BEYOND THE BASICS

PCOS

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DISCLOSURES

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

I will be discussing “off-label” uses of the following medications and classes:

- GLP-1 agonists
- Spironolactone

OBJECTIVES

Objective n° 1

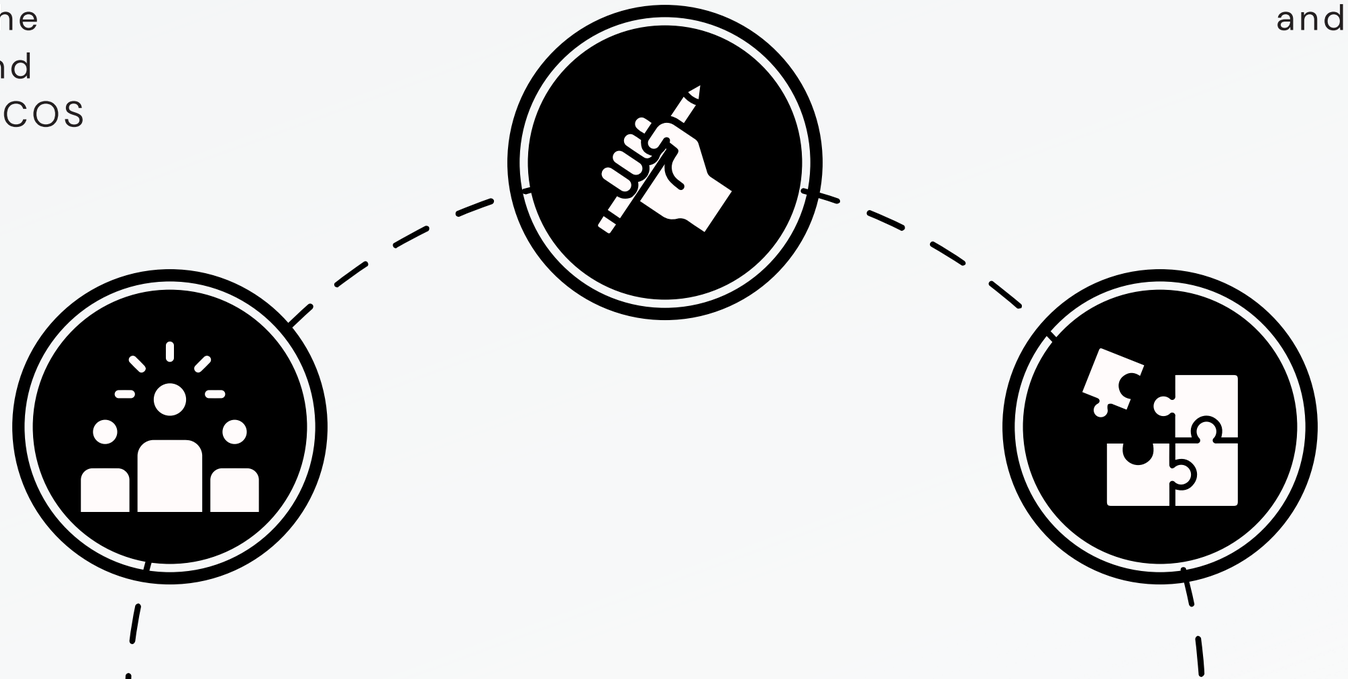
Summarize recommendations from the 2023 International Evidence-Based Guideline for the Assessment and Management of PCOS

Objective n° 2

Outline treatment modalities for PCOS symptoms

Objective n° 3

Discuss lifestyle interventions and prevention strategies for cardiometabolic and other sequelae of PCOS



2003

ROTTERDAM CRITERIA

2 of 3 criteria:

- Hyperandrogenism
- Oligo-anovulation
- Polycystic ovaries on ultrasound

2018

2018 INTERNATIONAL CRITERIA

2 of 3 criteria:

- Hyperandrogenism
- Ovulatory dysfunction
- Polycystic ovaries on ultrasound

2023

2023 INTERNATIONAL CRITERIA

- Refinement of diagnostic criteria
- Use of AMH as an alternative to ultrasound in adults
- Recognition of broader features of PCOS

&...

FUTURE RESEARCH

- Close key evidence-practice gaps
- Fund research for higher quality evidence

STATISTICS

PCOS is the most common endocrinopathy affecting reproductive-aged women

Prevalence: 10-13%

Delayed diagnosis is common

10%

PATIENT CASE

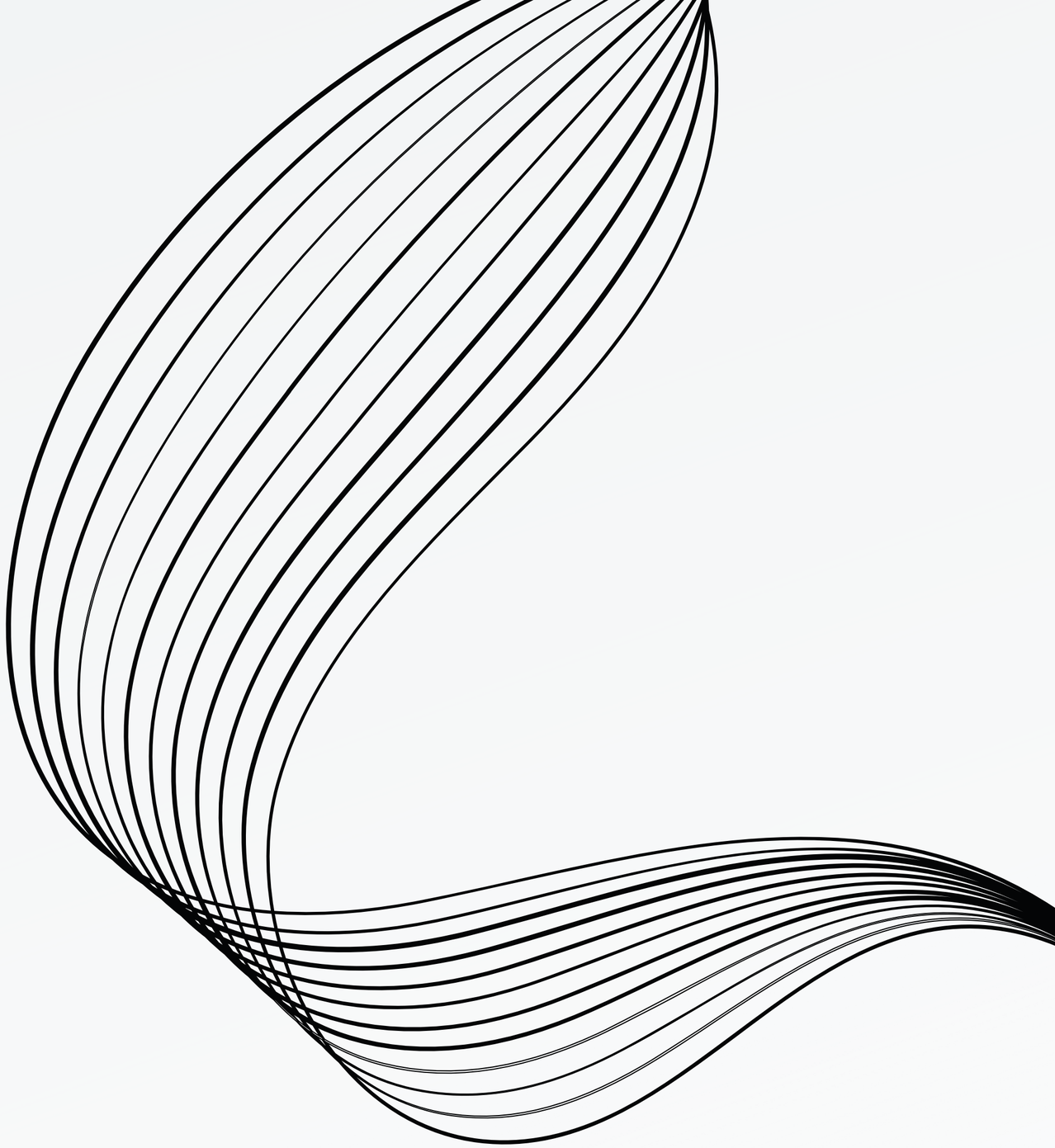
A 15 y.o. patient presents with irregular menses (every 22-35 days) and mild acne but no hirsutism. Her mother has a history of PCOS and is concerned her daughter has inherited this. She underwent menarche at age 12.

A) Diagnose with PCOS
B) Assess serum testosterone levels
C) Perform ultrasound to assess ovaries
D) B + C

PATIENT CASE

You ordered total and free testosterone, which both returned within normal parameters. What is the next best step?

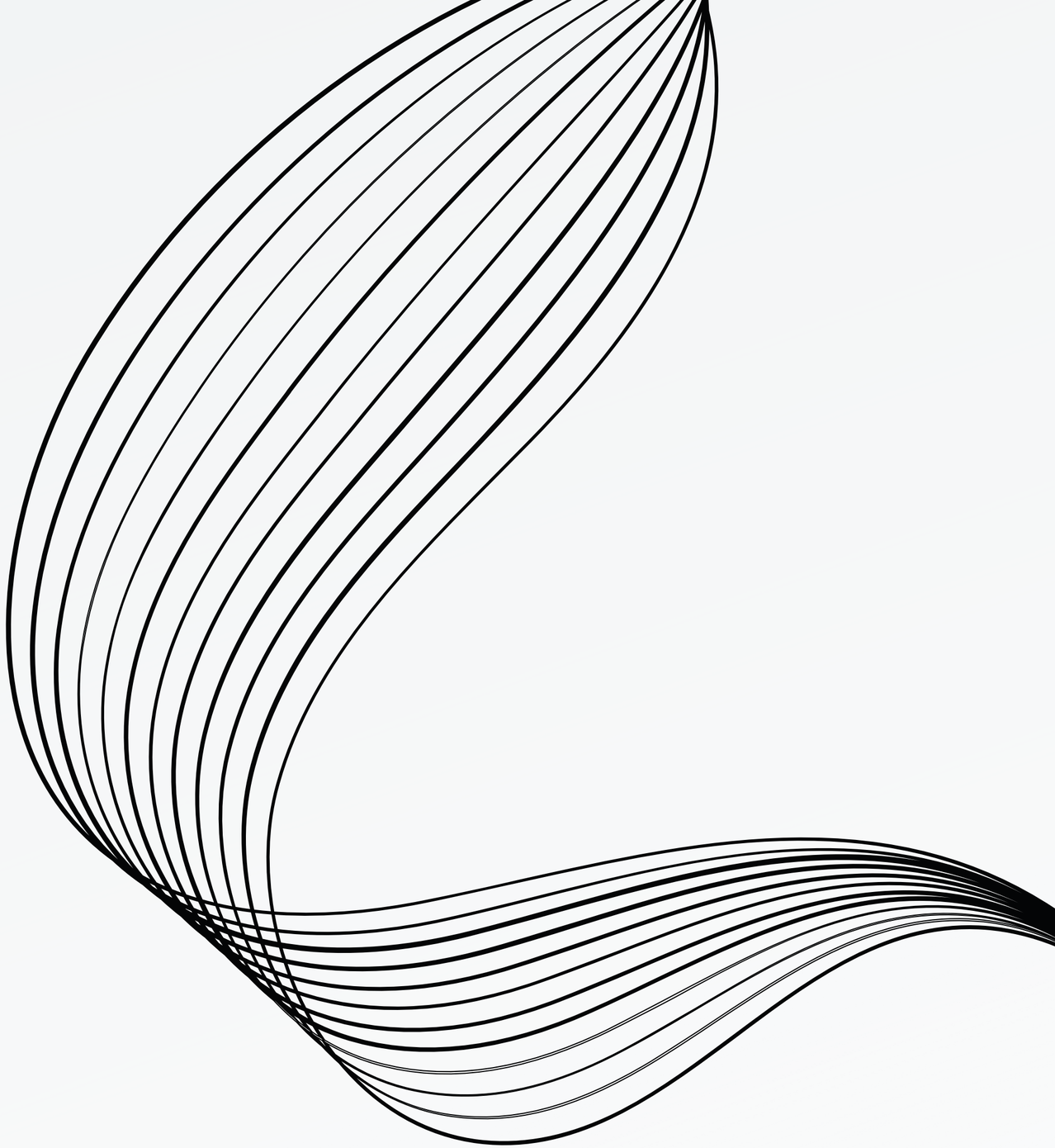
A) Diagnose with PCOS
B) Perform ultrasound to assess ovaries
C) Counsel regarding treatment options and reassess for PCOS at a later stage



PATIENT CASE

Which of the following is the first-line therapeutic agent for hirsutism in PCOS patients?

A) Spironolactone
B) Finasteride
C) Combined oral contraceptive pills



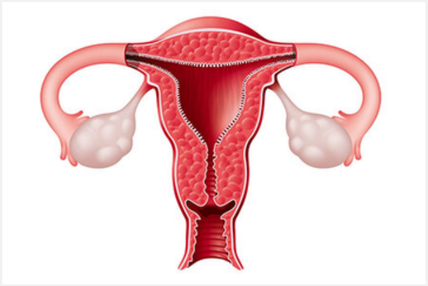
PATIENT CASE

PCOS patients should be screened for which of the following?

