

DR. HYMAN+



Polycystic Ovary Syndrome (PCOS)

Functional Medicine Deep Dive

By: Carrie Jones, ND, FABNE, MPH

www.dr-carriejones.com

Overview

1. Facts
2. Signs and Symptoms
3. Rotterdam Criteria
4. Hormone Pulses
5. Insulin, Inflammation and Visceral Obesity
6. The PCOS Evaluation
7. PCOS Treatment - Conventional
8. PCOS Treatment - More Functional

A few caveats before we get started:



- This is a 90min webinar on PCOS - It's more focused on insulin and inflammation.
- Introducing interesting research the average practitioner may not know.
- Not focusing much on conventional therapies such as the birth control pill.
- It's okay to get second opinions about your health status.
- It's also okay to have multiple practitioners on your health team.



5 Quick PCOS Facts

1. **Number 1** endocrine disorder in females

(But it's thought as many as **75% of patients** with PCOS are unidentified in clinical practice)

2. It's a major reason for
oligomenorrhea and fertility challenges

3. There are **genetic, environmental,**
and lifestyle factors at play

4. Long term sequelae such as cardiovascular disease and type 2 diabetes must routinely be evaluated especially with hyperandrogenism.

5.It is most commonly diagnosed by the **Rotterdam Criteria**

Ajmal N, Khan SZ, Shaikh R. Polycystic ovary syndrome (PCOS) and genetic predisposition: A review article European Journal of Obstetrics & Gynecology and Reproductive Biology: X. 2019; 3:100060-.



What is the Rotterdam Criteria?

First, What might PCOS look like?

Irregular or absent menstrual cycles

Hirsutism - darker hair growth on chin, down neck, around nipple or umbilicus

Acne- particularly cystic acne at the chin and jawline

Hair loss at the crown or temples

Central visceral adiposity

Skin tags

Acanthosis nigricans - darker/thicker skin in the armpits, nape of the neck, skin folds

Metabolic dysfunction - glucose, insulin, lipids, inflammatory markers

Fertility challenges

★ Rotterdam Criteria:

Must be 2 out of 3 to be considered PCOS

1. **Oligo (irregular >35 days) or amenorrhea (absence)**
2. **Hyperandrogenism** (Androgen labs and androgenic symptoms)
3. **Polycystic ovaries** seen on ultrasound (PCOM)

Ajmal N, Khan SZ, Shaikh R. Polycystic ovary syndrome (PCOS) and genetic predisposition: A review article European Journal of Obstetrics & Gynecology and Reproductive Biology: X. 2019; 3:100060-.

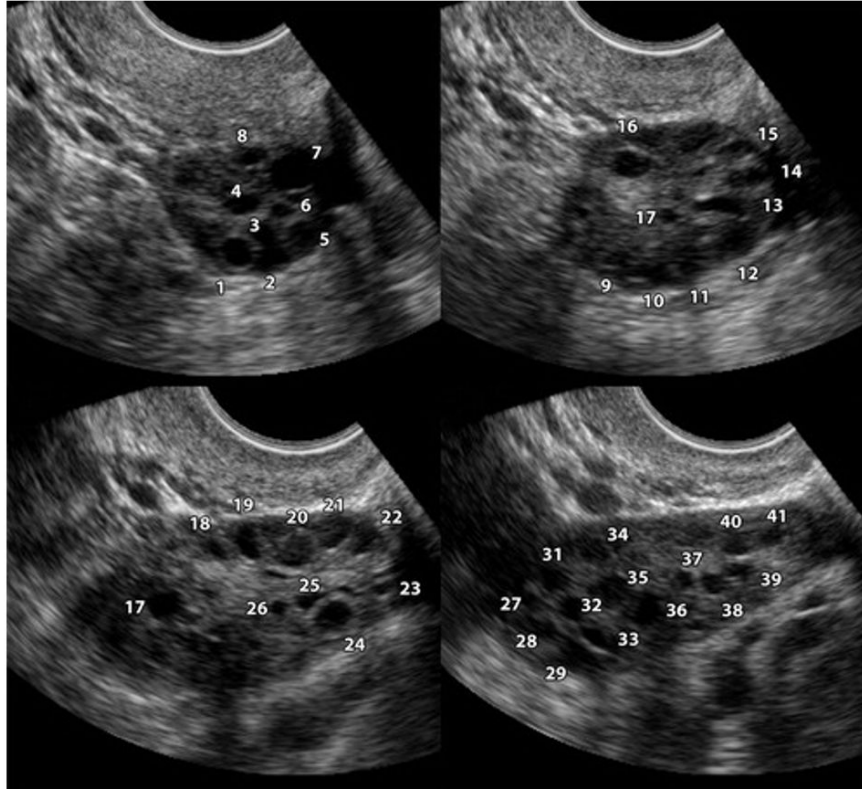
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***Ultrasound:** Either 12 or more follicles measuring 2-9 mm in diameter and/or an increased ovarian volume $>10\text{ cm}^3$



Lee TT, Rausch ME. Polycystic Ovarian Syndrome: Role of Imaging in Diagnosis *RadioGraphics*. 2012; 32(6):1643-1657.

<https://emedicine.medscape.com/article/404754-overview>

Do all ovarian cysts mean PCOS?

Do all ovarian cysts mean PCOS?



The 4 Phenotypes of PCOS

Phenotype	Ultrasound	Menses	Androgens	Prevalence
A	Polycystic	<u>Oligoanovulation</u>	Hyperandrogenism	44–65%
B	Not polycystic	<u>Oligoanovulation</u>	Hyperandrogenism	8–33%
C	Polycystic	Normal Menses	Hyperandrogenism	3–29%
D	Polycystic	<u>Oligoanovulation</u>	Normal Androgens	0-23%

Khan MJ, Ullah A, Basit S. Genetic Basis of Polycystic Ovary Syndrome (PCOS): Current Perspectives. Appl Clin Genet. 2019; 12:249-260. [\[PDF\]](#)

“The proposed **pathophysiology** of PCOS is a synergistic relationship between perturbed gonadotrophin releasing hormones (GnRH) **pulsatility** and **hyperandrogenism** probably accompanied by **hyperinsulinemia**, **insulin resistance**, and **inflammation**.”



**Hormones are pulsed out.
Like Morse Code.
They are not continuous
like a hose**



**Hormones are pulsed out.
Like Morse Code.
They are not continuous
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Think of your heartbeat - it pulses



Your brain starts the first pulse = GnRH

Hypothalamus → GnRH

This pulses to the pituitary = LH or FSH

Hypothalamus → GnRH

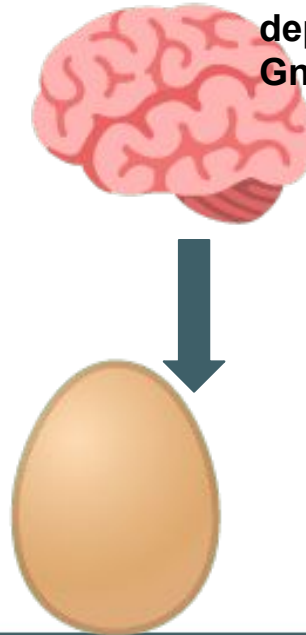


Pituitary → LH or FSH
depending on the type of
GnRH pulse

LH and FSH are different pulse types = stimulate different things

Hypothalamus → GnRH

Pituitary → LH or FSH
depending on the type of
GnRH pulse



- FSH = stimulates follicles to grow and estradiol
- LH = stimulates androgens, ovulation and progesterone

What affects these pulses?

Everything. Especially dysfunctional insulin & Inflammation

SNPS Being Studied with PCOS

- Insulin receptor
- Insulin gene variable number of tandem repeats (INS-VNTR)
- Insulin Receptor Substrate-1 and 2 (IRS-1 and IRS-2)
- Transcription Factor 7-Like 2 (TCF7L2) (adipogenesis)
- Calpain-10 (↑ risk type 2DM)
- Adiponectin
- CYP1A1
- CYP11A1
- DENN domain containing 1A (DENND1A)
- Paraoxonase 1 (PON1) (↑ risk type 2DM & CVD)
- Follicle Stimulating Hormone Receptor (FSHR)
- Androgen Receptor (AR)
- CYP17/HSD 17
- HSD3B
- Anti-müllerian hormone (AMH)
- Anti-müllerian hormone receptor II (AMHR2)
- TNF-α
- IL-6
- And more

Hiam , Moreno-Asso , Teede , et al. The Genetics of Polycystic Ovary Syndrome: An Overview of Candidate Gene Systematic Reviews and Genome-Wide Association Studies JCM. 2019; 8(10):1606-.

“If I have genetic variants around PCOS, that seems overwhelming. What do I do?”


Your best. You do your best with what you know.



