Polycystic Ovary Syndrome

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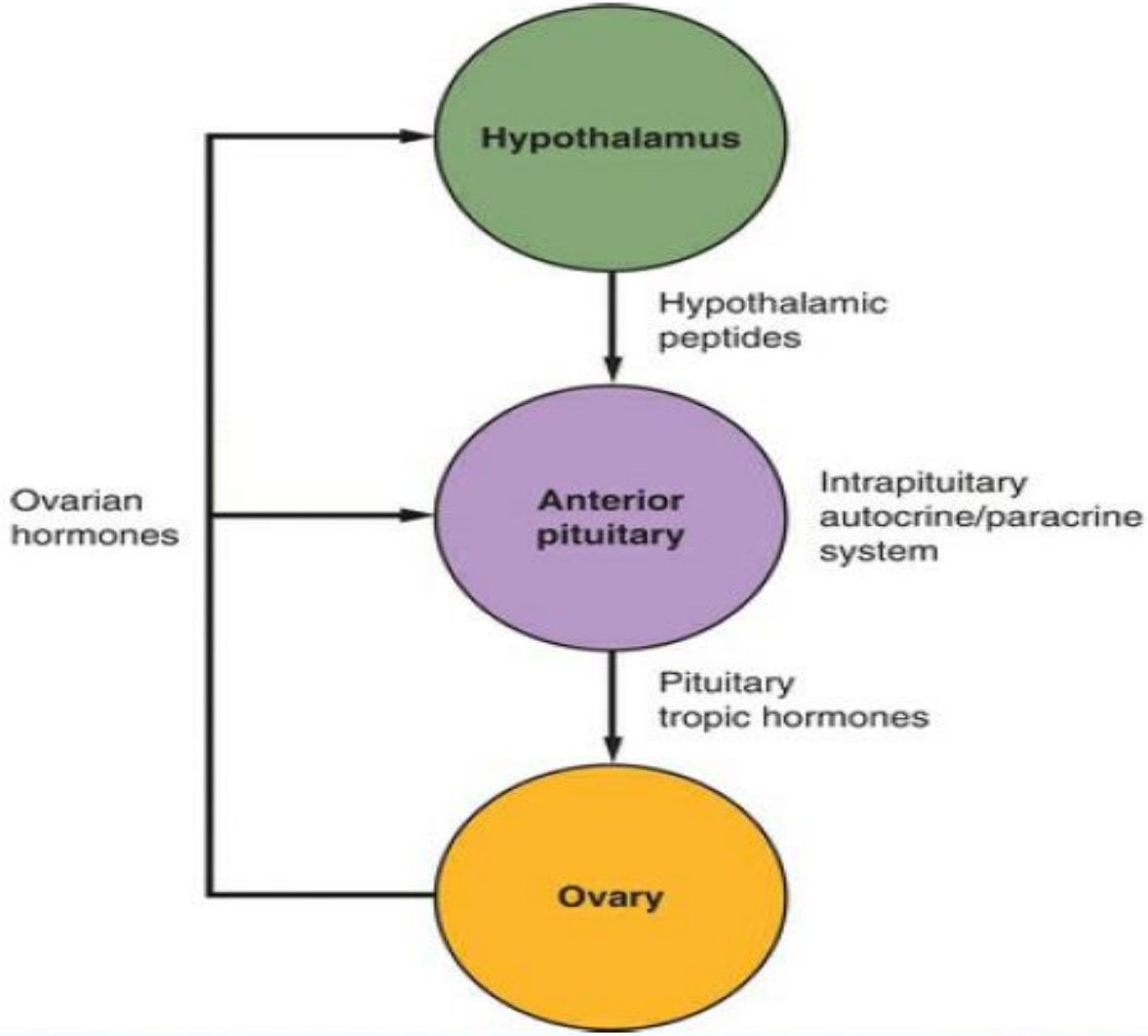
PCOS

- PCOS is the most obvious and common condition associated with chronic anovulation
- Affecting 4–6% of reproductive-age women

- PCOS is the most common “cause” of anovulation because PCOS does not cause anovulation is commonly encountered in women with PCOS.