A) Glycemic abnormalities
B) Dyslipidemia
C) Depression and anxiety
D) All of the above

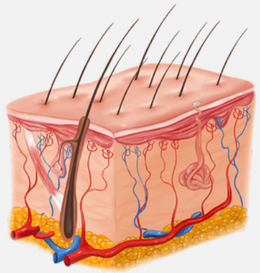
DIAGNOSTIC ALGORITHM

Exclusion of other causes: TSH, Prolactin, 17-OHP, FSH; Cushing’s, adrenal tumors., etc.



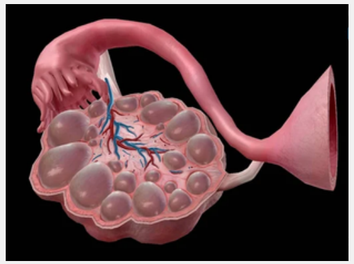
STEP 1

Irregular cycles + Clinical hyperandrogenism (exclude other causes) = **DIAGNOSIS**



STEP 2

If no clinical hyperandrogenism, **Test for biochemical = DIAGNOSIS**



STEP 3

If ONLY irregular cycles OR hyperandrogenism, **Ultrasound VS AMH in adults**

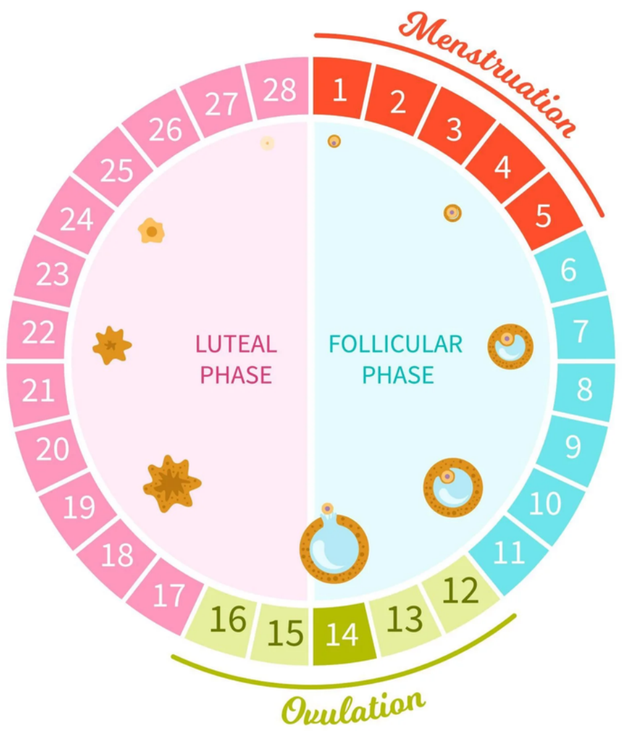
Adolescents: not indicated

IRREGULAR CYCLES

If present, consider PCOS

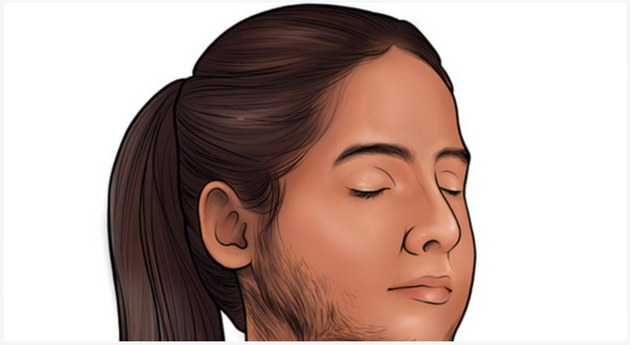
- Menarche and shortly after
  - First year post-menarche: NORMAL
  - 1 to <3 years post-menarche: <21 or >45 days

- Adolescence to Adulthood
  - 3 years post-menarche to perimenopause: <21 or >35 days or <8 cycles per year
  - 1 year post menarche > 90 days for ANY ONE CYCLE
  - Primary amenorrhea by age 15 or > 3 years post thelarche



HYPERANDROGENISM

Clinical



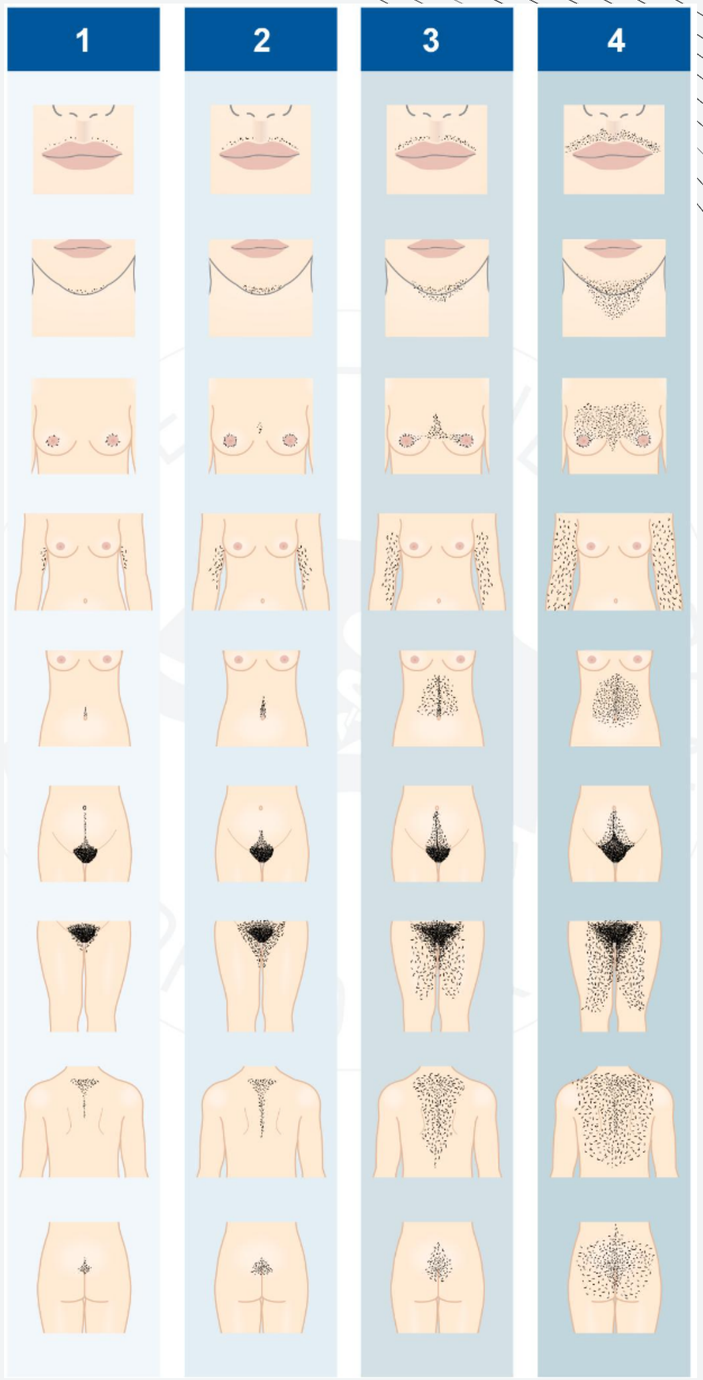
- The presence of hirsutism alone should be considered predictive of biochemical hyperandrogenism in adults
- Hirsutism affects 65-75% of patients
- Acne and female pattern hair loss are poor predictors, although acne affects >50%

- Biochemical assessment is of greatest value in patients with minimal or no clinical signs of hyperandrogenism
- Laboratories should use LC-MS/MS assays over direct immunoassays for assessing testosterone due to limited accuracy

Biochemical

HIRSUTISM

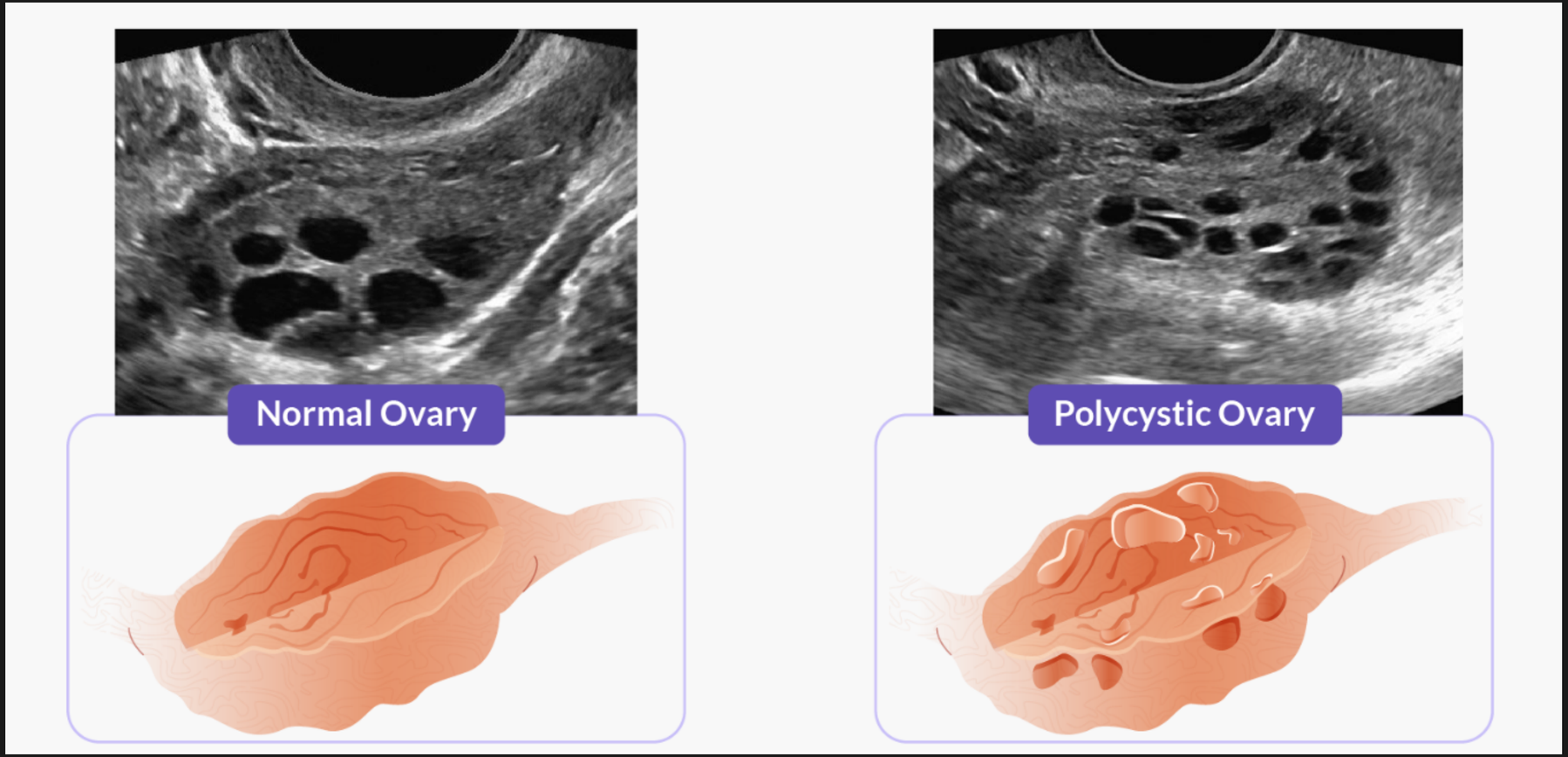
- **Modified Ferriman Gallwey**
  - 9 body areas
  - **Score of 4-6** = hirsutism per 2023 guidelines
  - Only account for terminal hairs
- Self-treatment can limit clinical assessment
- New-onset severe or worsening hirsutism warrants evaluation for other pathology
- Terminal hair growth is permanent

