
2nd Annual Diabetes Symposium
MONUMENT HEALTH

Polycystic Ovary Syndrome

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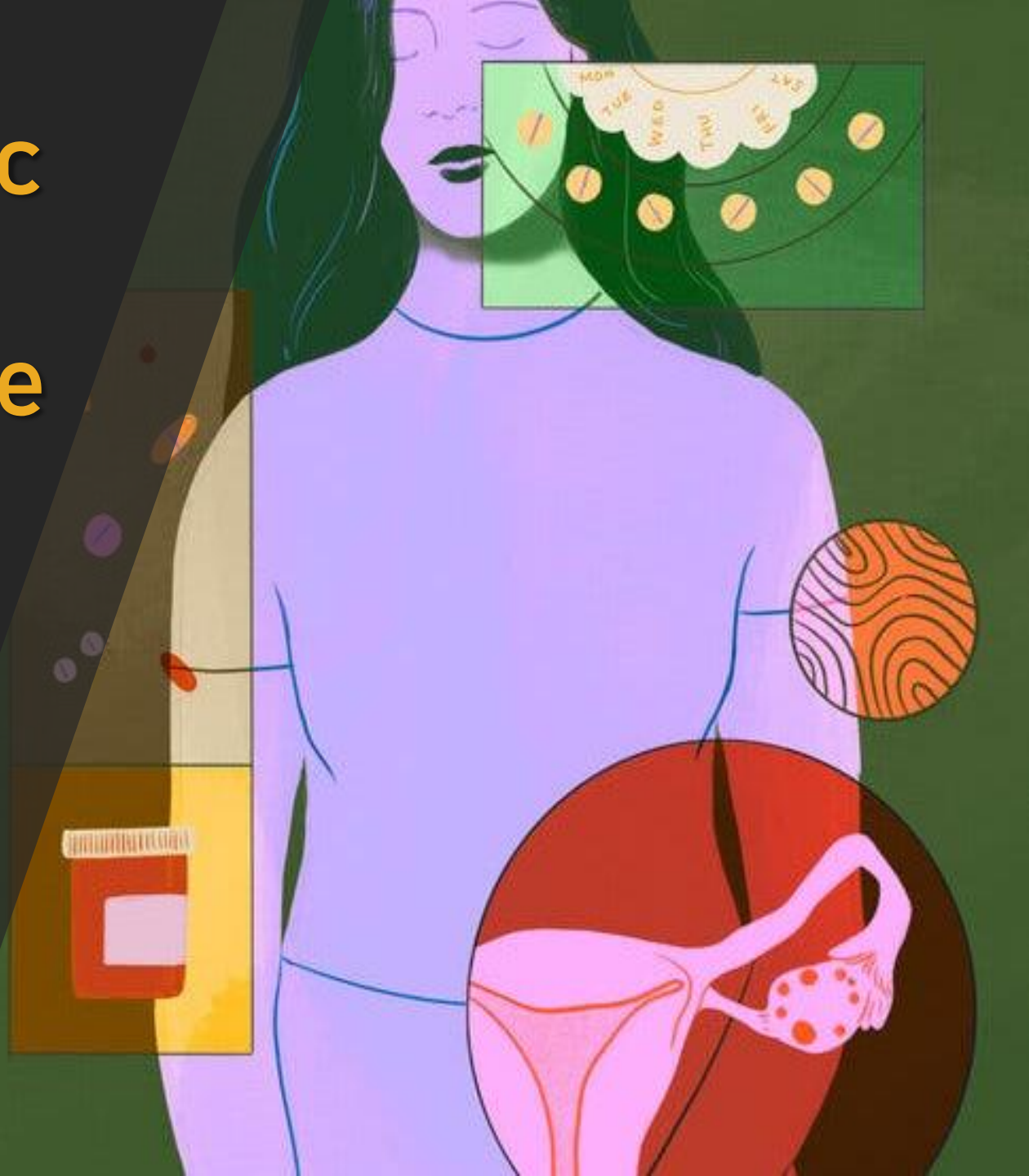
Endocrinology
January 21, 2022



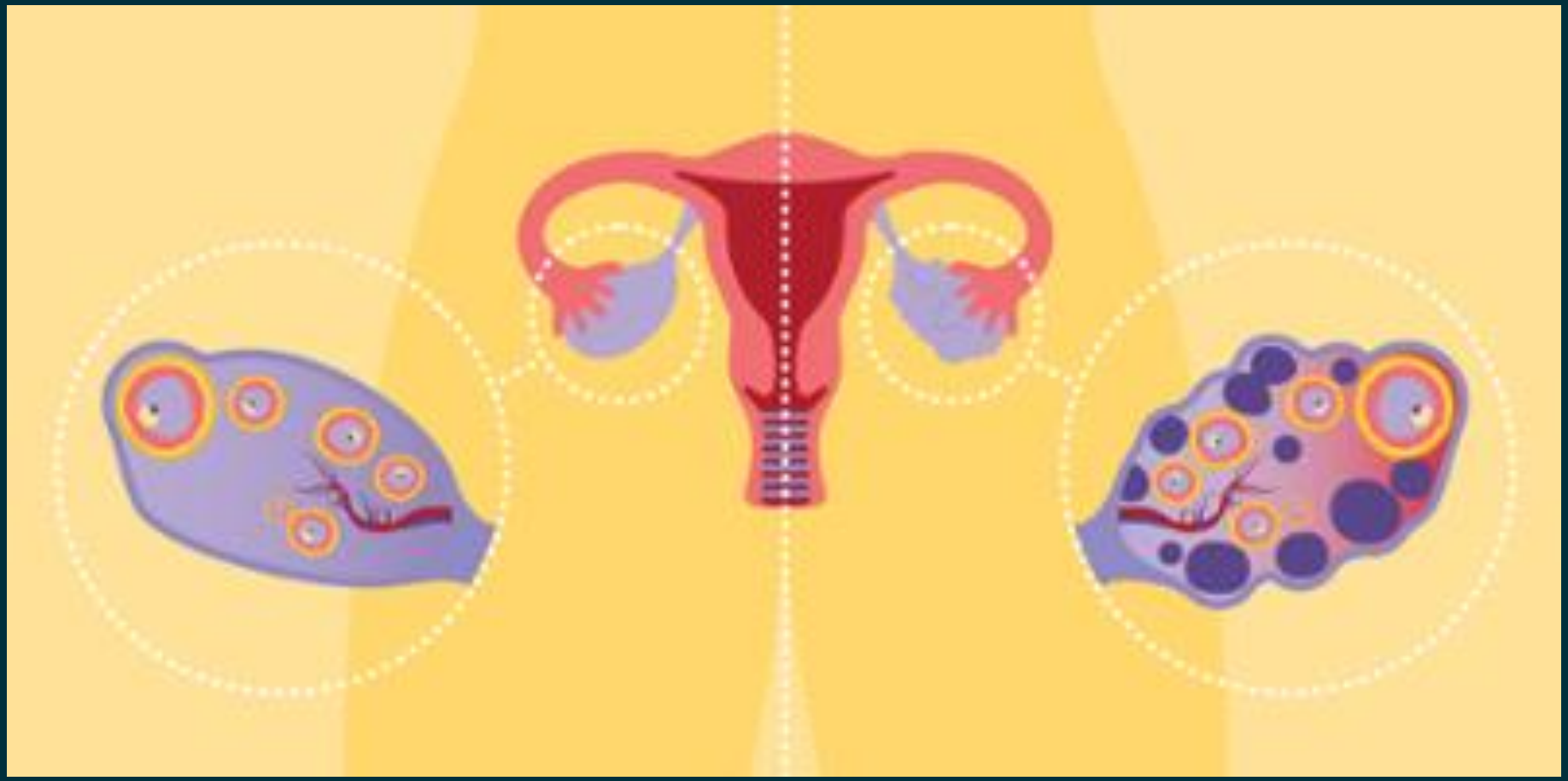
Michelle Mildenberg New York Times 9/4/2020

Disclosure

I have no actual or potential conflict of interest in relation to this program/presentation.

Outline

- Prevalence, significance, & diagnostic definition of PCOS
- Physiology of menstrual cycling
- Pathophysiology of PCOS
- Evaluation of PCOS
  - History
  - Exam
  - Differential diagnosis
  - Diagnostic testing
- Management



PCOS prevalence

The most common endocrine disorder in reproductive age women.

Affects 5-20% of reproductive-aged women

Accounts for about 20% of oligmenorrhea/amenorrhea

Dumesic DA, etl al. Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. Endocr Rev 2015

PCOS comorbidities and sequelae

- Increased ASCVD risk*
- Obesity and difficulty with weight loss (50-80%)
- Impaired glucose tolerance (30-35%)
- Type 2 diabetes (8-10%)
- Increased risk of pregnancy complications (Gestational diabetes, preeclampsia)
- Sleep apnea
- Depression & anxiety
- Endometrial cancer (2.7x risk, lifetime risk up to 9%)*

- Wild RA, et al. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. JCEM 2010
- Dumesic DA, Lobo RA. Cancer risk and PCOS. Steroids 2013

PCOS diagnostic criteria

NIH Consensus criteria (1990)

Must have both:

a. Androgen excess (clinical or biochemical)

b. Oligo-anovulation

Other causes must be excluded

Rotterdam criteria (2003)

Must have 2 or more:

a. Androgen excess (clinical or biochemical)

b. Oligo-anovulation

c. Polycystic ovaries on TVUS

Other causes must be excluded

Androgen Excess Society criteria (2006)

Must have both:

a. Androgen excess (clinical or biochemical)

b. Oligo-anovulation **or** Polycystic ovaries on TVUS

Other causes must be excluded

Polycystic ovarian morphologic features are defined as 12 or more antral follicles (2 to 9 mm in diameter) in either ovary, an ovarian volume that is greater than 10 ml in either ovary, or both.

Menstrual physiology

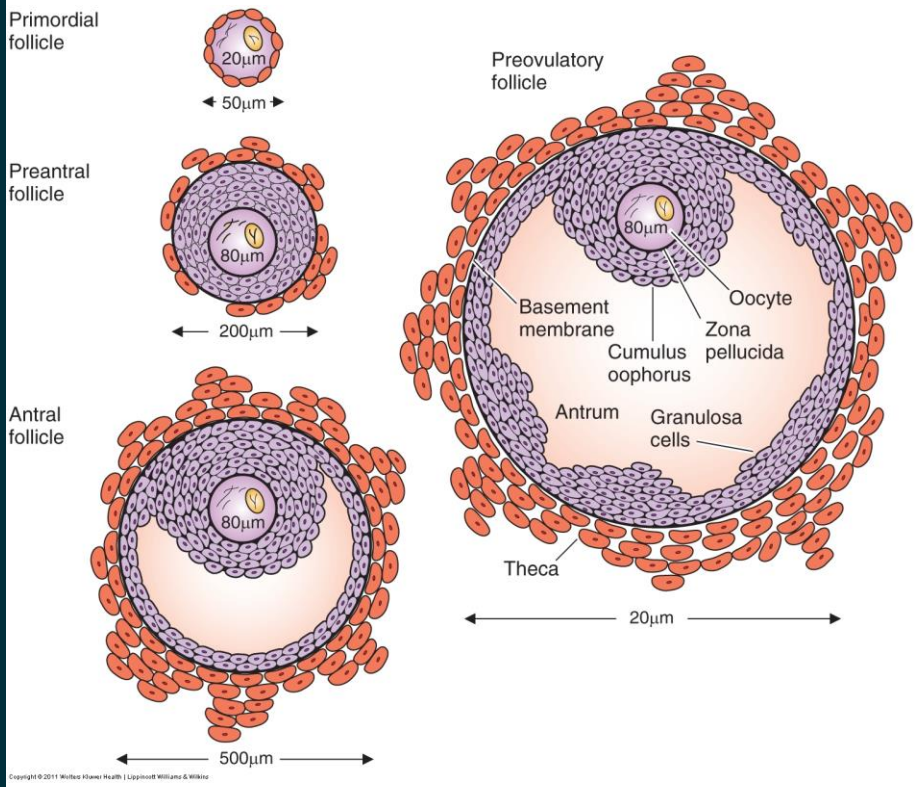
Menstrual cycle

- Normal menstrual cycle is 21-35 (28 days most common)
- By convention, the 1st day of menstruation is “day 1” of a cycle.
- Menstrual cycles have 3 phases
  - Follicular phase
  - Ovulatory phase
  - Luteal phase

Follicular phase

An orderly sequence of events over 10-14 days to ensure the proper number of follicles are ready for ovulation.

The result of this follicular development is (usually) one surviving mature follicle.