Let's Look at High Insulin

It's not a criteria for PCOS

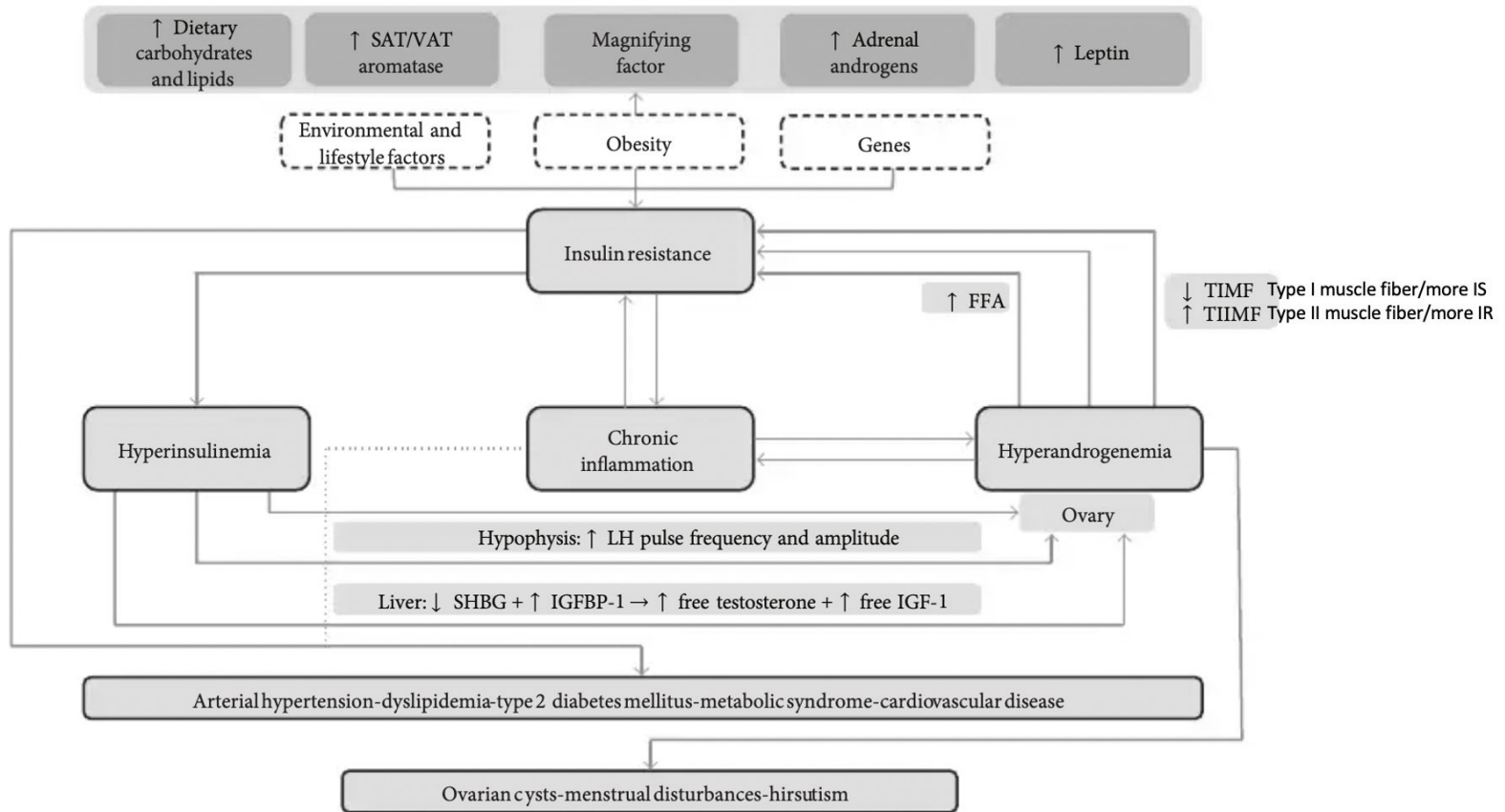
Insulin: 4 Major PCOS Effects

↑ GnRH pulse 
= ↑ LH = ↑ androgens
& don't ovulate

↑ insulin = ↑ androgen
production from the
ovary cells directly

↑ insulin = ↓ SHBG
= ↑ free testosterone

↑ insulin favors the
development of obesity
= ↑ inflammation, ↑ E2,
↑ cardiovasc. problems



Rojas J, Chávez M, Olivar L, et al. Polycystic Ovary Syndrome, Insulin Resistance, and Obesity: Navigating the Pathophysiologic Labyrinth International Journal of Reproductive Medicine. 2014; 2014:1-17.



Increased insulin and insulin resistance (IR) are extremely common in PCOS





Increased insulin and insulin resistance (IR) are extremely common in PCOS



**Both obese and non-obese
PCOS can have
insulin problems**

What is considered “normal” insulin levels?

	Insulin Level	Insulin Level (SI Units*)
Fasting	< 25 mIU/L	< 174 pmol/L
30 minutes after glucose administration	30-230 mIU/L	208-1597 pmol/L
1 hour after glucose administration	18-276 mIU/L	125-1917 pmol/L
2 hour after glucose administration	16-166 mIU/L	111-1153 pmol/L
≥3 hours after glucose administration	< 25 mIU/L	< 174 pmol/L
*SI unit: conversional units x 6.945		

<https://emedicine.medscape.com/article/2089224-overview>

What is considered “normal” insulin levels?

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<https://emedicine.medscape.com/article/2089224-overview>

Why a “low” fasting insulin?

A study in 2018 evaluated fasting insulin (FI) and the risk of **metabolic syndrome (MetS)**.

- Obesity
- High blood pressure
- High blood triglycerides
- Low levels of HDL cholesterol
- Insulin Resistance

Chen, Y. H., Lee, Y. C., Tsao, Y. C., Lu, M. C., Chuang, H. H., Yeh, W. C., Tzeng, I. S., & Chen, J. Y. (2018). Association between high-fasting insulin levels and metabolic syndrome in non-diabetic middle-aged and elderly populations: a community-based study in Taiwan. *BMJ open*, 8(5), e016554. <https://doi.org/10.1136/bmjopen-2017-016554>

Why a “low” fasting insulin?


- “After adjusting for gender, age, BMI, smoking status, hypertension and dyslipidaemia, the middle-aged and elderly populations in the high FI group were at significant risk for developing MetS (OR=5.04, 95% CI=2.15 to 11.81; P<0.01). This conclusion is consistent with previous findings.”

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- In this study, **high fasting insulin of n=104 was >7.9mIU/L (55pmol/L)**
- **Moderate** fasting insulin levels were 4.9-7.8mIU/L (34-54pmol/L)

Chen, Y. H., Lee, Y. C., Tsao, Y. C., Lu, M. C., Chuang, H. H., Yeh, W. C., Tzeng, I. S., & Chen, J. Y. (2018). Association between high-fasting insulin levels and metabolic syndrome in non-diabetic middle-aged and elderly populations: a community-based study in Taiwan. *BMJ open*, 8(5), e016554. <https://doi.org/10.1136/bmjopen-2017-016554>



Functional Perspective:
Practitioners suggest a fasting insulin in blood between 2-5mIU/L
to reduce the risk of metabolic syndrome/cardiometabolic disease



Inflammation and PCOS

Finding and Fighting Fires 🔥

PCOS Inflammation


“Reports show that women with PCOS, both with obesity and normal weight, exhibit elevated serum TNF, C-reactive protein (CRP), monocyte and lymphocyte circulating levels, and inflammatory infiltration in ovarian tissue.”

Rojas J, Chávez M, Olivar L, et al. Polycystic Ovary Syndrome, Insulin Resistance, and Obesity: Navigating the Pathophysiologic Labyrinth International Journal of Reproductive Medicine. 2014; 2014:1-17.

Inflammation Origin Story

- Microbiome problems
- Pathogens (stealth and overt)
- Foods
- Toxicants/chemicals
- Extra adipose tissue
- Injury
- Stress
- Trauma (big and little T's)
- Genetically prone
- Sleep/circadian rhythm dysfunction
- Etc.

