



The University of Utah
Department of Pathology

Laboratory Diagnosis of Polycystic Ovary Syndrome (PCOS)

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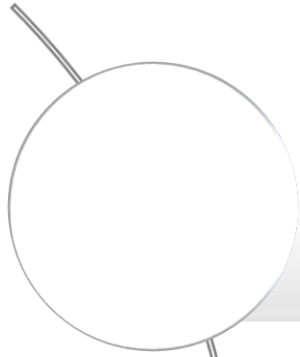
Continuing Education Seminar

5/21/2021

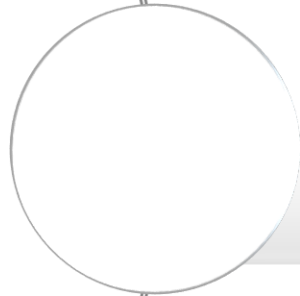


*An enterprise of the University of
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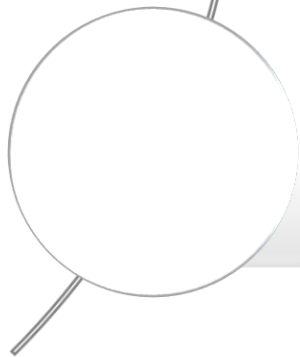
Learning objectives



Describe the common signs and symptoms associated with PCOS



Define the Rotterdam criteria for PCOS diagnosis



List the laboratory tests for evaluation of suspected PCOS

Outline

- Overview of the female reproductive system
- PCOS definition and criteria for diagnosis
- Key diagnostic features of PCOS
- Disorders that mimic PCOS
- Clinical manifestations and common interventions
- FAQ and conclusion

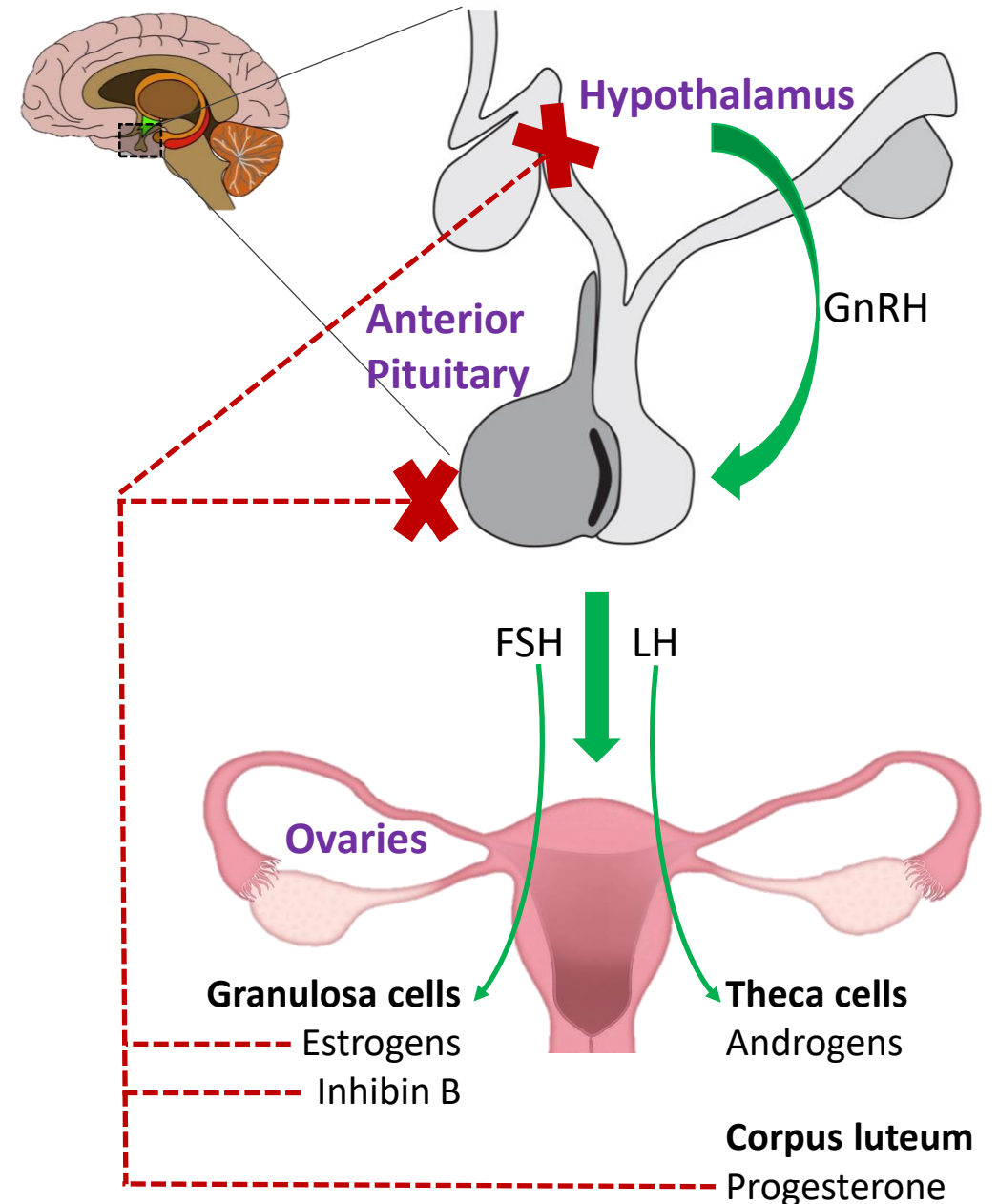
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Female reproductive system