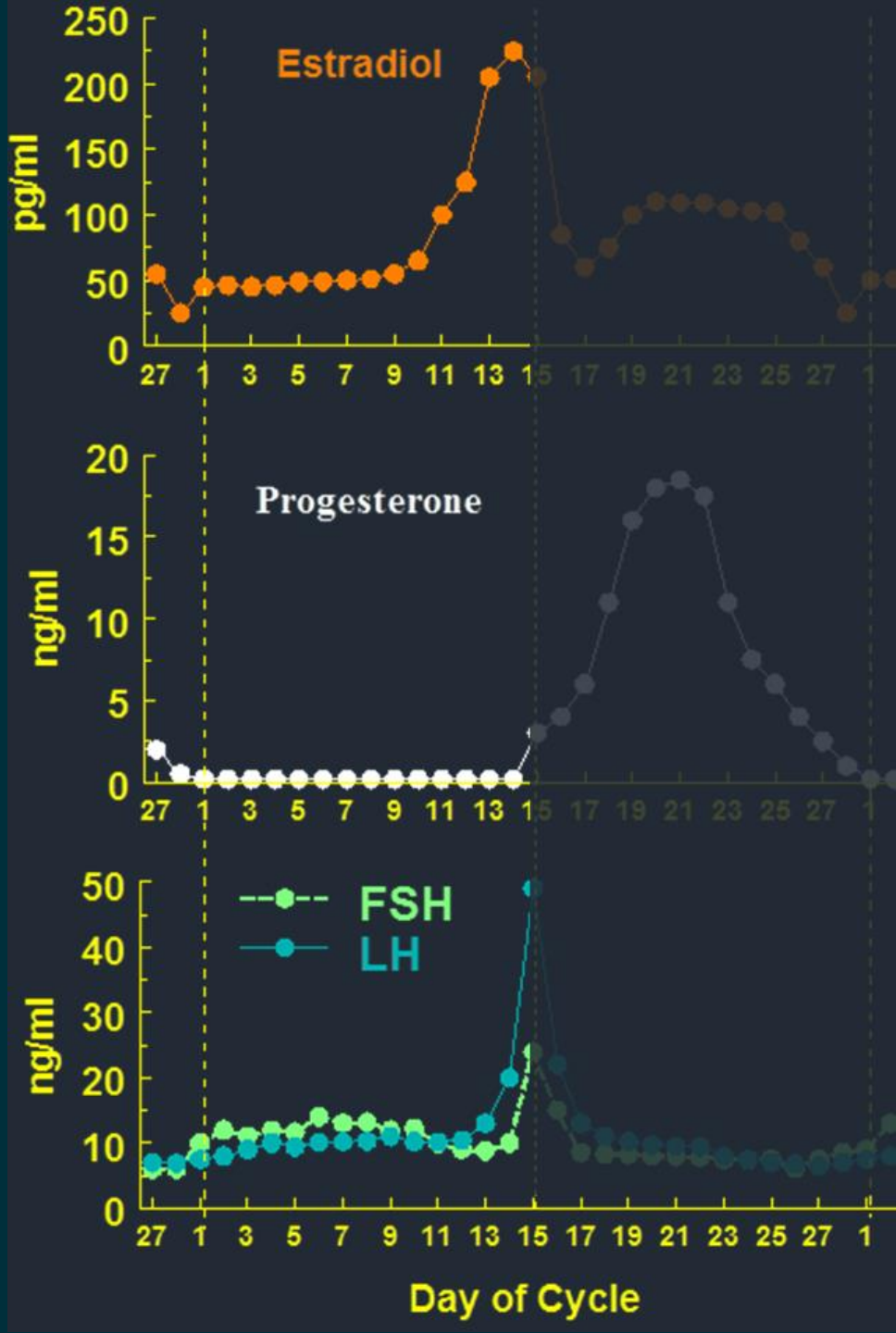


Follicular phase

FSH stimulates a group of follicles to grow

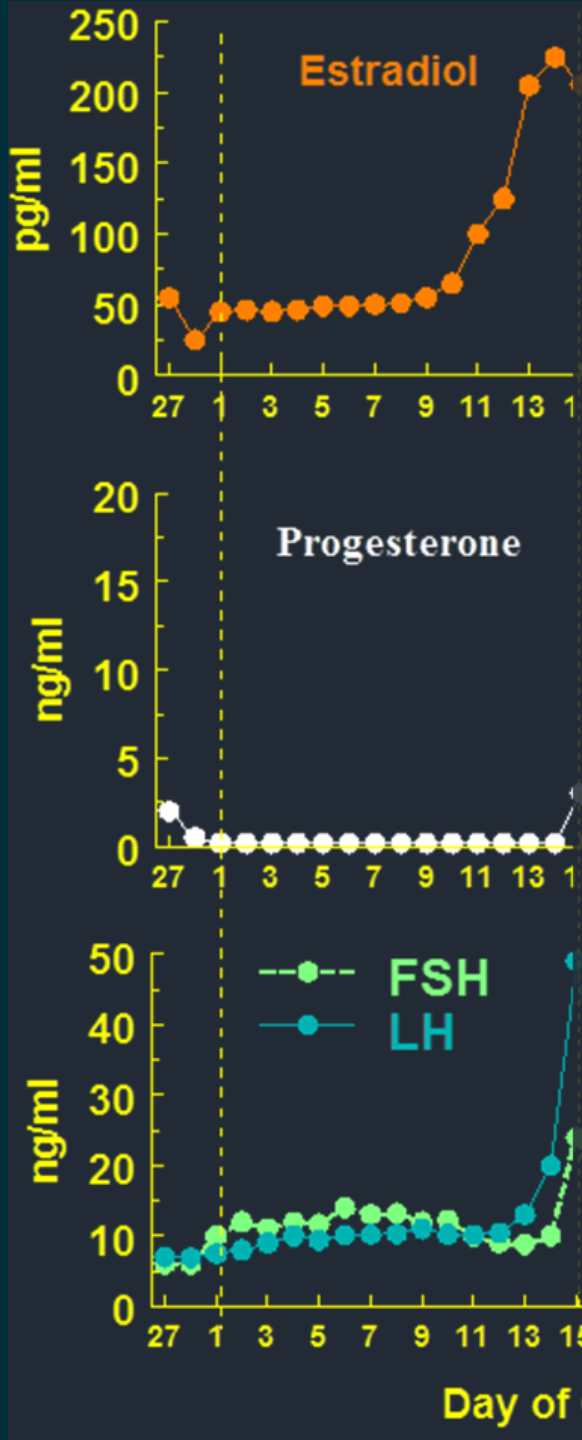
- These follicles secrete **estradiol**
  - stim growth of endometrium
  - stim growth of vasculature
  - paracrine effects on follicles

- Selection of a dominant follicle occurs around day 7
  - dominant follicle enlarges rapidly
  - ↑↑↑ **estradiol** secretion

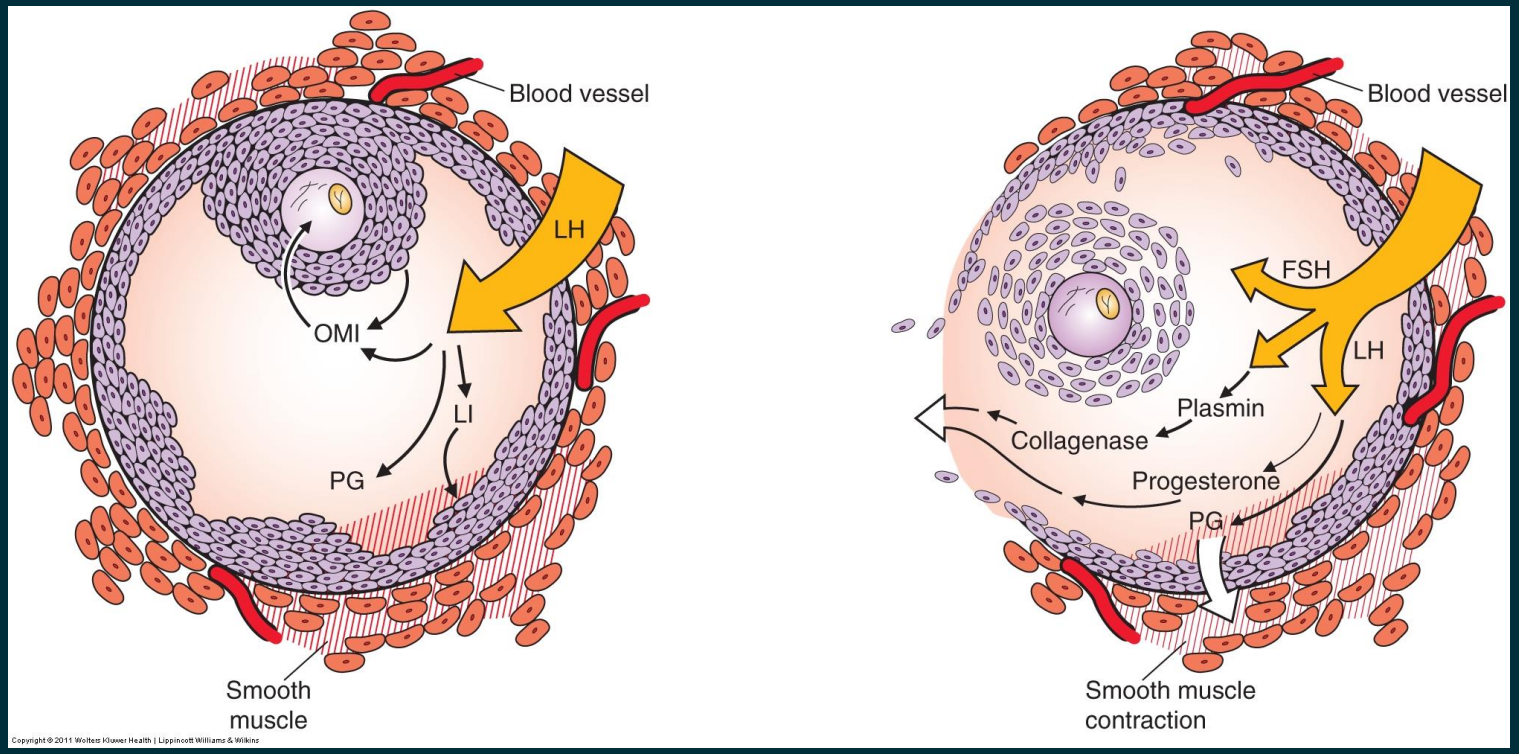


Follicular phase

- FSH induces granulosa cells in the follicle
  - to proliferate
  - express LH receptors
- As estradiol levels rapidly rise around day 7:
  - negative feedback effect on FSH release
  - positive feedback effect on LH release
- LH levels rise steadily in late follicular phase, which stimulates:
  - Differentiation of granulosa cells → luteal cells
    - Luteal cell start producing **progesterone**.
  - Theca cells to produce androgens



Luteinization is the differentiation of granulosa cells and theca cells to luteal cells

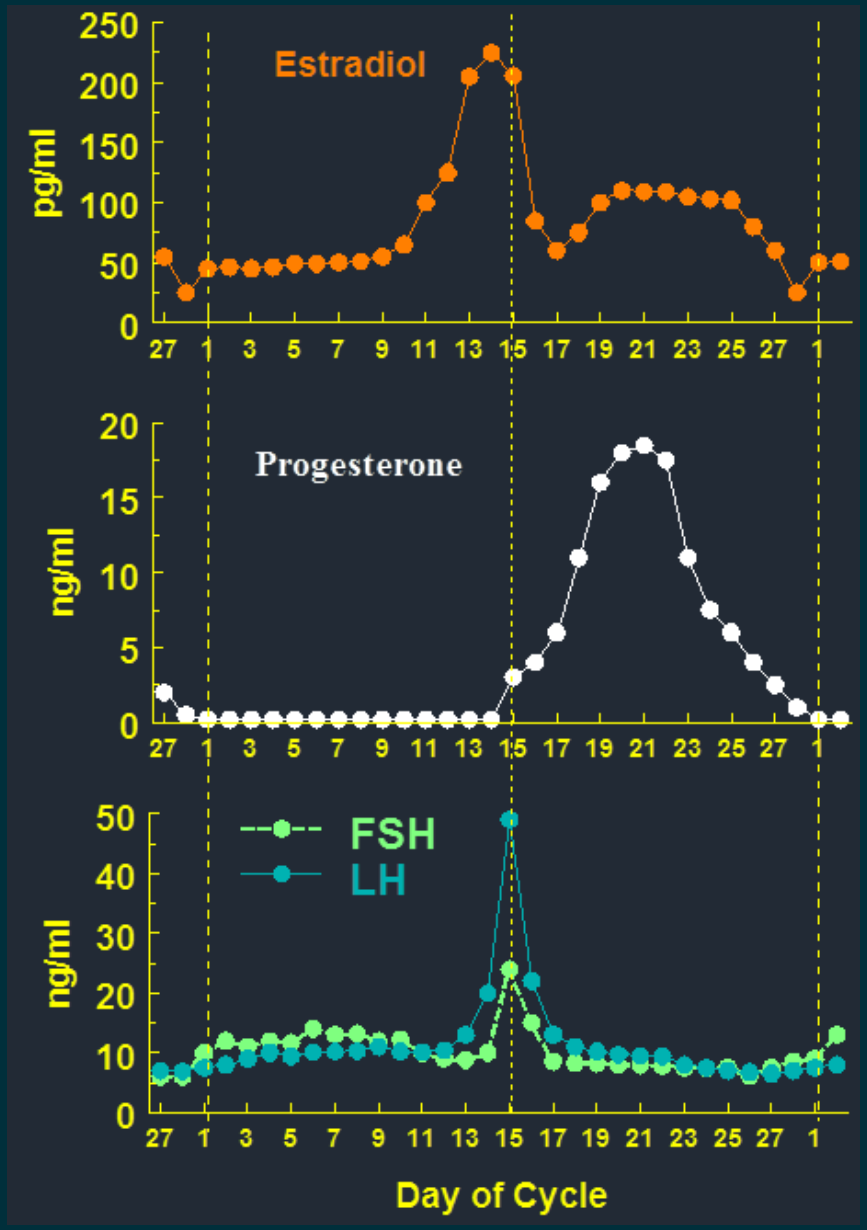


Ovulatory phase

- Around day 10-14, estradiol levels exceed a critical threshold in the hypothalamus, triggering large pulses of GnRH
- This results in a large surge of LH and FSH
- This surge permits the final maturation of the dominant follicle, leading to ovulation.
- In the fallopian tube, fimbria captures egg & sweeps it into oviduct

