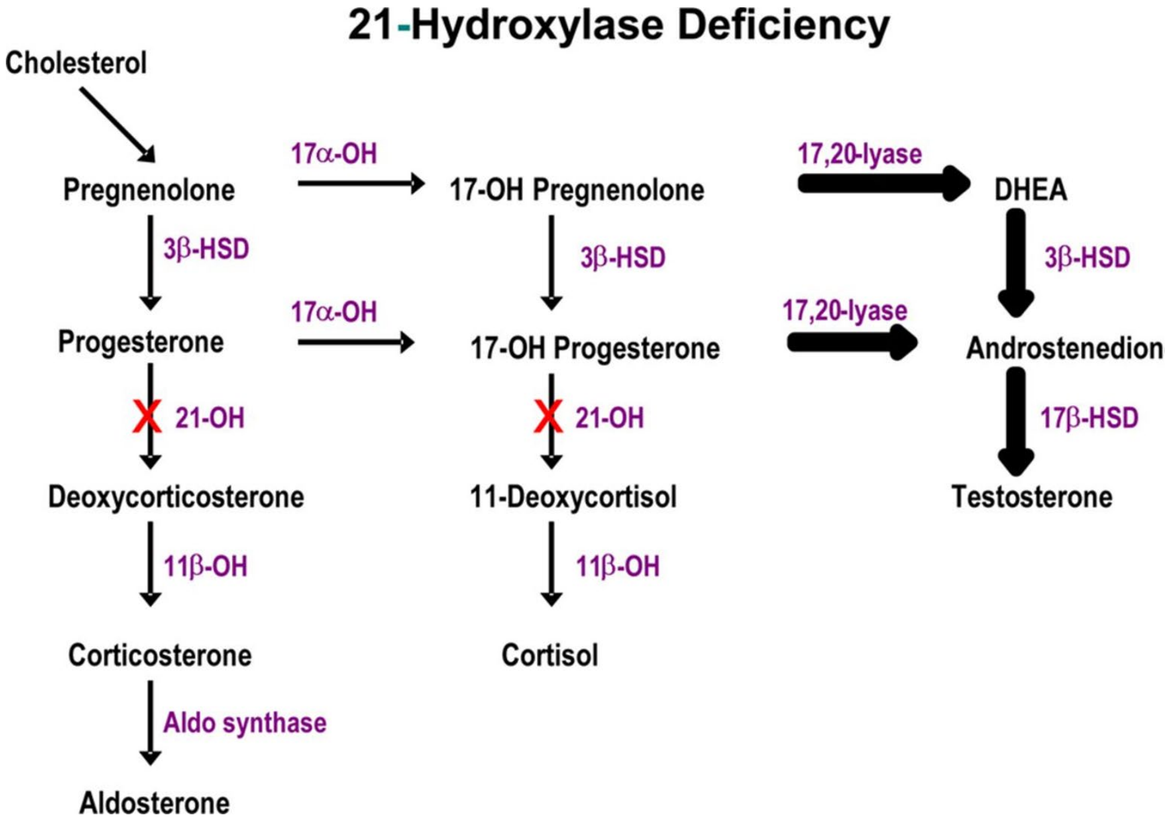
Diagnosis	Prevalence
Androgen-secreting neoplasm	.23%
Classical CAH	0.69%
Nonclassical CAH	2.06%
HAIR-AN syndrome	3.78%
PCOS	82%
Idiopathic	4.47%
Hyperandrogenemia, hirsutism, and normal ovulation	6.75%

Differential Diagnosis of Hirsutism and Amenorrhea

- DHEA- S- produced almost exclusively by the adrenals
  - 100 - 350 mcg/ dL
  - Can be in upper normal range or mildly elevated with PCOS, but if very high, suspect adrenal tumor
- Testosterone produced from the adrenals (25%), ovaries (25%) and peripheral conversion of androstenedione (50%)
  - In women, 80% of circulating T is bound to SHBG
- 17 OHP
  - Elevated in CAH (adrenal deficiency resulting in excess production of 17 OHP)

Congenital Adrenal Hyperplasia

- Inherited genetic defect that limits production of one of the enzymes the adrenal glands use to make cortisol, aldosterone or both(most commonly 21 - hydroxylase).
  - Usually will need to take steroids to replace cortisol.
  - Adequate cortisone replacement is needed to suppress androgens
- Autosomal recessive
- Excess production of male hormones prenatally (by 8 to 10 weeks gestation) and can lead to ambiguous genitalia, enlarged clitoris, virilization .
- Blood test would reveal elevated 17 OHP (usually >1000ng/dl). 17 OHP is overproduced and converted outside of adrenal gland to T.



