THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER

Polycystic Ovarian Syndrome

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38th Annual Contemporary Issues in Obstetrics and Gynecology

July 2024

Learning Objectives

1. Describe the complex pathophysiologic basis of PCOS and its role within the wider “metabolic syndrome”
2. Improve ability to execute a diagnostic work-up that is both comprehensive and pertinent
3. Discuss how to effectively counsel patients regarding the etiology of PCOS, risks, and treatment goals

Disclosures

- I have no relevant conflicts of interest to disclose.

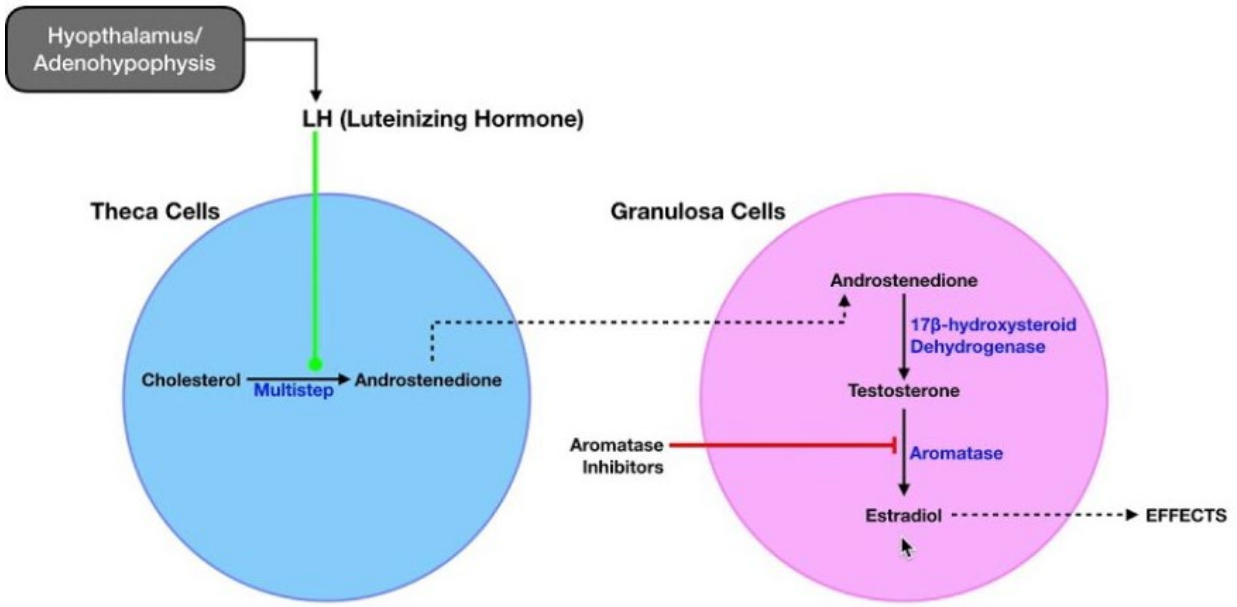
A Brief History: “Stein-Leventhal Syndrome”

- 1935: “Amenorrhea associated with polycystic ovaries”
  - Seminal publication: report of 7 cases of amenorrhea/oligomenorrhea with bilateral polycystic ovaries
  - Noted among these women obesity, hirsutism, acne, infertility

Pathophysiology

(Not quite as simple as you might think…)