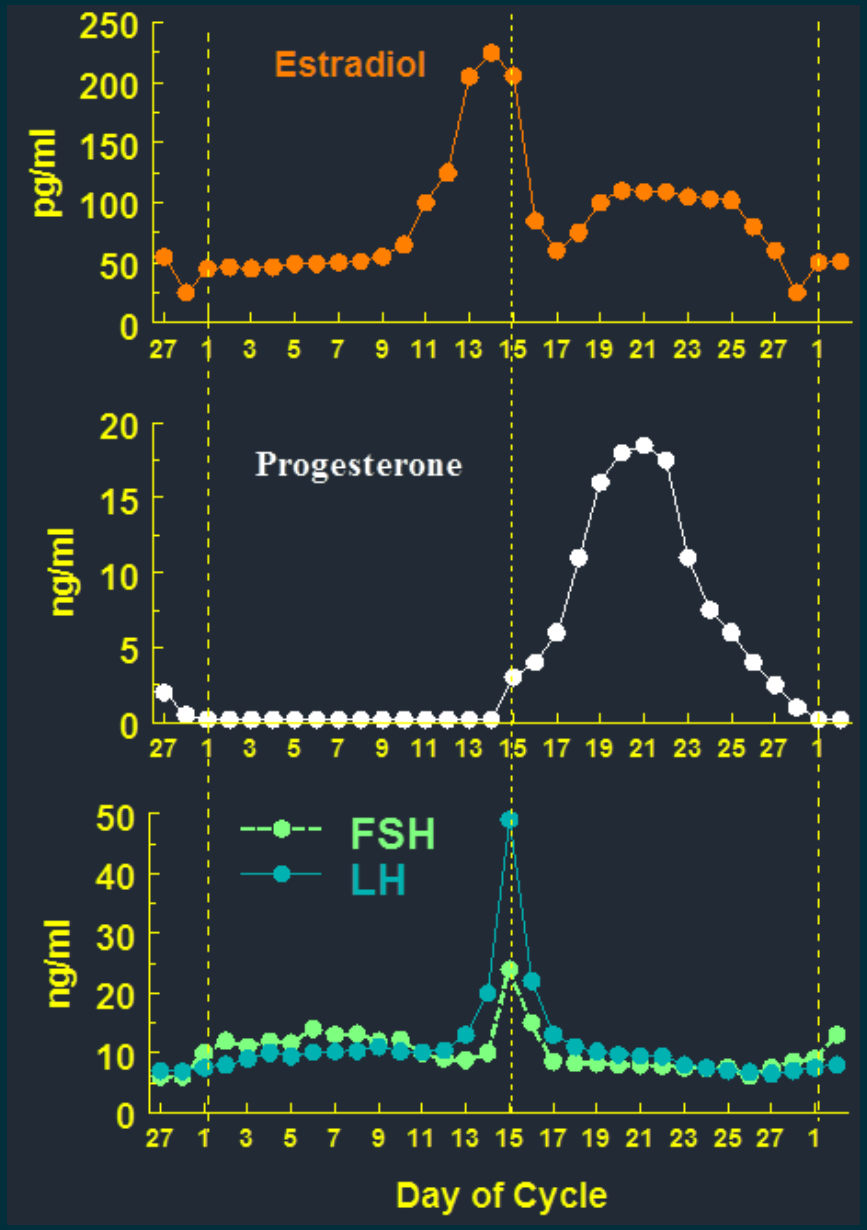
Luteal phase

- Ovulated follicle reorganizes into corpus luteum and starts to secrete **progesterone** and estradiol.
- Rising progesterone levels inhibit GnRH pulses, which leads to decreasing LH and FSH
- Final maturation of uterine endometrium occurs

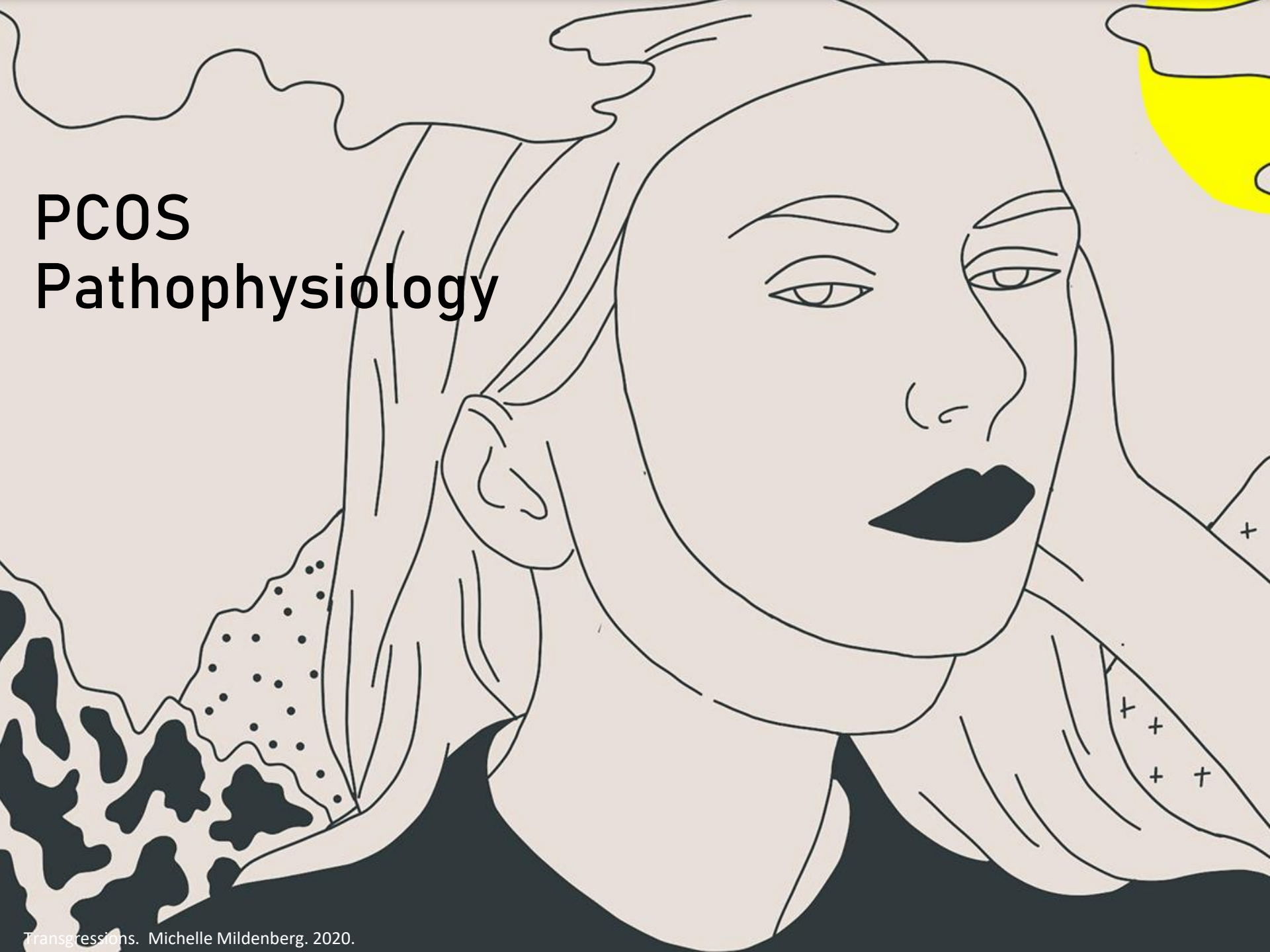


End of cycle

- The corpus luteum becomes insensitive to amount of LH available.
- Steroid secretion declines
- Arteries constrict, and the endometrium becomes ischemic & cells start dying
- As cells die arteries rupture, resulting in menses



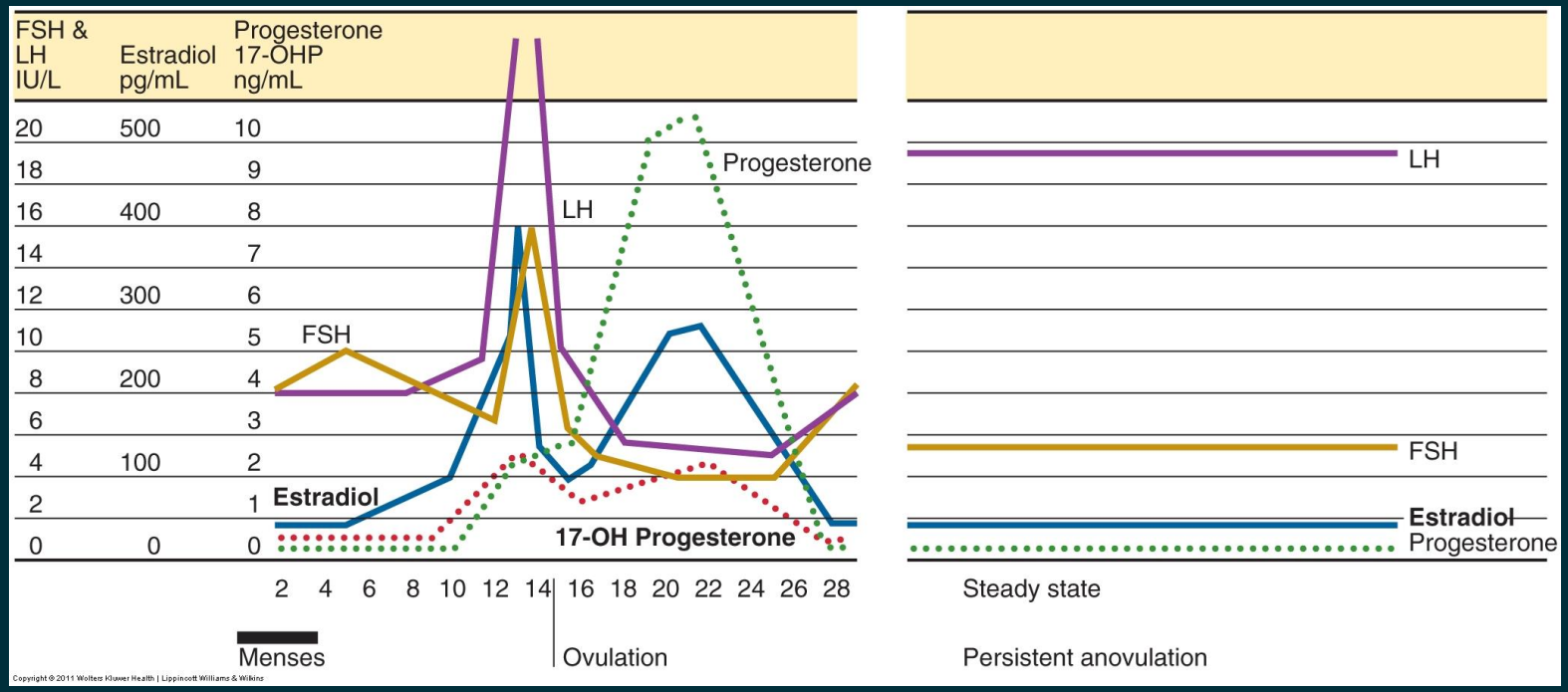
PCOS
Pathophysiology



Transgressions. Michelle Mildenberg. 2020.