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Varying degrees of genital ambiguity in girls with CAH

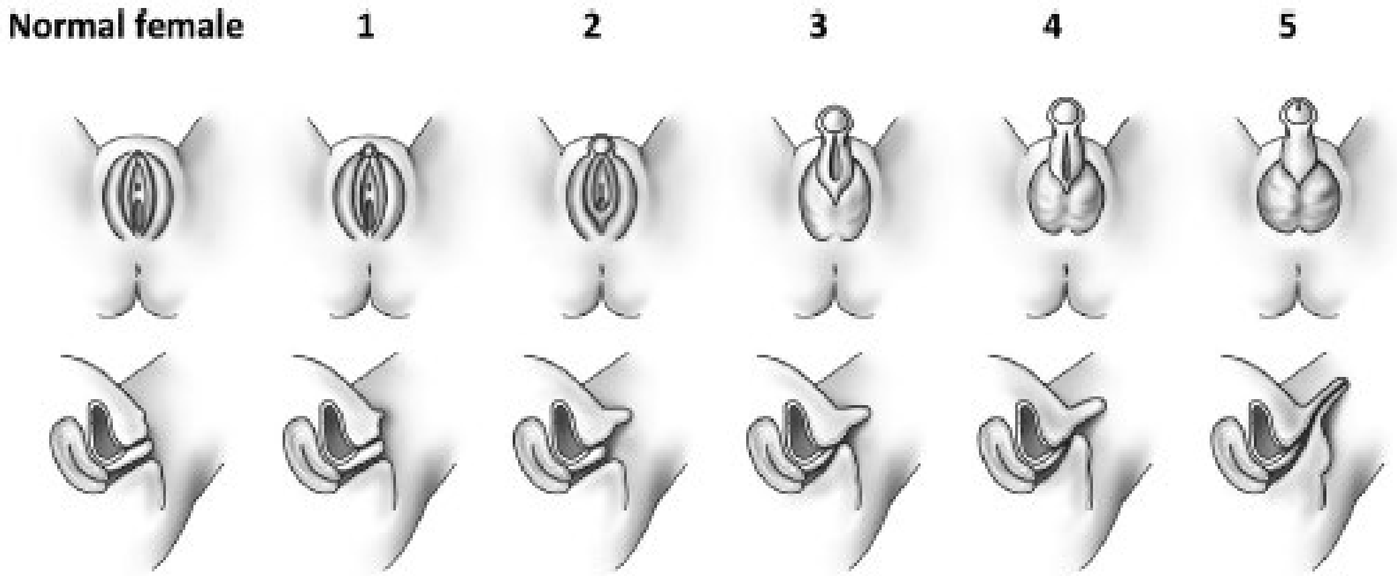


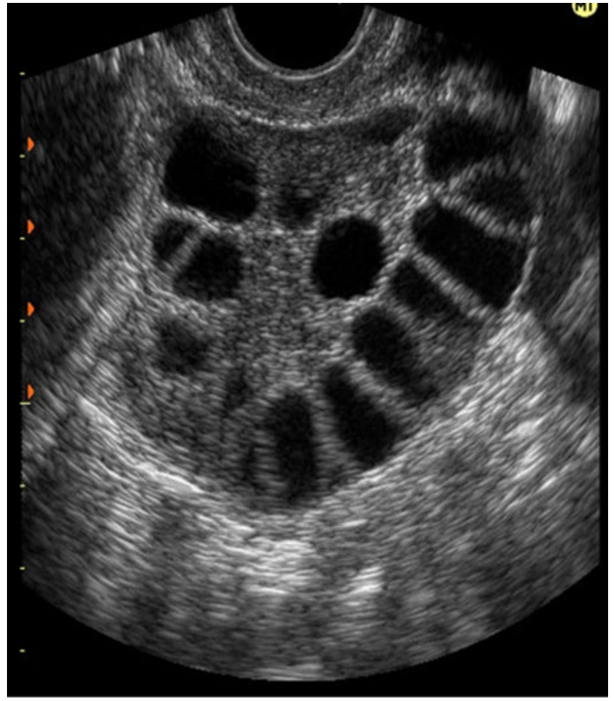
Fig. 4. Prader scale, female external genitalia viewed from above (*top*) and in cross-section (*bottom*).