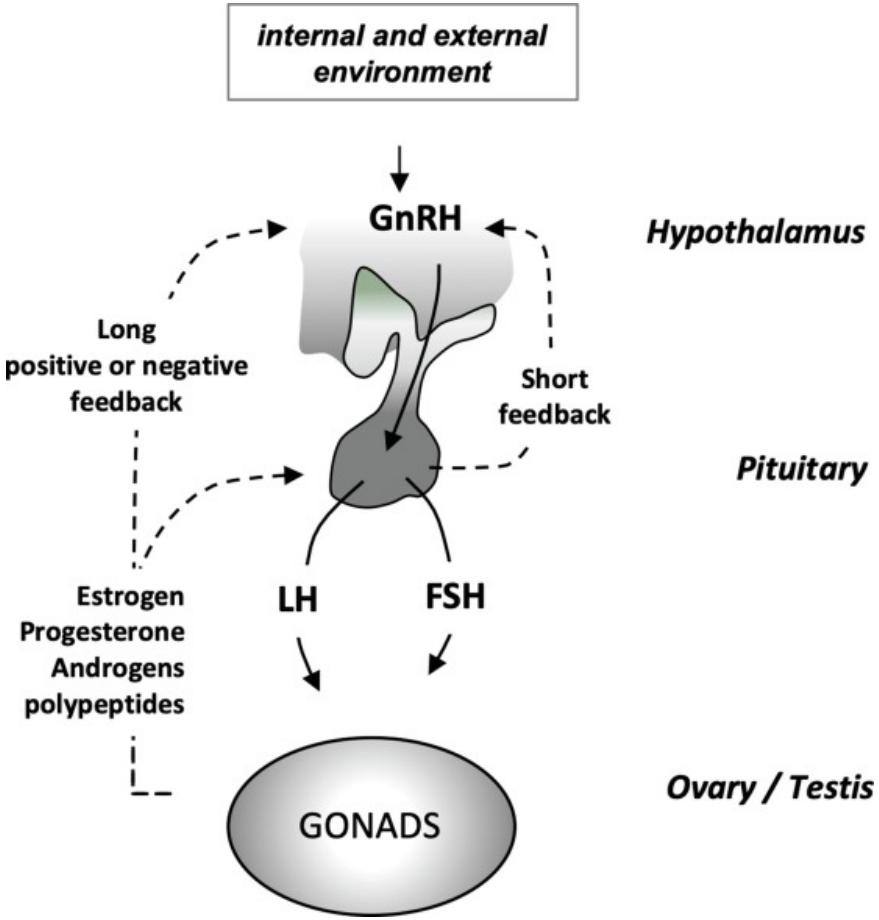
Theory #1: PCOS is a disorder of ovarian steroidogenesis



- Hypertrophic theca layer secretes **excessive androgens**
- Ovarian androgens exhibit a trophic effect on follicular cells
- Hyperstimulation by LH or insulin leads to arrested folliculogenesis → **PCO morphology, oligomenorrhea**

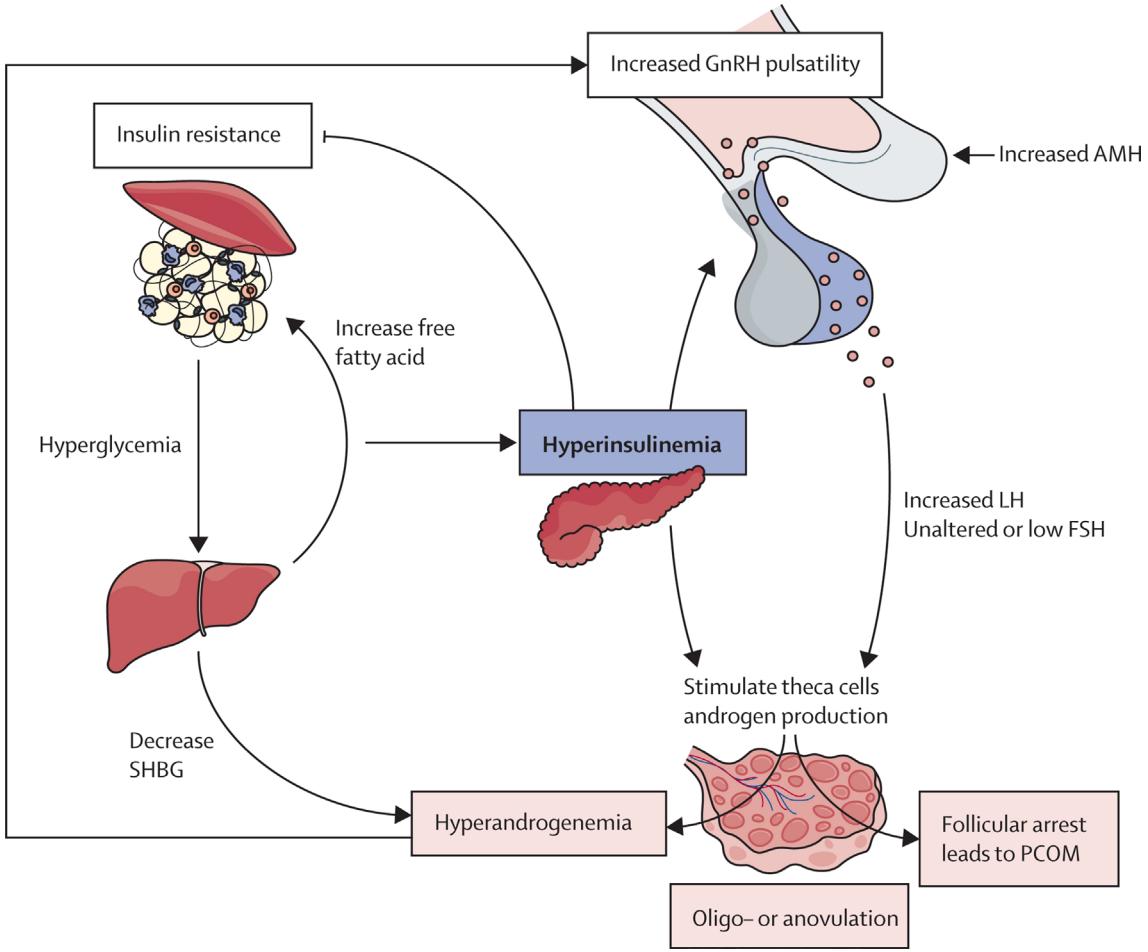
Theory #2: PCOS is a neuroendocrine disorder