Ovulation

- Normal ovulatory function requires coordination at all levels of the hypo thalamic pituitary-ovarian (HPO) axis


Hypothalamus
Hypothalamic peptides
Anterior pituitary
Intrapituitary autocrine/paracrine system
Ovarian hormones
Pituitary tropic hormones
Ovary

Ovarian follicular menstrual

- HPO axis matures and the positive feedback relationship between estradiol and gonadotropin secretion and ovulation becomes established.

Anovulation

- Disruption of functioning at any level of the HPO axis
- Amenorrhea, Oligomenorrhea
- Hirsutism
- Abnormal uterine bleeding

- Insulin resistance
- Increased type II diabetes mellitus
- Cardiovascular
- Endometrial hyperplasia cancer
- Infertility

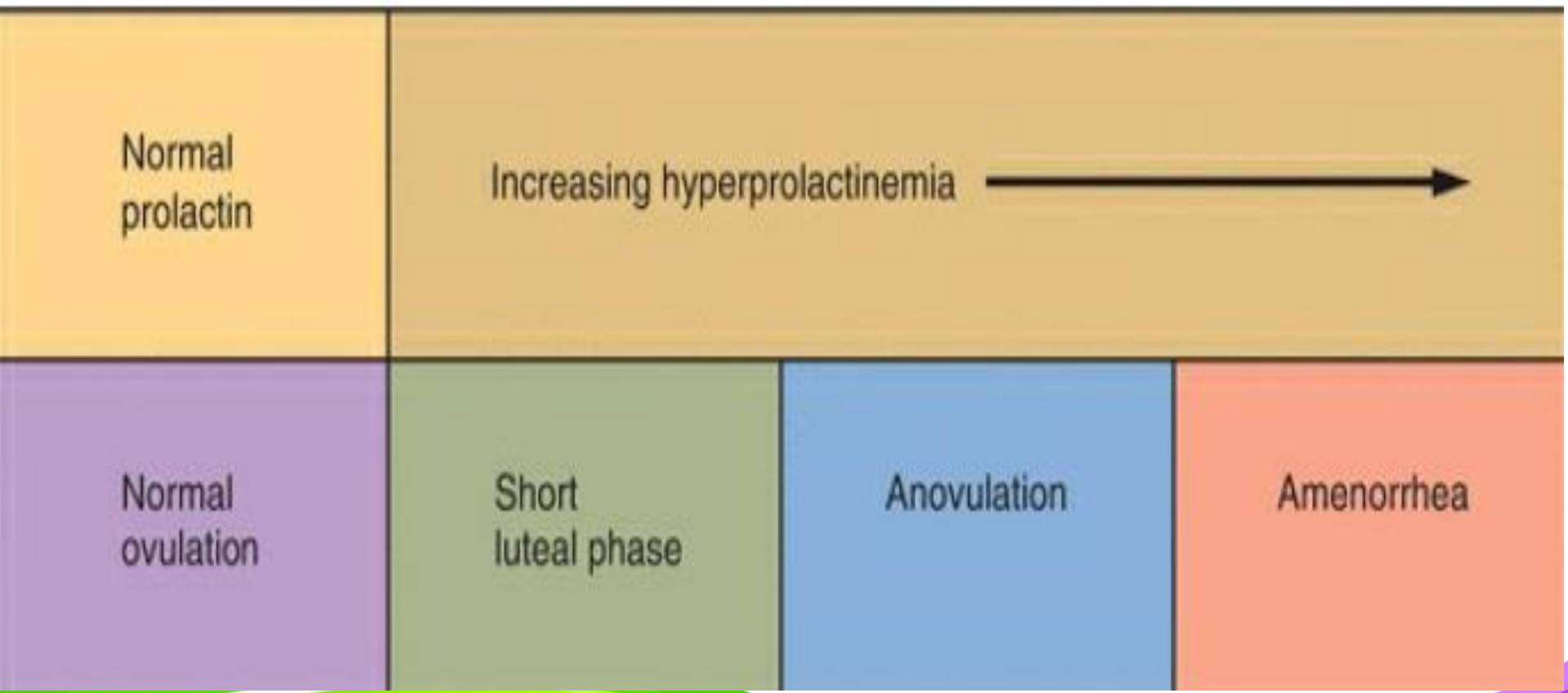
Common Causes of Anovulation

- Central defects, Hypo gonadotropic hypo gonadism reflecting hypothalamic
- HPO dysfunction, resulting in asynchronous gonadotropin and estrogen production
- Ovarian failure, Hyper gonadotropic hypo gonadism

Cause of Anovulation

- Emotional, nutritional (weight loss, eating disorders)
- Pharmacologic (opiates or dopaminergic agonists)
- Physical stress (excessive exercise)
- Can suppress GnRH neuronal activity ,dysfunctional patterns of gonadotropin secretion that fail to promote progressive follicular development, resulting in anovulation.