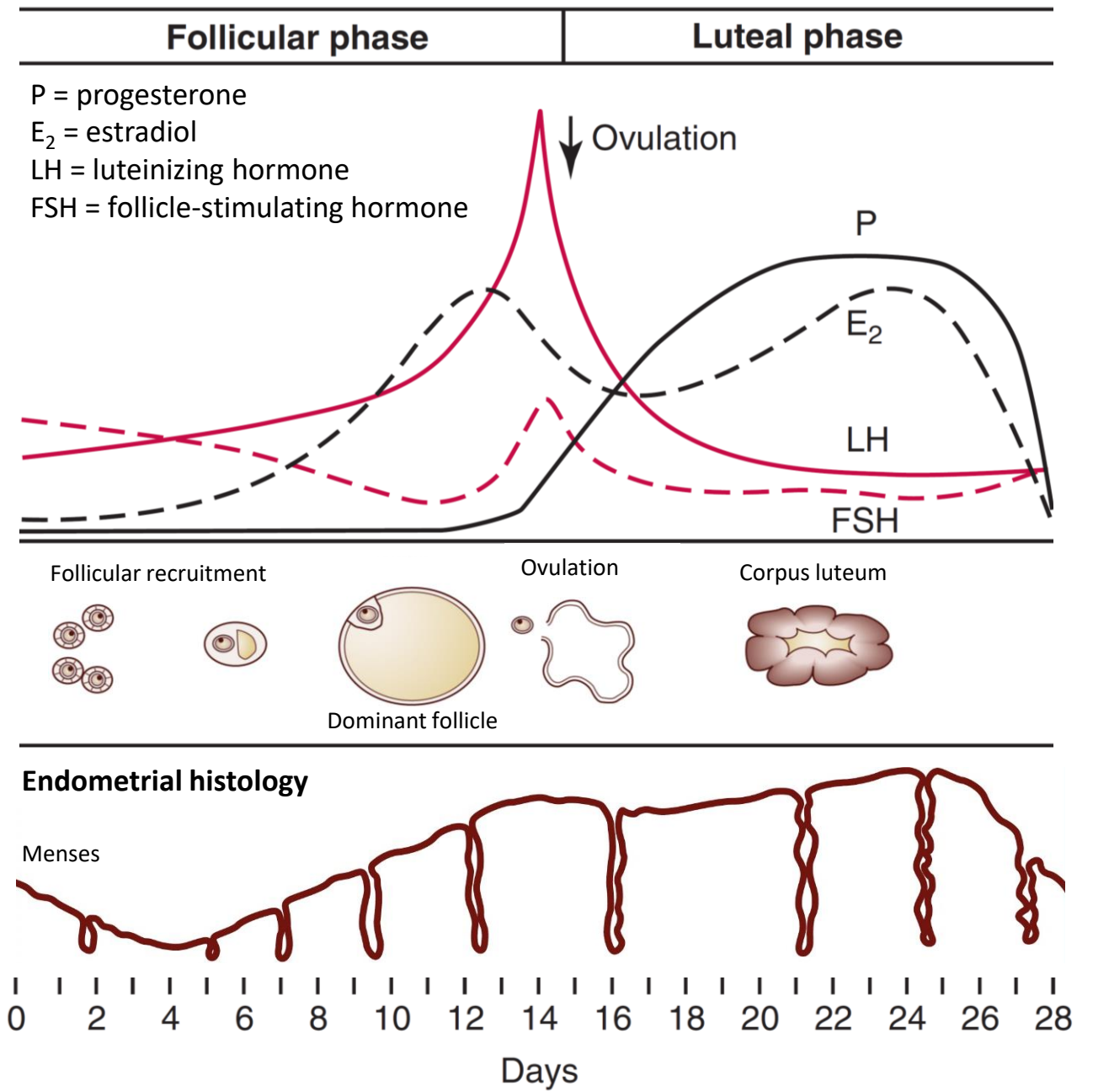
- Gonadotropin-releasing hormone (GnRH) stimulates release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH)
- FSH regulates estradiol and inhibin B production in the granulosa cells of the ovary
 - Also stimulates follicular growth
- LH stimulates androstenedione production in theca cells of the ovary
 - Also stimulates ovulation and progesterone secretion from the developing corpus luteum
- Negative feedback

Hypothalamic-Pituitary-Ovarian (HPO) Axis

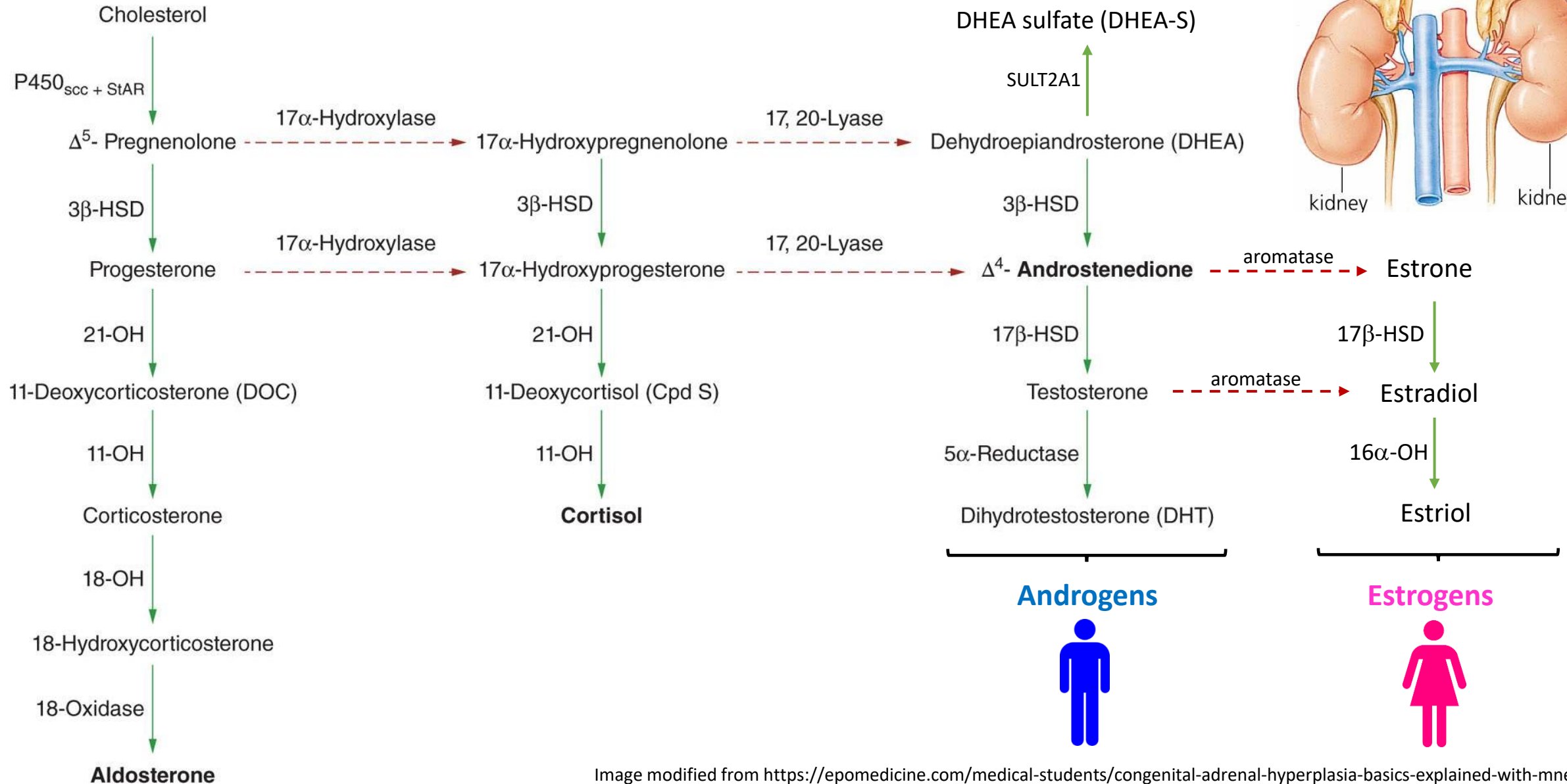
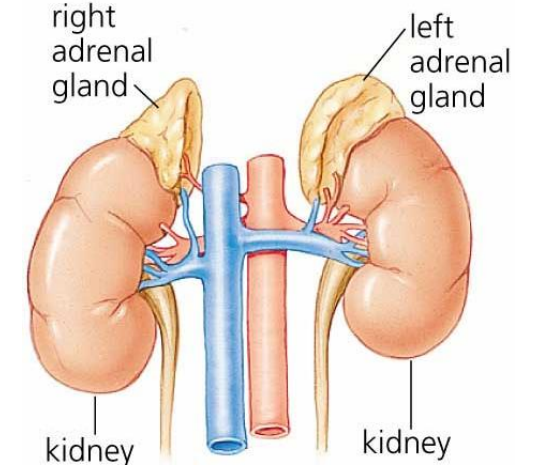