PCOS pathophysiology

- Polycystic ovary syndrome develops when a chronic anovulatory state persists for a sufficient length of time and is a result of the disordered endocrine milleu caused by chronic anovulation.
- There are currently 3 mechanisms thought to be involved, to different degrees depending on the patient's phenotype



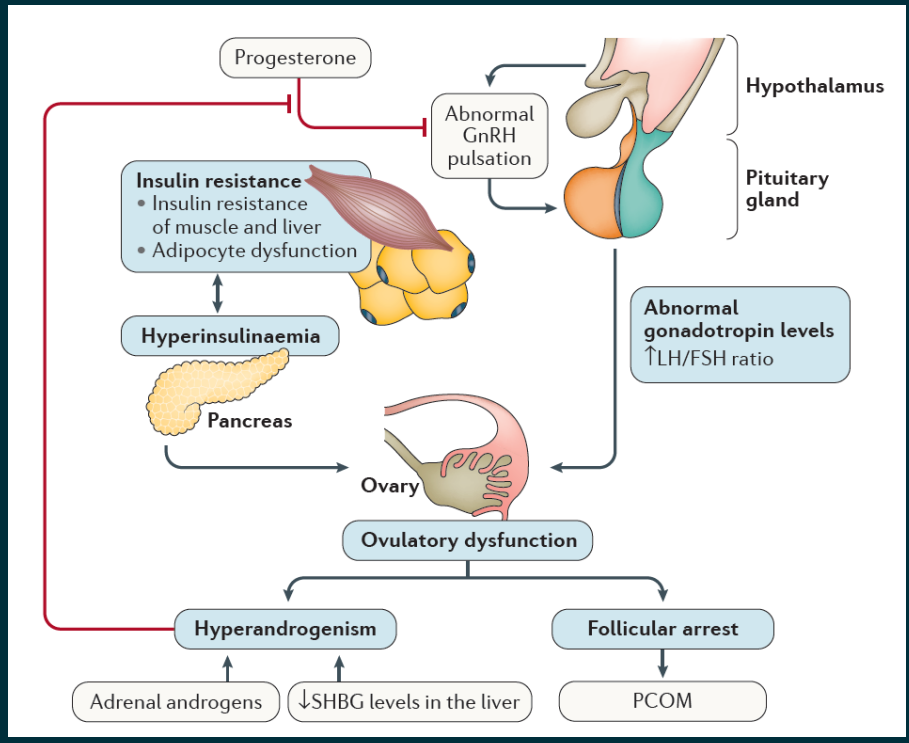
PCOS pathophysiology

1: Increased GnRH pulse frequency

- Increased GnRH pulse frequency results in increased LH secretion and decreased FSH secretion.

- ↑LH ↓FSH results in:
  - increased androgen production
  - interference with normal follicular development

- ↑ androgens further exacerbate the problem by inhibiting progesterone-mediated inhibition of GnRH pulses.

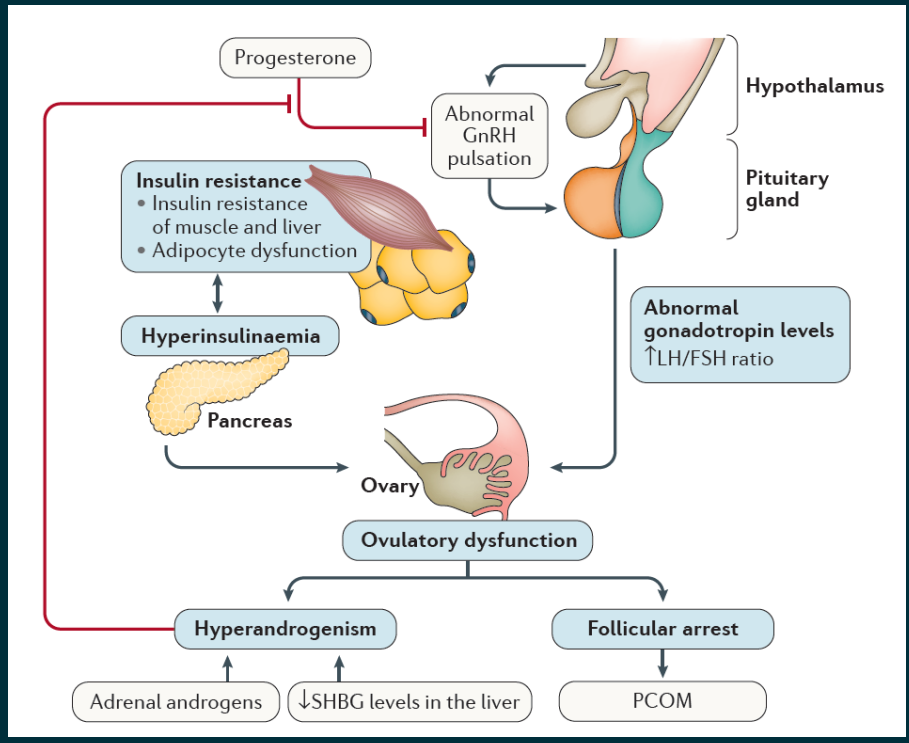


† Azziz R, et al. Polycystic ovary syndrome. Nature Reviews Disease Primers. 2016

PCOS pathophysiology

2. Inherent abnormalities of ovarian (and adrenal) steroidogenesis.

- Theca cells have increased sensitivity to LH and secrete more androgens.
- Adrenal androgen production (DHEA-S) is increased in at least 30% of women with PCOS, but the mechanism is unknown.



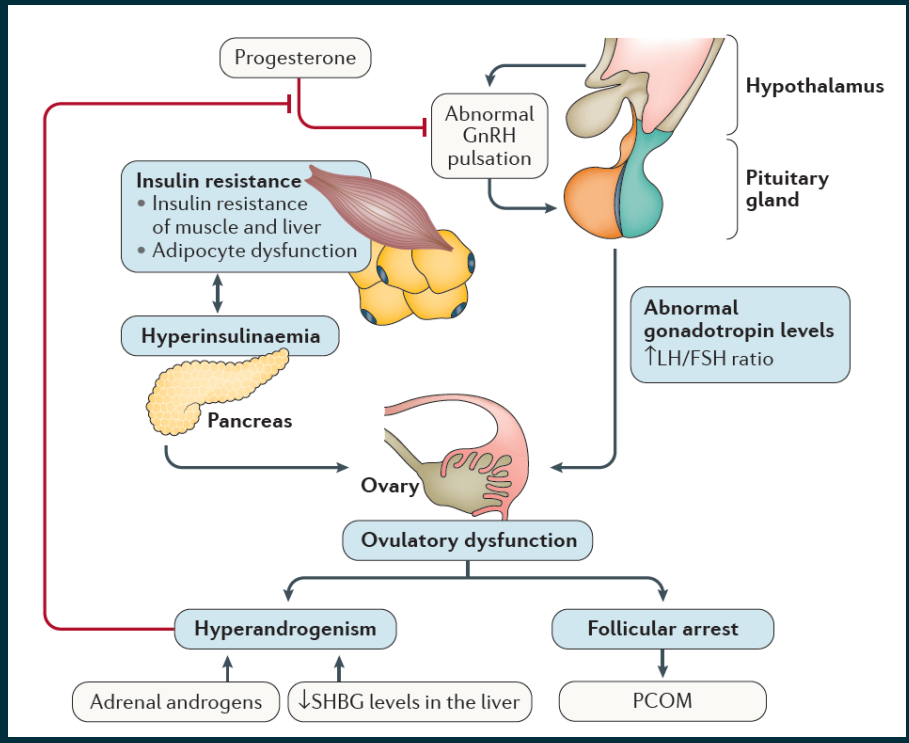
† Azziz R, et al. Polycystic ovary syndrome. Nature Reviews Disease Primers. 2016

PCOS pathophysiology

3. Insulin resistance and hyperinsulinemia

Insulin resistance:

- ↑ LH-stimulated androgen production by ovarian theca cells
- potentiates corticotropin-mediated adrenal androgen production
- inhibits hepatic synthesis of sex hormone–binding globulin (SHBG), which increases free testosterone levels.



† Azziz R, et al. Polycystic ovary syndrome. Nature Reviews Disease Primers. 2016

PCOS Genetics

- Familial clustering and twin studies strongly support an underlying genetic basis for PCOS.
  - Having mother or sister with PCOS confers a 30-50% risk
- Genomewide association studies implicate:
  - Gonadotropin receptors, Beta-subunit of FSH, Insulin receptor, DENND1A*, THADA**
- Note that obesity-assc'd genes have **not** been implicated, and data supporting a link between obesity as a driver of PCOS is lacking†.
  - Studies showing association of BMI and PCOS are selected hospital/clinic populations.
  - In a study of an unselected population in the US, there was no difference in PCOS prevalence based on BMI. ‡

* differentially expressed in normal and neoplastic cells domain-containing protein 1
** thyroid adenoma-associated protein
† Azziz R, et al. Polycystic ovary syndrome. Nature Reviews Disease Primers. 2016
‡ Yildiz, B, et al. Impact of obesity on the risk for polycystic ovary syndrome. JCEM. 2008

History and Exam

Patient history: Irregular menstrual frequency

- All patients with PCOS will have ovulatory dysfunction.
- Ovulatory dysfunction is presumed if there is irregular menstrual cycle frequency, def
  - From 3 years post-menarche to menopause: < 21 days or > 35 days or < 8 cycles/yr
  - In adolescents, the following are also irregular:
    - From one year post-menarche: > 90 days from prior cycle
    - Primary amenorrhea 3 years post-thelarche or after age 15

- Ovulatory dysfunction can also be present in women with regular menses
  - 15-40% of hyperandrogenemic patients have regular menses[†].
  - Serum progesterone during midluteal phase (days 21-22) < 7 c/w anovulation[*].

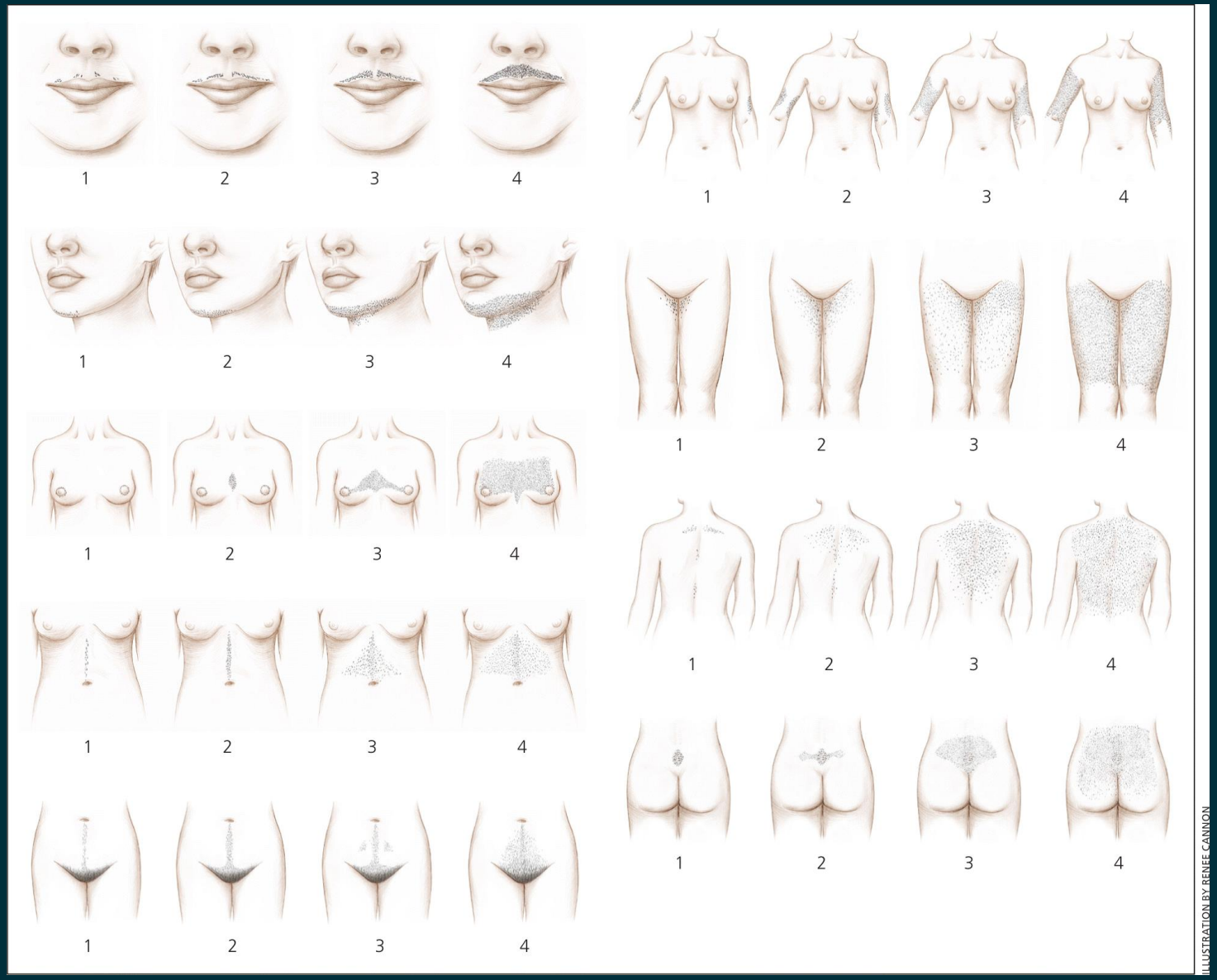
* Hull MG, et al. The value of a single serum progesterone measurement in the midluteal phase as a criterion of a potentially fertile cycle ("ovulation") derived from treated and untreated conception cycles. Fertil Steril. 1982