- Pituitary Tumors ,hyperprolactinemia ,abnormal Gonadotropin Secretory
- Hyperthyroidism and hypothyroidism can cause chronic anovulation


Normal prolactin
Increasing hyperprolactinemia
Normal ovulation
Short luteal phase
Anovulation
Amenorrhea

Diagnostic Criteria for PCOS

- Having a clear and specific definition for PCOS is important
- Women increased risk for variety of problems: Infertility ,abnormal uterine bleeding, endometrial cancer, obesity, type 2 diabetes mellitus, dyslipidemia, hypertension, and cardiovascular disease.

Diagnostic criteria of PCOS

- European Society of Human Reproduction and Embryology (ESHRE),American Society for Reproductive Medicine (ASRM) Rotterdam, at least two of the three major criteria:
- (1) oligo anovulation (oligo-/amenorrhea)
- (2) clinical or biochemical signs of hyperandrogenism
- (3) polycystic-appearing ovary assessed by ultrasonography, ovarian volume of more than 10 mL or more than 12 follicles measuring between 2 and 9 mm in size in at least one ovary

- Androgen Excess and PCOS Society (AE-PCOS) in 2006, diagnosis of PCOS requires:
- (1)hyperandrogenism(hirsutism,hyperandrogenemia)
- (2)ovarian dysfunction(oligoanovulation or PCO)
- (3)exclusion of other androgen excess or related disorders

Criteria		National Institute of Health (NIH) Criteria 1990	Rotterdam Criteria 2003	Androgen Excess and PCOS Society Criteria 2006
1	Irregular periods[b]	1 and 2[a]	Any 2 of 3[a]	1 and 2[a]
2	Elevated serum androgens or			or
	Hyperandrogenism			2 and 3[a]
	Hirsutism			
	Acne			
	Androgenetic alopecia			
3	Polycystic ovarian morphology (PCOM) or polycystic ovary (PCO)[c]			

- To diagnose PCOS, it is important to rule out common causes of anovulation

Common Causes of Anovulation	Diagnosis
Pregnancy	Elevated hCG
Thyroid dysfunction	Elevated TSH—primary hypothyroidism Suppressed TSH—primary hyperthyroidism
Hyperprolactinemia	Elevated prolactin Abnormal pituitary imaging
Late-onset CAH	Elevated total testosterone, DHEA-S, 17-OH progesterone
Obesity/insulin resistance	Elevated fasting and/or provoked insulin levels
Ovarian failure	Elevated FSH Suppressed estradiol, undetectable inhibin B, AMH
Iatrogenic Antianxiety/antidepressant Androgens	Elevated prolactin Elevated testosterone depending on the type of formulation
Psychological stress	Prolactin may be elevated Normal or low-normal FSH/LH Low estradiol
Eating disorders	Low to low-normal FSH/LH Low estradiol Low free T3 (anorexia)

Pathophysiology

- PCOS is most likely multifactorial involving:
- Endocrine ,metabolic , genetic, epigenetic, and environmental factors.

Compared normally cycling women with PCOS

- Increased serum LH concentrations
- low-normal FSH levels
- Increased LH to FSH ratios