Inflammation and Visceral Obesity

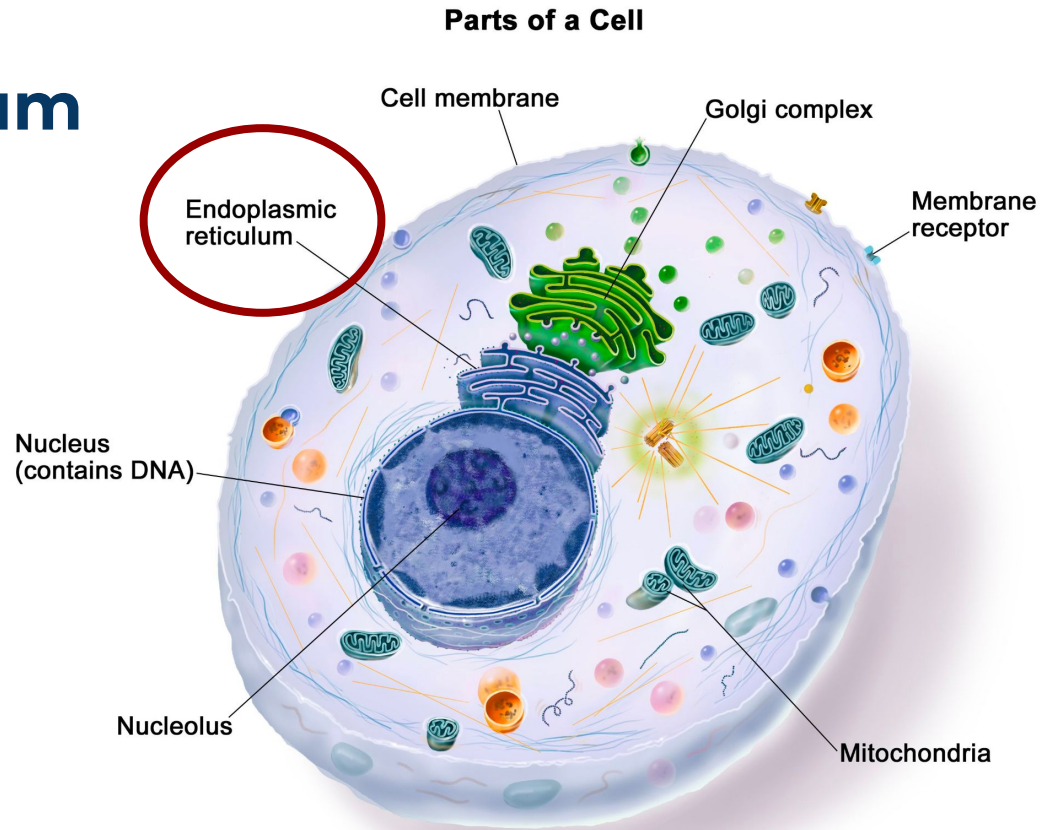
- Weight gain/obesity are not a diagnostic criteria of PCOS
- It is, however, a common feature (25-70%)
- IR-PCOS tend to have \uparrow visceral and truncal adipose accumulation that create low grade inflammation 

- Barrea L, Frias-Toral E, Verde L, et al. PCOS and nutritional approaches: Differences between lean and obese phenotype Metabolism Open. 2021; 12:100123-.
- Calcatera V, Verduci E, Cena H, et al. Polycystic Ovary Syndrome in Insulin-Resistant Adolescents with Obesity: The Role of Nutrition Therapy and Food Supplements as a Strategy to Protect Fertility Nutrients. 2021; 13(6):1848-

Endoplasmic Reticulum Stress in the Ovaries and PCOS

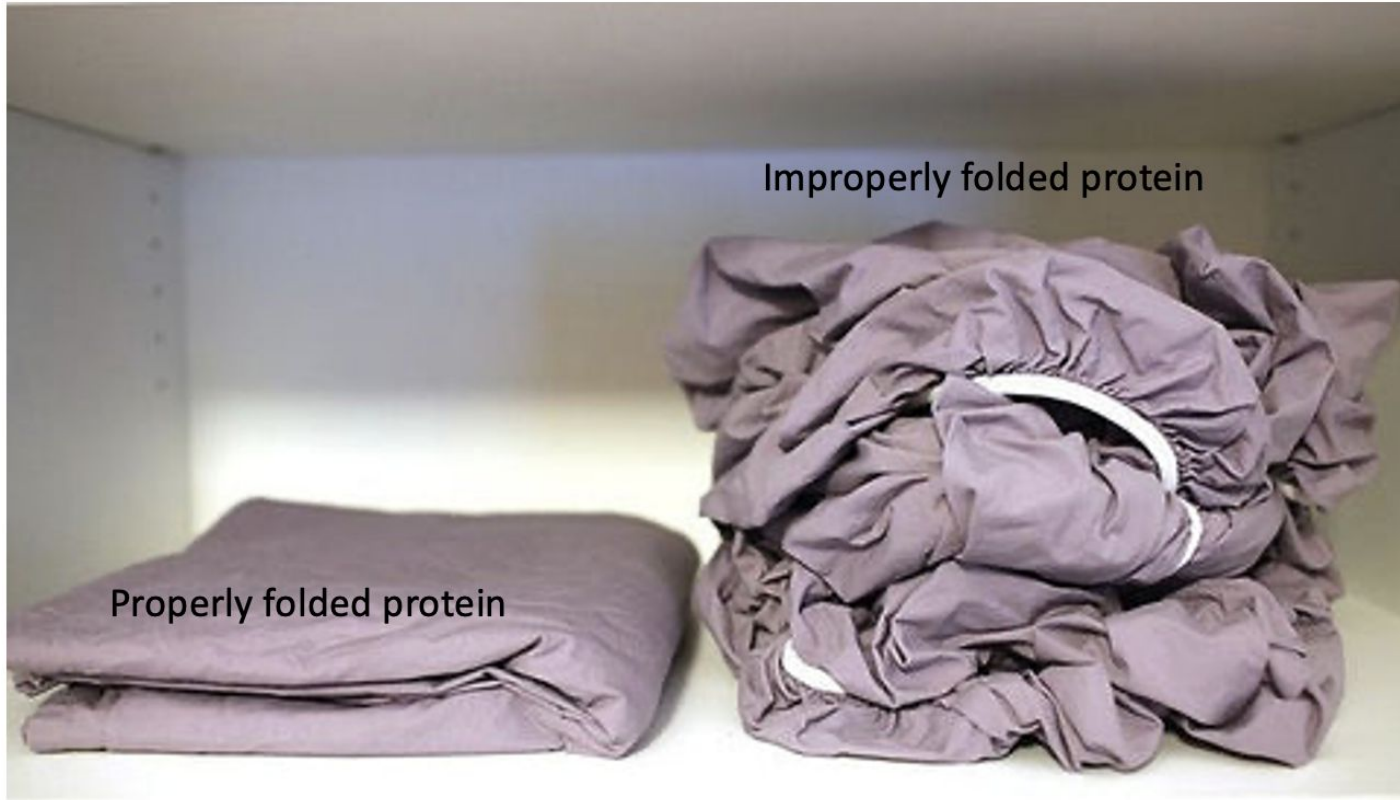
“ER stress is defined as a condition in which unfolded or misfolded proteins accumulate in the ER because of an imbalance in the demand for protein folding and the protein-folding capacity of the ER...In principle, the UPR restores homeostasis and keeps the cell alive. However, if the ER stress cannot be resolved, **it induces programmed cell death.**”

Koike H, Harada M, Kusamoto A, et al. Roles of endoplasmic reticulum stress in the pathophysiology of polycystic ovary syndrome Front. Endocrinol.. 2023; 14.



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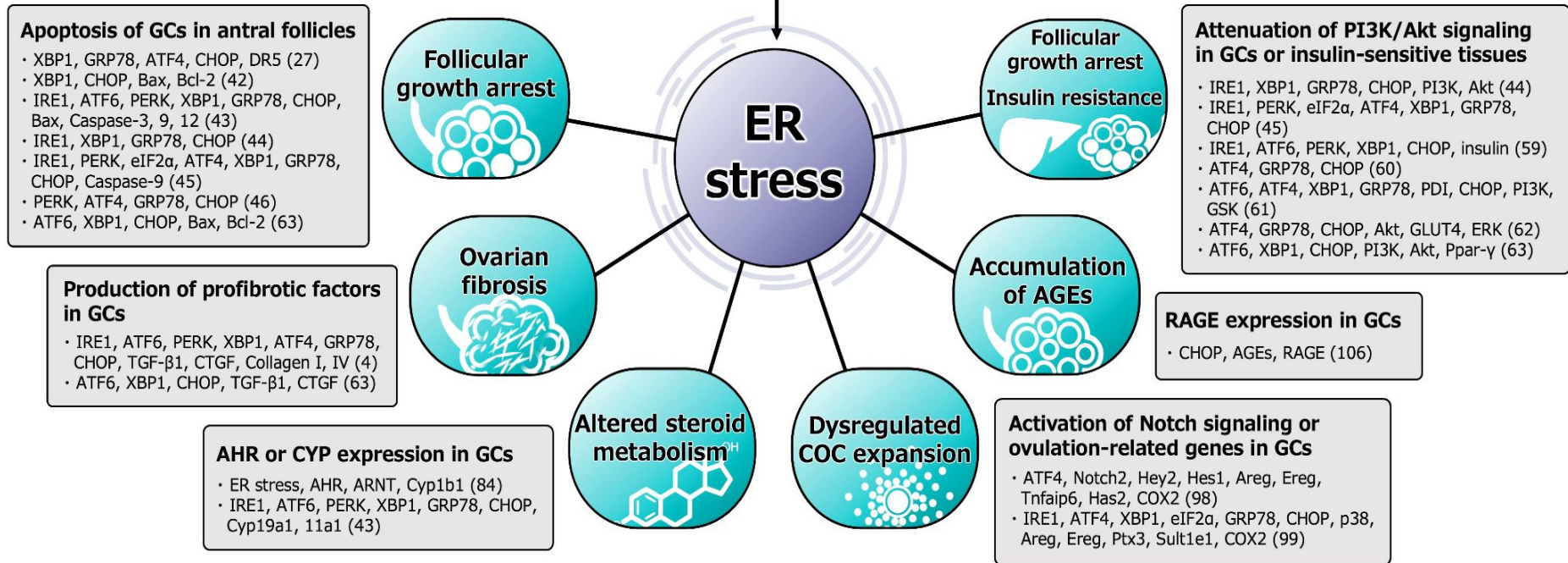
Folded vs Poorly Folded Protein Analogy