- Altered GnRH pulsatility leads to aberrant (↑)LH:(↓)FSH ratio
  - Increased LH leads to **ovarian hyperandrogenism**
  - Decreased FSH leads to arrested folliculogenesis **(PCO morphology, oligomenorrhea)**



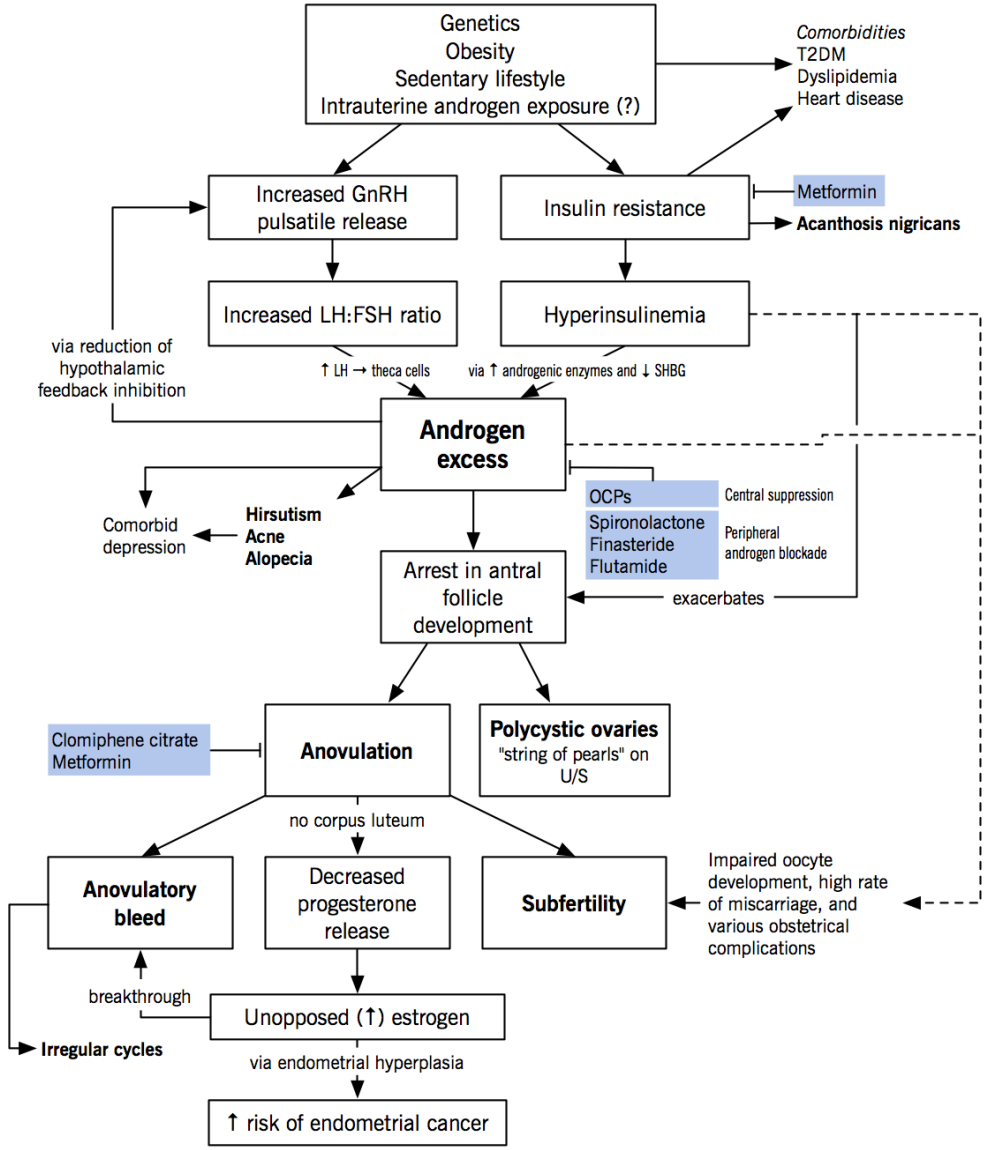
Theory #3 : PCOS is a disorder of insulin resistance