- LH levels increase
- FSH typically are normal or low : Decrease

  hypothalamic dopamine or opioid inhibition of

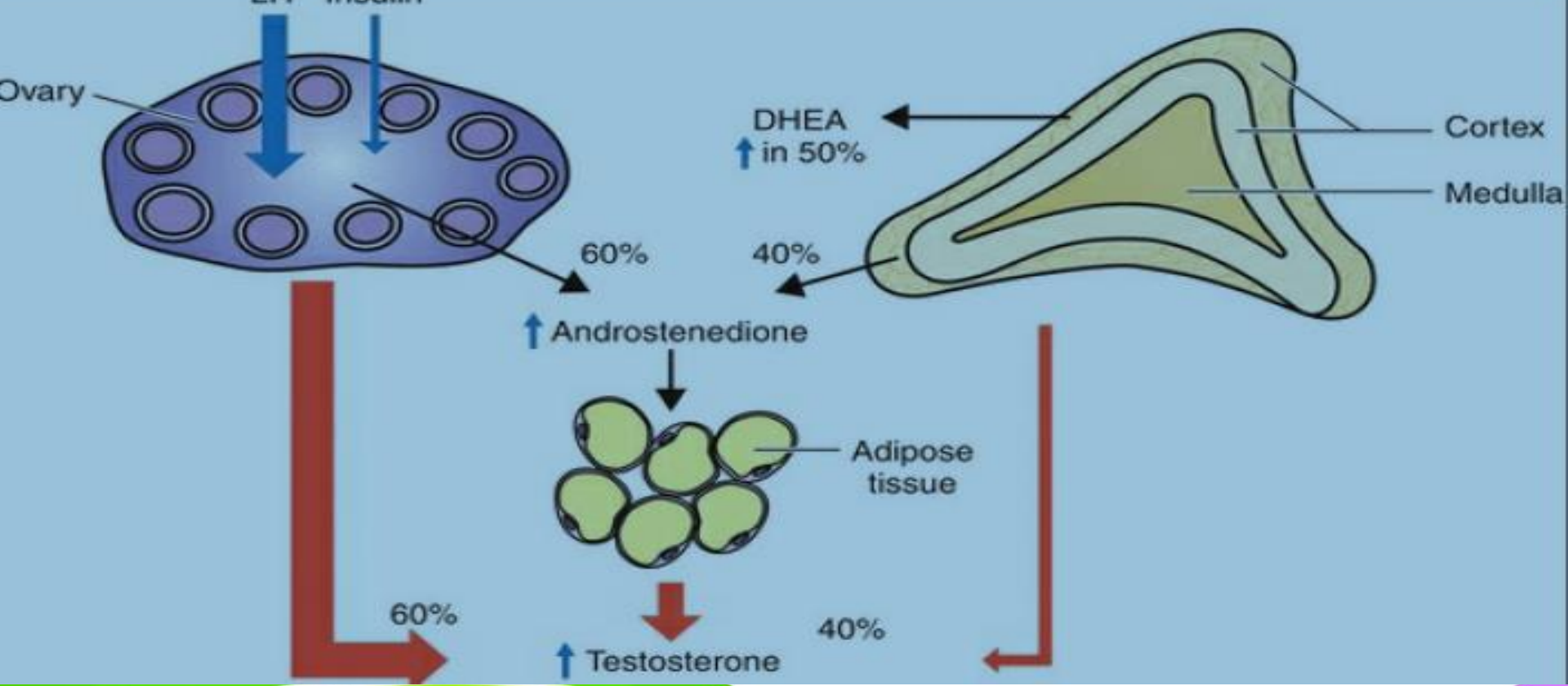
  pulsatile Increased circulating androgen levels

- Excessive LH secretion
- Important cause of disordered follicular development and anovulation, but is not the proximate cause of PCO or increased ovarian androgen production in women with PCOS.

High local androgen concentrations

- Impede follicular maturation
- Promote follicular atresia
- Predispose to a chronic anovulatory state

- Both androgens and estrogens is increased in PCOS
- Elevated serum testosterone ,androstenedione, (DHEA), (DHEA-S), (17-OHP), and estrone


Ovary
DHEA
in 50%
Cortex
Medulla
60%
40%
Androstenedione
Adipose
tissue
60%
40%
Testosterone

- AMH is produced by greatest in the granulosa cells of follicles measuring less than 4 mm (pre antral and antral follicles).
- In women with PCOS, there is an excessive amount of AMH, which is likely explained by increased follicles in the antral and preantral ,produce the greatest amounts of AMH

- AMH production is increased in anovulatory PCOS and normo-ovulatory PCOS women when compared to “normal” ovaries

- Proposed as an inclusion criteria for the diagnosis of PCOS
- AMH of 5 ng/mL has a high specificity (97%) and greater sensitivity than the current criteria for PCO morphology