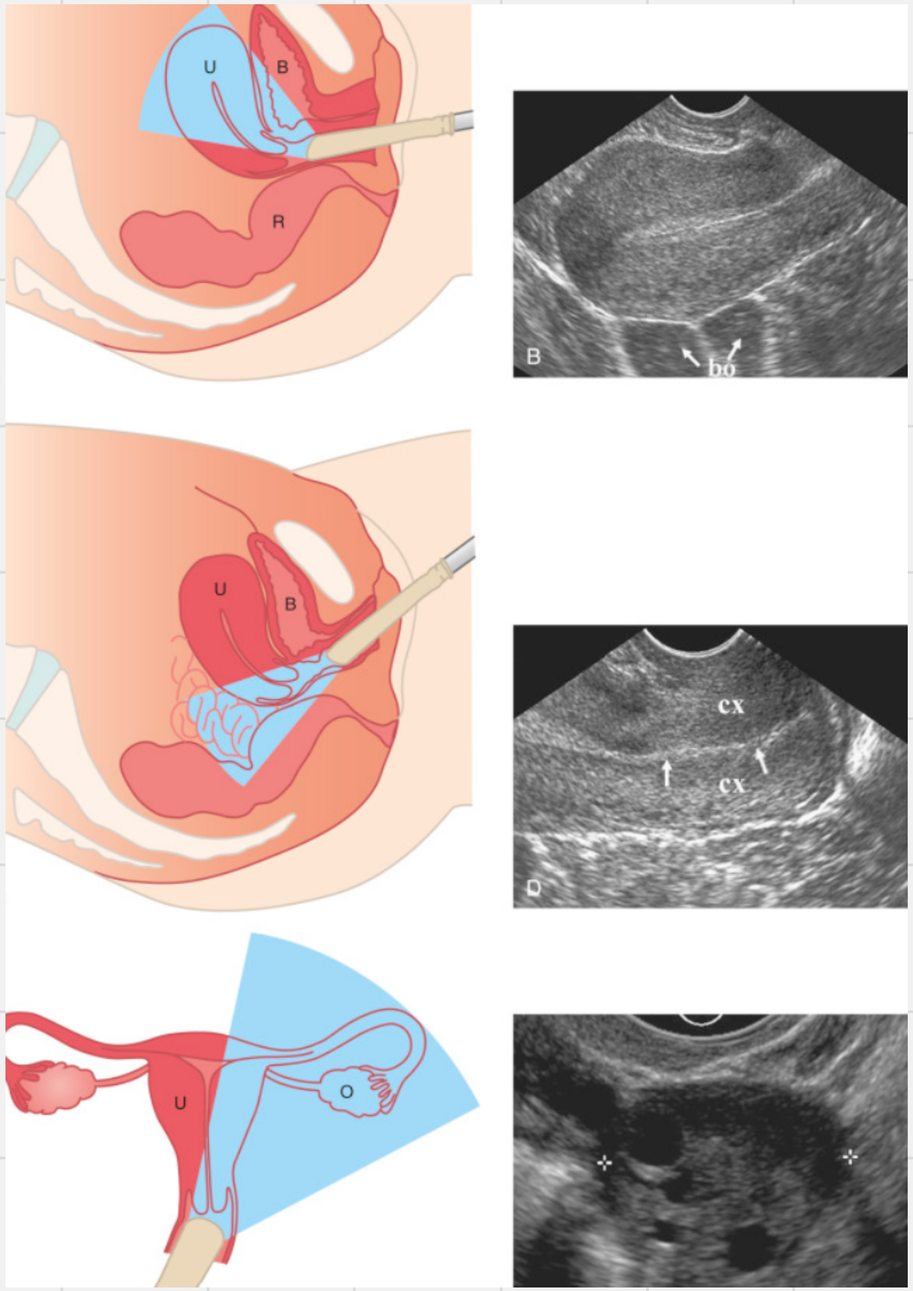


ULTRASOUND

FNPO ≥ 20 in at least one ovary

Ovarian volume ≥ 10 mL or FN per section ≥ 10

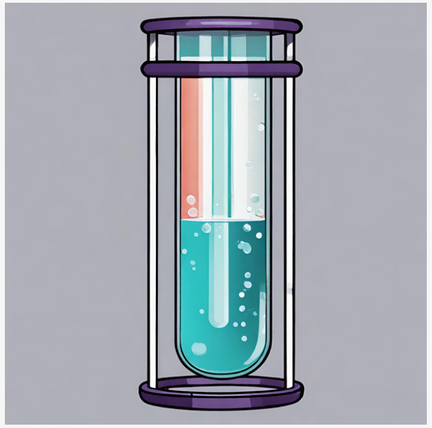




COMPONENTS

- Last menstrual period (or stage of cycle).
- Measurements in 3 dimensions (in cm) or volume of each ovary.
- Corpus lutea, dominant follicles (>10 mm) should not be included in ovarian volume calculations
- Reliance on the contralateral ovary FNPO for diagnosis of PCOM, where a dominant follicle is noted
- Uterine features and/or pathology including endometrial thickness and pattern

Transabdominal ultrasound should primarily report ovarian volume (OV) with a threshold of ≥ 10 ml or follicle number per section (FNPS) ≥ 10 in either ovary due to difficulty of assessing follicle counts throughout the entire ovary with this approach



Anti-Mullerian Hormone

01

Mechanism

Expressed in preantral and small antral follicles
Inhibits recruitment of primordial follicles
Suppresses FSH signaling

02

Expression

Peaks at 20-25 years of age
Lower in those with higher BMI
Suppressed by recent/current OCP use

03

Diagnostic Value

Should not be used as a single test for PCOS diagnosis
Poor specificity, particularly in adolescents

CLINICAL SUBGROUPS “Phenotypes”

44.8%

- Hyperandrogenism
- Oligo/Anovulation
- Polycystic ovaries

15-20%

- Hyperandrogenism
- Oligo/Anovulation

15-20%

- Hyperandrogenism
- Polycystic ovaries

15-20%

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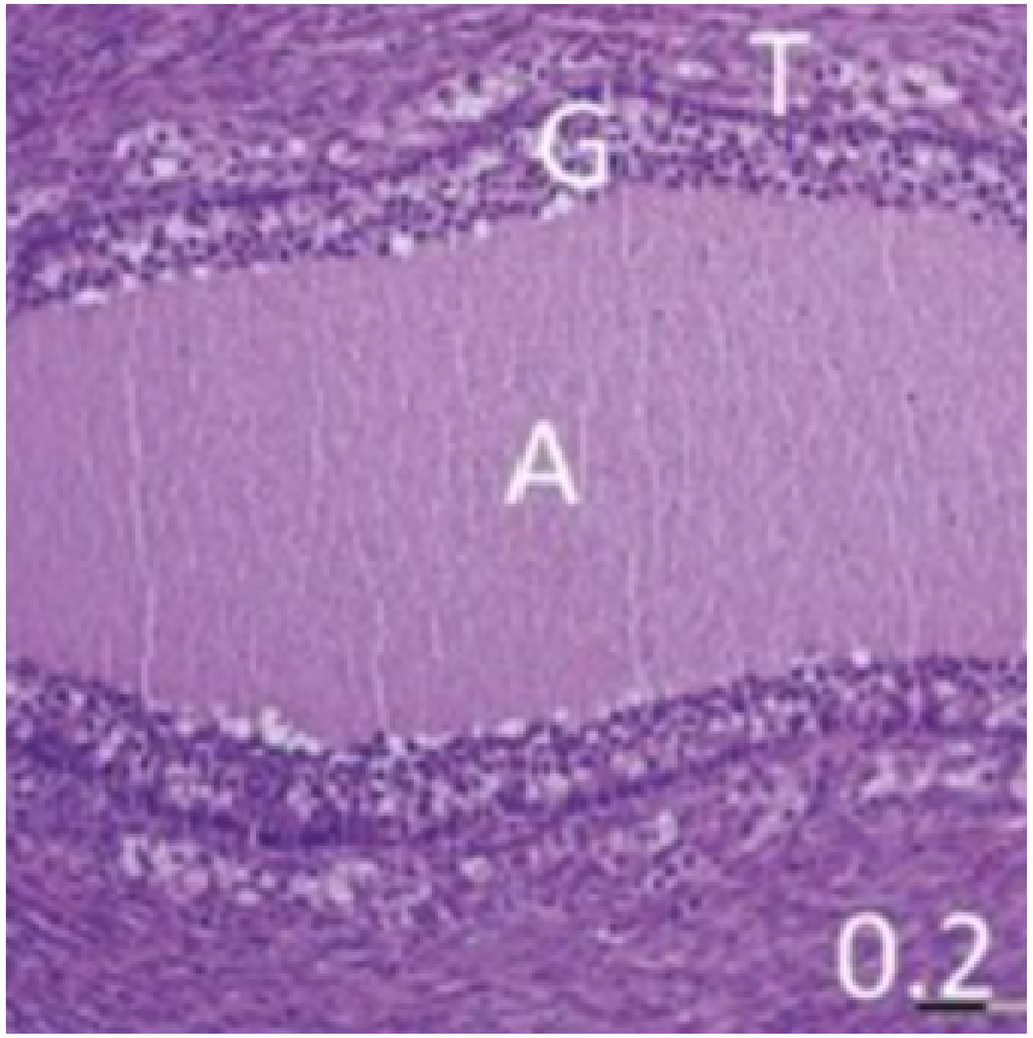
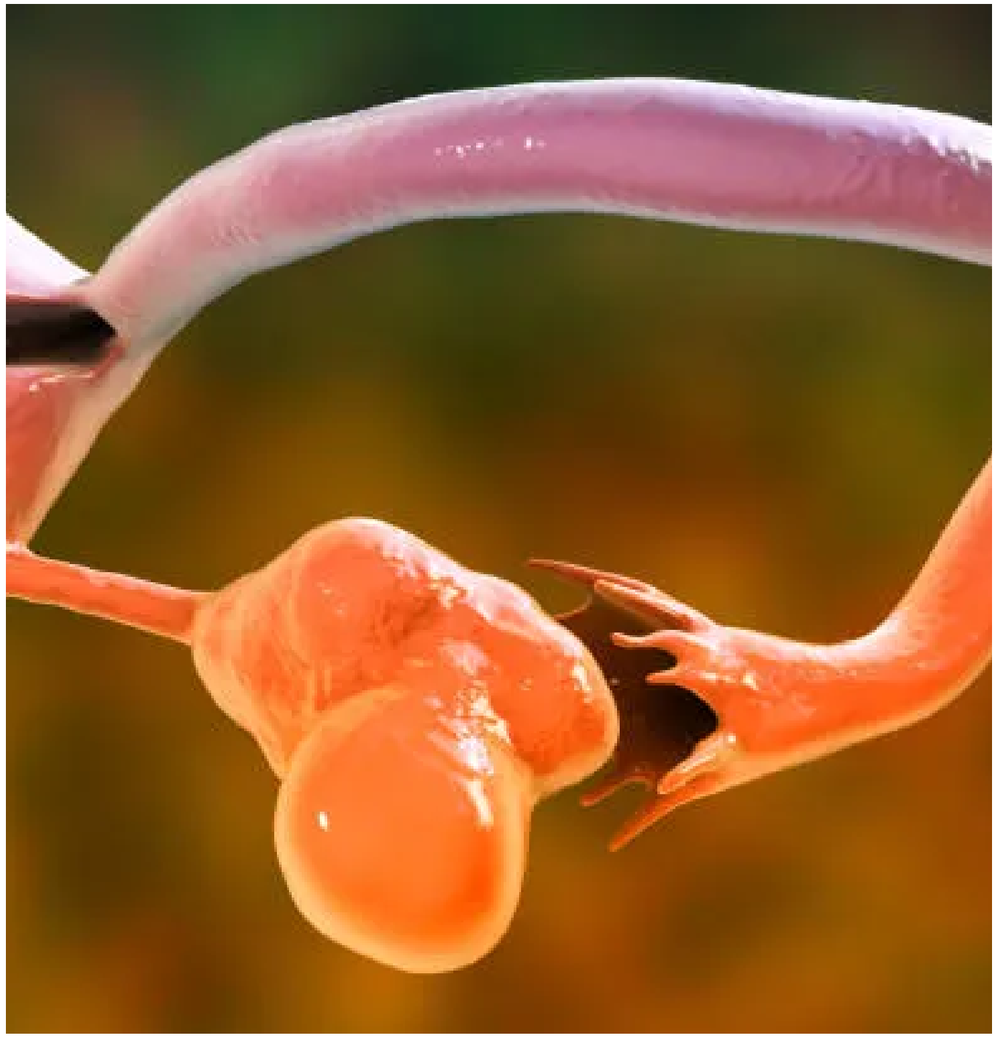


LH

LUTEINIZING HORMONE

- Increased LH:FSH in some but not all cases
- Receptors found in theca cells and mature granulosa cells
- Androstenedione and testosterone converted to estrogens
- Impaired follicular development
- Reduced inhibition of GnRH pulse frequency by progesterone



SUBTYPE D

GYNECOLOGIC ONLY

- IGF-1 is thought to arrest follicle growth leading to formation of follicular ovarian cysts
- Lean PCOS women are more commonly characterized by an increase in LH pulse amplitude