- Insulin resistance → hyperinsulinemia → **increased androgen production**
- Insulin resistance → decreased (SHBG) → **Increased bioavailable serum testosterone**
- Hyperinsulinemia → altered hypothalamic GnRH secretion **(PCOM, oligomenorrhea)**
  - **Direct and indirect mechanisms**



Pathophysiology of PCOS

Alex Rotstein, Ragini Srinivasan, and Eric Wong



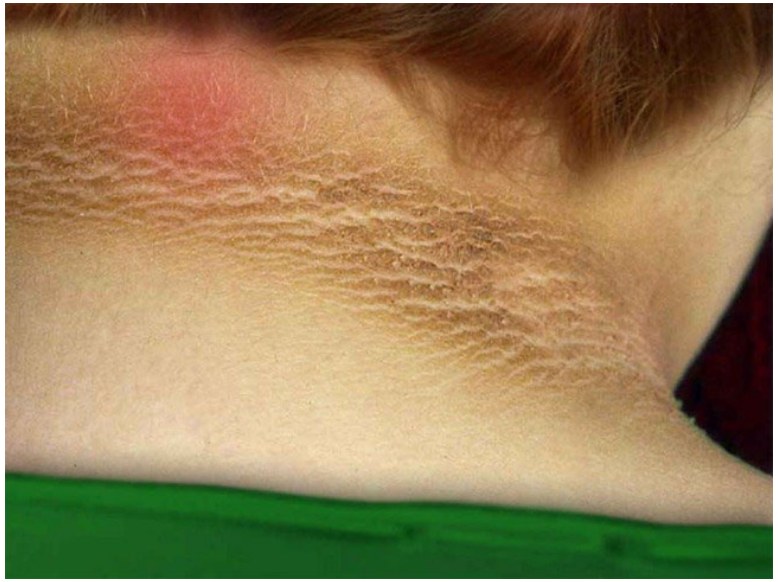
Diagnostic Criteria

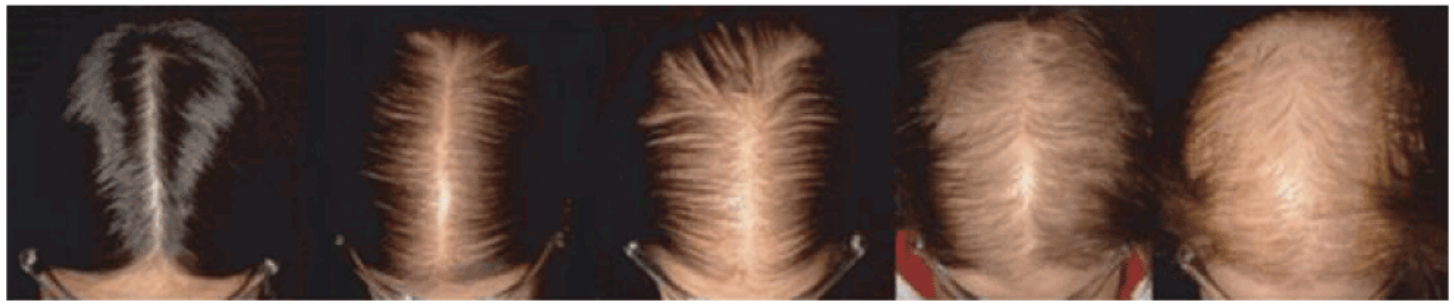
	NIH (1990) (both required)	Rotterdam (2003) (2 of 3)	Androgen Excess Society (2006) (Hyperandrogenism + 1 other)
Hyperandrogenism	+	+/-	+
Oligomenorrhea/amenorrhea	+	+/-	+/-
PCO morphology on US	---	+/-	+/-
Incidence among anovulatory women	55%	91%	

- 2018 International Evidence-Based Guideline for Assessment and Management of PCOS ratified Rotterdam criteria for diagnosis of PCOS
- Insulin resistance nearly always present
- PCOS diagnosed by NIH criteria have greatest risk of metabolic syndrome

Clinical Manifestations

- Menstrual irregularity
- Sub-fertility
- Hyperandrogenism: hirsutism, acne, androgenic alopecia
- Insulin resistance: acanthosis nigricans
- Metabolic syndrome





Diagnosis

PCOS as a “rule-in/rule-out” disorder

Differential Diagnosis