† Azziz R, Carmina E, Dewailly D, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril 2009

Patient history

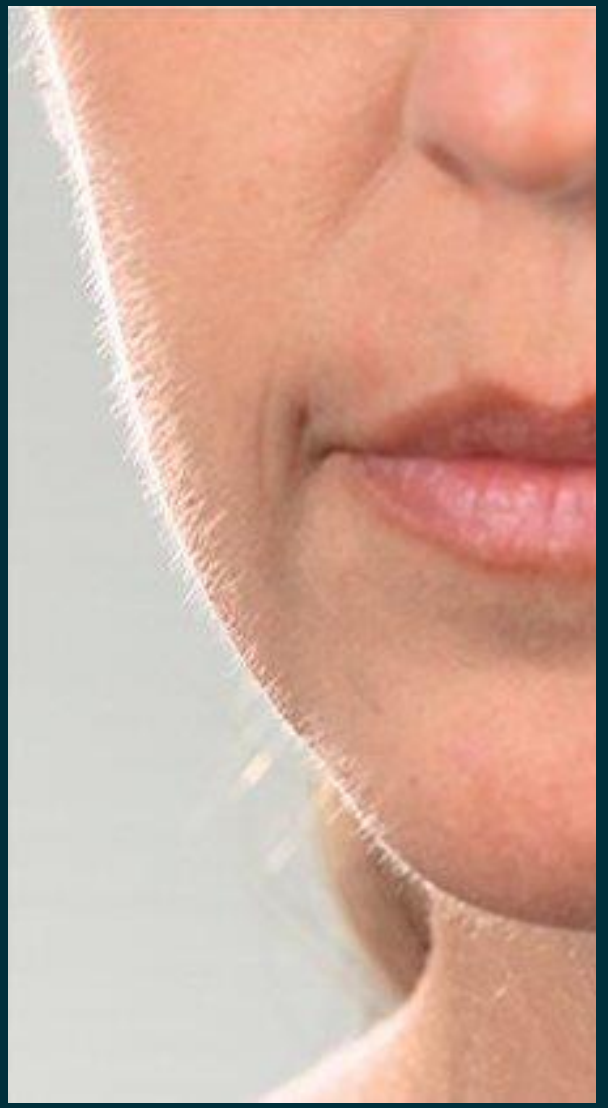
- Hirsutism
  - Less prominent in women of eastern Asian descent
  - More prominent in Hispanic, Mediterranean, and Middle Eastern women.
- Acne
- Excess hair loss
- Acanthosis nigricans and skin tags
- Weight gain
- Clitoromegaly (>10mm in length)

Physical exam: Hirsutism

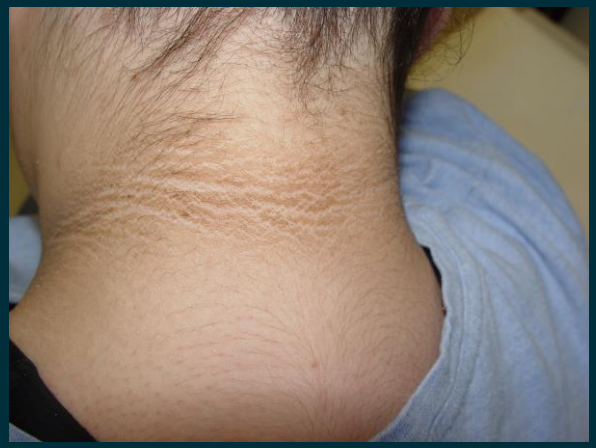


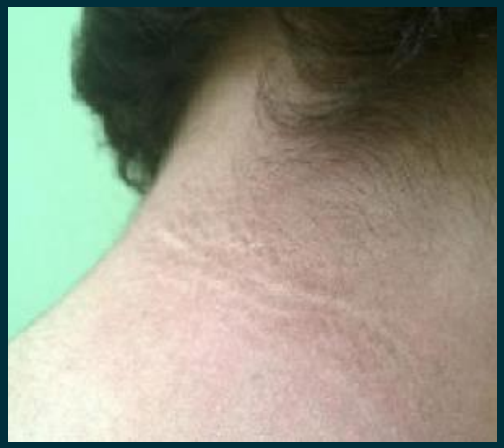
Physical exam: Vellus hairs

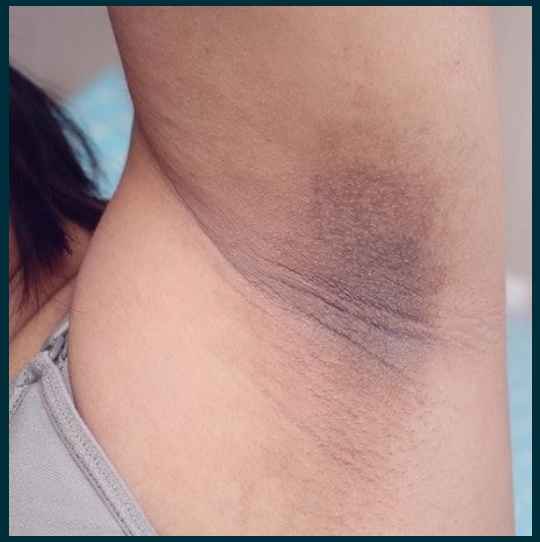
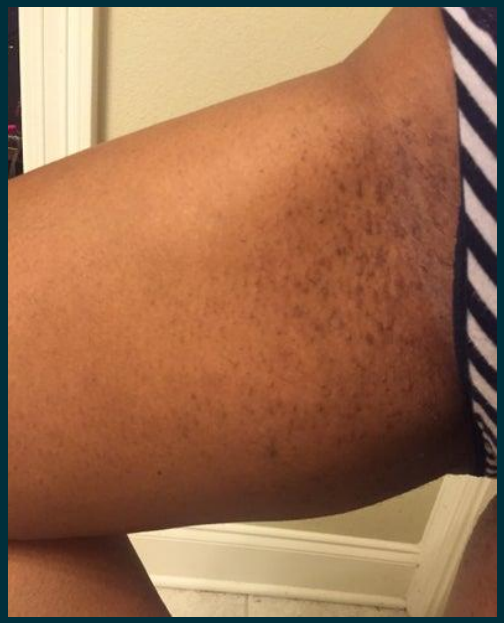
- Vellus hairs are not hirsutism. These are non-pigmented and also found in locations that not androgen-dependent
- Hypertrichosis (Excessive vellus hair) ddx
  - Medications
    - cyclosporine, cetirizine, citalopram, topical corticosteroids, diazoxide, implanon, phenytoin, streptomycin
  - Diseases
    - Hypothyroidism
    - Anorexia nervosa
    - Dermatomyositis
    - Malnutrition
    - Epidermolysis Bullosa
    - Porphyria
  - Congenital syndromes
    - Hurler's syndrome
    - Trisomy 18
    - Fetal alcohol syndrome
  - Normal states
    - Advanced age
    - Ethnic background
    - Pregnancy



Physical exam: Acanthosis nigricans & skin tags





Differential diagnosis

Differential diagnosis of PCOS

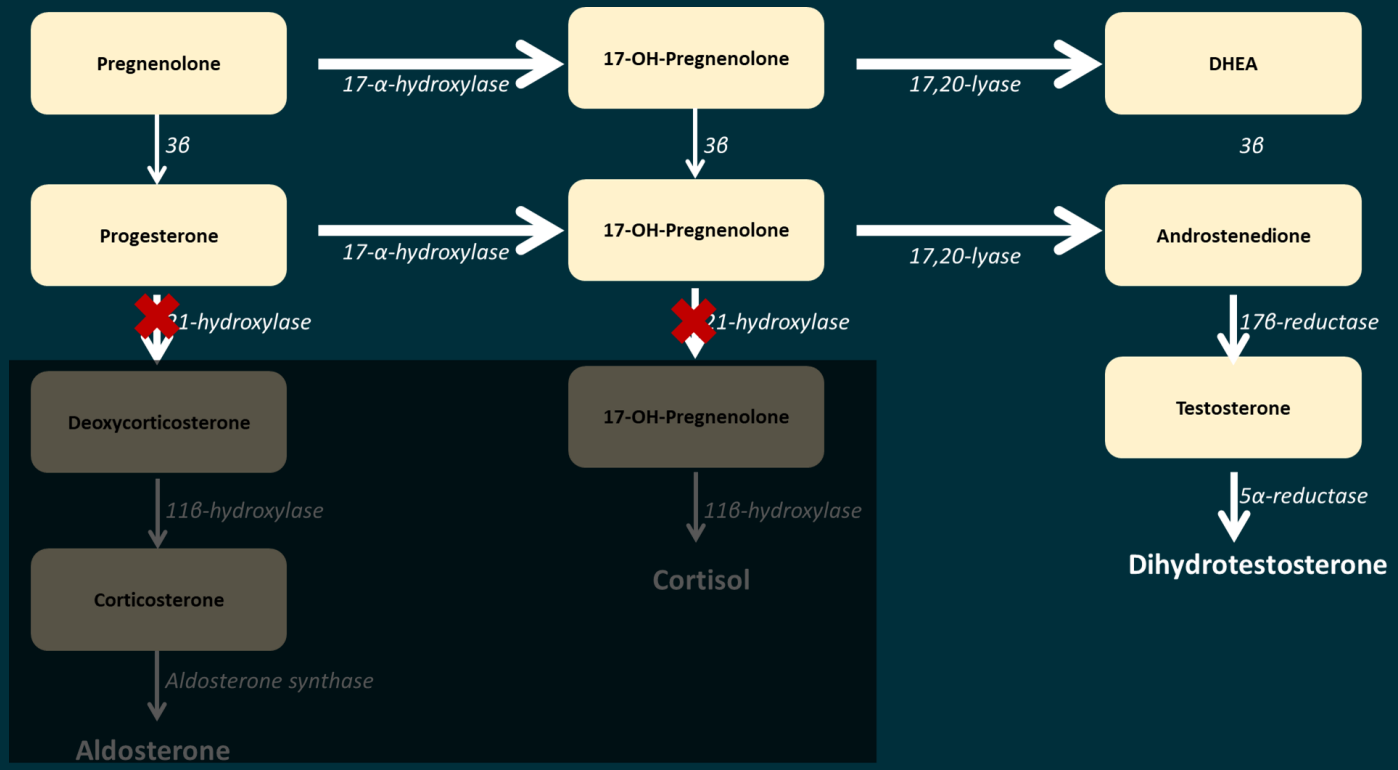
- Idiopathic hirsutism
- Nonclassical CAH
- Virilizing tumors of the adrenal or ovary
- Cushings syndrome
- Hypothyroidism
- Acromegaly
- Prolactinoma
- Premature ovarian insufficiency
- Functional hypothalamic amenorrhea
- Medication-induced hyperandrogenism
  - androgens, danazol, glucocorticoids, dilantin, diazoxide, minoxidil
- Partial androgen insensitivity
- 5α-reductase deficiency

Differential diagnosis of PCOS: Nonclassical ("late onset") CAH

Caused by autosomal recessive defect of 21-hydroxylase

1-4% prevalence in American white and Hispanic women.