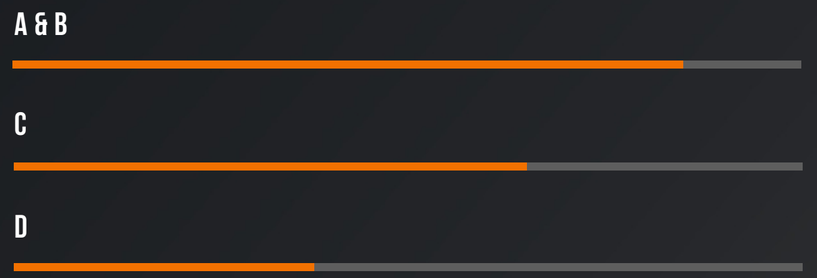
METABOLIC GROUPS

A, B, C

Insulin

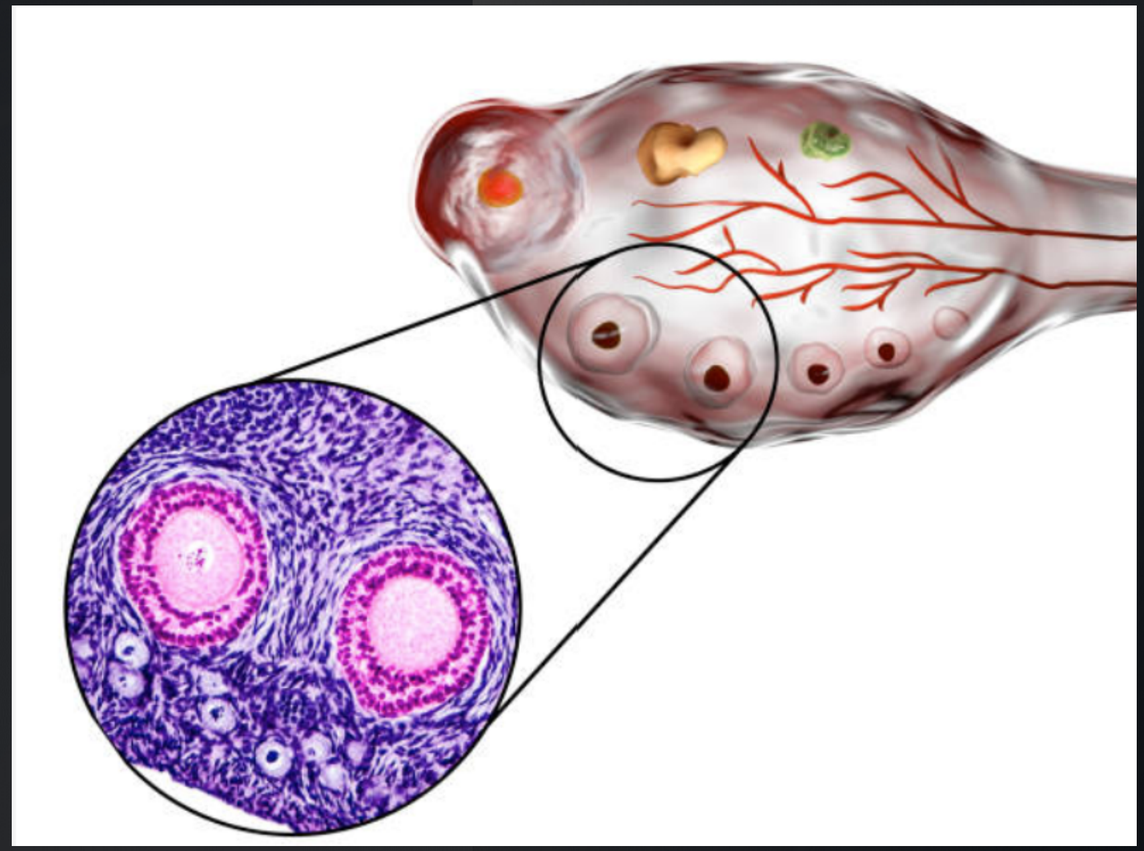
- Co-gonadotropin effects on ovary
- Facilitates androgen secretion from adrenal gland
- Modulates release of LH

Insulin resistance is present in 80.4% of classic phenotype (A & B), 65% of ovulatory phenotype (C), and 38.1% of normoandrogenic phenotype (D).



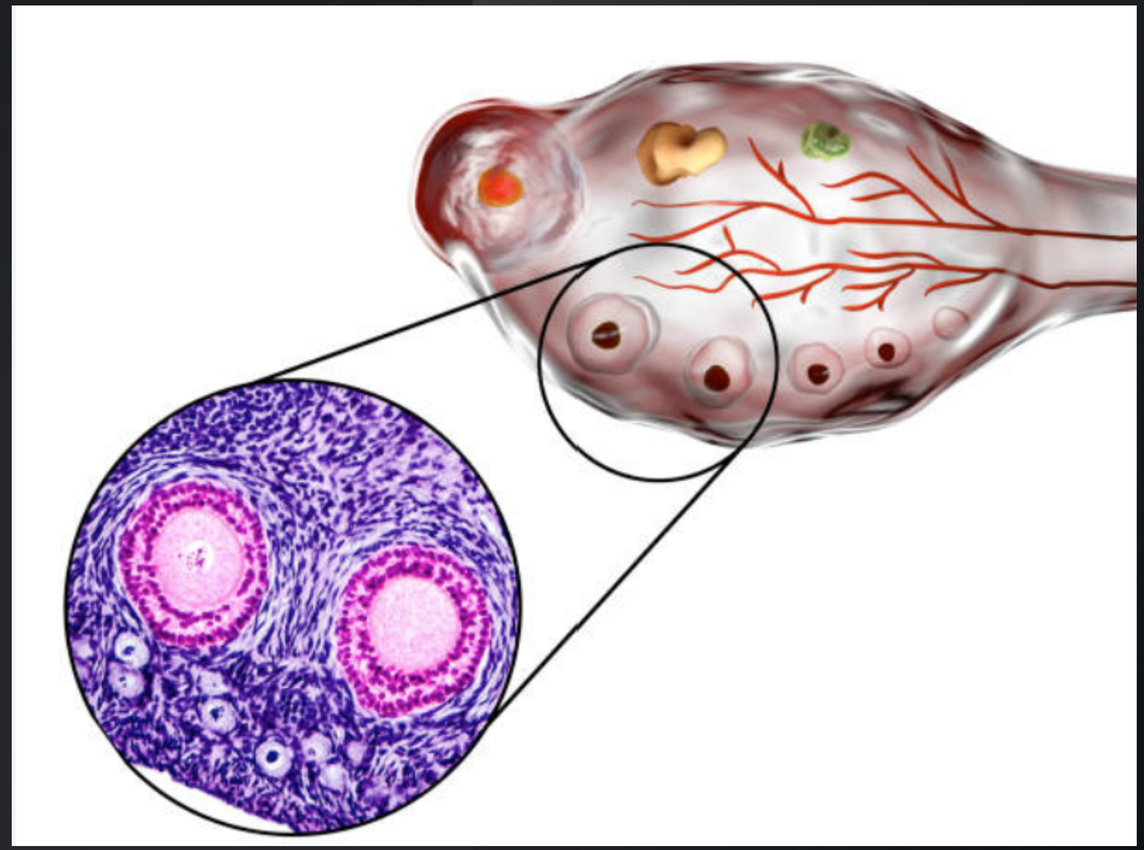
HYPERINSULINEMIA

- Ovarian Paradox: despite systemic resistance, ovaries remain sensitive to insulin signaling
- Insulin receptors on theca cell membranes
- Direct stimulatory effect on steroidogenesis
- Intracellular signaling stimulates 17-OH activity
- Ovarian testosterone synthesis activated

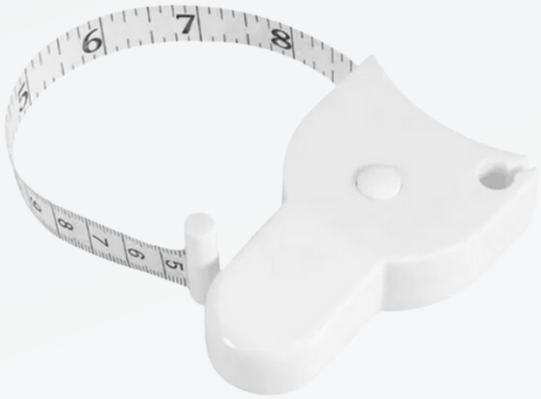


HYPERINSULINEMIA

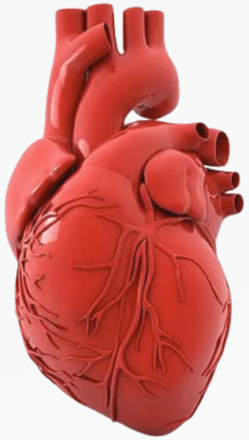
- Stimulates epimerase activity
- Converts myo-inositol to D-chir-inositol
- Downregulates aromatase-mediated androgens to estrogen: Increased androgen levels
- Stimulates LH Rc expression
- Stimulates SHBG: impaired synthesis in IR
- Oocyte maturation failure, anovulation, decreased oocyte quality



CO-MORBIDITIES



- Cardiovascular disease/Coronary heart disease
- Diabetes
- Sleep disorders



- Metabolic syndrome
- Endometrial cancer
- Psychological disorders

RISK ASSESSMENT

·A lifelong health plan is recommended including a focus on healthy lifestyle, prevention of excess weight gain, optimization of fertility and preconception risk factors, and prevention of metabolic risk factors/diabetes/CV disease/sleep disorders

- Lipid profile
- BP annually
- Frequency thereafter on global risk factors

CARDIOVASCULAR

- Assess glycemic status at diagnosis
- Reassess every 1-3 yr

ENDOCRINE

- Screen for anxiety and depression in all patients with PCOS
- Higher risk of eating disorders

PSYCHOSOCIAL

MENSTRUAL CYCLE

Individualize treatment based upon symptoms

METFORMIN

Alone or in Combination

- Option in adolescents for cycle regulation
- Metformin + COCP most beneficial in high metabolic risk group

HORMONAL

Alone or in Combination

- Ideal for irregularity
- COCP first-line therapy
- Patch, vaginal ring, progestin-only, IUD alternatives

LIFESTYLE

Primary

- 5 to 10 percent reduction in body weight
- Not all individuals have restoration of ovulation or menses despite similar weight reduction

COCP

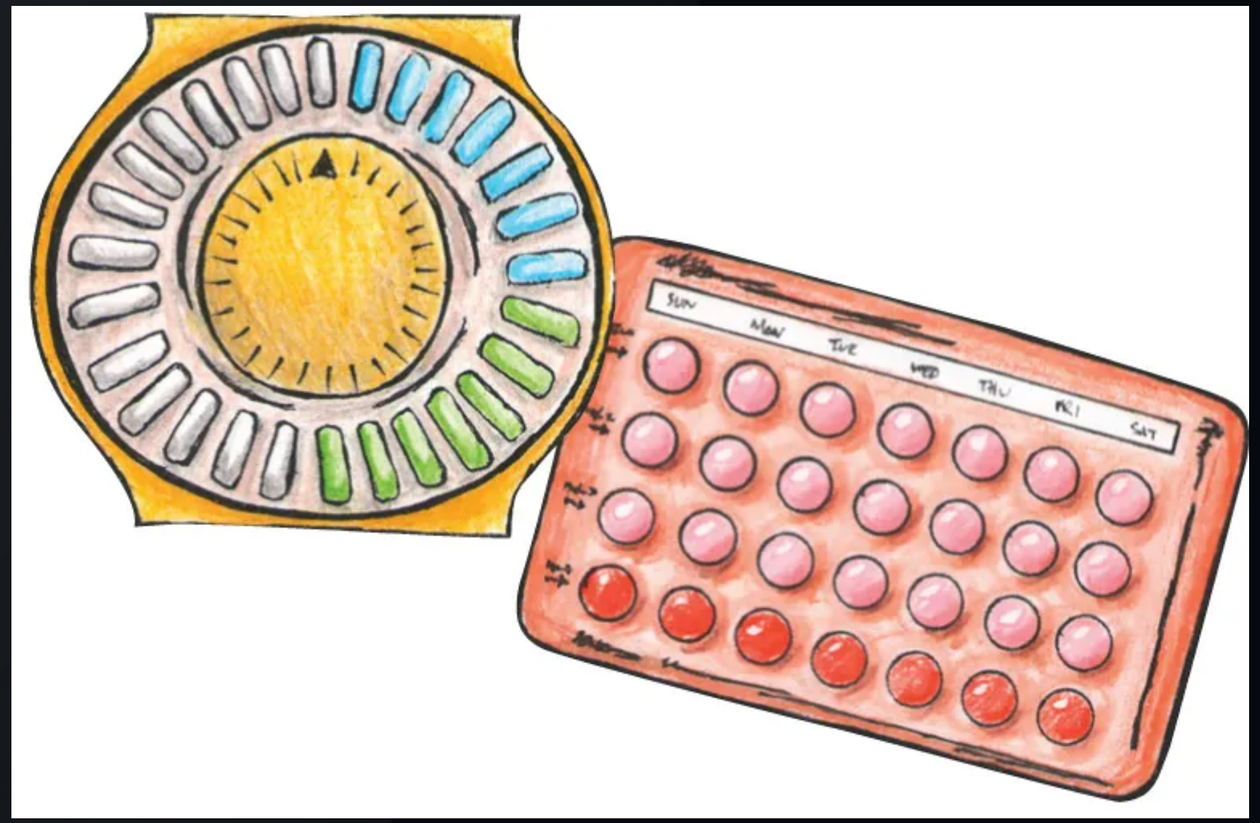
- Endometrial protection
- Contraceptive effect
- Cutaneous benefits