- Amenorrhea:
  - Hypogonadotropic hypogonadism
  - Premature ovarian insufficiency
  - Thyroid disorder
  - Hyperprolactinemia
  - Pregnancy!

- Acanthosis:
  - Primary insulin resistance
  - Malignancy
  - Iatrogenic

- Hirsutism:
  - Androgen-secreting tumor
  - Exogenous androgen
  - Non-classical CAH

Diagnosis

- History: menstrual history, onset of androgen excess, medication usage (including exogenous androgens, steroids), family history of DM2, CVD
- Physical:
  - Vitals
  - BMI
  - Acne
  - Balding
  - Distribution of hirsutism
  - Acanthosis nigricans
  - Waist circumference

Diagnosis, continued

- **Labs**:
  - FSH/estradiol [rule out hypogonadotropic hypogonadism or primary ovarian insufficiency]
  - Total testosterone + SHBG vs. serum free testosterone [rule in serum hyperandrogenism]
  - TSH [rule out thyroid disease]
  - Prolactin [rule out prolactinoma]
  - 17-OH-P (normal <4 ng/mL) [rule out congenital adrenal hyperplasia]

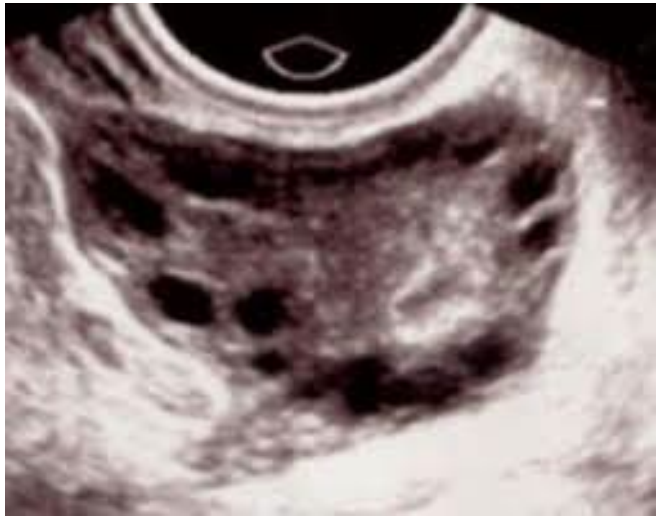
  - 2h GTT
  - Lipid panel

  - Consider:
    - DHEA-S if rapid virilization (adrenal androgen secreting tumor)
    - 24h serum cortisol if stigmata of Cushing syndrome
    - Fasting insulin if severe stigmata of insulin resistance