Menstrual cycle



- **Follicular phase** → selection and growth of the dominant follicle
 - Estradiol secretion by developing follicle
 - LH surge before ovulation
- **Luteal phase** → ruptured follicle differentiates into corpus luteum
 - Synthesizes progesterone and estradiol
 - Preparation of endometrium for implantation



Production of sex steroid hormones in adrenal glands



Summary of key reproductive hormones

- **GnRH** → stimulates release FSH and LH
- **FSH** → stimulates follicular growth; regulates estradiol release
- **LH** → stimulates ovulation; regulates progesterone and **androstenedione** release
- **Progesterone** → prepares endometrium for implantation; maintains pregnancy
- **Estrogens** (e.g., estradiol) → female sex hormones 
- **Androgens** (e.g., **androstenedione**, **testosterone**) → male sex hormones 

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Case study about my good friend “wonder woman”

- 29 year old Caucasian female in post-graduate medical training
- Married to a healthy male partner
- Chief complaint → ***unable to get pregnant*** after one year of trying
- Normal physical exam findings; healthy BMI; no alcohol or drug use
- ***Irregular and painful periods*** post-menarche (age 13) for which oral contraceptives were prescribed

Pathophysiology of PCOS

- Complex, multi-factorial, heterogeneous

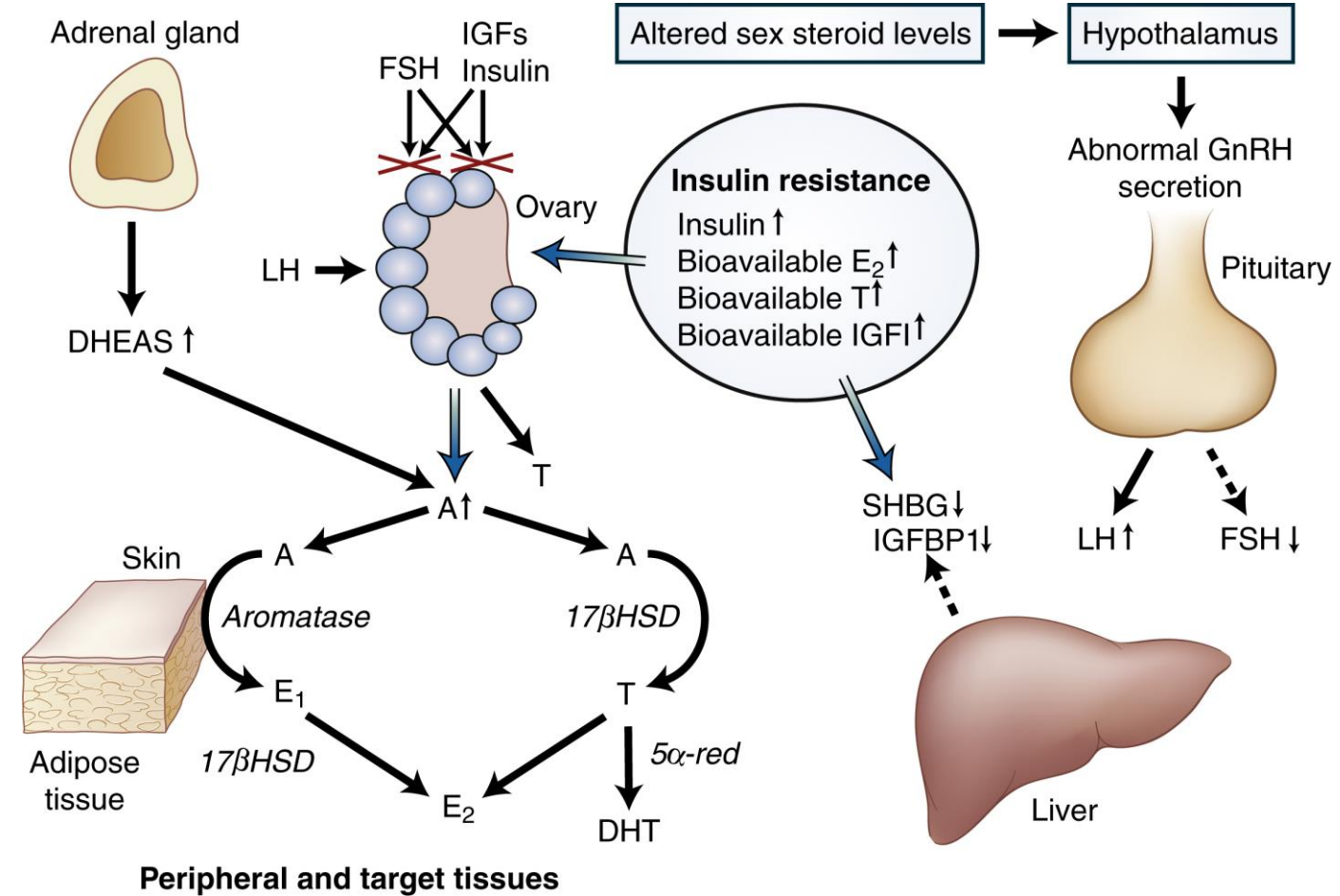
- Exact cause is still poorly understood!**

- ↑ GnRH/LH pulsatile activity

- ↑ LH : FSH ratio
 - ↑ LH = ↑ androgens

- Insulin resistance / hyperinsulinemia

- ↓ SHBG = ↑ bioavailable testosterone
 - ↑ peripheral conversion of androstenedione to estradiol and dihydrotestosterone



Signs and symptoms of PCOS

Psychological



- Anxiety
- Depression
- Negative body image
- Eating disorders

Reproductive



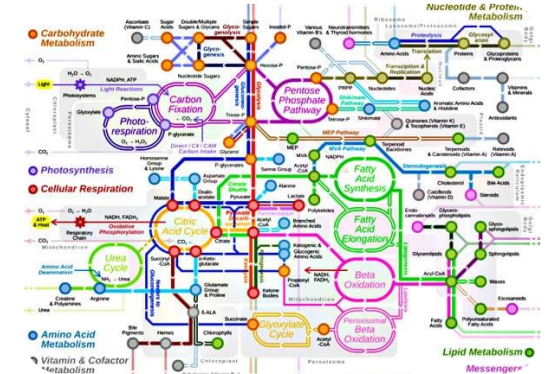
- Irregular menstruation
- Infertility
- Pregnancy complications

Dermatological



- Acne
- Alopecia
- Acanthosis nigricans
- Hirsutism

Metabolic



- Obesity
- Metabolic syndrome
- Type 2 diabetes
- Cardiovascular risk

Criteria for PCOS diagnosis

- Diagnosis of exclusion

- Rule out disorders that mimic the clinical features of PCOS

- ***Rotterdam criteria*** *

- Two of the three following criteria
 - Androgen excess
 - Ovarian dysfunction
 - Polycystic ovarian morphology



Defining PCOS through the years

Criteria	NIH 1990	ESHRE/ASRM (Rotterdam) 2003	AE-PCOS 2006
Hyperandrogenism	✓	✓	✓ required
Ovarian dysfunction	✓	✓	✓
Polycystic ovarian morphology		✓	✓
	2 of 2 required	2 of 3 required	2 of 3 required
Exclusion of conditions that mimic PCOS	✓	✓	✓
<small>NIH = National Institutes of Health ; ESHRE = European Society of Human Reproduction and Embryology ASRM = American Society for Reproductive Medicine ; AE-PCOS = Androgen Excess and PCOS Society</small>			

Rotterdam criteria was endorsed by

- NIH in 2012
- 2018 international **evidence-based** guideline for the assessment and management of PCOS *

PCOS is not primarily defined by polycystic ovaries

* Human Reproduction. 2018; 33(9): 1602–1618

Is PCOS an ancient disorder?