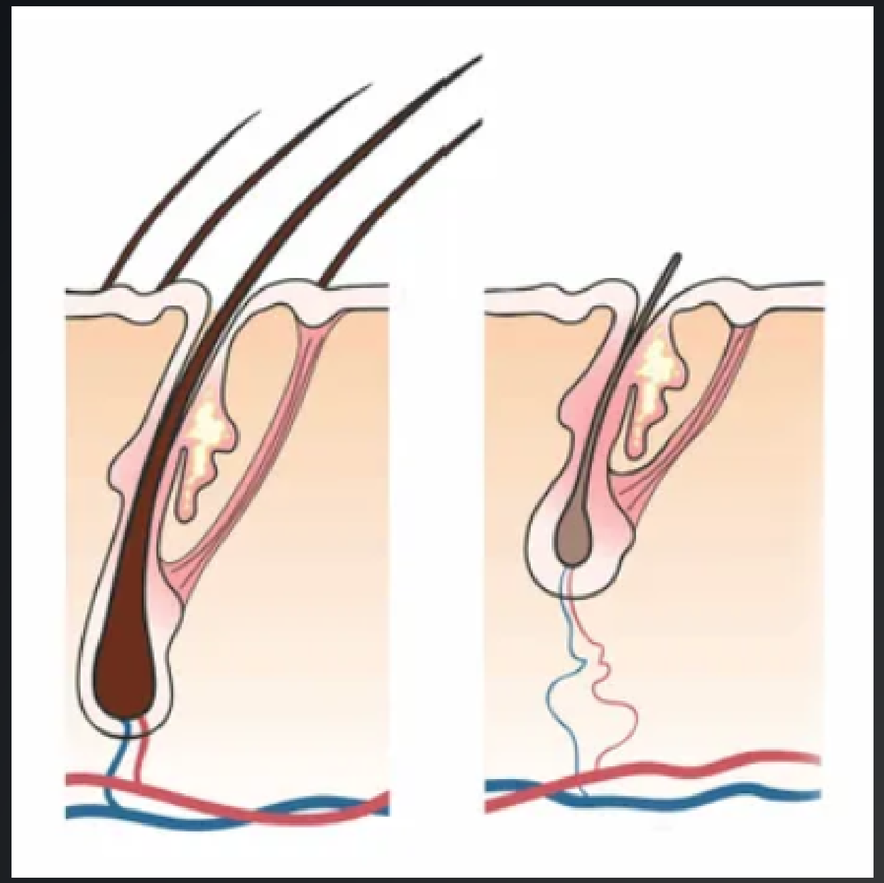
Progestin-Only

- Intermittent progestin therapy
- Continuous (mini-pill)
- Endometrial protection
- Mini-pill has contraceptive effect

IUD

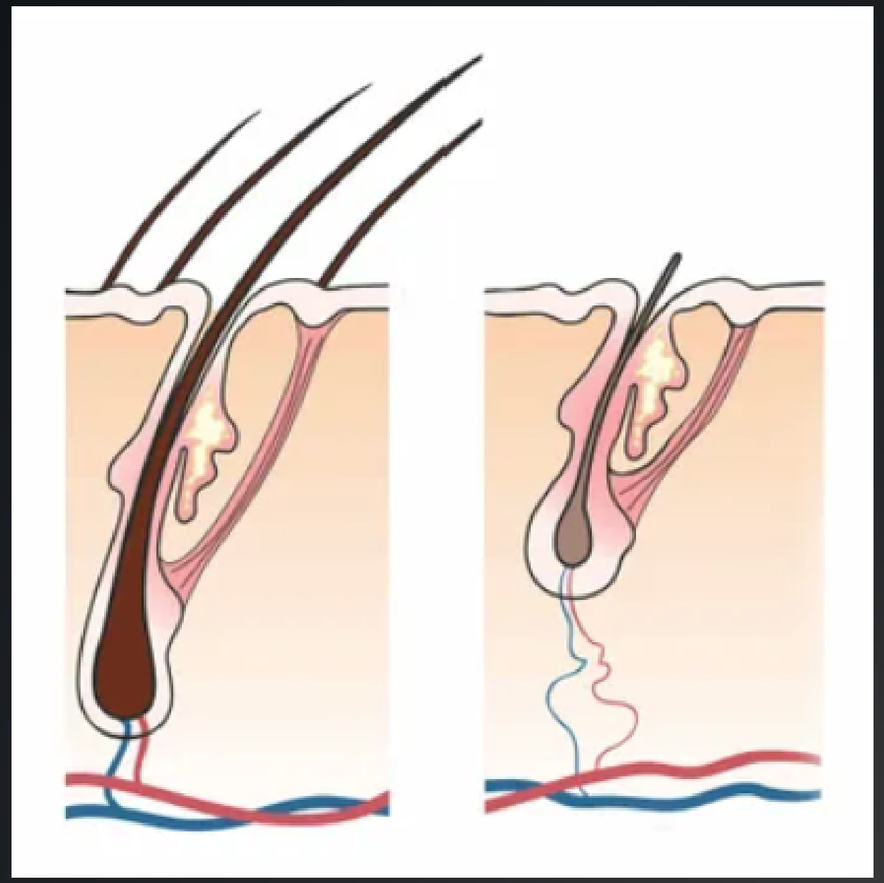
- Progesterone-containing IUD
- Endometrial protection
- Contraceptive effect
- Less regularity





HYPERANDROGENISM

- Peripheral 5α-reductase catalyzes the conversion of testosterone to dihydrotestosterone (DHT). In body hair DHT stimulates
  - Increased sebum production
  - Vellus to terminal hair transformation
  - Prolongation of the anagen phase resulting in longer thicker hairs
- Terminal hairs are “medullated.” Lanugo and vellus hairs are non-medullated.



HYPERANDROGENISM

HIRSUTISM AND ACNE

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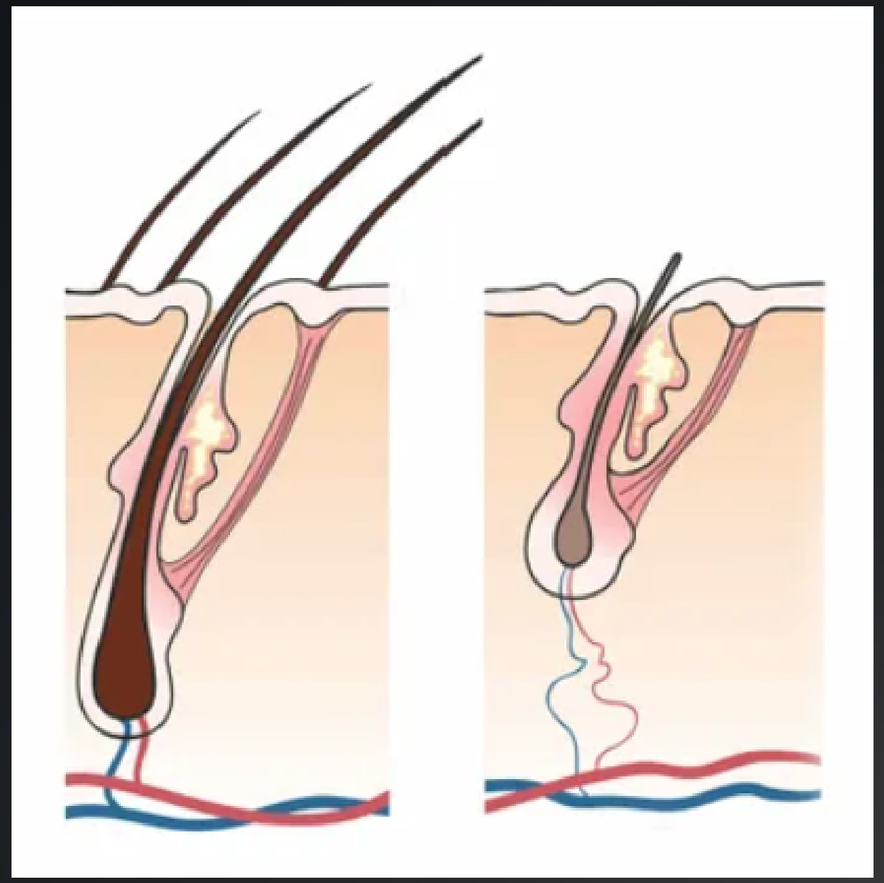
- COCP first-line therapy
- Anti-androgens: consider after 6 months OR not a candidate for COCP
- Transdermal and vaginal ring preparations have not been well studied



HYPERANDROGENISM

HIRSUTISM AND ACNE

.....

- Spironolactone: competes at androgen receptor and SHBG, suppressive effect on androgen synthesis
- Finasteride: inhibits 5-alpha-reductase type 2 and thus DHT to testosterone conversion
- Flutamide: inhibits androgen binding and uptake in target tissue
- Counsel regarding risks of incomplete development in male fetuses

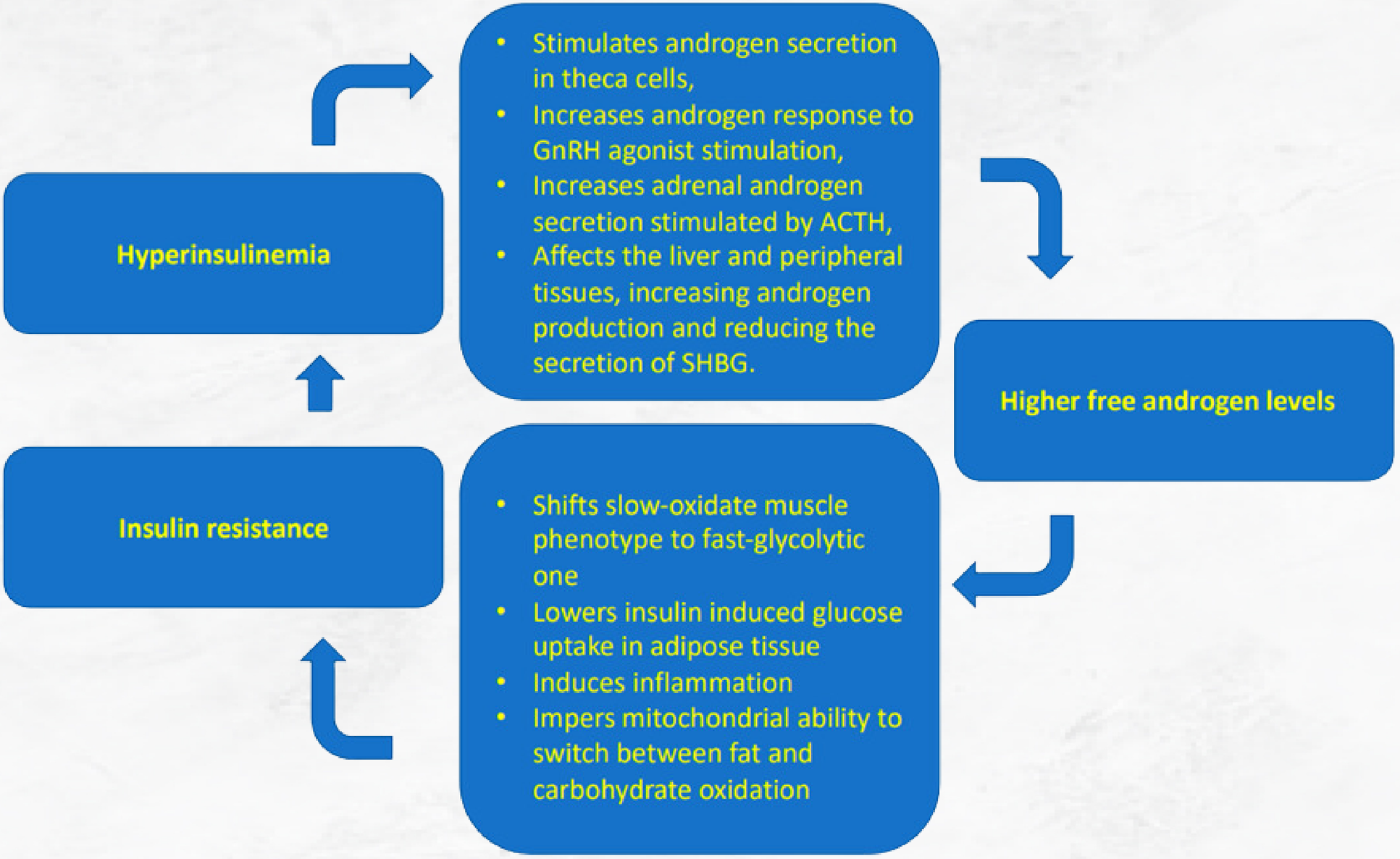
OBESITY

ADIPOSITY

- Visceral adipose tissue in women with PCOS is similar to male visceral adipose tissue
- Favors androgen excess in response to insulin and other triggers
- Hypertrophy/hyperplasia of adipocytes induces insulin resistance, hyperinsulinemia, lipogenesis, and increased fat storage in the liver, pancreas, and skeletal muscles

ADIPOSITY

- Adiponectin promotes storage of TG in adipose tissue, increases muscle fat oxidation and glucose uptake, and increases insulin signaling
- Adiponectin is decreased in concentration as adipose tissue volume increases
- Increased adiposity without vascularization induces hypoxia and TNF-alpha
  - Decreased GLUT-4 expression
  - Decreased glucose transport intracellularly
- Impaired insulin sensitivity, reduced glycogen synthesis, increased hepatic gluconeogenesis, and pro-inflammation


Hyperinsulinemia
• Stimulates androgen secretion in theca cells,
• Increases androgen response to GnRH agonist stimulation,
• Increases adrenal androgen secretion stimulated by ACTH,
• Affects the liver and peripheral tissues, increasing androgen production and reducing the secretion of SHBG.
Higher free androgen levels
Insulin resistance
• Shifts slow-oxidate muscle phenotype to fast-glycolytic one
• Lowers insulin induced glucose uptake in adipose tissue
• Induces inflammation
• Impers mitochondrial ability to switch between fat and carbohydrate oxidation

2023 IEBG Guidelines

DIET
No evidence to support superiority of any one type for anthropometric, metabolic, hormonal, reproductive or psychological outcomes