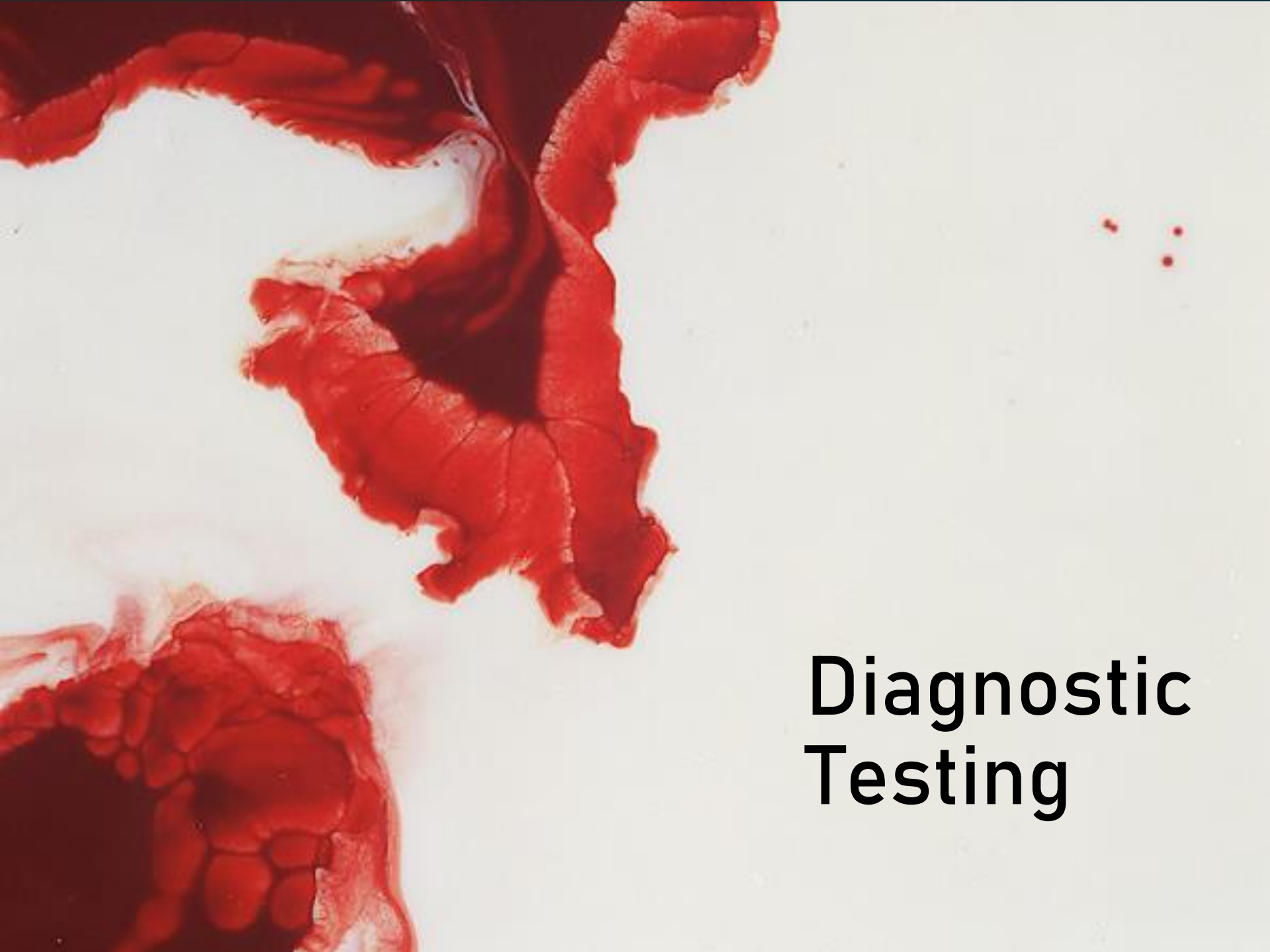
Highest prevalence: Mediterranean, Hispanic, Slavic, Ashkenazi Jewish



Differential diagnosis of PCOS
Virilizing tumor

- Rare
  - Prevalence of androgen-secreting ovarian tumor in women with hyperandrogenism: 1 in 300-1000*
  - Adrenal virilizing tumors are even more rare†
- Consider if serve or abrupt signs of hyperandrogenism
- Suggestive labs:
  - High T (>150 ng/dl) and or DHEA-S (>800 mcg/dl)

*Fritz MA, Speroff L. Clinical Gynecology Endocrinology and Infertility, 8th Edition. Lipincott Williams & Wilkins. 2011
†cannot find any citations giving an estimated prevalence



Diagnostic Testing

Lab evaluation: assessing for hyperandrogenemia

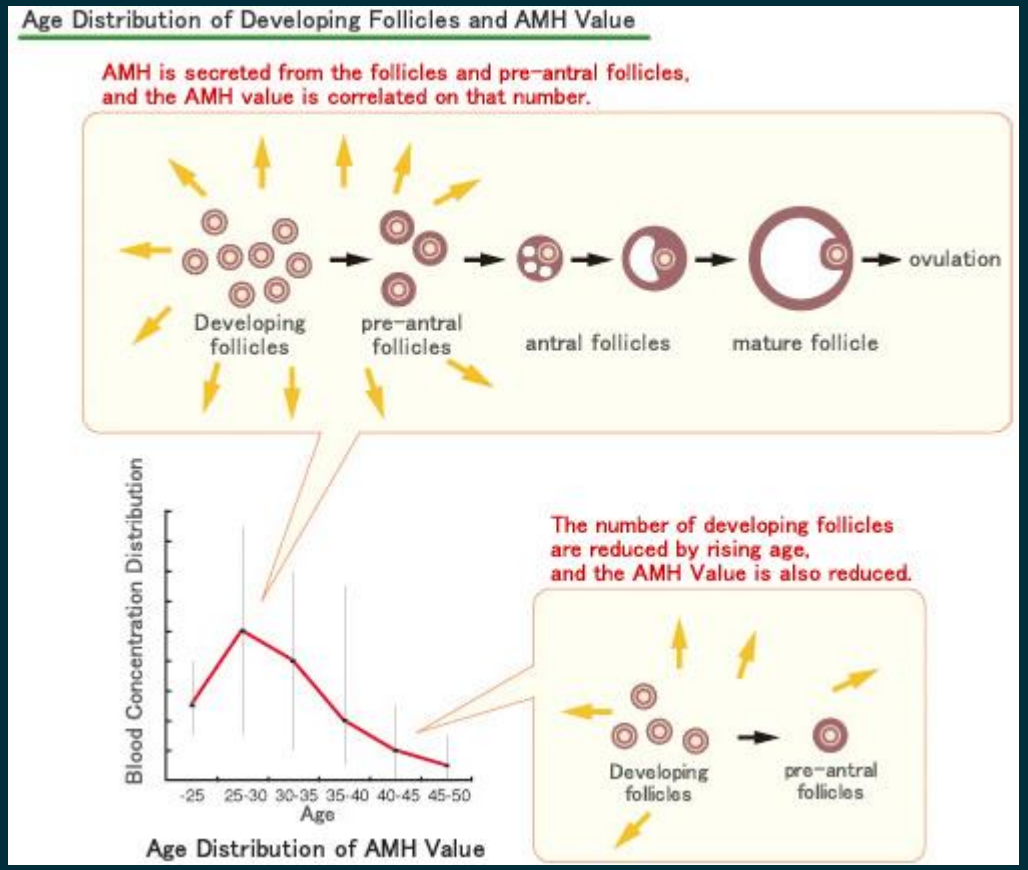
- Total testosterone (ONLY USE LC-MS)
  - Elevated in most, but not all, pts with PCOS
  - Immunoassays on the scale of levels present in women are inaccurate. For testosterone levels below 100ng/dL, 56–90% were ± 20% of those measured by the gold standard*†.
- Free testosterone (by equilibrium dialysis)
  - Guidelines recommend this as the gold standard but is expensive.
- SHBG
  - Allows you to calculate free testosterone, but this is typically unnecessary.

* Wang C, et al. Measurement of total serum testosterone in adult men: comparison of current laboratory methods versus liquid chromatography-tandem mass spectrometry. JCEM 2004.
† Miller KK, et al. Measurement of free testosterone in normal women and women with androgen deficiency: comparison of methods JCEM. 2004.
‡ Carmina E. Ovarian and adrenal hyperandrogenism. Ann N Y Acad Sci. 2006

Lab evaluation: assessing for hyperandrogenemia

- DHEA-S
  - Some pts will also have excessive adrenal androgen production
  - Increased in at least 30% of patients with PCOS, and 5% of PCOS patients only have DHEA-S elevation‡
- DHEA
  - Little diagnostic value; levels have a diurnal pattern and high between-subject variability, and are sensitive to stress
- 11B-hydroxyandrostenedione and androstenedione
  - Generally not needed in clinical use

‡ Carmina E. Ovarian and adrenal hyperandrogenism. Ann N Y Acad Sci. 2006



Lab evaluation: assessing for ovulatory dysfunction

Anti-Mullerian Hormone

Checked more frequently now, particularly in unclear cases.

Elevated levels (>4.5ng/mL) can be a useful substitute for ovarian morphology

Lab evaluation: excluding other disorders

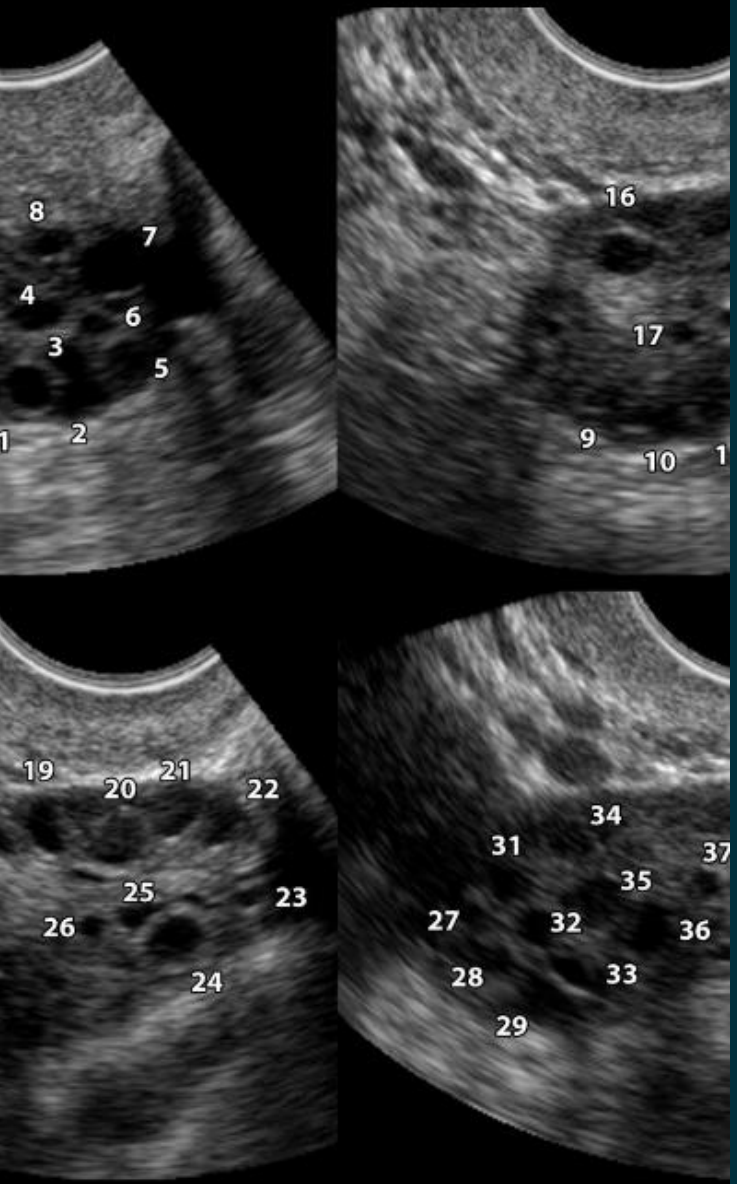
The following should be checked to rule out other causes of androgen excess and anovulation:

- TSH
- Prolactin
- Fasting glucose

Lab evaluation: excluding other causes

- 17-hydroxyprogesterone
  - Check in women with early-onset hirsutism, FHx of NCCAH, or in high risk ethnic groups*
  - Should be checked in early follicular phase (first few days after onset of menses). Should be checked in the AM
  - < 200 ng/dl rules this out, >800 is nearly diagnostic
- Dexamethasone-suppressed cortisol
  - in pts with other suggestive features of Cushing syndrome
  - (don't do this on woman on OCP, which causes false positives)
- LH and FSH:
  - While PCOS is associated with increased LH, and LH:FSH ratio of 2:1 was previously regarded as a marker of PCOS, this is not a reliable.

*Fritz MA, Speroff L. Clinical Gynecology Endocrinology and Infertility, 8th Edition. Lipincott Williams & Wilkins. 2011.