ER Stress and PCOS

“ER stress pathways are activated in the ovaries of both a mouse model of PCOS and in humans, and local hyperandrogenism in the follicular microenvironment associated with PCOS is responsible for activating these.”

Hyperandrogenism \rightleftharpoons Hyperinsulinemia



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Speaking of Inflammation, Stress and Adipose Tissue...

Testosterone

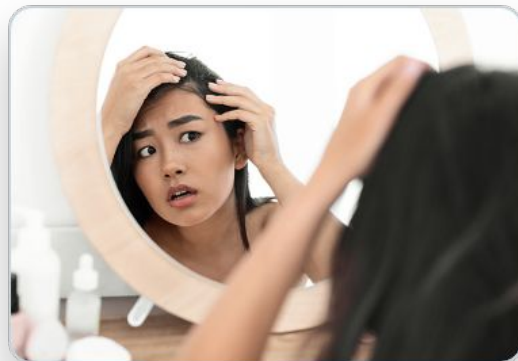
5a-Reductase Enzyme

```
graph LR; A[Testosterone] -- "5a-Reductase Enzyme" --> B["5a-DHT  
(2-5x stronger than T)"]
```

5a-DHT
(2-5x stronger than T)

What are the Sx of higher 5a-DHT (and testosterone)?

- Cystic acne especially along the jaw and chin
- Hirsutism
- Female pattern baldness or androgenic alopecia
- Mood swings - anger/irritation



Testosterone

5a-Reductase Enzyme

5a-DHT
(2-5x stronger than T)

**High Insulin
High Inflammation
High Triglycerides**



How is PCOS Evaluated?

Lab work & Imaging

As many as 75% of women aren't identified as PCOS by their clinician.

💡 **A good intake is critical!** 💡

Symptoms, systems review, period history, pregnancy history, medications, family history, etc.



Have a proper physical exam



Symptoms of PCOS can Overlap with Other Conditions

Irregular or absent cycles:

- Thyroid issues, Elevated prolactin, High stress, Overtraining, Undereating, Puberty/Perimenopause, Certain Medications, Head Trauma/Traumatic Brain Injury, etc.

Hyperandrogenic symptoms - cystic acne, hirsutism, hair loss

- Diet/lifestyle, Products/Chemicals, Thyroid issues, Elevated prolactin, High stress, Overtraining, Undereating, Puberty/Perimenopause, Certain Medications, Ethnicity, NC-Congenital Adrenal Hyperplasia, etc.

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Hyperandrogenic symptoms - c

- Diet/lifestyle, Products/Chemicals, Thyroid issues, Elevated prolactin, High stress, Overtraining, Undereating, Puberty/Perimenopause, Certain Medications, Ethnicity, NC-Congenital Adrenal Hyperplasia, etc.

Note:
**You can have any of these conditions
and PCOS**

Labs Specifically for PCOS

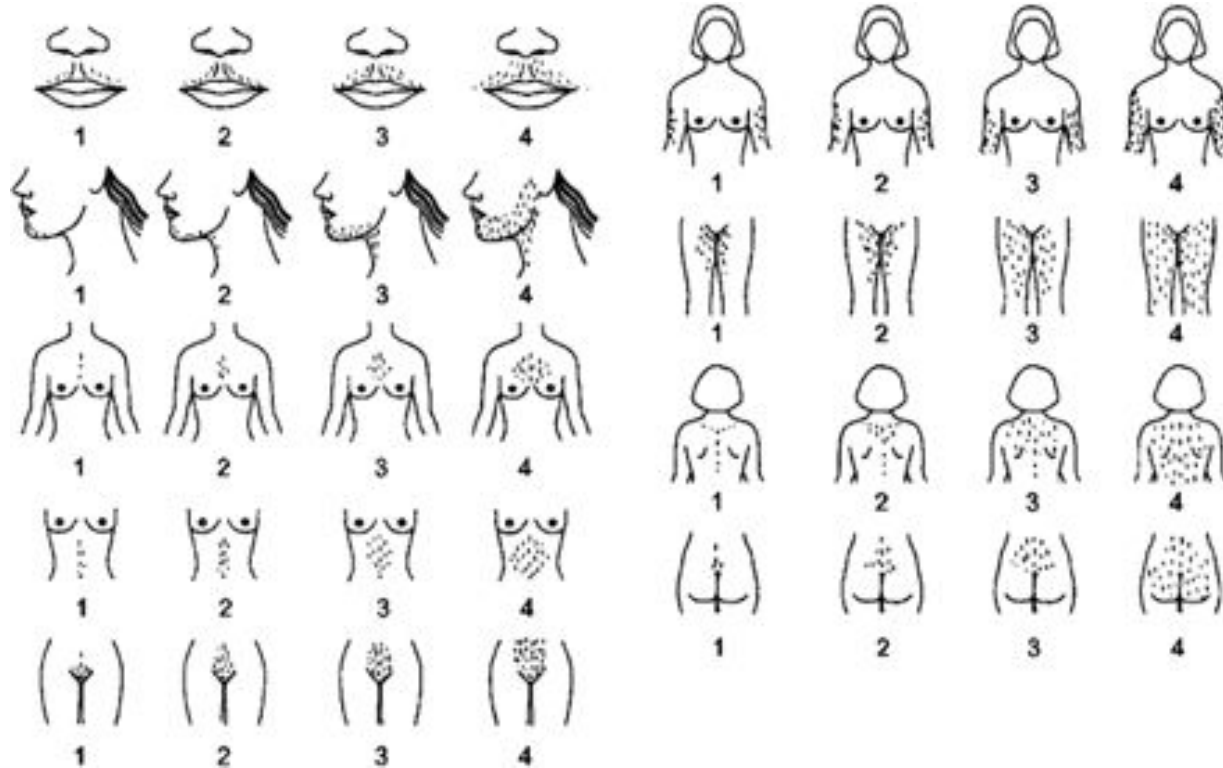
- **Free Testosterone**
 - Elevated in up to 89% with PCOS
- **Total Testosterone**
 - Elevated in 49-80% with PCOS
- **Sex Hormone Binding Globulin (SHBG)**
 - Typically reduced if insulin is high
- **DHEA-S**
 - Elevated in 25-35% with PCOS

*Be sure to choose mass spectrometry

*Can be done at any point in her cycle if she cycles

Christ JP, Cedars MI. Current Guidelines for Diagnosing PCOS Diagnostics. 2023; 13(6):1113. <https://escholarship.org/uc/item/3qm2m390>

Ferriman-Gallwey Scoring



Testing Reproductive Hormones: Progesterone/Estradiol

- This may be challenging if someone has oligomenorrhea or amenorrhea
- If they still cycle, first work to determine if they ovulate.
 - LH strips/ovulation predictor kits can help.
- If they do ovulate, testing **progesterone and estradiol** 5-7 days after ovulation (luteal phase) is ideal.



Testing Reproductive Hormones: Estrone/Estradiol

- In general, consider testing **estrone (E1) and Estradiol (E2)** regardless
- Why?
- **Androgens can convert (aromatize) into estrogens** in adipose tissue
- High insulin and inflammation can increase this!
- You may not cycle often, but you're estrogens can still be high!