Insulin resistance

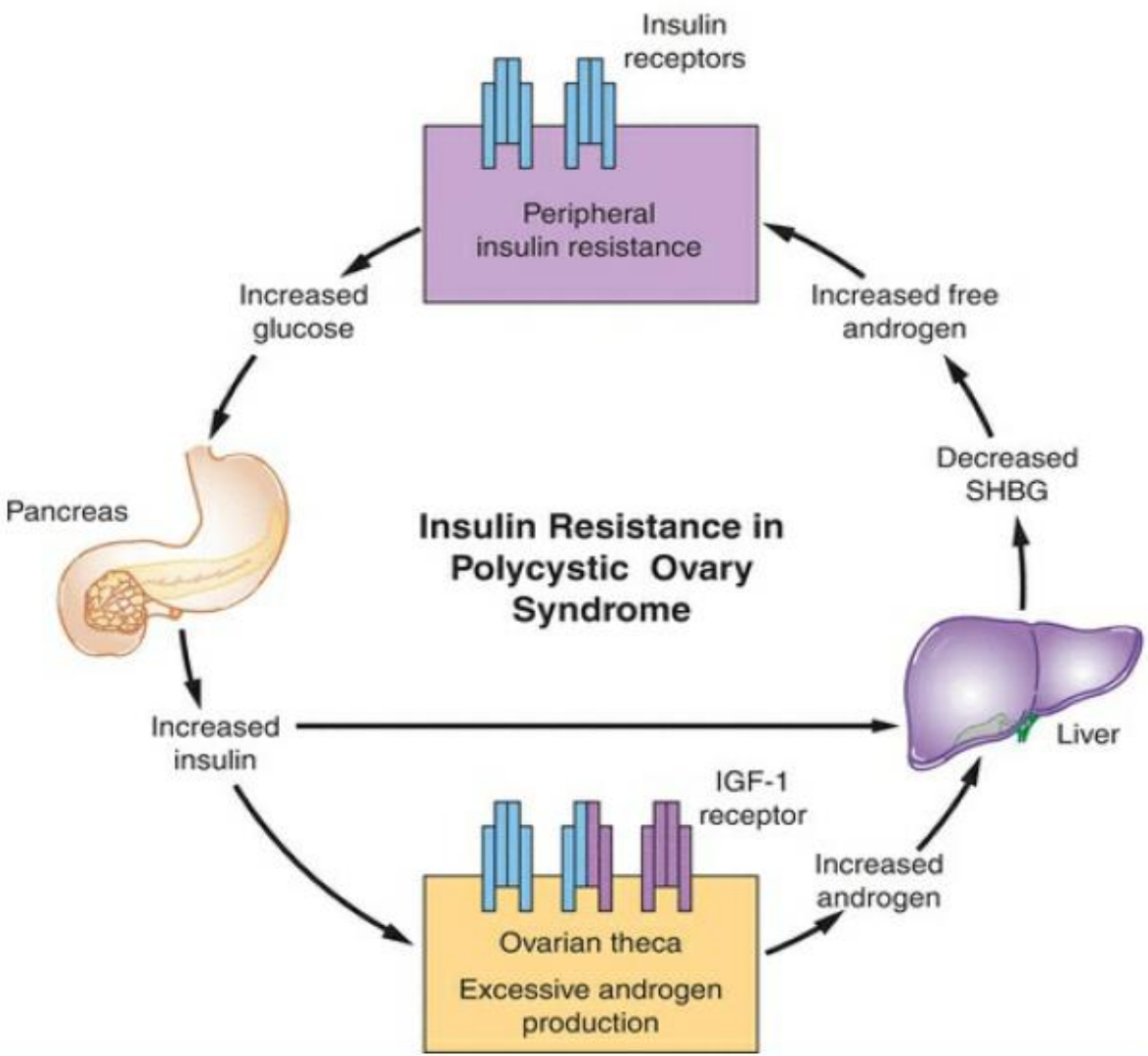
- 50% and 75%, Obese women with PCOS
- 20–25% lean women with PCOS
- 35% women with PCOS impaired glucose tolerance
- 7–10% type 2 diabetes mellitus

- Increased insulin levels cause:
- Hyper androgenism in women with PCOS increased ovarian androgen production
- Inhibiting hepatic SHBG production.