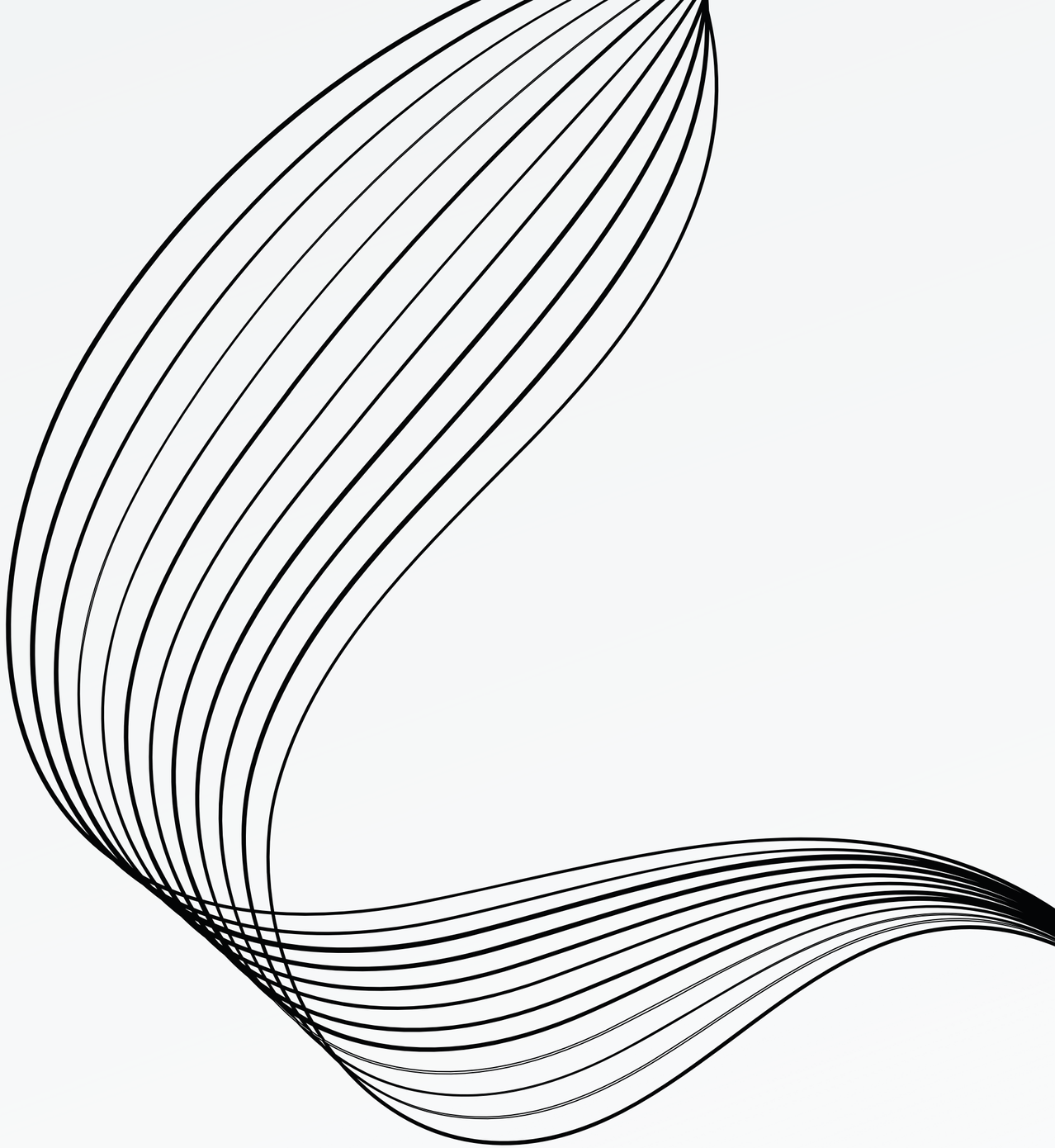
EXERCISE
Minimum of 250 min/week moderate intensity or 150 min/week vigorous and muscle-strengthening activities on 2 non-consecutive days/week

MEDICATIONS
Anti-obesity medications should be considered
- Pregnancy data lacking
- Inositol could be considered due to limited harm, potential improvement

SURGERY
Bariatric surgery could be considered for all side effects of PCOS including pregnancy rates
- Counsel on reliable contraception until advised safe to conceive

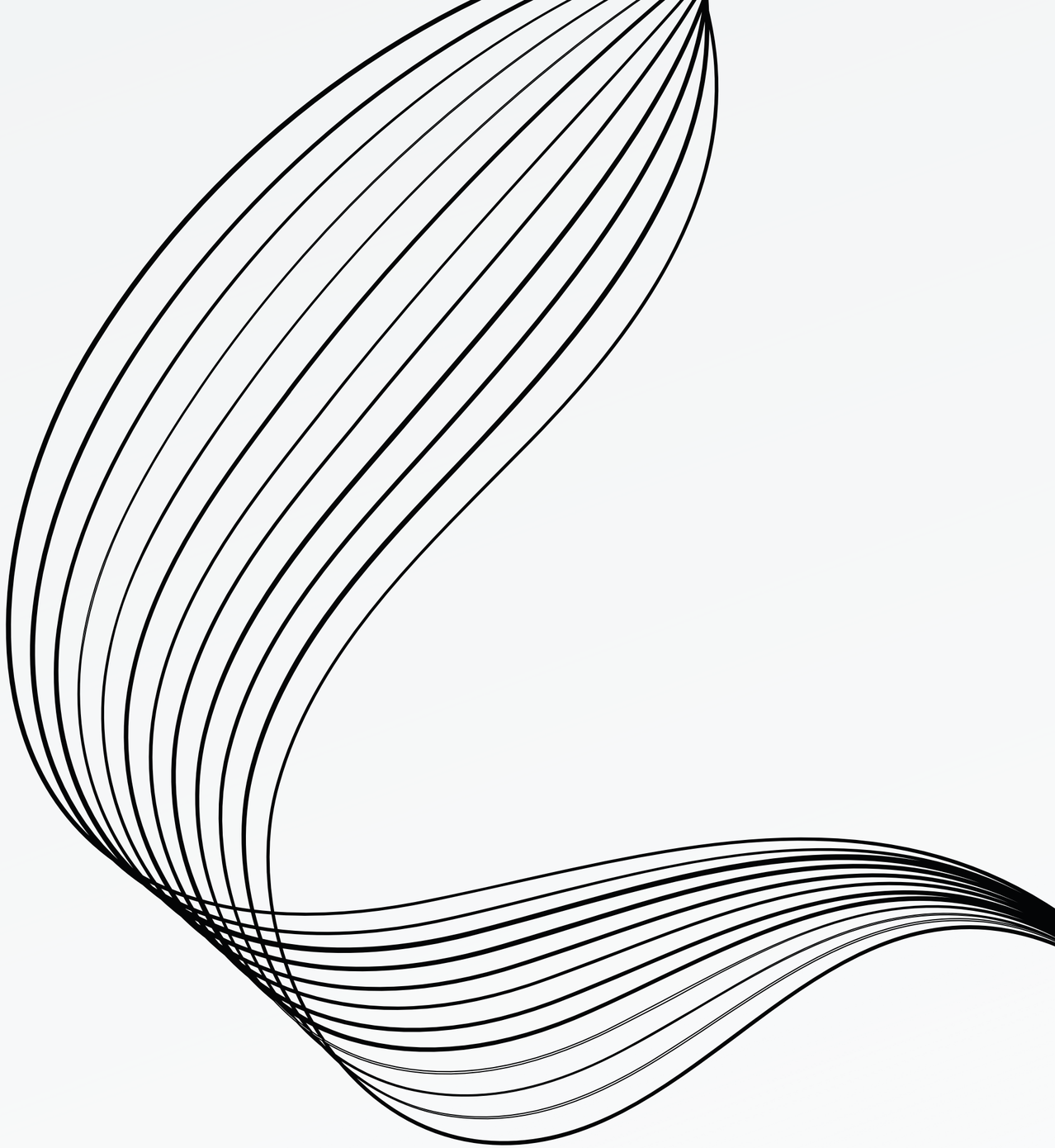
METFORMIN

- *Decreases gluconeogenesis*
- *Decreases lipogenesis*
- *Enhances uptake of glucose in skeletal muscle, liver, and adipose tissue*
- *Recommend in PCOS patients with BMI ≥ 25 kg/m2 in**



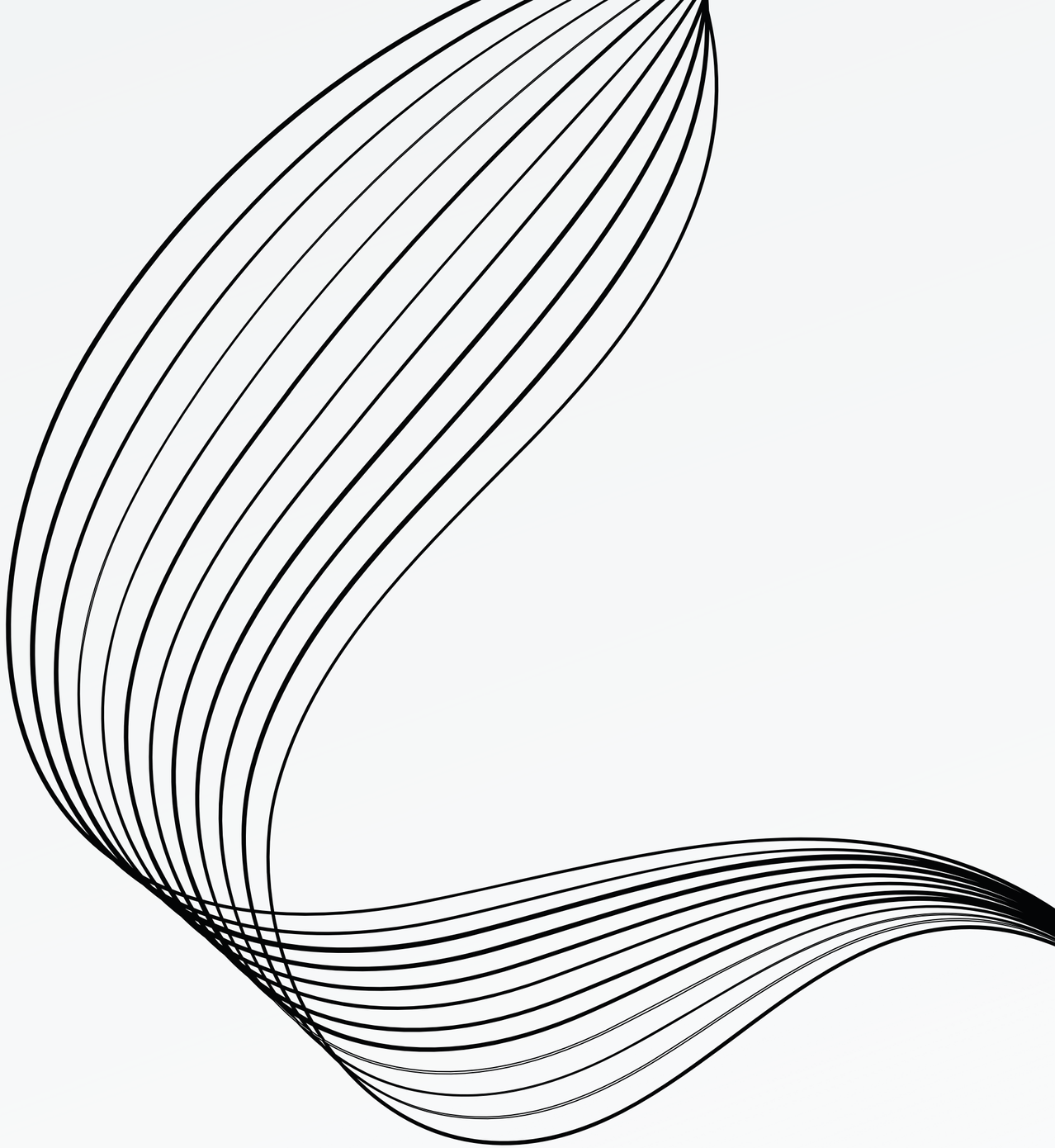
INOSITOL

- *Act as secondary messenger for insulin*
- *Myoinositol improves ovulatory function*
- *DCI reduces peripheral insulin resistance*
- *MI and DCI reduce LH, LH/FSH, and testosterone levels*
- *Proposed ratio of MI:DCI 40:1*



BERBERINE

- *Decreases insulin resistance*
- *Lowers lipid profile*
- *Improves ovulatory function**