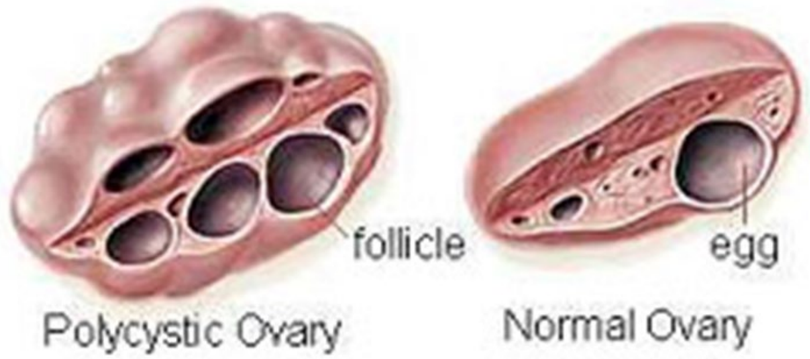
Endocrinol Metab Clin N Am 44 (2015) 275–296

Part 4: Intro to PCOS

PCOS

- Most common endocrine disorder in women (bet 6 and 10%).
  - Begins as early as menarche
- Characterized by oligo- or anovulation, polycystic ovaries and elevated androgens (2 out of 3 as defined by Rotterdam Criteria, 2004).
- Insulin Resistance is not necessary for the diagnosis of PCO, but it very prevalent in this population





Rotterdam ESHRE/ASRM - Workshop group. Hum Reprod 19:41, 2004

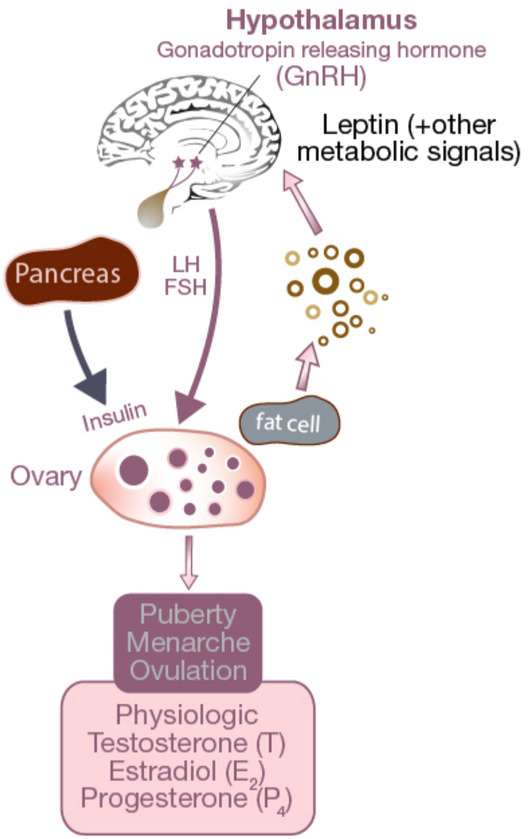
Etiology

- NO specific cause discovered for PCOS
- NO specific mode of inheritance
- Many candidate genes profiles are under investigation
  - Familial clustering of PCOS
  - *40% of (premenopausal) sisters of women with PCOS have elevations of total or biologically available testosterone levels
- Complex interplay between genes and the environment