“But those women whose menstruation is less than three days or is meagre, are robust, with a healthy complexion and a masculine appearance; yet they are not concerned about bearing children nor do they become pregnant”

Hippocrates (460 BC-377 BC)

“Sometimes it is also natural not to menstruate at all... It is natural too in persons whose bodies are of a masculine type... we observe that the majority of those not menstruating are rather robust, like mannish and sterile women”

Soranus of Ephesus (c. 98-138 AD)

“Married, infertile woman with shiny ovaries with a white surface the size of pigeon eggs”

Vallisneri (1721)

Stein and Leventhal (1935) → regarded as the first investigators of PCOS

- Described a group of 7 women with menstruation disturbances, hirsutism and enlarged ovaries with many small follicles

Proposed PCOS phenotypes

Phenotype A

Androgen excess + ovulatory dysfunction + PCOM

Phenotype B

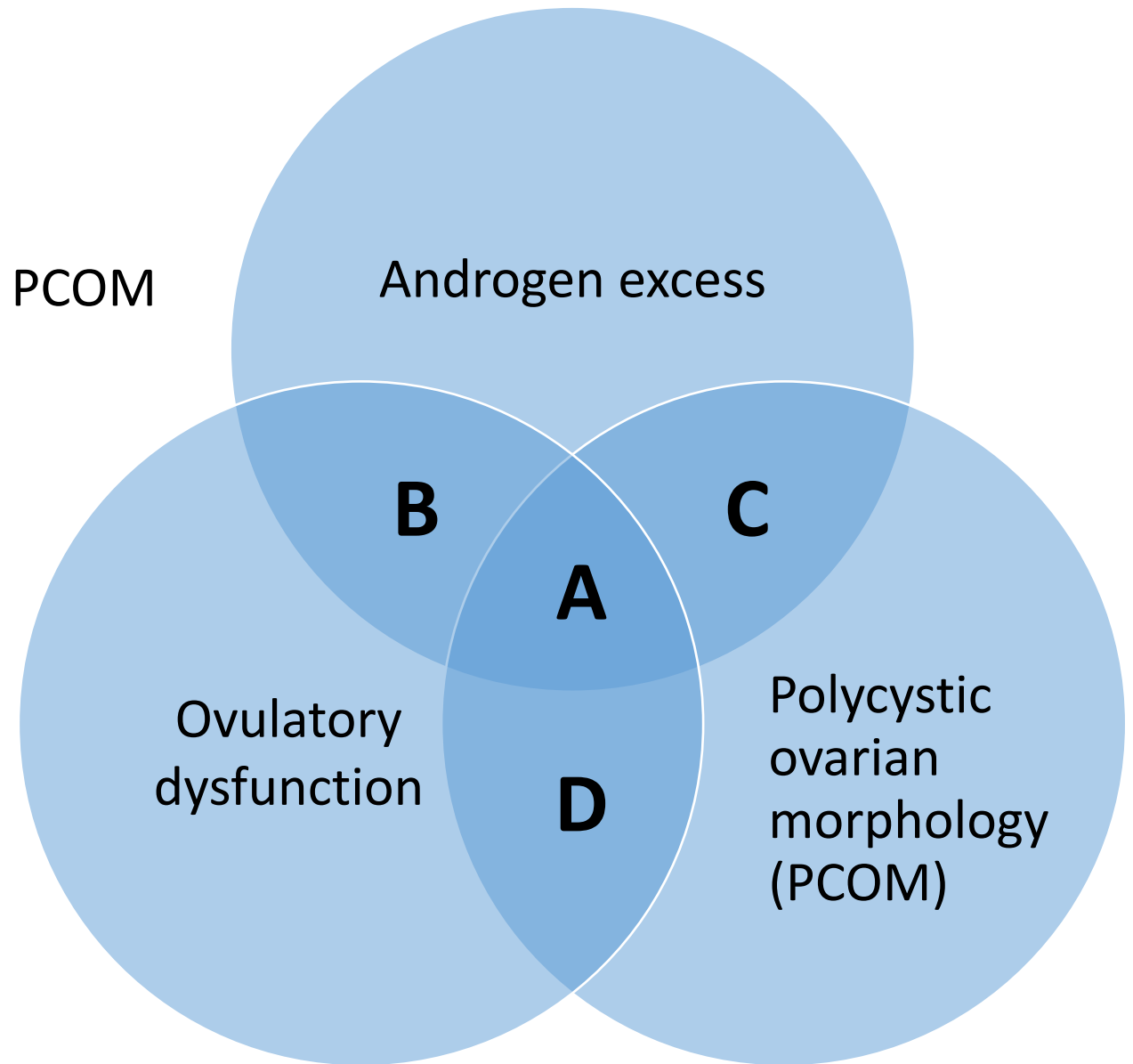
Androgen excess + ovulatory dysfunction

Phenotype C

Androgen excess + PCOM

Phenotype D

Ovulatory dysfunction + PCOM



Outline

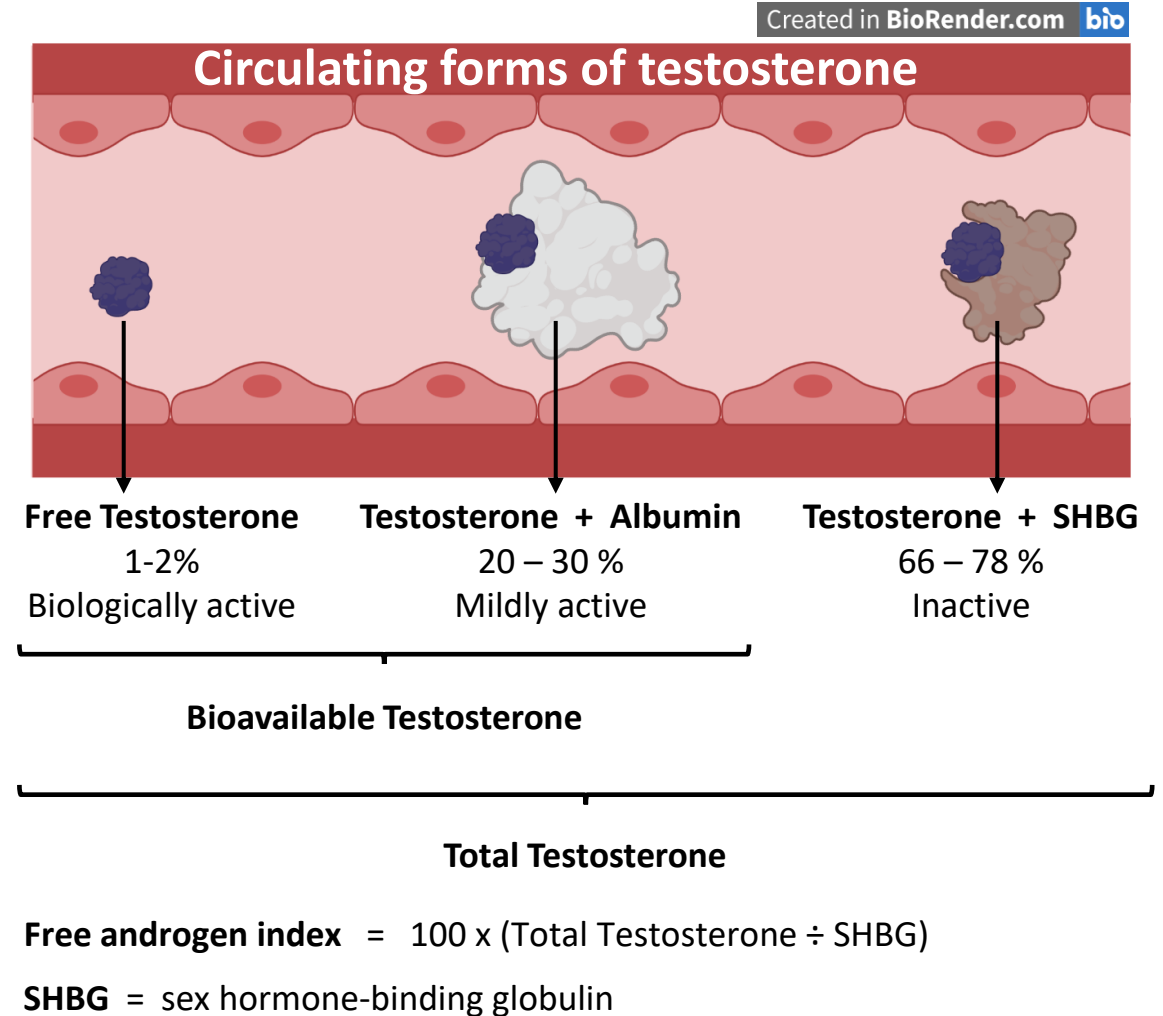
- Overview of the female reproductive system
- PCOS definition and criteria for diagnosis
- **Key diagnostic features of PCOS**
 - Androgen excess
 - Biochemical
 - Clinical
 - Ovarian dysfunction
 - Polycystic ovaries
- Disorders that mimic PCOS
- Clinical manifestations and common interventions
- FAQ and conclusion