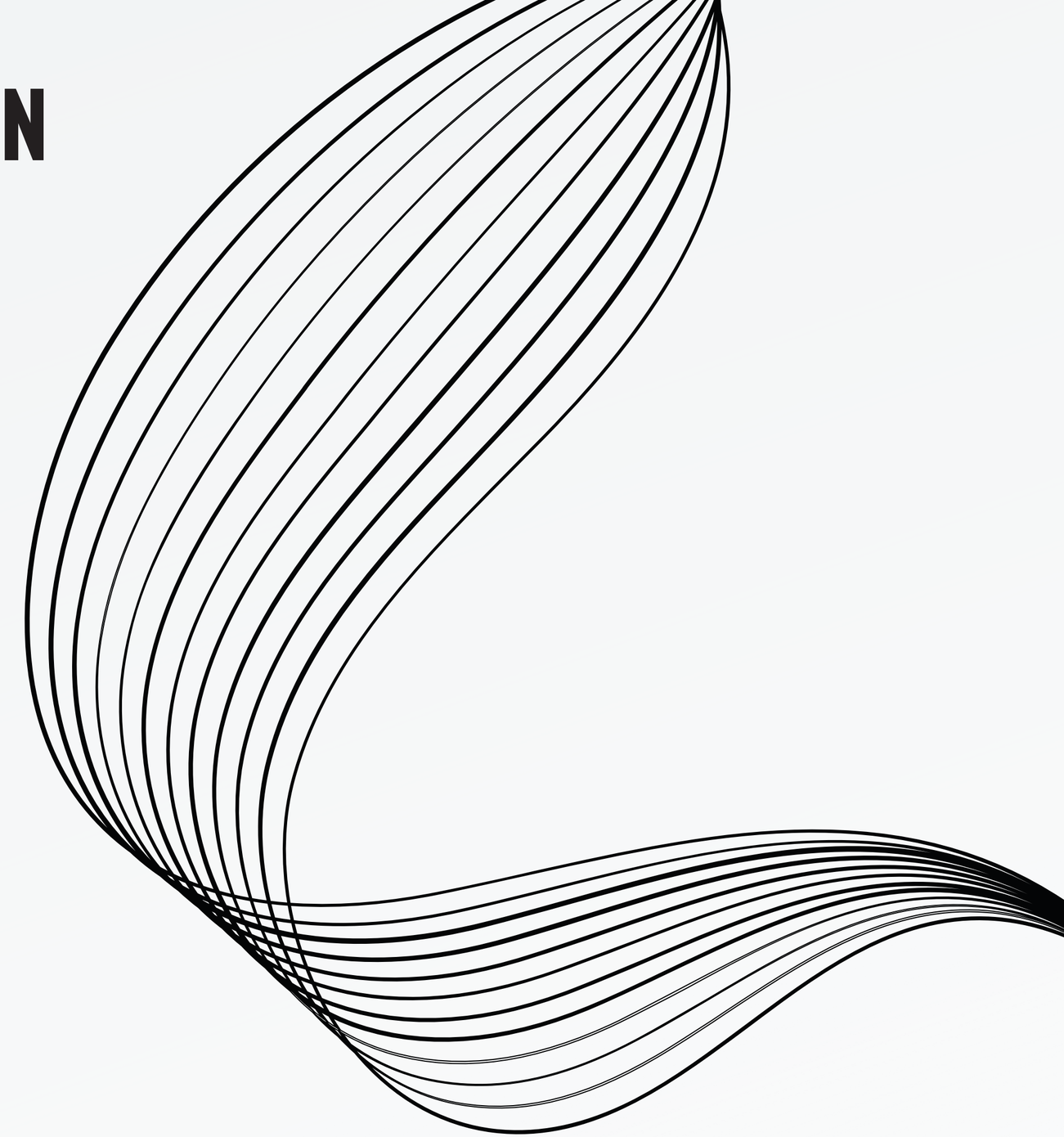


THIAZOLIDINEDIONES

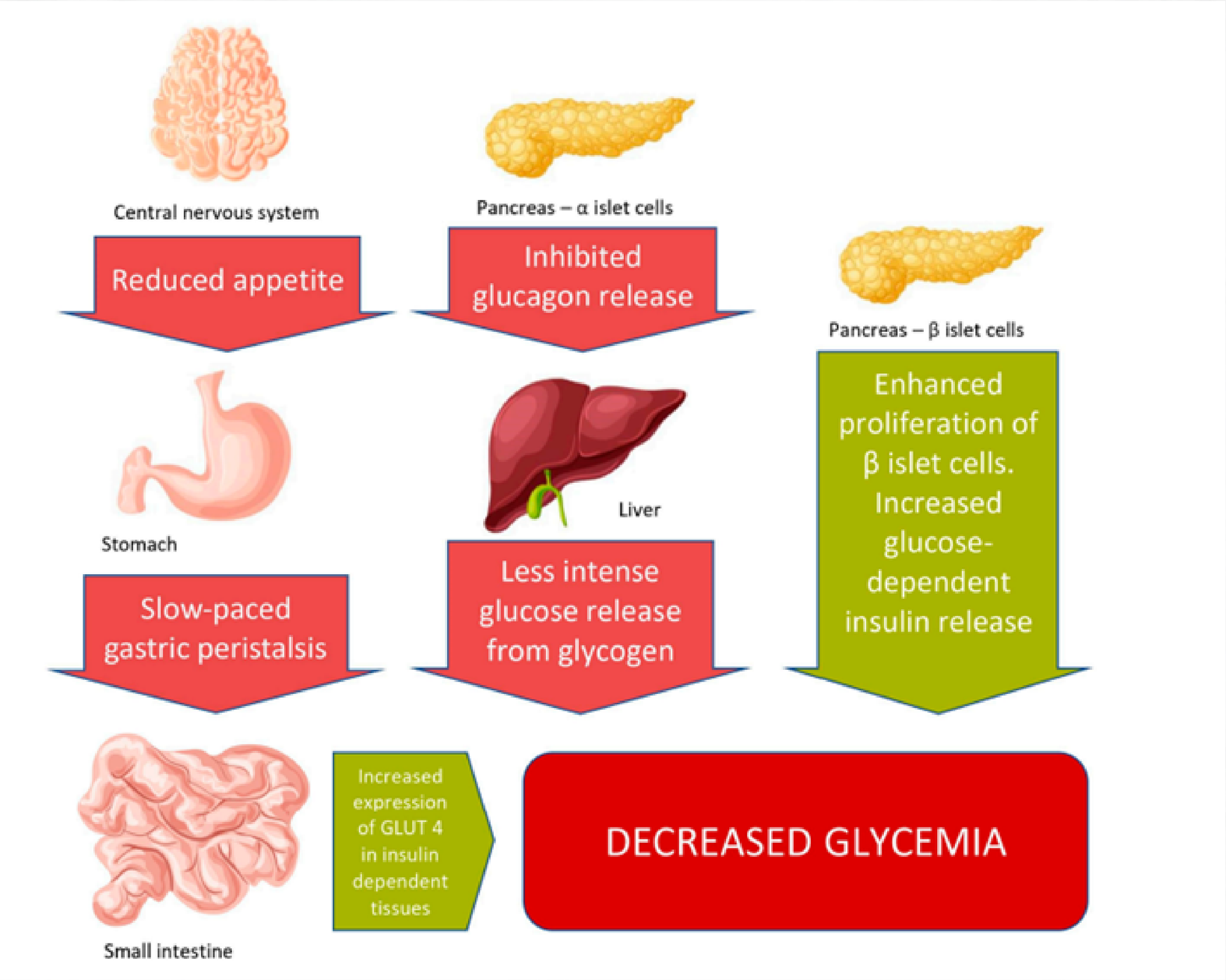
- *Decrease hepatic and peripheral insulin resistance*
- *Improve menstrual cycle and ovulation*
- *Reduce androgen levels in PCOS patients*
- *Side effects include weight gain, peripheral edema, heart failure, fractures*

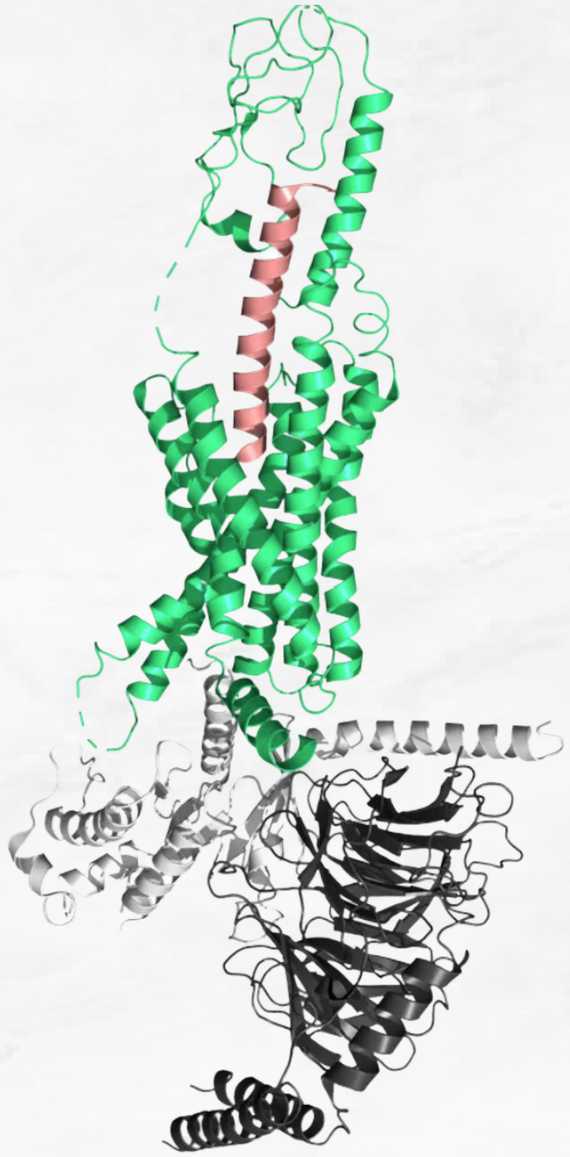
CLINICAL COMPARISON

- *Myoinositol + DCI, Metformin + TZDs, and Metformin + BBR superior to Metformin for total testosterone reduction*
- *Metformin + DCI, Metformin + TZDs, and TZDs lowered HOMA-IR significantly in comparison to Metformin alone*
- *TZDs superior to Metformin in decreasing FPG, TG, LDL levels and increasing HDL*
- *Metformin + TZDs associated with lower TG compared to Metformin and TZD monotherapy*
- *Metformin + BBR more effective in reduction of BMI than Metformin alone*



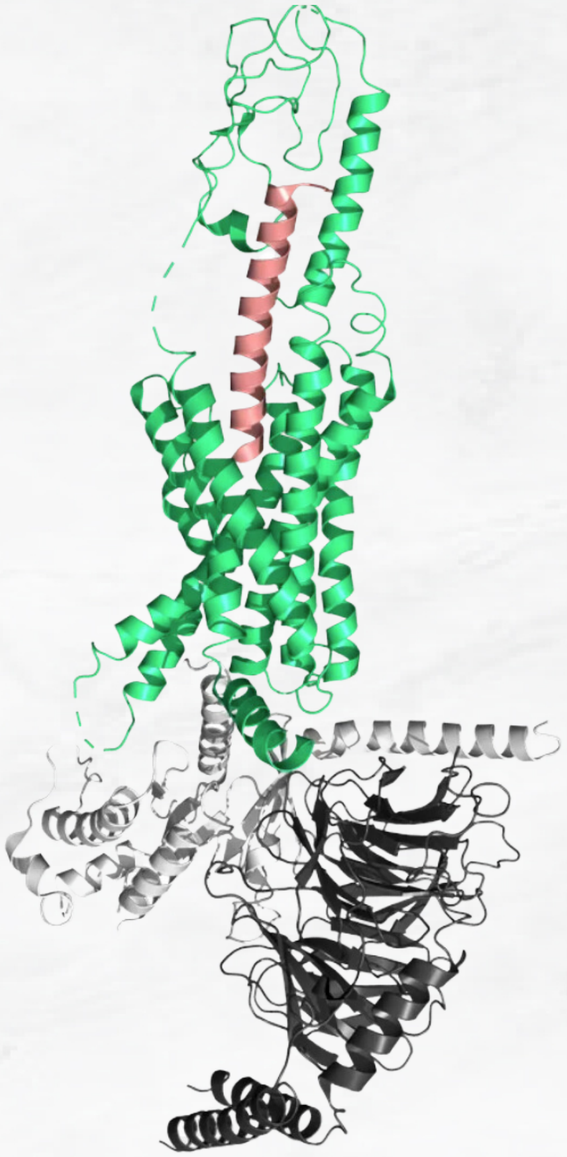
GLP-1


Central nervous system
Reduced appetite
Pancreas – α islet cells
Inhibited glucagon release
Pancreas – β islet cells
Enhanced proliferation of β islet cells. Increased glucose-dependent insulin release
Stomach
Slow-paced gastric peristalsis
Liver
Less intense glucose release from glycogen
Small intestine
Increased expression of GLUT 4 in insulin dependent tissues
DECREASED GLYCEMIA