Imaging evaluation of PCOS

PCO Morphology*

- ≥ 20 follicles (2-9mm) on either ovary and/or Increased volume (≥ 10 ml) on either ovary
- These are updated based on newer US technology

Very Important notes

- Up to 30% of normal women can have PCOM*. (that is not a typo)
- PCOM can be seen in patients with functional hypothalamic anovulation and hyperprolactinemia.
- Do not use these criteria in women on OCPs (OCPs may cause false negative findings)

Polycystic ovaries do not establish and are not required for diagnosis of PCOS

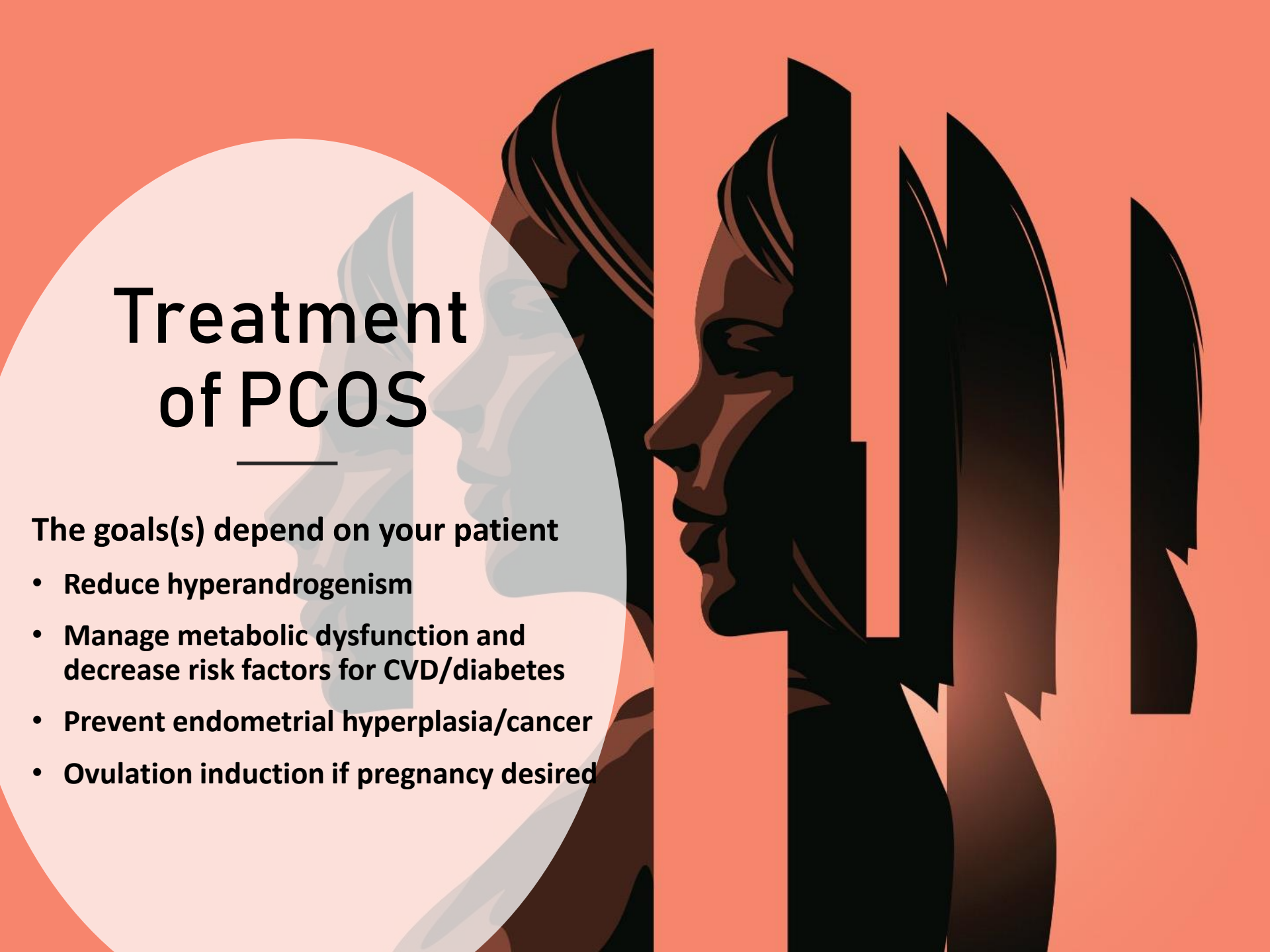
* Dewailly D, et al. Definition and significance of polycystic ovarian morphology: a task force report from the Androgen Excess and Polycystic Ovary Syndrome Society. Hum Reprod Update. 2014

Management of PCOS

Workup after diagnosis of PCOS is made

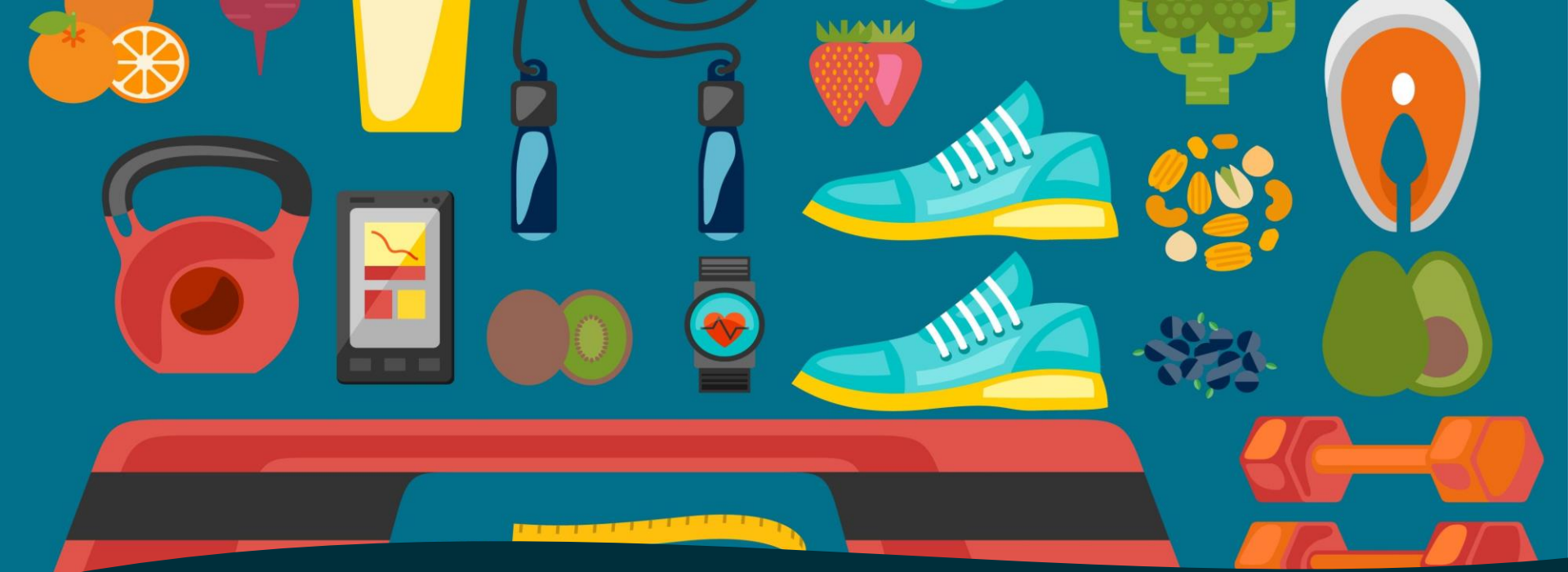
- 2hr OGTT
  - 35% have impaired glucose tolerance, 10% have diabetes
- Fasting insulin/HOMA-IR (this is Controversial)
- Fasting lipid profile
- Screening questions for sleep apnea
- Screen for depression and anxiety
- Check blood pressure
- Check BMI

Treatment of PCOS



The goals(s) depend on your patient

- **Reduce hyperandrogenism**
- **Manage metabolic dysfunction and decrease risk factors for CVD/diabetes**
- **Prevent endometrial hyperplasia/cancer**
- **Ovulation induction if pregnancy desired**



Lifestyle intervention improves ovulation in 40-50% of women with PCOS, 30-40% can subsequently achieve spontaneous pregnancy[*†ϕ].

Lifestyle changes

No specific diet has been found to be superior[‡]. The goal is long-term calorie restriction to trigger weight loss. Even 5% weight loss can improve ovulation.

Guidelines recommend minimum of 150 min/wk of moderate intensity exercise[ℐ], with muscle strength activity 2 days/wk[ℐ]

* Moran, L., et al. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database Syst. Rev. 2011*
†Carmina, E. PCOS: metabolic impact and long-term management. Minerva Ginecol . 2012.
ϕKiddy, D. S. et al. Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. Clin. Endocrinol. 1992
‡Moran, L. J. et al. Dietary composition in the treatment of polycystic ovary syndrome: a systematic review to inform evidence-based guidelines. J. Acad. Nutr. Diet.2013
ℐ Moran LJ, et al. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. Fertil Steril 2009.

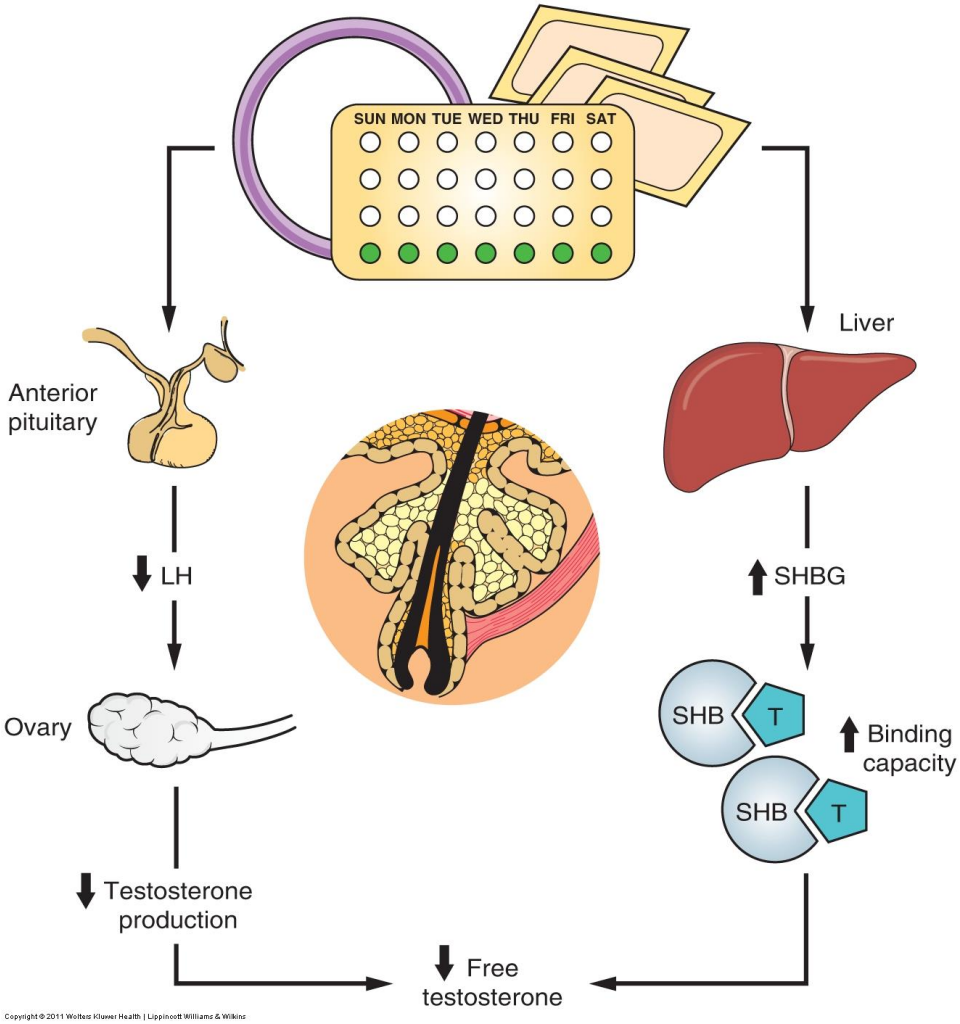
Combined Oral Contraceptives

Mechanism of Action

- Suppress of LH secretion and ovarian androgen production
- Stimulate SHBG, thereby lowering free testosterone levels

Benefits

- Reduces ovarian androgens
- Corrects irregular menstrual cycles
- Reduces risk of endometrial hyperplasia and cancer



*Fritz MA, Speroff L. Figure 13.11. Clinical Gynecology Endocrinology and Infertility, 8th Edition. Lipincott Williams & Wilkins. 2011.