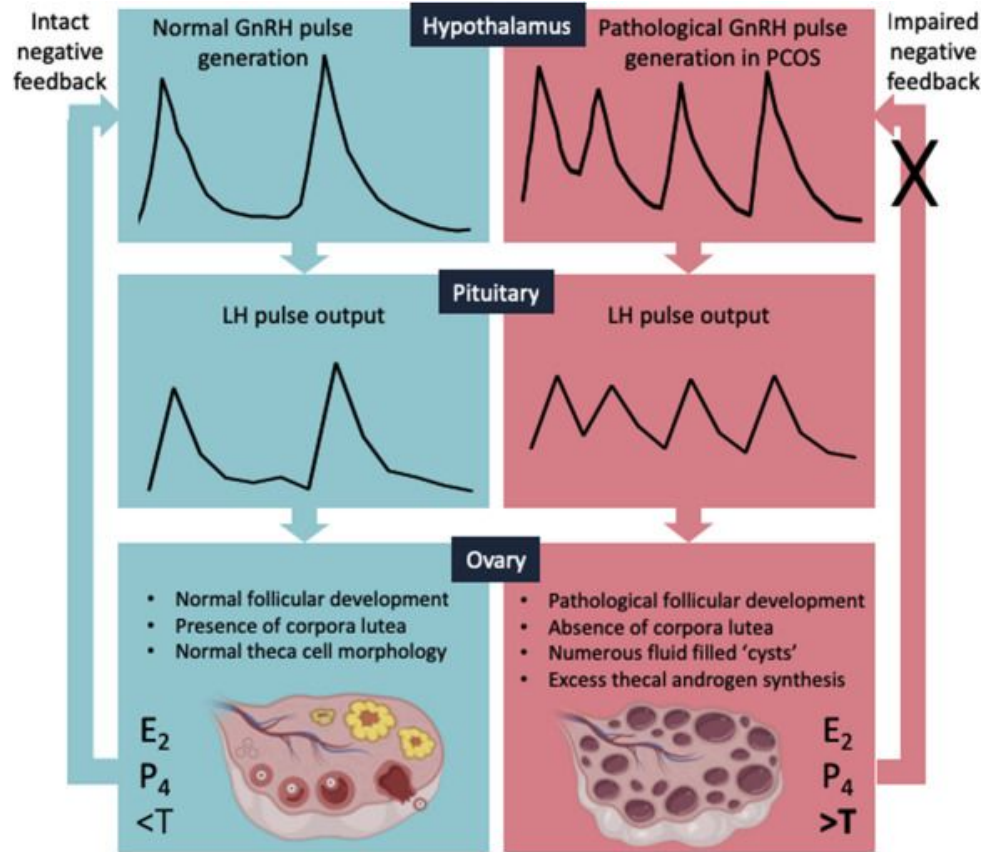
Testing Reproductive Hormones: LH and FSH

- **Follicle stimulating hormone (FSH):**
 - Generally tested with estradiol on day 2, 3 or 4 of the menstrual cycle via blood
- **Luteinizing hormone (LH):**
 - Should rise sharply before ovulation to help trigger that egg release when cycling
 - Testing usually done via LH strips or ovulation predictor kits
 - Can test via blood

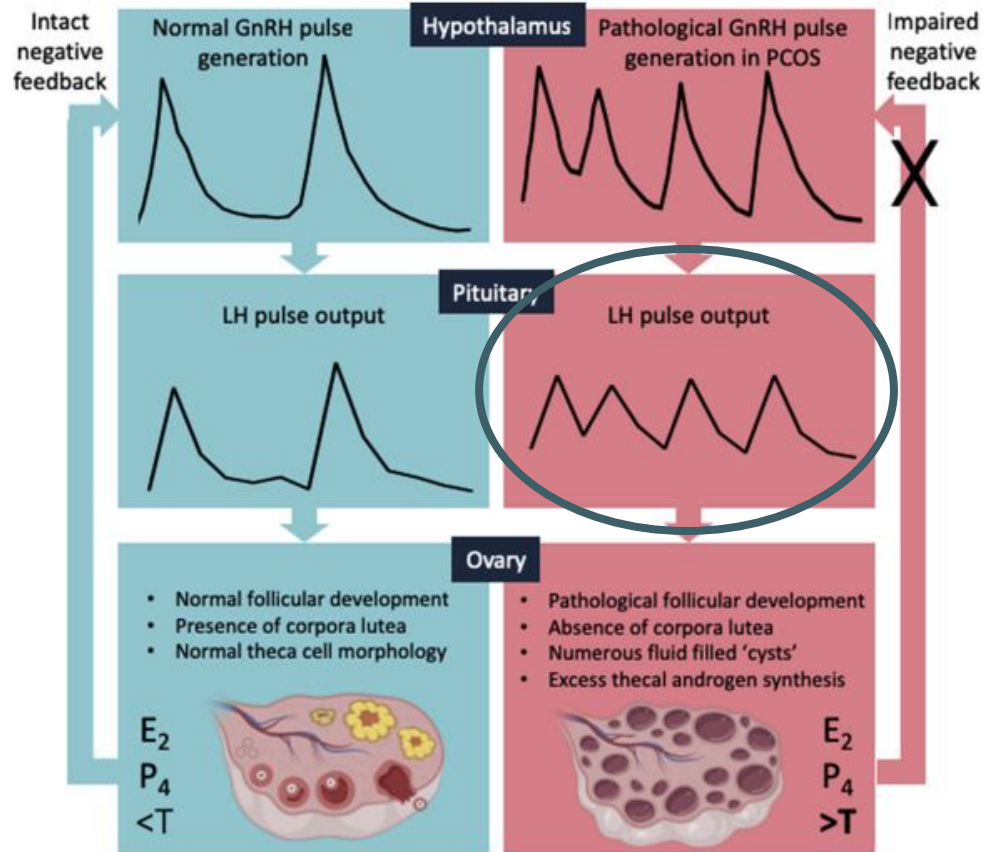
Testing Reproductive Hormones: LH and FSH

- **With anovulatory PCOS:**
 - LH is often continually elevated
 - FSH is usually in range or low
 - An **LH/FSH ratio of 2 or 3** may help indicate anovulation and PCOS

Saadia Z. Follicle Stimulating Hormone (LH: FSH) Ratio in Polycystic Ovary Syndrome (PCOS) - Obese vs. Non- Obese Women. Med Arch. 2020; 74(4):289-293. [PDF]



Coyle C, Campbell RE. Pathological pulses in PCOS Molecular and Cellular Endocrinology. 2019; 498:110561-.



Coyle C, Campbell RE. Pathological pulses in PCOS Molecular and Cellular Endocrinology. 2019; 498:110561-.

Testing Glucose and Insulin: Options

- **Fasting Glucose**
 - TyG Index (Triglyceride Glucose Index)
- **Fasting Insulin**
 - HOMA-IR calculation
- **Liver function tests** - 24% adults have Nonalcoholic Fatty Liver Dz
- Hemoglobin A1C
- Continuous Glucose Monitoring (CGM)
- Glucose Insulin Tolerance Test

Anti-Mullerian Hormone (AMH)

- Hormone made inside the follicles in the ovaries
- Sometimes used with fertility testing for ovarian reserve testing
 - Low levels indicate lower ovarian reserve
- Higher levels indicate more preantral and small antral follicles
 - Depending on the lab, **results >4 or >5ng/ml suggest PCOS**
 - **Do a pelvic ultrasound to evaluate for cysts if AMH is high**

Ran Y, Yi Q, Li C. The Relationship of Anti-Mullerian Hormone in Polycystic Ovary Syndrome Patients with Different Subgroups. Diabetes Metab Syndr Obes. 2021; 14:1419-1424. [\[PDF\]](#)

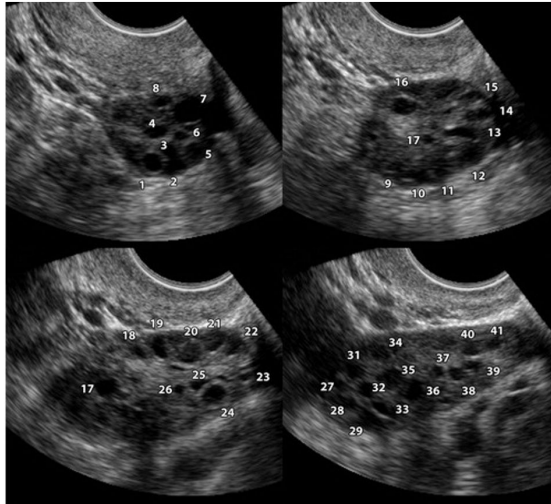
Other Testing to Consider Regarding PCOS:

- **Lab testing for the ‘overlap’ conditions**
- **Do a Lipid panel (consider a more advanced panel)**
 - Particle count, Lp(a), apolipoprotein B (ApoB), oxLDL, ex.
- Fasting Leptin
- Uric Acid (Fructose → purines → uric acid)
- Inflammatory markers such as hsCRP
- GI Testing - 🦌 more on this
- Vitamin D

Evaluating for PCOM:

- Pelvic Ultrasound

***Ultrasound:** Either 12 or more follicles measuring 2-9 mm in diameter and/or an increased ovarian volume $>10\text{ cm}^3$



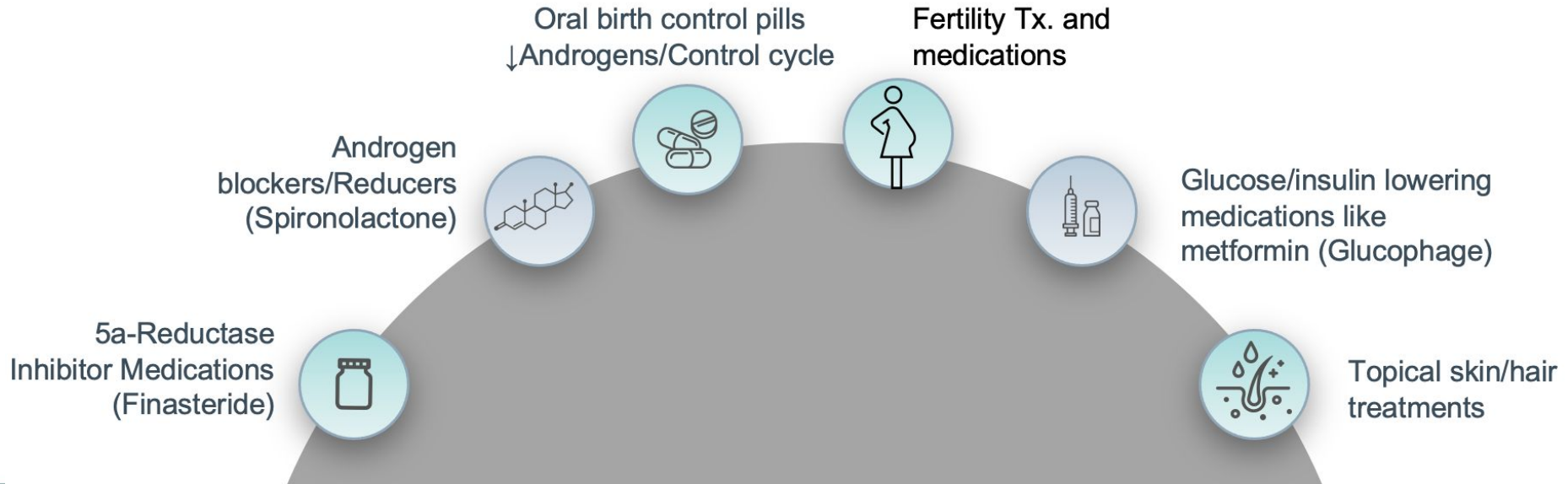
Lee TT, Rausch ME. Polycystic Ovarian Syndrome: Role of Imaging in Diagnosis *RadioGraphics*. 2012; 32(6):1643-1657.
<https://emedicine.medscape.com/article/404754-overview>



How is PCOS Treated?

Conventional & Functional

Conventional Treatment for PCOS





PCOS involves every system in the body

Therefore, treatment should be a whole systems approach

First thing's first

What can be done to:

**Reduce
fasting Insulin**

**Reduce
Inflammation**

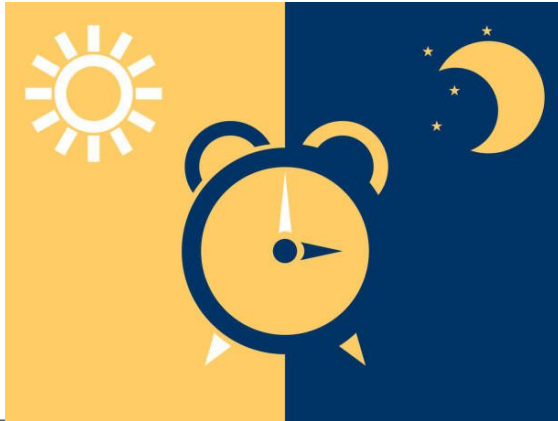
**Reduce
Visceral
Adiposity**

Foundational Work

- Do you need to evaluate the way you eat, what you eat or the timing of what you eat? Do you need support with that?
- Do you need to evaluate how you do or don't move or exercise? Do you need support with that?
- Do you need to evaluate any habits not serving you for the better?
- Do you need support with the mental emotional aspect?
- Do you need to evaluate the stress in your life?
- Do you need bodywork? Massage? Acupuncture? Chiropractic?
- Do you find joy in life? Do you have a community? Are you happy?

Foundational Work ☐

- ☐ Are you getting enough sleep?
- ☐ Are you sleeping in darkness?
- ☐ Are you working with your circadian rhythm instead of against it?
- ☐ **Your circadian rhythm helps set your reproductive rhythm!**



Women with polycystic ovary syndrome (PCOS) have reduced melatonin concentrations in their follicles and have mild sleep disturbances

[Hongwanyu Li](#), [Mei Liu](#) & [Cong Zhang](#) 

BMC Women's Health **22**, Article number: 79 (2022) | [Cite this article](#)

5534 Accesses | **6** Citations | **14** Altmetric | [Metrics](#)

Abstract

Background

Polycystic ovary syndrome (PCOS) is a common gynecologic disorder related to abnormal circadian rhythm. Therefore, we aimed to find whether the level of melatonin, a rhythm regulating hormone changed in the ovarian microenvironment in this disease.

Methods

The melatonin concentrations in follicular fluid (FF) were measured in 35 PCOS and 36 non-PCOS women undergoing in vitro fertilization (IVF) treatment.

Results

The FF melatonin concentration was significantly lower in PCOS women than non-PCOS

Do your best to minimize endocrine disrupting chemicals



“A wide variety of chemical compounds, both natural and synthetic, have been recognized to possess endocrine disrupting activity, including phytoestrogens, compounds in pharmaceutical and cosmetic products (e.g., parabens, triclosan (TCS)), pesticides, **plastics (bisphenol A (BPA) and its alternatives)**, plasticizers (phthalates), metals (heavy metals, trace elements) and industrial chemicals with by-products”

Smovršnik T, Virant-Klun I, Pinter B. Polycystic Ovary Syndrome and Endocrine Disruptors (Bisphenols, Parabens, and Triclosan)-A Systematic Review. Life (Basel). 2023; 13(1):. [[PDE](#)]

Reduce/minimize fragrances To reduce phthalates



Al-Saleh I, Elkhatib R. Screening of phthalate esters in 47 branded perfumes Environ Sci Pollut Res. 2015; 23(1):455-468.

Hlišníková H, Petrovičová I, Kolena B, Šidlovská M, Sirotkin A. Effects and Mechanisms of Phthalates' Action on Reproductive Processes and Reproductive Health: A Literature Review. Int J Environ Res Public Health. 2020; 17(18):. [\[PDF\]](#)

**A lot of your health
starts in the gut!**

Central Regulation of PCOS: Abnormal Neuronal-Reproductive-Metabolic Circuits in PCOS Pathophysiology

Baoying Liao^{1 2 3 4}, Jie Qiao^{1 2 3 4}, Yanli Pang^{1 2 3 4}

Affiliations + expand

PMID: 34122341 PMID: [PMC8194358](#) DOI: [10.3389/fendo.2021.667422](#)

[Free PMC article](#)

Abstract

Polycystic ovary syndrome (PCOS) is a common reproductive endocrine disease. PCOS patients are characterized by hyperandrogenemia, anovulation, and metabolic dysfunction. Hypothalamus-pituitary-ovary axis imbalance is considered as an important pathophysiology underlying PCOS, indicating that central modulation, especially the abnormal activation of hypothalamic GnRH neurons plays a vital role in PCOS development. Increased GnRH pulse frequency can promote LH secretion, leading to ovarian dysfunction and abnormal sex steroids synthesis. By contrast, peripheral sex steroids can modulate the action of GnRH neurons through a feedback effect, which is impaired in PCOS, thus forming a vicious cycle. Additionally, hypothalamic GnRH neurons not only serve as the final output pathway of central control of reproductive axis, but also as the central connection point where reproductive function and metabolic state inter-regulate with each other. Metabolic factors, such as insulin resistance and obesity in PCOS patients can regulate GnRH neurons activity, and ultimately regulate reproductive function. Besides, gut hormones act on both brain and peripheral organs to modify metabolic state. Gut microbiota disturbance is also related to many metabolic diseases and has been reported to play an essential part in PCOS development. This review concludes with the mechanism of central modulation and the interaction between neuroendocrine factors and reproductive or metabolic disorders in PCOS development. Furthermore, the role of the gut microenvironment as an important part involved in the abnormal

**A lot of your health
starts in the gut!**

Central Regulation of PCOS: Abnormal Neuronal-Reproductive-Metabolic Circuits in PCOS Pathophysiology