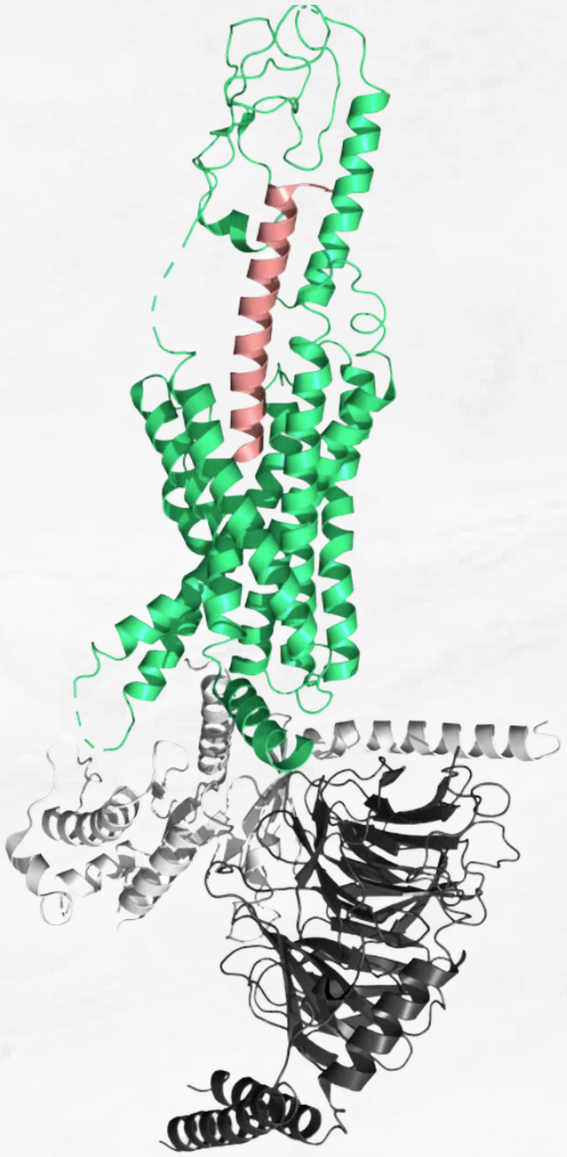
GLP-1 AND PCOS

- Improves insulin sensitivity which reduces LH
- Increase SHBG secretion which reduces bioavailability of androgens
- In animal models: increases mature Graafian follicle number (fertility) and endometrial function (reduce implantation failure, pregnancy loss, defective placentation)
- May be combined with metformin
  - Lower doses with combined therapy



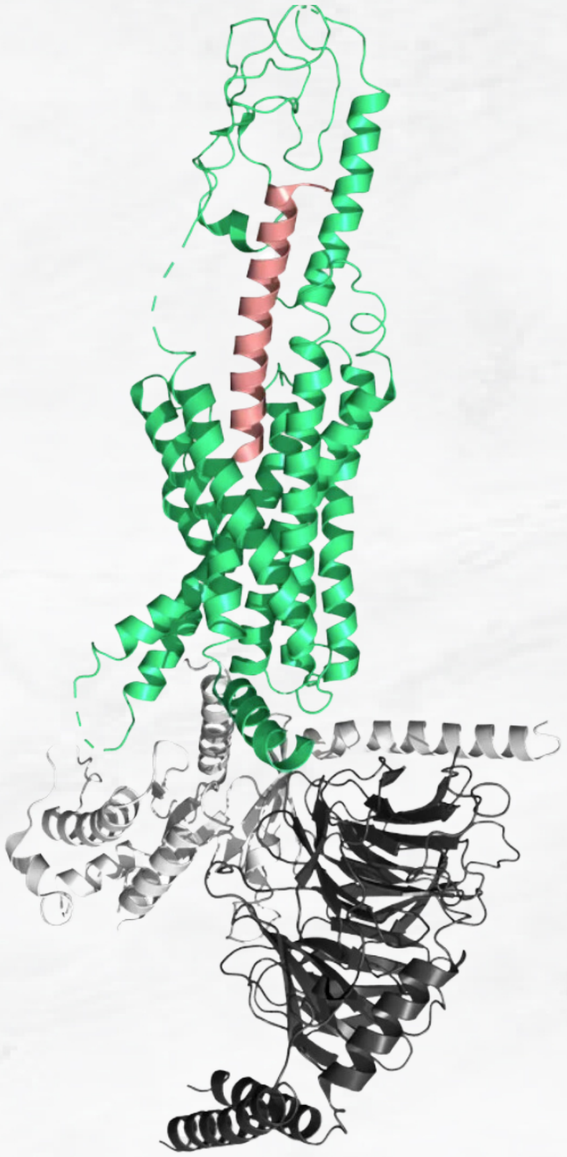
GLP-1 AND PCOS

Study of 72 PCOS patients with BMI > 25 and/or IR showed 5 kg avg reduction in body weight, reduced liver fat content, visceral adipose tissue and prevalence of NAFLD; SHBG increased by 19%, free testosterone decreased by 19%, and A1c, fasting glucose, and leptin decreased. Ovarian volume reduced by 1.6 mL. Menses incidence improved with bleeding ratio 0.28 vs 0.14.



GLP-1 AND FERTILITY

- Preconception liraglutide + metformin superior to metformin alone in IVF pregnancy rates
- Increased number of spontaneous pregnancies with exenatide in comparison to metformin
- Exenatide alone or in combo with metformin improves menstrual irregularity and ovulation rate in overweight/obese PCOS women
- No conclusive safety data for pregnancy



GLP-1 COUNSELING

- Screen PCOS patients for metabolic syndrome
- Screen for contraindications: h/o pancreatitis, diabetic retinopathy, medullary thyroid cancer
- Caution when in use with renin-angiotensin inhibitors due to susceptibility to AKI from dehydration and volume contractions

PATIENT CASE

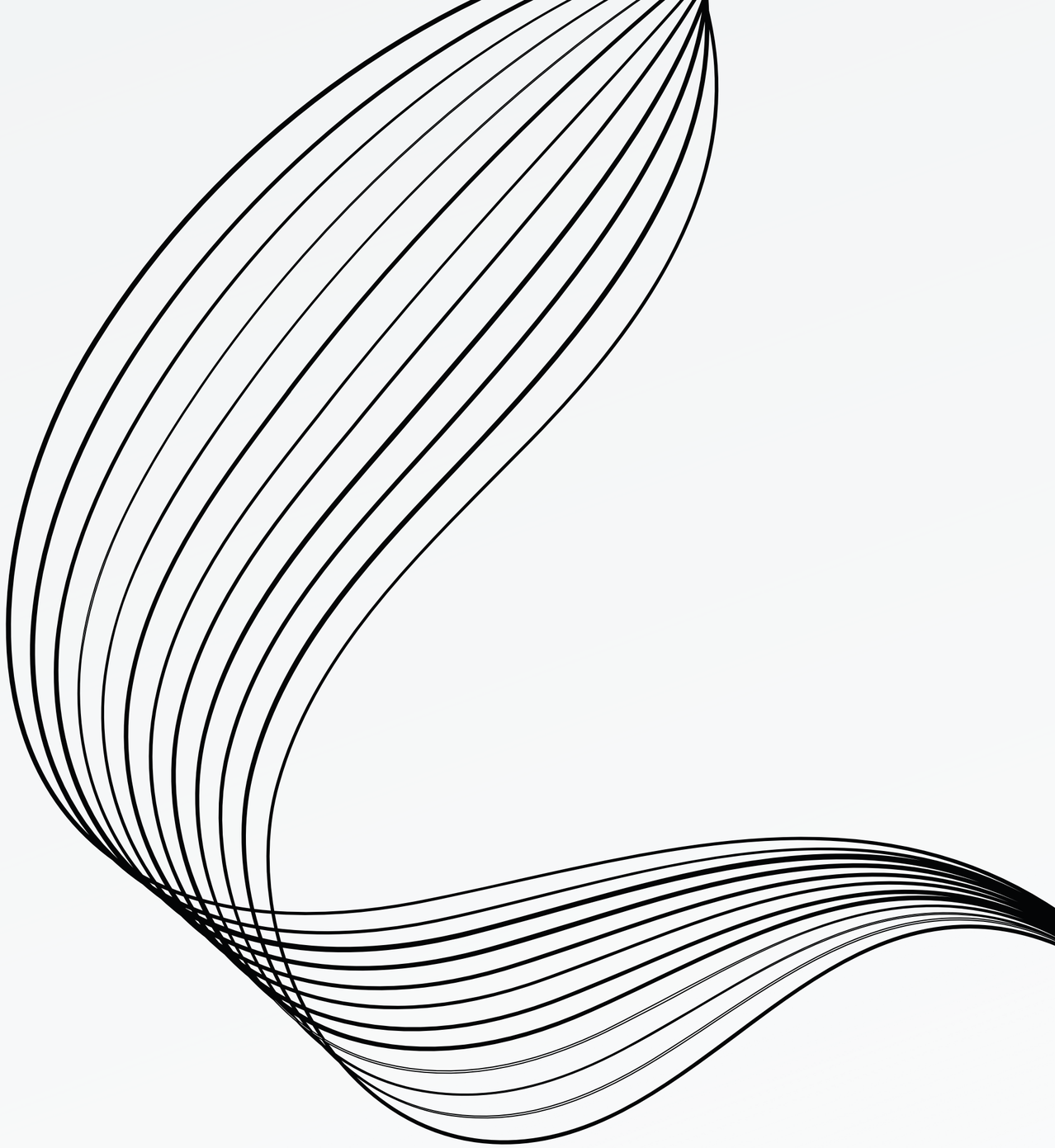
A 15 y.o. patient presents with irregular menses (every 22-35 days) and mild acne but no hirsutism. Her mother has a history of PCOS and is concerned her daughter has inherited this. She underwent menarche at age 12.

A) Diagnose with PCOS
B) Assess serum testosterone levels
C) Perform ultrasound to assess ovaries
D) B + C

PATIENT CASE

You ordered total and free testosterone, which both returned within normal parameters. What is the next best step?

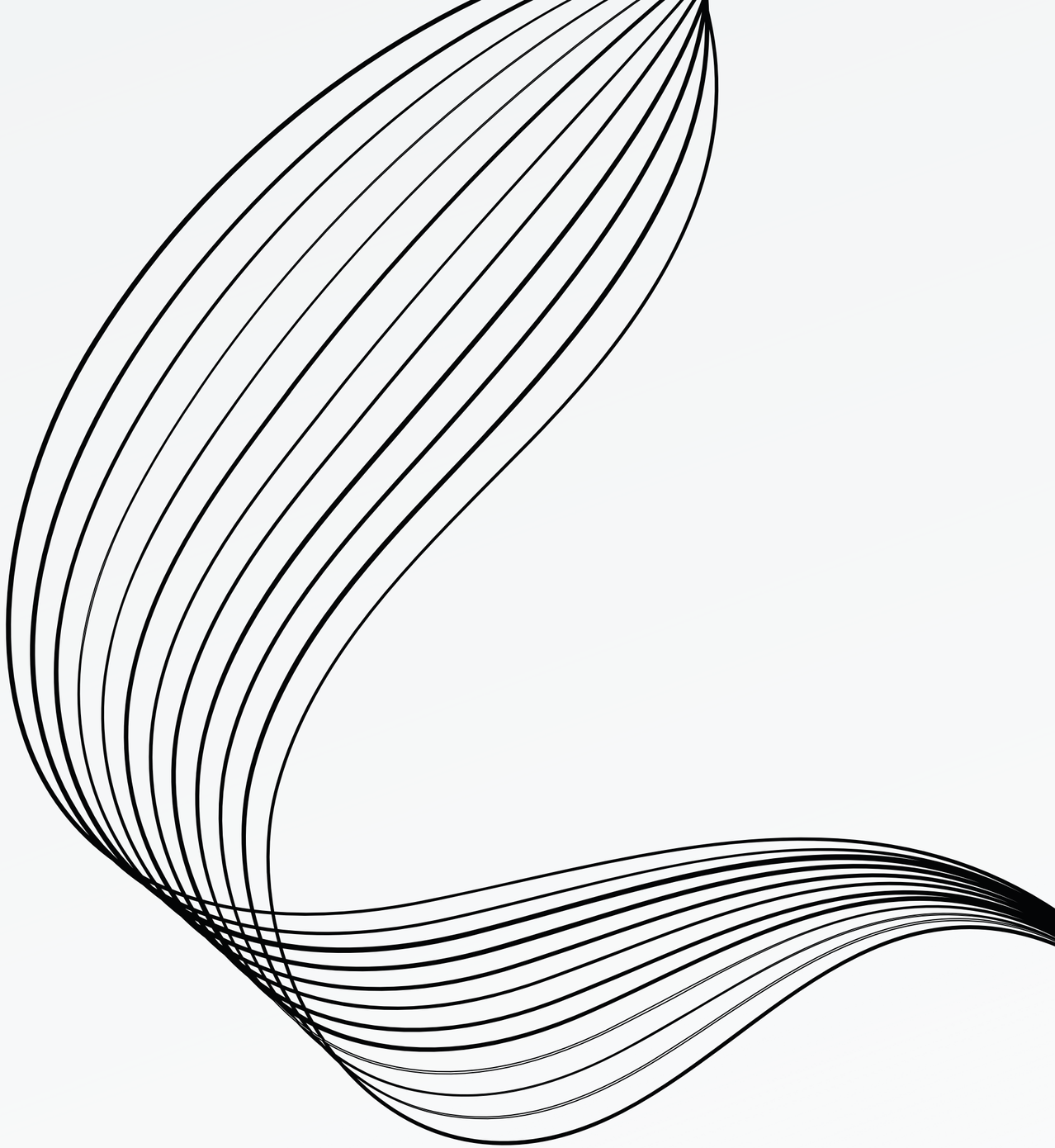
A) Diagnose with PCOS
B) Perform ultrasound to assess ovaries
C) Counsel regarding treatment options and reassess for PCOS at a later stage



PATIENT CASE

Which of the following is the first-line therapeutic agent for hirsutism in PCOS patients?

A) Spironolactone
B) Finasteride
C) Combined oral contraceptive pills



PATIENT CASE

PCOS patients should be screened for which of the following?

A) Glycemic abnormalities
B) Dyslipidemia
C) Depression and anxiety
D) All of the above

QUESTIONS?

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