Biochemical hyperandrogenism

■ *Free and/or total testosterone?*

- *No consensus* on which analyte(s) to measure, methodology, reference intervals ¹
- LC-MS/MS recommended for most accurate measurement
- Calculated values also acceptable ²
(free T, bioavailable T, or free androgen index)
- Reference ranges may vary between laboratories
- Hormonal contraception affects SHBG
(withdrawal recommended for ≥ 3 months)
- Markedly high levels may suggest an androgen-secreting tumor

■ *Androstenedione and DHEAS* → limited additional information



¹ Human Reproduction. 2018; 33(9): 1602–1618

² J Clin Endocrinol Metab. 1999; 84(10):3666–3672



**CDC LABORATORY/MANUFACTURER
HORMONE STANDARDIZATION (HOST) PROGRAM**

STANDARDIZATION OF SERUM TOTAL TESTOSTERONE MEASUREMENTS

- Started in January 2010
- Evaluates the performance (bias and imprecision) of participants (i.e., commercial assays manufactures, reference/research laboratories)
- $\pm 6.4\%$ mean bias to the CDC testosterone reference method is required for certification

Clinical hyperandrogenism

Comprehensive physical examination for

■ Hirsutism

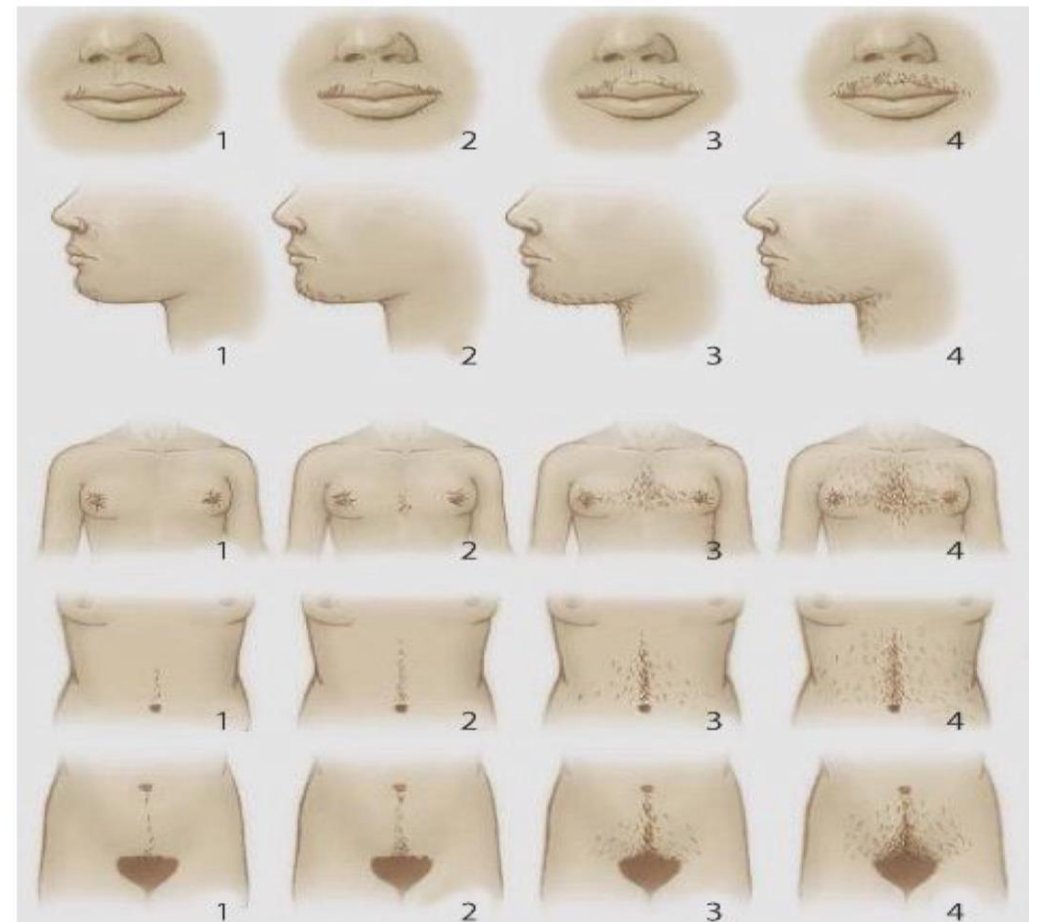
- Excessive terminal hair in male-like pattern
- Modified Ferriman-Gallwey score ($\geq 4 - 6$)

■ Androgenic alopecia

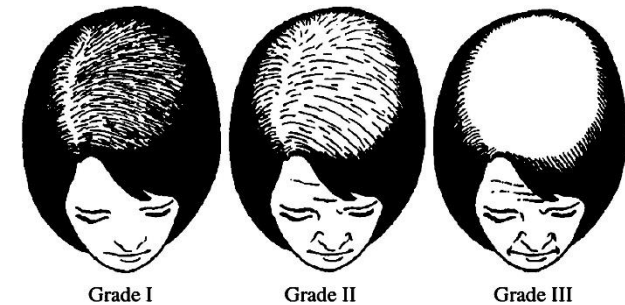
- Hair loss
- Ludwig visual score

■ Acne

- No universally accepted visual assessment



Int J Res Pharm Biomed Sci. 2012; 3(4): 1476-82




J. Eur. Acad. Dermatol. Venereol. 2016; 30(4): 667-676

Case study about my good friend “wonder woman”