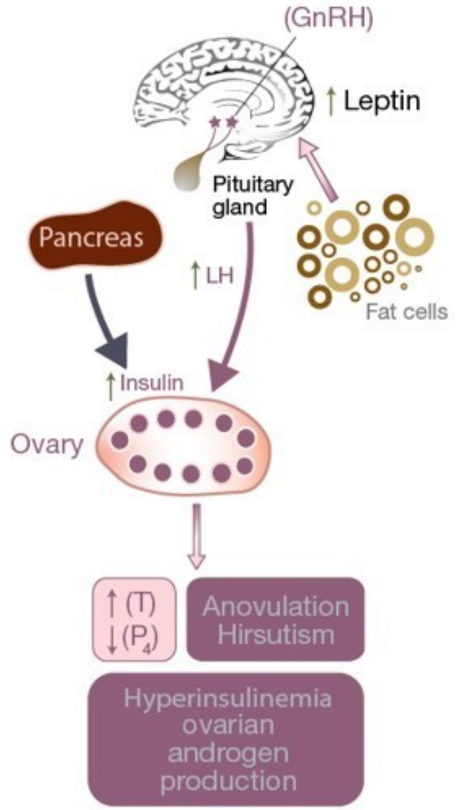
*Legro 1998 PNAS

PATHOPHYSIOLOGY OF PCOS

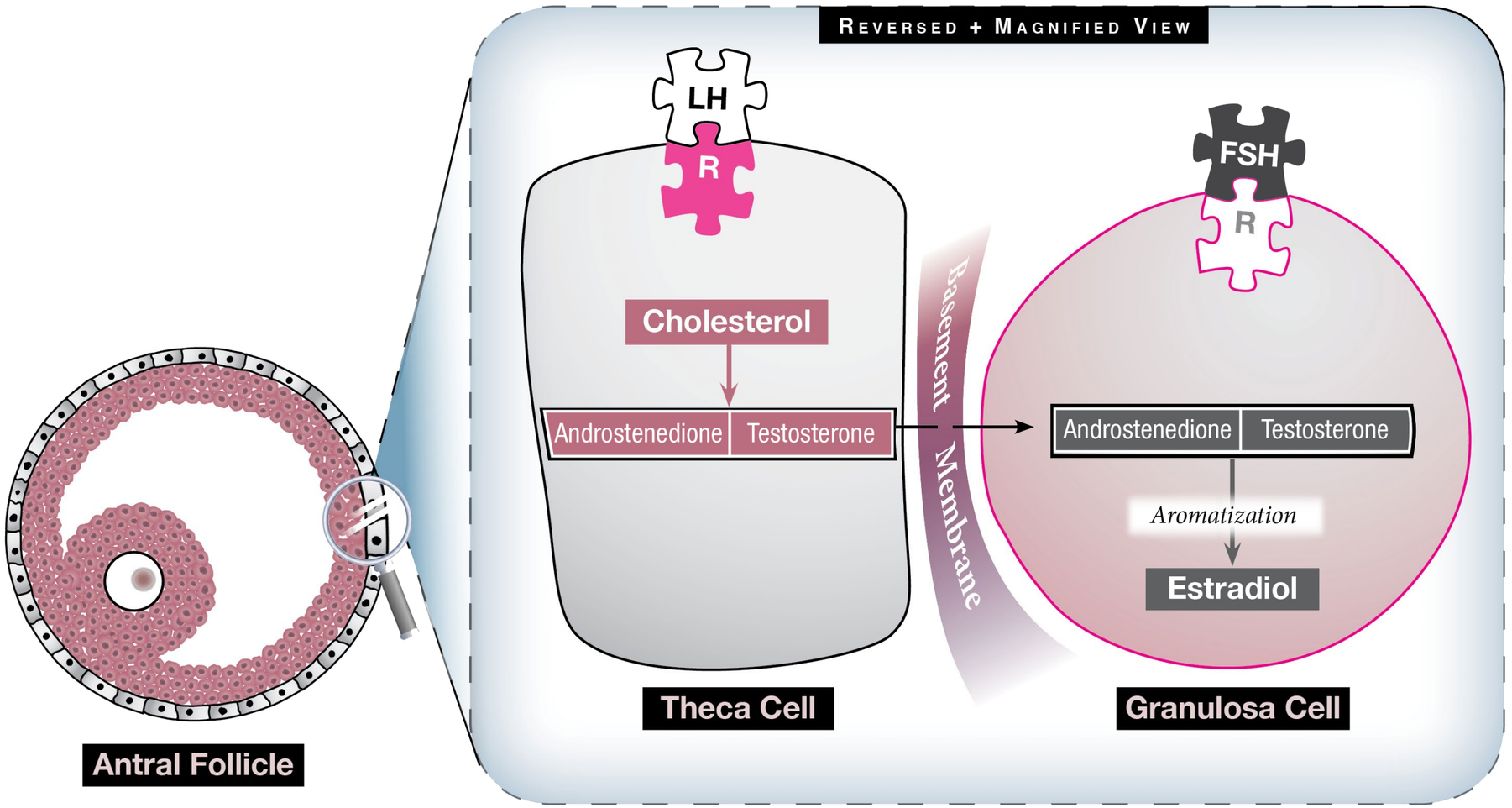
Normal nutrition



Over-weight/PCOS



Estrogen Production



Insulin Resistance

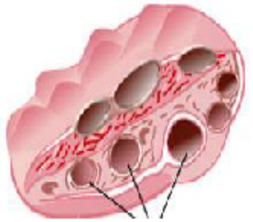
↓

Compensatory Hyperinsulinemia
(elevated insulin levels)