Combined Oral Contraceptives

Estrogen (essentially all are ethinyl estradiol):

- Dose must be at least 20mg to suppress LH

Progestin

- Avoiding progestins with high androgenic effects. (Ex: norgestrel, levonorgestrel, norethindrone)
- Newer progestins have greater progestogenic and lower androgenic effect (Norgestimate, desogestrel, drospirenone)

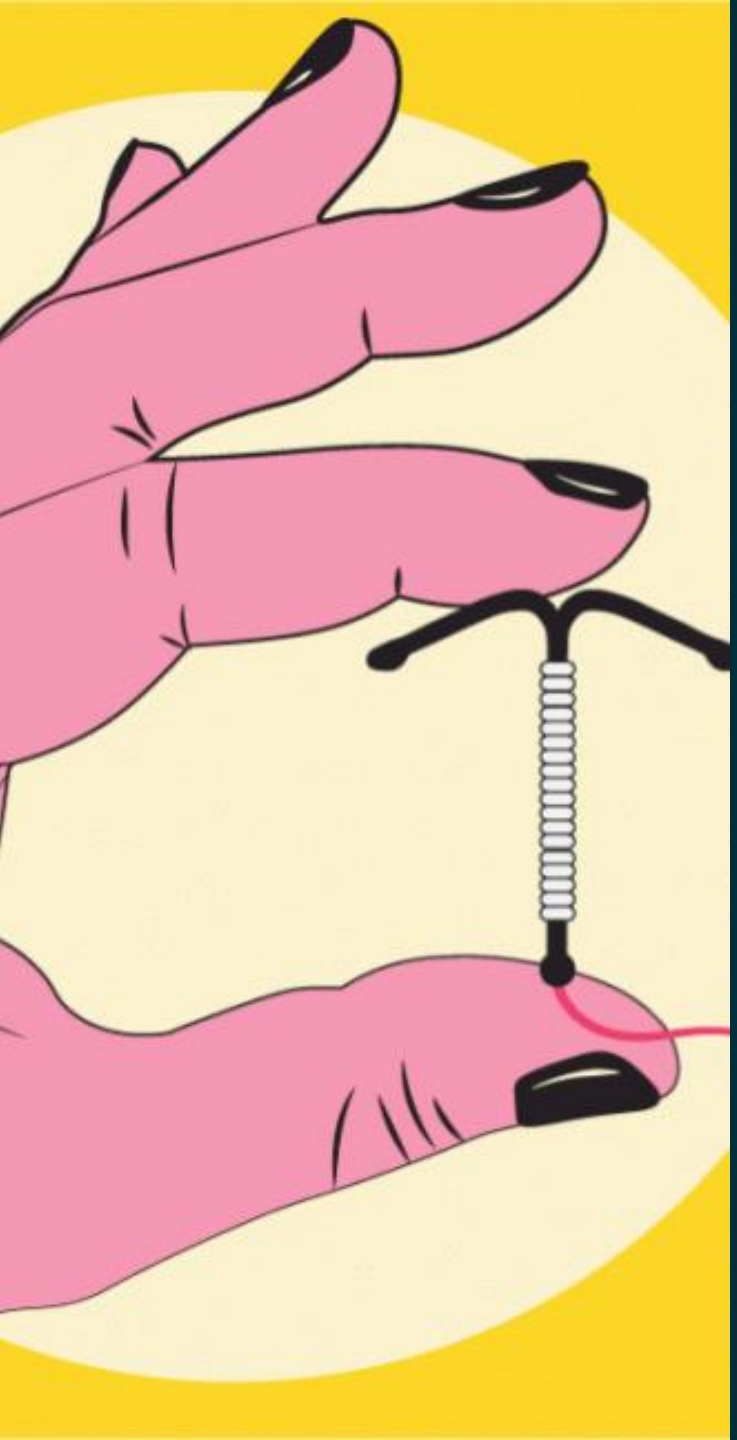
Which COCP to choose?

- No one formulation is superior*
- Most OCPs have adequate ethinyl estradiol (20-35mg), so initial choice is more based on the progestin
- OCPs with Norgestimate or Desogestrel are a good initial choice

	Estrogen (mcg)	Progestin (mg)
MonoNessa	Ethinyl estradiol 35mg	Norgestimate 0.25mg
OrthoCyclen	Ethinyl estradiol 35mg	Norgestimate 0.25mg
Previfem	Ethinyl estradiol 35mg	Norgestimate 0.25mg
Sprintec	Ethinyl estradiol 35mg	Norgestimate 0.25mg
Apri	Ethinyl estradiol 30mg	Desogestrel 0.15mg
Desogen	Ethinyl estradiol 30mg	Desogestrel 0.15mg
OrthoCept	Ethinyl estradiol 30mg	Desogestrel 0.15mg
Reclipsen	Ethinyl estradiol 30mg	Desogestrel 0.15mg
Solia	Ethinyl estradiol 30mg	Desogestrel 0.15mg
Ocella	Ethinyl estradiol 30mg	Drospirenone 3mg
Safyral	Ethinyl estradiol 30mg	Drospirenone 3mg
Syeda	Ethinyl estradiol 30mg	Drospirenone 3mg
Yasmin	Ethinyl estradiol 30mg	Drospirenone 3mg
Zarah	Ethinyl estradiol 30mg	Drospirenone 3mg
Beyaz	Ethinyl estradiol 20mg	Drospirenone 3mg
Gianvi	Ethinyl estradiol 20mg	Drospirenone 3mg
Loryna	Ethinyl estradiol 20mg	Drospirenone 3mg
Vestura	Ethinyl estradiol 20mg	Drospirenone 3mg
Yaz	Ethinyl estradiol 20mg	Drospirenone 3mg

per FDA, OCPs with Drospirenone have increased risk of DVT compared to other OCPs

Legro, R. S. et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J. Clin. Endocrinol. Metab



What if the patient can't/won't take an OCP?

If OCP contraindicated or declined, recommend progestin-only therapy to prevent endometrial hyperplasia.

- Cyclic progestin: Medroxyprogesterone 5-10mg 10-14 days /month
- continuous progestin (mini-pill)
- progestin IUD (Mirena)
- progestin depo injection (Depo provera)
- Progestin implant (Implanon)

Downsides of progestin-only

- Will not improve acne or hirsutism
- Cyclic progestin will not provide contraception

Metformin†

Role in treating PCOS is debated.

Consider off-label use for patients with evidence of insulin resistance, for the following potential benefits:

- Reduced risk of diabetes
- Decrease in hyperinsulinemia→ lower androgens
- Can restore ovulatory cycles in ~50% of patients‡
- Mild weight loss

†N estler JE. Metformin for the treatment of the polycystic ovary syndrome. NEJM. 2008

‡ Moghetti P, et al. Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation.

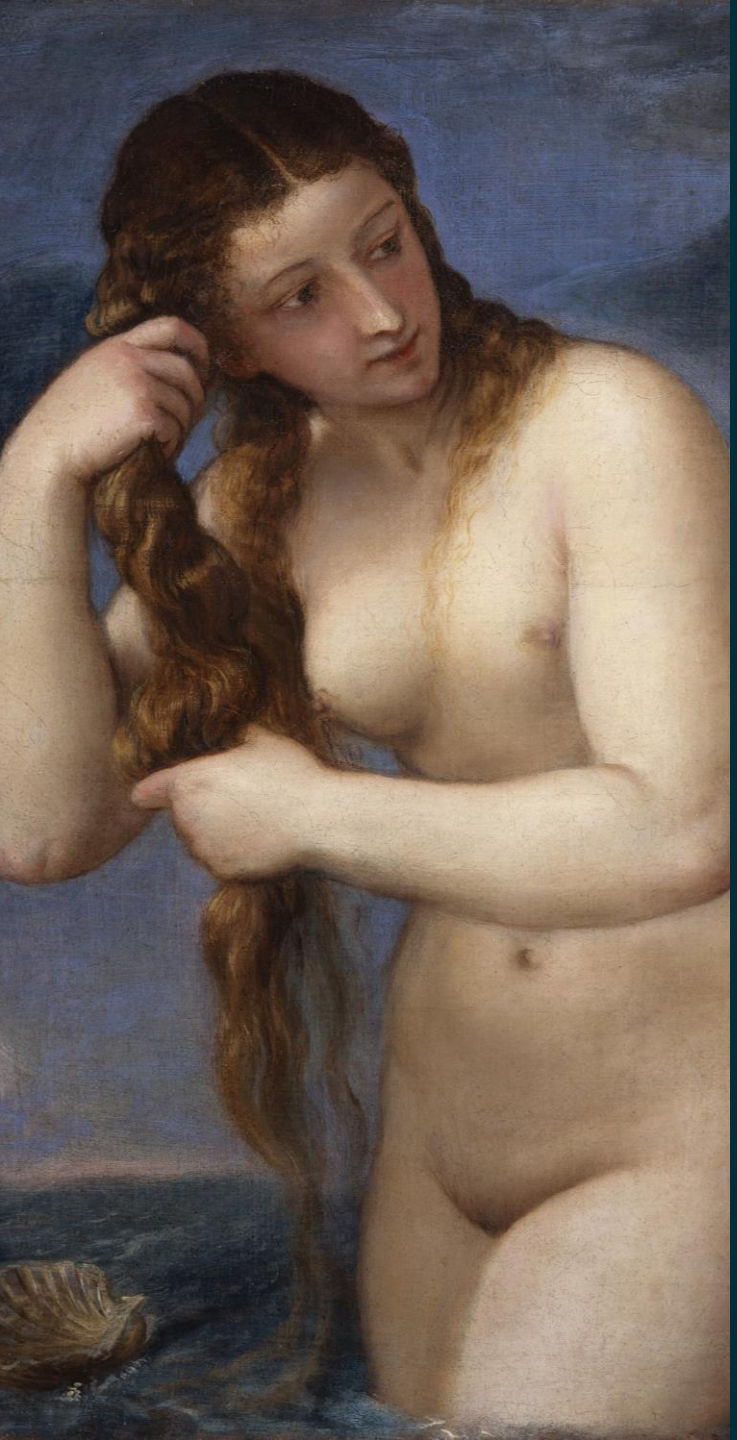
Treatment of hirsutism

- 1st line: OCP
- 2nd line: spironolactone 50-100mg BID
- 3rd line: Finasteride 5mg QD or

  Flutamide 150-250mg QD

- Improvement can take >6 months
- Anti-androgens must be used with contraception due to their teratogenic potential

Swiglo, B. A. et al. Clinical review: antiandrogens for the treatment of hirsutism: a systematic review and metaanalyses of randomized controlled trials. JCEM. 2008

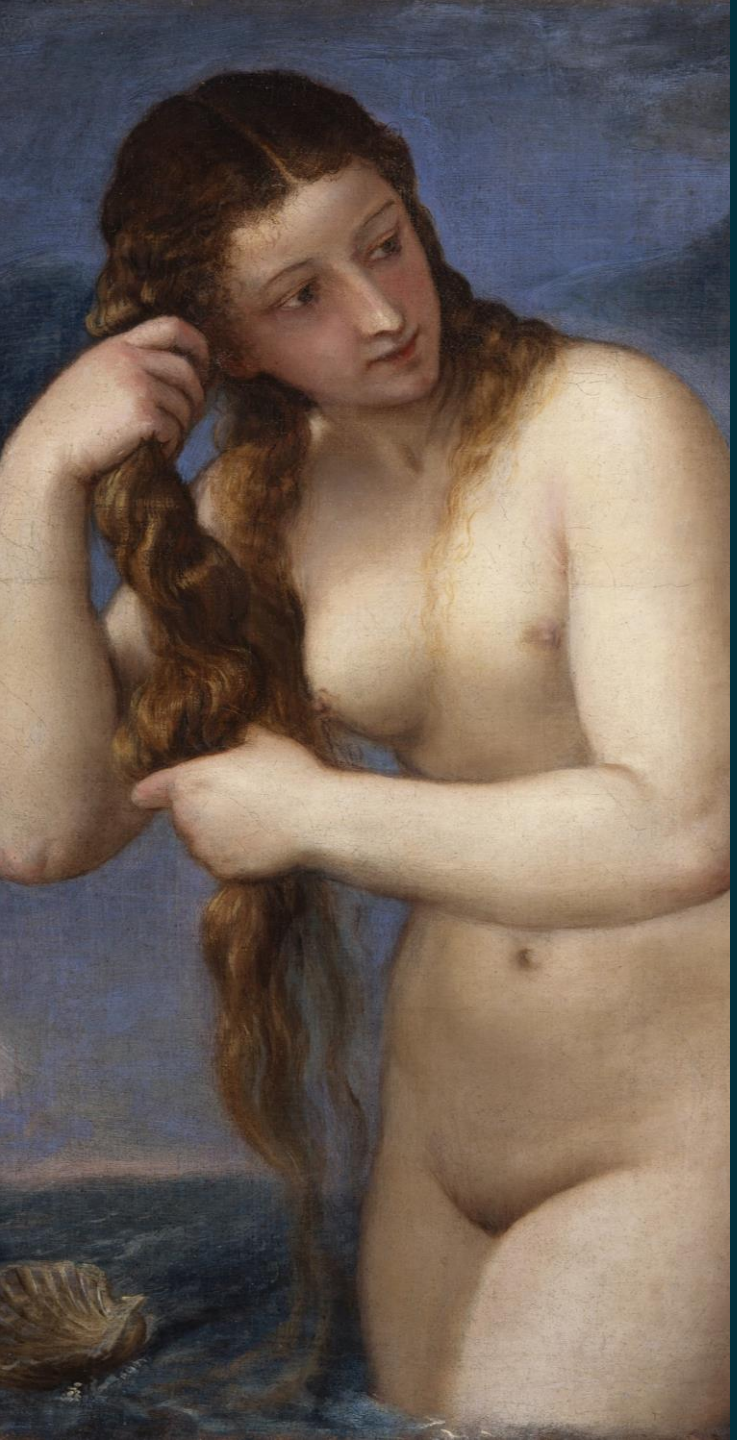


Treatment of Infertility

Goal is to restore ovulatory cycles with lifestyle interventions +/- medical therapy.

Set appropriate expectations. Odds of woman with PCOS conceiving is 5–10% per ovulatory cycle, compared to 10–15% per cycle in women without PCOS*.

* Legro, R. S. et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. NEJM. 2008



Treatment of Infertility

First line therapy is either Letrozole or Clomiphene citrate

- Letrozole
  - Mechanism: aromatase inhibitor, decreases estrogen production
  - Superior to Clomiphene in achieving pregnancy, but increased rate of multiple pregnancies (3-8%)
- Clomiphene citrate
  - Mechanism: SERM, decreases inappropriate estrogen feedback to CNS to restore ovulation

Thank you