- Normal physical exam
 - No sign of hirsutism, alopecia, or acne
- Serum testosterone not tested
- FSH = 7 IU/L
- LH = 19 IU/L
- LH:FSH ratio = **2.7** (normal < 2)

PCOS Diagnosis Checklist

 Hyperandrogenism

Definition of irregular menstrual cycle and ovulatory dysfunction

- **Amenorrhea → absence of menstrual periods**
 - **Primary** → no menstruation by age 15 or > 3 years post breast development
 - **Secondary** → lack of menstruation for > 3-6 months post menarche
- **Oligomenorrhea → infrequent menstrual periods**
 - Menstrual cycle < 21 days or > 35 days
 - < 8 menstrual cycles per year
- **Anovulation → lack or absence of ovulation**





<https://www.newyou.com/wp-content/uploads/2016/06/Irregular-Period.png>

Case study about my good friend “wonder woman”

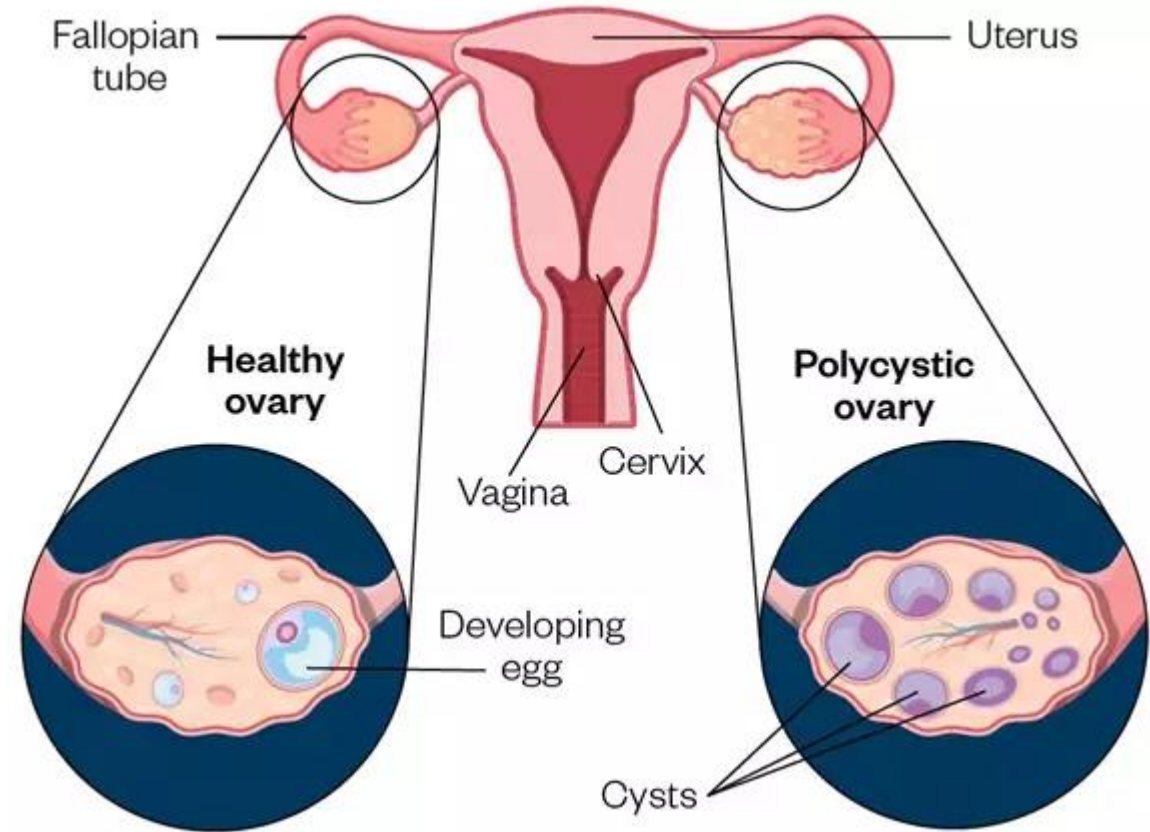
- History of irregular and painful menstruation post-menarche
- At the time she presented for infertility evaluation, she had ***no menstruation for the last 3 months***

PCOS Diagnosis Checklist

-  Hyperandrogenism
-  Ovarian dysfunction

Ultrasound and polycystic ovarian morphology

- ≥ 20 follicles (2-9 mm in diameter) per ovary
- and/or*
- Ovarian volume ≥ 10 mL
 - Excluding corpora lutea, cysts or dominant follicles
 - Based on 8 MHz bandwidth endovaginal ultrasound transducers *
 - *May change with improved ultrasound technology*
 - Not applicable in women < 8 years after menarche *



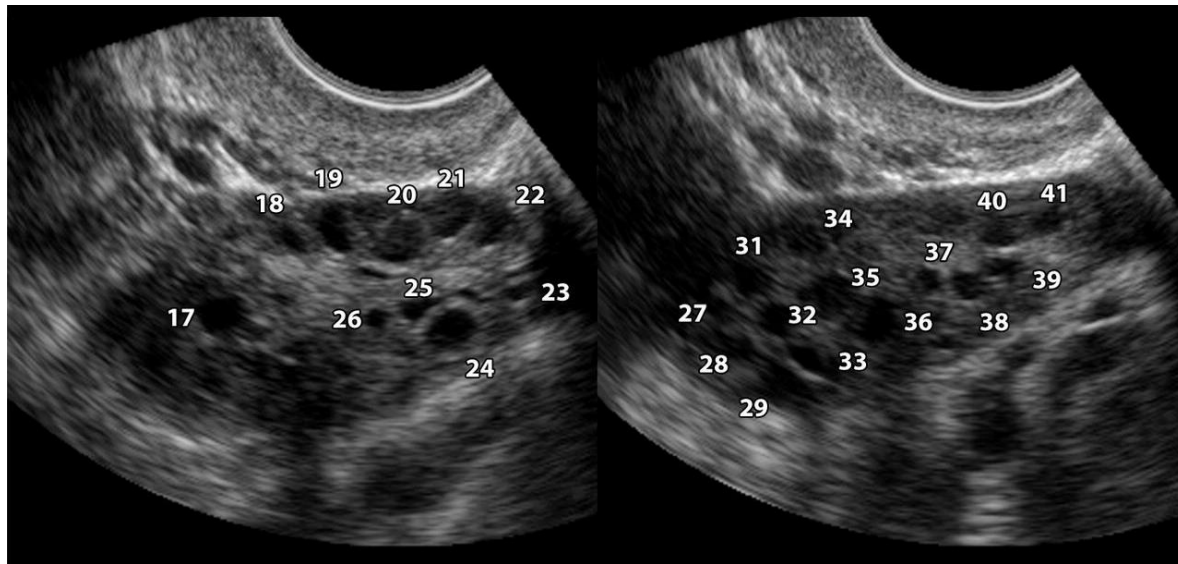
<https://www.sifsof.com/clinical-apps/polycystic-ovarian-syndrome-assessment/>

Not all women diagnosed with PCOS have polycystic ovaries

* Human Reproduction. 2018; 33(9): 1602–1618

Case study about my good friend “wonder woman”