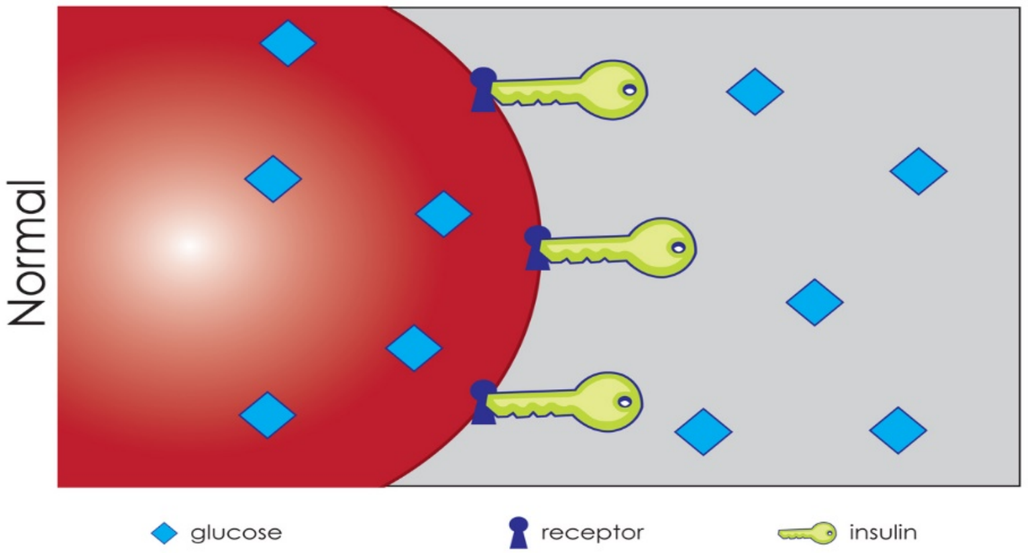
↓

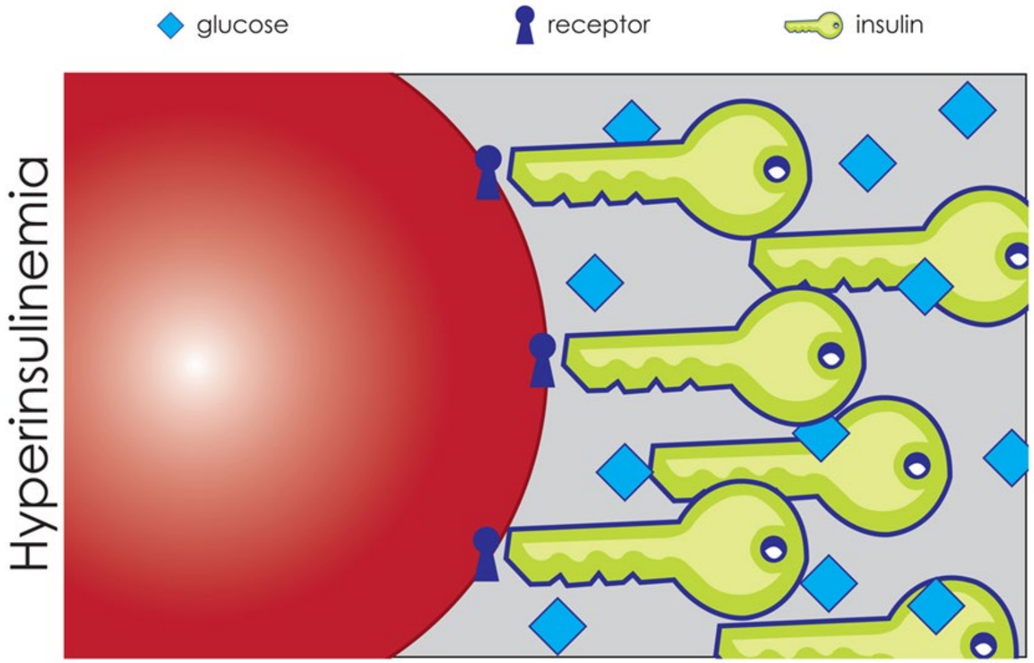
Increased androgen production
inhibits follicle development and
prevents ovulation