Diagnosis, continued

- Imaging:
  - TVUS: PCO morphology, identification of endometrial abnormalities
    - ≥ 12 follicles <10 mm in diameter

      OR
    - Ovarian volume >10 mm^3
    - Can be one ovary alone



Diagnostic Phenotypes

PCOS phenotype A (Classical PCOS)	PCOS phenotype B (Hyperandrogenic anovulatory PCOS)	PCOS phenotype C (Ovulatory PCOS)	PCOS phenotype D (Non-hyperandrogenic PCOS)
Hyperandrogenism	Hyperandrogenism	Hyperandrogenism	X
Oligo-amenorrhea	Oligo-amenorrhea	X	Oligo-amenorrhea
PCOM	X	PCOM	PCOM

Clinical Considerations

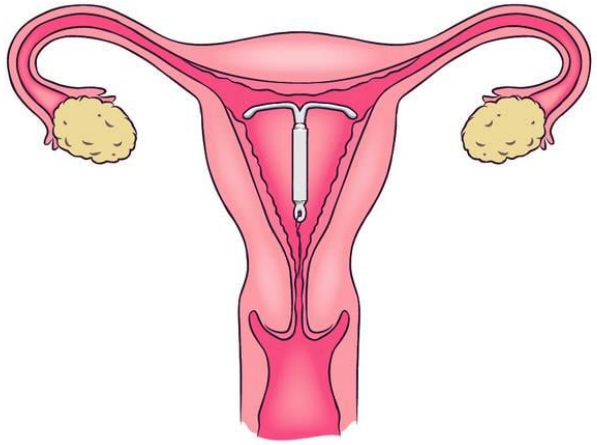
- Risk of diabetes:
  - 40% of patients with PCOS have impaired glucose tolerance at time of diagnosis
  - 10% of women with PCOS develop diabetes during their 20s or 30s
  - Patients with PCOS have 2-5x lifetime risk of developing diabetes compared to those without
- Risks during pregnancy:
  - Increased pregnancy weight gain
  - Increased risk of gestational diabetes and hypertensive disorders of pregnancy independent of BMI
  - Decreased placental weight

Clinical Considerations, continued

- Heritability:
  - Female offspring of patients with PCOS have 5x greater likelihood of being diagnosed with PCOS than those born to patients without PCOS
- Risk of endometrial cancer:
  - Patients with PCOS have 2.7x higher risk of developing endometrial cancer than those without PCOS

Treatment

- Patients seeking fertility:
  - Weight loss improves ovarian function and fertility and improves pregnancy outcomes
  - Metformin
    - Improves insulin resistance
    - Enhances fertility
  - Letrozole first-line for ovulation induction



Treatment, continued

- Patients not seeking immediate fertility:
  - Combined oral contraceptives:
    - Decrease hyperandrogenism: decreased LH production, suppression of ovarian androgen secretion, increased SHBG
    - Endometrial protection
  - Progesterone:
    - Endometrial protection
  - Metformin:
    - Improves insulin resistance
    - Mild weight loss
    - May delay onset of diabetes

Treatment

- Hirsutism:
  - Depilatories/laser hair removal
  - Combined oral contraceptives (first-line)
    - Consider drosperinone (Yaz, Slynd) for antiandrogenic properties
  - Spironolactone (second-line)
    - Binds to androgen receptor as an antagonist
    - Decreases ovarian and adrenal androgen production
    - Full clinical effect takes 6 months or more
    - Must be administered concurrently with contraceptive due to anti-androgenic effects on fetus

Areas of Continued Research

- Heritability of PCOS (genetic susceptibility)
- Transgenerational transmission of PCOS (epigenetic modification)
- Relationships between obesity and development of PCOS

References

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Thank you!