- Polycystic ovarian morphology identified by ultrasound



Radiographics. 2012; 32(6): 1643-57

PCOS Diagnosis Checklist

- Hyperandrogenism
- Ovarian dysfunction
- Polycystic ovaries

Emerging biomarker for evaluating polycystic ovaries

Anti-Müllerian Hormone (AMH)

- Dimeric glycoprotein in transforming growth factor beta (TGF- β) family
 - Solely secreted by granulosa cells of the pre-antral and small antral ovarian follicles
- Commonly used in assisted reproduction clinics
 - Assessment of ovarian reserve
 - Identify risk of ovarian hyperstimulation syndrome
 - Strong association between AMH and follicle count
 - Generally higher in women with PCOS than in normal ovulatory women
 - Proposed as surrogate to ultrasound
 - ***Current guidelines do not recommend AMH as an alternative to ultrasound***
 - May change with improved assay standardization and established cut off levels

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Disorders that mimic PCOS

▪ Thyroid dysfunction/hypothyroidism

- \uparrow TRH/TSH = \uparrow prolactin secretion = inhibition of GnRH pulses = ovulatory dysfunction/infertility
- **Laboratory test** → measure serum TSH

▪ Prolactinoma (prolactin-secreting tumor)

- \uparrow prolactin secretion = inhibition of GnRH pulses = ovulatory dysfunction/infertility
- **Laboratory test** → measure serum prolactin

▪ Nonclassic congenital adrenal hyperplasia

- 21-hydroxylase enzyme insufficiency = excess androgen = ovulatory dysfunction/infertility
- **Laboratory test** → early morning (before 8 AM) serum 17-hydroxyprogesterone

Disorders that mimic PCOS

■ Adrenal hyperfunction (Cushing syndrome)

- ↑ serum cortisol = suppression of GnRH = ovulatory dysfunction/infertility
- *Laboratory test* → 24-hour urine free cortisol or midnight saliva cortisol

■ Androgen-secreting tumors

- ↑ androgens = ↓ LH-pulse frequency = ovulatory dysfunction/infertility

■ Acromegaly

- ↑ growth hormone levels = ↓ LH and estradiol levels = ovulatory dysfunction/infertility

■ Others causes of amenorrhea*





- **Pregnancy!!!**, hypogonadotropic hypogonadism, primary ovarian insufficiency

*J Clin Endocrinol Metab. 2015; 100(3): 812–824

Case study about my good friend “wonder woman”

- Pregnancy test (serum HCG) → *negative*
- Thyroid function (serum TSH) → *normal*
- Adrenal function (24-hour urine free cortisol) → *normal*
- Serum prolactin → *normal*
- HbA1C → *normal*
- Serum 17-hydroxyprogesterone → *normal*

PCOS Diagnosis Checklist

-  Hyperandrogenism
-  Ovarian dysfunction
-  Polycystic ovaries
-  Condition that mimics PCOS

Final Diagnosis → PCOS Phenotype D (ovulatory dysfunction + polycystic ovaries)

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Common clinical manifestations associated with PCOS

- Obesity
 - Affects ~80% of women with PCOS in US ¹
- Type 2 diabetes, gestational diabetes, and impaired glucose tolerance
 - Up to 5-fold increased risk ²
- Insulin resistance
- Increased risk for cardiovascular disease
- Endometrial cancer
 - 2 to 6 times higher risk ²
- Obstructive sleep apnea

1. Endocrine Reviews. 2015; 36(15): 487–525

2. Human Reproduction. 2018; 33(9): 1602–1618

Interventions for PCOS

Lifestyle

- Healthy diet
- Regular physical activity
- Maintain healthy weight
- Behavioral strategies

Note: interactions around healthy lifestyle should be respectful, patient-centered and individualized

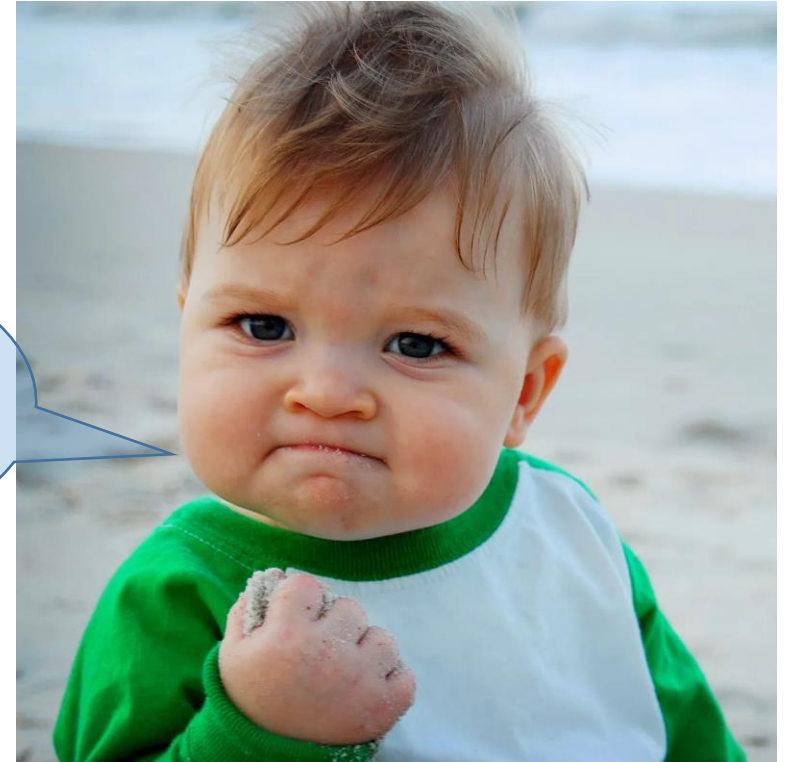
Pharmacological

- Hormonal contraceptives
 - For hyperandrogenism and menstrual abnormalities
- Metformin
 - For metabolic disorders and weight management
- Letrozole (1st line) or clomiphene citrate
 - For anovulatory infertility
- Anti-androgen medications
 - For hirsutism and androgen-related alopecia

Case study about my good friend “wonder woman”

- Prescribed clomiphene citrate for ovulation induction
- Had successful conception (mono-mono twins)

Oh YES!



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Other PCOS FAQ

- **Does an irregular menstrual cycle mean you have PCOS?**

There are so many conditions (including PCOS) that can cause an irregular menstrual cycle.

- **Can I still get pregnant if I have PCOS?**

Yes. Having PCOS does not mean you can't get pregnant.

- **How does PCOS affect pregnancy?**

Women with PCOS may have higher rates of miscarriage, gestational diabetes, preeclampsia, preterm birth, and C-section delivery.

- **Is there a cure for PCOS?**

There is currently no cure for PCOS, but there are treatments to help minimize symptoms and associated health risks.

<https://www.womenshealth.gov/a-z-topics/polycystic-ovary-syndrome>

<https://www.hormone.org/support-and-resources/resource-library/pcos-myths-debunked>

Other PCOS FAQ

- **Does PCOS affect only overweight women?**

No. Women with healthy BMI could be affected with PCOS. However, risk of PCOS may be higher if you are obese.

- **Is PCOS unique to one ethnicity/race?**

PCOS can occur in women of all races and ethnicities.

- **Is PCOS a genetic disorder?**

Inconclusive evidence. No established genetic marker for PCOS has been identified. *PCOS is a complex and polygenic disease*. You may be at higher risk if you have a mother, sister or aunt with PCOS.