- Insulin also potentiates the action of LH
- Insulin and LH act synergistically to stimulate androgen production

- PCOS have demonstrated that insulin stimulates ovarian androgen production
- Rise in serum androstenedione and testosterone above baseline concentrations

- The combined actions of insulin and androgens
- lower SHBG concentrations
- Increased free androgen levels, which aggravate the underlying insulin resistance

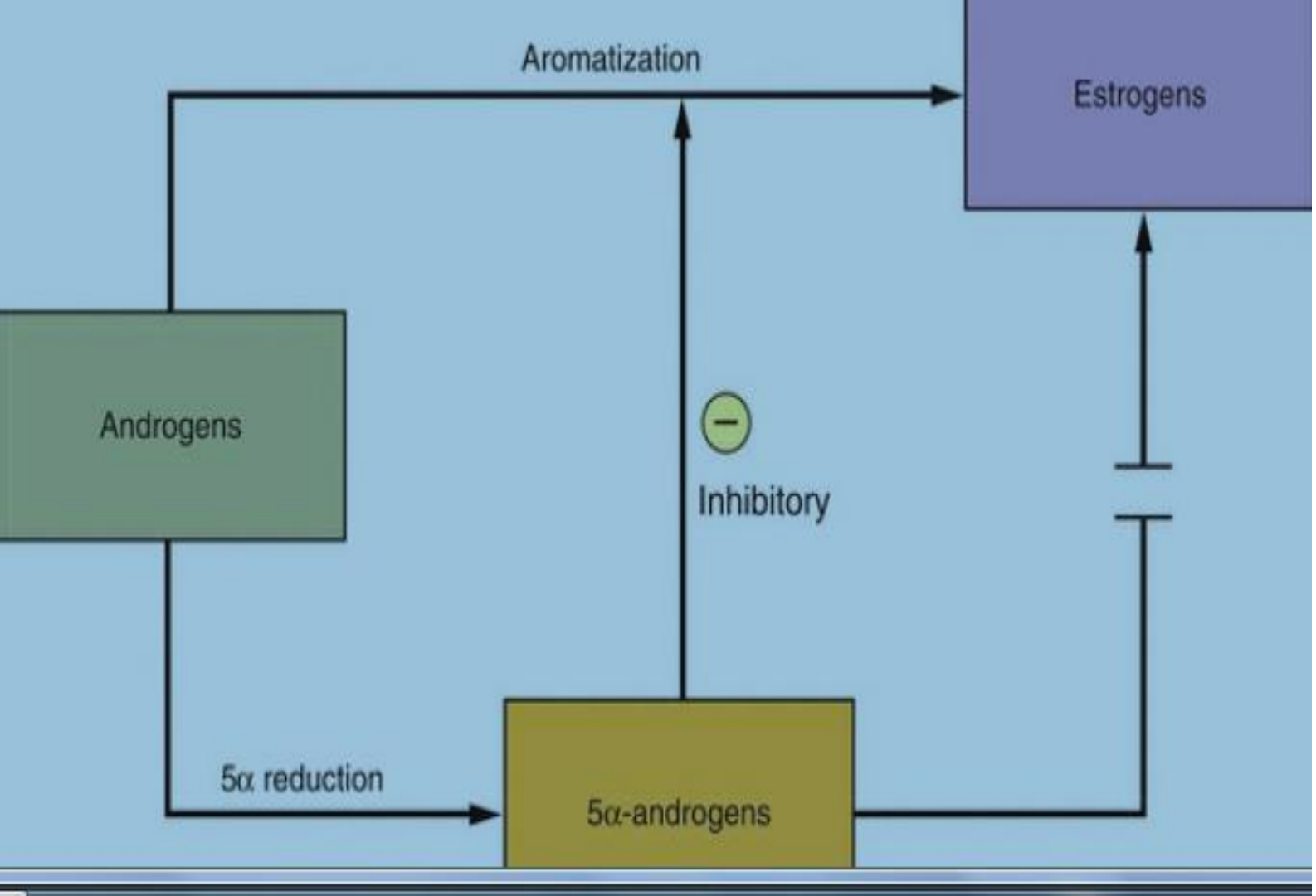

Insulin receptors
Peripheral insulin resistance
Increased glucose
Increased free androgen
Pancreas
Decreased SHBG
Insulin Resistance in Polycystic Ovary Syndrome
Increased insulin
Liver
IGF-1 receptor
Increased androgen
Ovarian theca
Excessive androgen production

- Insulin stimulates ovarian androgen production acting via insulin receptors on theca/interstitial cells in the ovarian stroma
- At high concentrations, insulin also binds to IGF-1 receptors Insulin

- Complexity and polygenic nature of the disorder Suggests that more than one mechanism may be involved.
- Insulin resistance and hyperinsulinemia an important part of the pathophysiology of PCOS.