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Abstract

Polycystic ovary syndrome (PCOS) is a common reproductive endocrine disease. PCOS patients are characterized by hyperandrogenemia, anovulation, and metabolic dysfunction. Hypothalamus-pituitary-ovary axis imbalance is considered as an important pathophysiology underlying PCOS, indicating that central modulation, especially the abnormal activation of hypothalamic GnRH neurons plays a vital role in PCOS development. Increased GnRH pulse frequency can promote LH secretion, leading to ovarian dysfunction and abnormal sex steroids synthesis. By contrast, peripheral sex steroids can modulate the action of GnRH neurons through a feedback effect, which is impaired in PCOS, thus forming a vicious cycle. Additionally, hypothalamic GnRH neurons not only serve as the final output pathway of central control of reproductive axis, but also as the central connection point where reproductive function and metabolic state inter-regulate with each other. Metabolic factors, such as insulin resistance and obesity in PCOS patients can regulate GnRH neurons activity, and ultimately regulate reproductive function. Besides, gut hormones act on both brain and peripheral organs to modify metabolic state. Gut microbiota disturbance is also related to many metabolic diseases and has been reported to play an essential part in PCOS development. This review concludes with the mechanism of central modulation and the interaction between neuroendocrine factors and reproductive or metabolic disorders in PCOS development. Furthermore, the role of the gut microenvironment as an important part involved in the abnormal

Address GI/Microbiome Issues:

- See the dentist regularly - The GI tract starts in the mouth! 
- Chew your food - you are not a snake.
- Consider GI Testing - see a trained practitioner
- Evaluate foods that are known to trigger symptoms
- Prebiotics, probiotics, postbiotics
- Stimulate the Vagus nerve

The Vagus Nerve: From the Brain to the GI

- Involved in several organs in the upper half of the body
- Very involved in communication **up to the brain**
- Largely considered important for the rest/digest/heal/repair functions
- **Try to stimulate it via:**
 - End a shower, swim, sit in cold water
 - Dip face in cold water
 - Singing, laughing, chanting, humming LOUDLY
 - Gargle “aggressively”
 - Meditation or breathing exercises
 - Address Gut health

Breit S, et al. Vagus Nerve as Modulator of the Brain–Gut Axis in Psychiatric and Inflammatory Disorders. *Front. Psychiatry*. 2018;9(44):<https://doi.org/10.3389/fpsy.2018.00044>

Zhao X, Jiang Y, Xi H, Chen L, Feng X. Exploration of the Relationship Between Gut Microbiota and Polycystic Ovary Syndrome (PCOS): a Review. *Geburtshilfe Frauenheilkd*. 2020; 80(2):161-171. [\[PDF\]](#).

Natural Treatments Studied For Metabolic Support & ER Stress

Movement after Meals

- **Walking** (or light movement) after meals helped reduce postprandial glucose
 - Take away - consider a walk, even around your house, after carb heavy meals
 - Reynolds A, Venn B. The Timing of Activity after Eating Affects the Glycaemic Response of Healthy Adults: A Randomised Controlled Trial *Nutrients*. 2018; 10(11):1743-.
- **Soleus push ups** (seated calf raise) can reduce postprandial glucose
 - Hamilton MT, Hamilton DG, Zderic TW. A potent physiological method to magnify and sustain soleus oxidative metabolism improves glucose and lipid regulation. *iScience*. 2022; 25(9):104869. [[PDF](#)]

Consider Time Restricted Feeding

Pros: TRF study on women! With improvements!

Cons: Only 15 were in the study

Research | [Open Access](#) | [Published: 13 April 2021](#)

Eight-hour time-restricted feeding improves endocrine and metabolic profiles in women with anovulatory polycystic ovary syndrome

[Chunzhu Li](#), [Chuan Xing](#), [Jiaqi Zhang](#), [Han Zhao](#), [Wenjing Shi](#) & [Bing He](#) 

Journal of Translational Medicine **19**, Article number: 148 (2021) | [Cite this article](#)

15k Accesses | 19 Citations | 37 Altmetric | [Metrics](#)

Abstract

Background

Time-restricted feeding (TRF) is a form of intermittent fasting, which is beneficial for weight loss and cardiometabolic health. Polycystic ovary syndrome (PCOS) is one of the most common reproductive endocrine and metabolic diseases affecting women of childbearing age. It is associated with an increased prevalence of metabolic syndrome, cardiovascular diseases and type 2 diabetes. The effects of TRF on PCOS patients remains undefined, here we investigated the impact of TRF on women with anovulatory PCOS.

Inositol = 2-4 grams

- Inositols: 2nd messenger for insulin = better sensitivity
- Myo-inositol:D chiro-inositol = 40:1 ratio
- Several human studies using a combination or **myo-inositol** alone
- **Pearl:** Sodium ions transport myo-inositol into the tissues and manganese helps store inositol

Be careful if on a glucose regulating medication

• Kalra, B.; Kalra, S.; Sharma, J.B. The inositols and polycystic ovary syndrome. Indian J. Endocrinol. Metab. 2016, 20, 720–724

• Sasseville LJ, Longpré JP, Wallendorff B, Lapointe JY. The transport mechanism of the human sodium/myo-inositol transporter 2 (SMIT2/SGLT6), a member of the LeuT structural family. Am J Physiol Cell Physiol. 2014; 307(5):C431-41. [\[PDF\]](#)

Alpha Lipoic Acid (ALA): 400-800 mg/day

- Powerful antioxidant especially to the mitochondria
- Helps regenerate other antioxidants like vitamin C, E and glutathione
- Inhibits NFkB (inflammation)
- Improves glucose utilization in muscles
- Improves insulin sensitivity
- Studied in human studies on PCOS alone and in combination with Inositol

Petrillo T, Semprini E, Tomatis V, et al. Putative Complementary Compounds to Counteract Insulin-Resistance in PCOS Patients. Biomedicines. 2022; 10(8):. [[PDF](#)]

Berberine = 500mg 3 times/day with meals

- Reduces glucose by improving insulin sensitivity
- Promotes proper glucose transport
- Increases anti-inflammatory cytokines
- Can reduce/kill the gut microbiome = be careful
- Don't use with glucose regulating medications without a practitioner's guidance

Calcaterra V, Verduci E, Cena H, et al. Polycystic Ovary Syndrome in Insulin-Resistant Adolescents with Obesity: The Role of Nutrition Therapy and Food Supplements as a Strategy to Protect Fertility Nutrients. 2021; 13(6):1848-

Petrillo T, Semprini E, Tomatis V, et al. Putative Complementary Compounds to Counteract Insulin-Resistance in PCOS Patients. Biomedicines. 2022; 10(8):. [\[PDF\]](#)

Gymnema sylvestre: 400-600 mg per day

- Helps reduce the taste for sugar
- Reduces sugar absorption in the intestines
- Reduces LDL and triglycerides

Kanetkar P, Singhal R, Kamat M. *Gymnema sylvestre*: A Memoir. J Clin Biochem Nutr. 2007; 41(2):77-81. [\[PDF\]](#)

Petrillo T, Semprini E, Tomatis V, et al. Putative Complementary Compounds to Counteract Insulin-Resistance in PCOS Patients. Biomedicines. 2022; 10(8):. [\[PDF\]](#)

Zuñiga LY, González-Ortiz M, Martínez-Abundis E. Effect of Administration on Metabolic Syndrome, Insulin Sensitivity, and Insulin Secretion Journal of Medicinal Food. 2017; 20(8):750-754.

Cinnamon

- Cinnamomum cassia studied regularly with glucose
- Can help reduce insulin sensitivity in women with PCOS
- Anti-inflammatory and antioxidant as a spice

Lakshmi JN, Babu AN, Kiran SSM, et al. Herbs as a Source for the Treatment of Polycystic Ovarian Syndrome: A Systematic Review. BioTech (Basel). 2023; 12(1):. [\[PDF\]](#)

Resveratrol = 1500 mg/day human PCOS study

- Shown to reduce enzyme CYP17 thus lowers high testosterone and DHEA
- Shown to lower insulin and improved insulin resistance
- Known for its antioxidant abilities = reduce inflammation
- (Note: Common smaller doses may not have this effect)

•Banaszewska B, Wrotyńska-Barczyńska J, Spaczynski RZ, Pawelczyk L, Duleba AJ. Effects of Resveratrol on Polycystic Ovary Syndrome: A Double-blind, Randomized, Placebo-controlled Trial The Journal of Clinical Endocrinology & Metabolism. 2016; 101(11):4322-4328.

TUDCA (bile acid) = Consider 250 or 500mg?