Case study about my good friend “wonder woman”

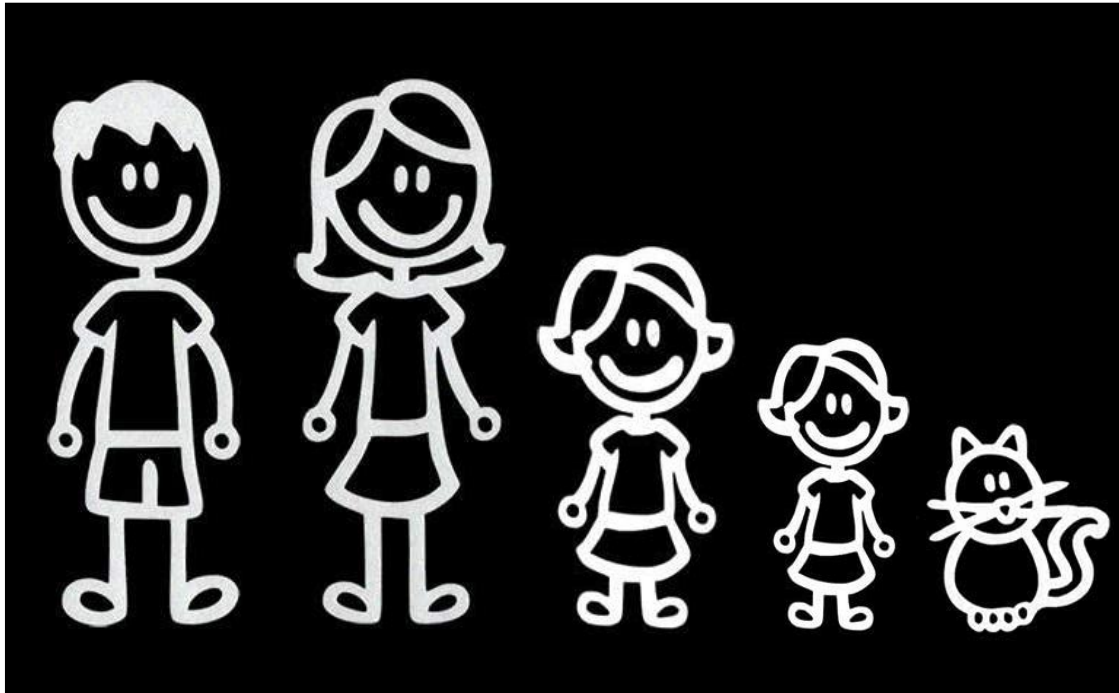
- Had successful conception (mono-mono twins)
 - Miscarried late in the first trimester
- Clomiphene citrate was restarted but ovulation was unsuccessful
- Switched to letrozole and conceived again
 - Two pregnancy losses



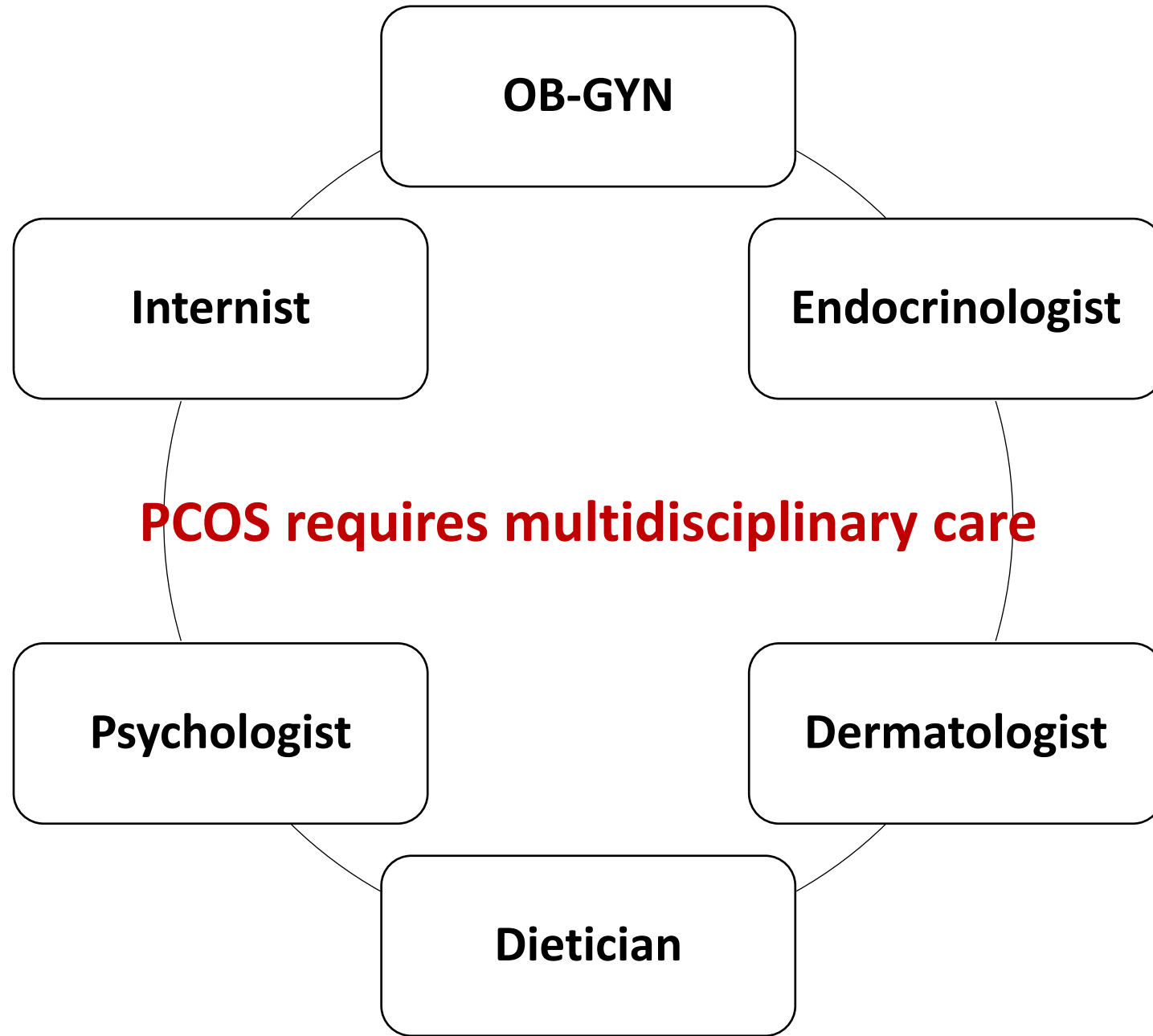
<https://i.redd.it/yb5hk3ut1yt41.png>

Case study about my good friend “wonder woman”

- **Now has 2 kids from separate pregnancies!!!**
 - Second baby was born premature at 34 weeks
- Later found out some other family members (sister and maternal aunt) have PCOS



AND
they lived
HAPPILY
ever after...



... you are not alone



JOIN OVER 55,000 WOMEN IN THE FIGHT AGAINST PCOS



SEPTEMBER IS POLYCYSTIC
OVARY/OVARIAN SYNDROME
(PCOS) AWARENESS MONTH

- ✓ **Join a support group**
- ✓ **Volunteer**
- ✓ **Spread awareness**
- ✓ **Become an advocate**
- ✓ **Donate**

pcoschallenge.com

pcosawarenessmonth.org

Thank You

Acknowledgements

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