Obesity

- Increased peripheral aromatization of androgens
- Elevated estrogen concentrations
- Decreased levels (SHBG) production
- Increased free estradiol and testosterone
- **I**nsulin resistance, increase in insulin levels that Stimulates androgen production in the ovarian stroma


Aromatization
Estrogens
Androgens
Inhibitory
5α reduction
5α-androgens

- Insulin resistance
- Elevated androgens
- Predispose to PCOS phenotype in obese adolescents.

Obesity(35% -60%)

- Increasing insulin resistance, hyperinsulinemia, ovulatory dysfunction and metabolic syndrome glucose intolerance, risk factors for cardiovascular disease, and sleep apnea
- Obesity in women with PCOS typically is centrally with a greater increase in visceral than in subcutaneous fat

- Obesity in it PCOS given the HPO dysfunction in
- Elevation in free testosterone levels due to suppressed hepatic production of SHBG.

- The high androgen levels ,elevated estrogen levels or increasing LH pulse frequency and amplitude and inhibiting FSH secretion
- Menstrual irregularity, dysfunctional bleeding, hirsutism, and infertility is higher in obese than in lean women with PCOS and obesity is an independent risk factor for developing glucose intolerance and diabetes.

- Obese women have a higher prevalence:
- Miscarriage
- Gestational diabetes
- Pre-eclampsia

weight loss

- Decreased circulating insulin and androgen
- Restores ovulatory function and normal menstrual cycle
- Therefore, in obese girls and women who are experiencing menstrual irregularity, weight reduction must be first-line management approach.

- Lean women with PCOS have a increased:
- percentage of body fat, a higher waist-hip ratio, and greater intra-abdominal, peritoneal, and visceral fat compared to normal women matched for BMI.

Genetic Considerations

- Familial clustering heritable X-linked or autosomal dominant inheritance
- Hyperandrogenism, anovulation, and PCO suggests an underlying genetic basis or cause.
- Observed a high prevalence of hyperinsulinemia and hypertriglyceridemia, PCOS in females

- 50% of sisters of women with PCOS
- 35% of mothers elevated total or bioavailable testosterone .
- The first-degree relatives of women with PCOS also exhibit other metabolic abnormalities such as dyslipidemia which may predispose to an increased risk for cardiovascular disease.
- These observations further suggest a genetic predisposition or susceptibility.

- PCOS is best seen as a polygenic
- Genomic variants
- Environmental factors.

Diagnosis of Polycystic Ovary Syndrome

- PCOS is not a specific endocrine disease but a syndrome represented by a collection of signs and symptoms and that no one sign, symptom, or test is diagnostic.