↓



Multiple small follicles that do
not ovulate


Normal
glucose
receptor
insulin


glucose
receptor
insulin
Hyperinsulinemia

DIAGNOSIS OF PCOS

New Patient Evaluation

- History
  - Menstrual cycle irregularities since menarche
  - Pt often c/o androgenic symptoms (alopecia, acne, hair growth)
- Physical
  - Often overweight/obese - android body type
  - Signs of insulin excess (acanthosis nigricans)
  - F- G score
  - Ultrasound: PCOS - appearing ovaries

New Patient Evaluation

- Blood:
  - FSH, LH, bHCG, TSH, Prolactin
    - Low FSH & LH- Be aware of possible HA
  - Androgens: total & free T, DHEAS
    - Total Testosterone >200 ng/ml
    - DHEAS >700- 800 g/dl
    - 17- OHP for any pt with hirsutism (follicular)
  - Lipid Panel
  - Glucose testing:
    - 2HR- OGT (with insulin levels)
    - HGbA1c?
    - Fasting Glucose ± Insulin level?

PART 5: AMENORRHEA WORKUP

Amenorrhea - Medical History

- Primary or Secondary?
- Time of onset (s/p D & C or uterine surgery)
  - Gradual (Ovarian failure)
- Other symptoms? Hot flashes, galactorrhea, hair growth?
- Weight gain or loss
  - Eating disorders, exercise
- Severe or chronic illness (diabetes, renal failure)
  - Radiation or chemo
- Cervical procedures (cone bx …etc)

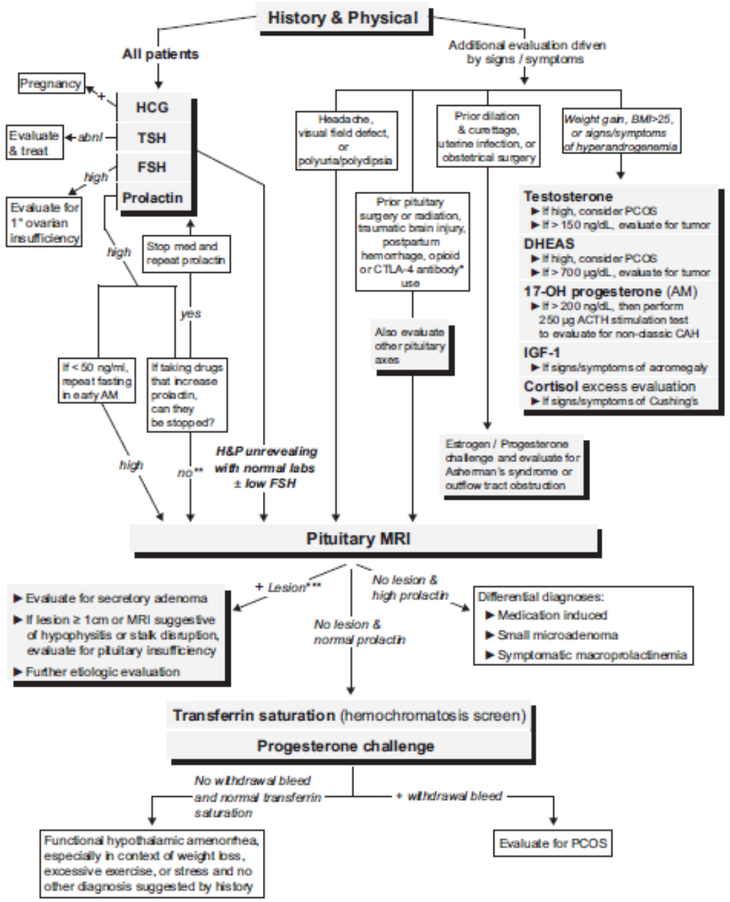
Amenorrhea - Physical Exam

- BMI/body habitus
- Goiter
- Galactorrhea
- Acanthosis nigricans
- Acne/hirsutism
- Vaginal ultrasound (ovary appearance, endo thickness, mullerian duct abnormalities)
- Speculum exam if primary amenorrhea (confirm patent vagina and visible cervix; cervical stenosis?)

Amenorrhea

- Evaluate ovaries - day 3 testing, AMH, ultrasound to look at ovaries and uterus
- Progesterone challenge:
  - –Both diagnostic and therapeutic
  - –Estrogen “priming” of uterus necessary
  - –If neg, then cyclic hormone therapy bleed
- Other labwork depending on exam
  - –Androgens, karyotype, PRL, TSH

Amenorrhea work-up



Retrieved from: J Clin Endocrinology Metab, March 2015, 100(3): 812-824