- The bile acid: tauroursodeoxycholic acid
- Really helpful to your bile, liver and gallbladder
- Helps reduce endoplasmic reticulum stress
 - Helps with proper protein folding in mitochondria and reduced cell death
- Done in mouse studies - no established dose in PCOS

Azhary JMK, Harada M, Kunitomi C, et al. Androgens Increase Accumulation of Advanced Glycation End Products in Granulosa Cells by Activating ER Stress in PCOS . 2020; 161(2).

Azhary JMK, Harada M, Takahashi N, et al. Endoplasmic Reticulum Stress Activated by Androgen Enhances Apoptosis of Granulosa Cells via Induction of Death Receptor 5 in PCOS . 2019; 160(1):119-132.

Khalaf K, Tomese P, Cocco A, Albanese A .2022). "Tauroursodeoxycholic acid: a potential therapeutic tool in neurodegenerative diseases". *Translational Neurodegeneration*. 11 (1): 33.

Zhang M, Hu R, Huang Y, et al. Present and Future: Crosstalks Between Polycystic Ovary Syndrome and Gut Metabolites Relating to Gut Microbiota Front. Endocrinol.. 2022; 13.

Natural Treatments Studied For Androgenic Symptoms

Spearmint Tea: 2 cups/day ↓ Total and Free T Seems better for reducing androgenic acne



Grant P, Ramasamy S. An update on plant derived anti-androgens. Int J Endocrinol Metab. 2012; 10(2):497-502. [\[PDF\]](#)

Anti-Androgenic Herbs

- Reishi Mushroom
- Licorice (be mindful of electrolytes and blood pressure)
- White peony
- Green Tea (EGCG)
- Saw Palmetto

Grant P, Ramasamy S. An update on plant derived anti-androgens. Int J Endocrinol Metab. 2012; 10(2):497-502. [PDE](#)

Natural Treatments Studied For Cycle Support

Chaste Tree Berry = 250-500 mg daily

- *Vitex agnus castus*
- Helpful to reduce mildly elevated prolactin not due to tumors and restore cycling and ovulation
- Potentially 'adaptogenic' to GnRH pulses
- Note: In some PCOS - it might make symptoms worse due to pulse changes or enhancements

Feyzollahi Z, Mohseni Kouchesfehiani H, Jalali H, Eslimi-Esfahani D, Sheikh Hosseini A. Effect of Vitex agnus-castus ethanolic extract on hypothalamic KISS-1 gene expression in a rat model of polycystic ovary syndrome. *Avicenna J Phytomed.* 2021; 11(3):292-301. [\[PDF\]](#)

Black Cohosh = 20-1500 mg/day

- *Cimicifuga racemosa*
- Possible mild aromatase inhibitor = ↓ Estrone/Estradiol
- Studied with clomid in PCOS fertility patients = positive outcomes by reducing LH, improving ovulation

Pourhoseini SA, Mahmoudinia M, Najaf Najafi M, Kamyabi F. The effect of phytoestrogens () in combination with clomiphene in ovulation induction in women with polycystic ovarian syndrome: A clinical trial study. Avicenna J Phytomed. 2022; 12(1):8-15. [\[PDF\]](#)

Fennel Seeds (*Foeniculum vulgare*)

- Phytoestrogen
- Used often in ayurvedic medicine in women with PCOS to restore menses
- Anti-oxidant

Lakshmi JN, Babu AN, Kiran SSM, et al. Herbs as a Source for the Treatment of Polycystic Ovarian Syndrome: A Systematic Review. BioTech (Basel). 2023; 12(1):. [\[PDF\]](#)

Fenugreek = 500mg 2-3 times/day

- *Trigonella foenum-graecum*
- Often mixed in supplements for diabetes or blood sugar
- Reduces cyst size thus ovarian volume
- Decreases the LH/FSH ratio

Lakshmi JN, Babu AN, Kiran SSM, et al. Herbs as a Source for the Treatment of Polycystic Ovarian Syndrome: A Systematic Review. BioTech (Basel). 2023; 12(1):. [\[PDF\]](#)

Tribulus = 750mg

Mixed reviews

- Might increase FSH and estradiol
- Might increase libido
- Might improve ovulation if done days 5-14 of the cycle

Lakshmi JN, Babu AN, Kiran SSM, et al. Herbs as a Source for the Treatment of Polycystic Ovarian Syndrome: A Systematic Review. *BioTech (Basel)*. 2023; 12(1):. [\[PDF\]](#)
Sirotkin AV, Kolesárová A. Puncture vine (*Tribulus Terrestris* L.) in control of health and reproduction. *Physiol Res*. 2021; 70(Suppl4):S657-S667. [\[PDF\]](#)

Quercetin: 1000 mg/day human studies

“The majority of studies supported the beneficial effects of quercetin on the ovarian histomorphology, folliculogenesis, and luteinisation processes. The effects of quercetin on reducing the levels of testosterone, luteinizing hormone (LH), and insulin resistance were also reported. Although quercetin improved dyslipidemia, no significant effect was reported for weight loss. It is suggested that the benefits of quercetin may be more closely related to antioxidant and anti-inflammatory features of quercetin rather than weight-reducing effects.”

Pourteymour Fard Tabrizi F, Hajizadeh-Sharafabad F, Vaezi M, Jafari-Vayghan H, Alizadeh M, Maleki V. Quercetin and polycystic ovary syndrome, current evidence and future directions: a systematic review. J Ovarian Res. 2020; 13(1):11. [\[PDF\]](#)

Newer Less Known Less Researched: Peptides & Bioregulators

Molecular role of peptides/proteins in subfertility of polycystic ovarian syndrome

Onder Celik ¹, Suleyman Aydin ², Nilufer Celik ³, Kader Ugur ⁴, Seyda Yavuzkir ⁵, Safak Hatirnaz ⁶, Meltem Yardim ², Sude Celik ⁷

Affiliations + expand

PMID: 30942166

Abstract

Obesity and hyperandrogenemia are known to have adverse effects on both developing follicle and endometrium receptivity in polycystic ovarian syndrome (PCOS). Insulin resistance also contributes to this dilemma as a cause or a consequence and leads to worsening of the clinical picture. The difficulty in obtaining pregnancy despite the presence of a large number of oocyte has concentrated our attention on oocyte quality and development. However, the occurrence of subfertility has also caused us to investigate the presence of different etiologic agents in non-obese PCOS women with normal androgen and insulin levels. In this context peptides have become the most accused and investigated molecules in cases of impaired fertility due to PCOS. Most of the studies investigating the relationship between PCOS and peptide did not support each other. The difficulties in measuring peptide levels as well as the individual variations in peptide synthesis and release are possible causes of this incongruity. For all these reasons, the incorporation of studies investigating the relationship between PCOS, peptide and subfertility in an article has become critical to pioneering future work. Understanding the association between peptides and subfertility will help us to understand the effects of peptides on failed fertility in PCOS. Moreover, updating our knowledge about peptides may allow us designing new drugs to to treat subfertility in

Kisspeptin treatment induces gonadotropic responses and rescues ovulation in a subset of preclinical models and women with polycystic ovary syndrome

A Romero-Ruiz, K Skorupskaite, F Gaytan, E Torres, C Perdices-Lopez, B M Mannaerts, S Qi, S Leon, M Manfredi-Lozano, C Lopez-Rodriguez ... [Show more](#)

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Abstract

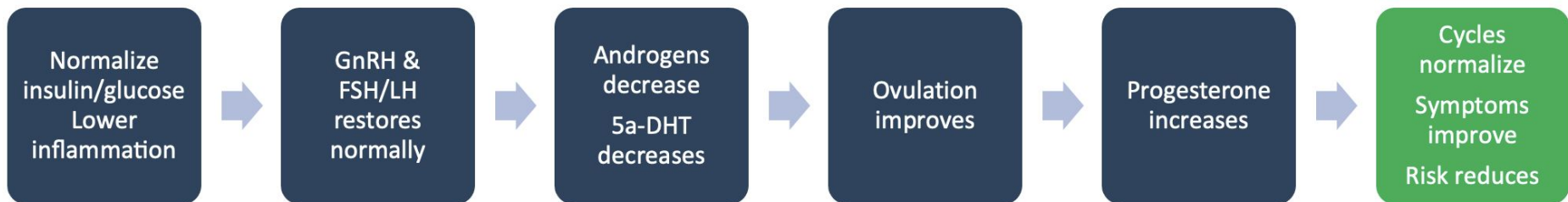
STUDY QUESTION

Can kisspeptin treatment induce gonadotrophin responses and ovulation in preclinical models and anovulatory women with polycystic ovary syndrome (PCOS)?

SUMMARY ANSWER

Kisspeptin administration in some anovulatory preclinical models and women with PCOS can stimulate reproductive hormone secretion and ovulation, albeit with incomplete efficacy.

The PCOS Goal!



DR. HYMAN+

Thank You!



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