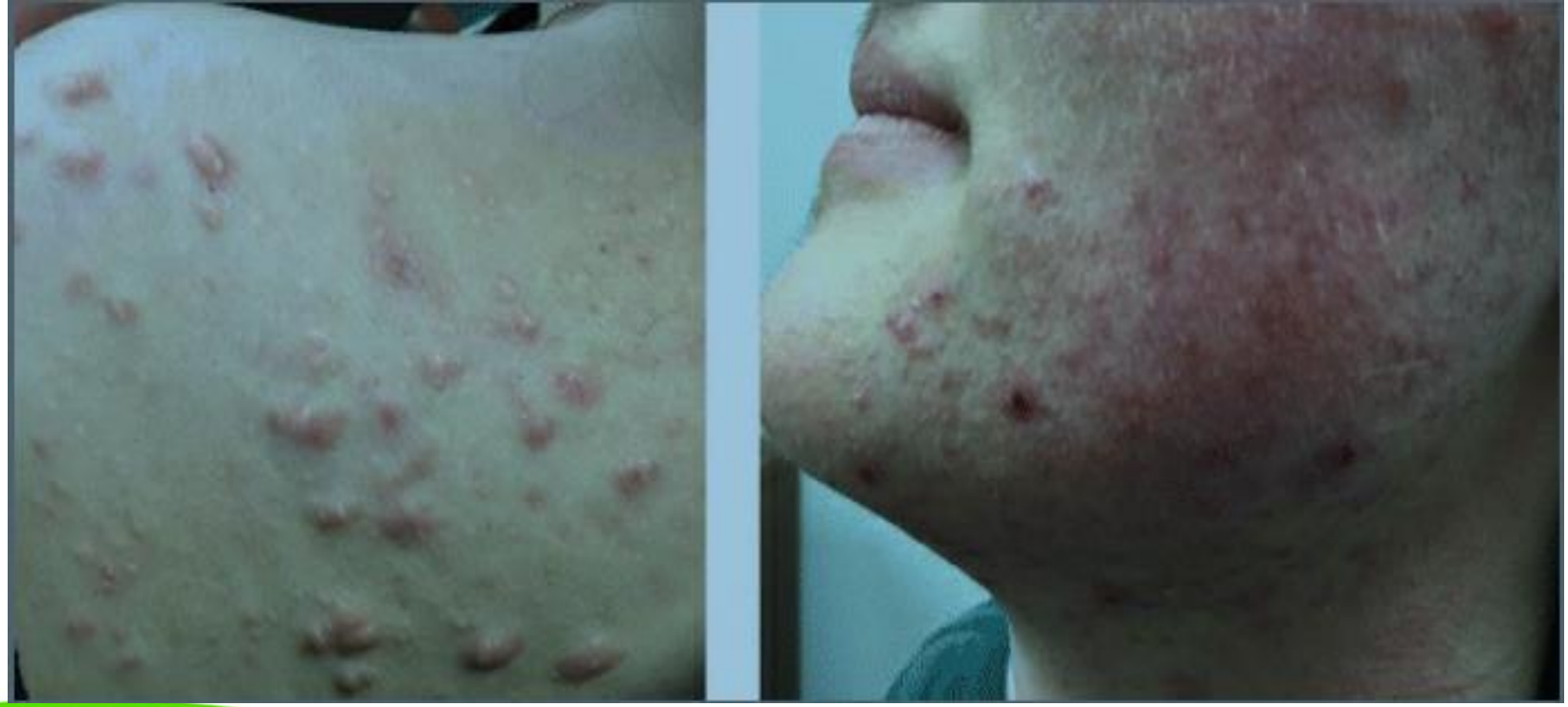
- For clinical purposes, measurement of the free testosterone level, or measurement of the serum total testosterone concentration Usually is unnecessary
- In most cases, clinical evidence of hirsutism provides evidence of hyper androgenism, and if severe, sudden in onset, rapidly progressive, or associated with symptoms or signs of virilization ,there is little reason for concern about an androgen-producing tumor

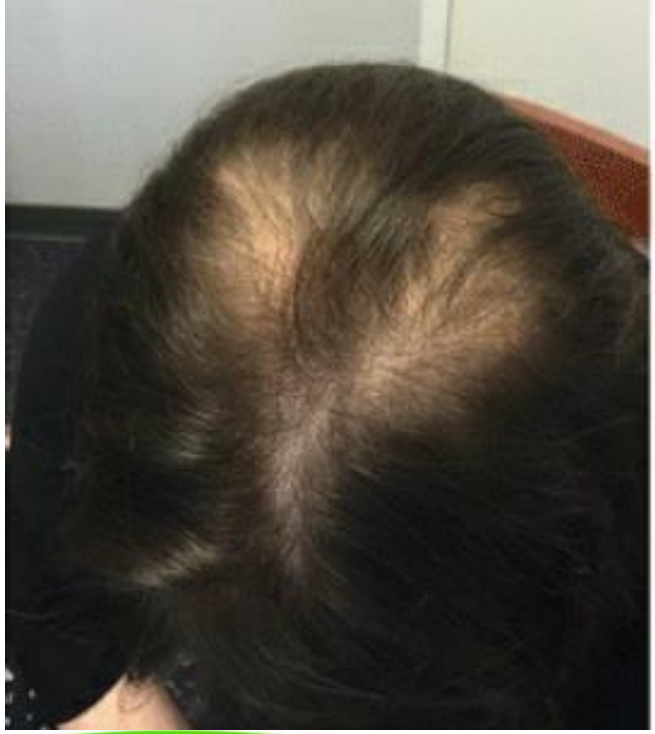
DHEA-S

- DHEA-S levels are however not considered when diagnosing PCOS per the Rotterdam criteria.
- Clinical routine testing of DHEA-S levels in settings of mild clinical hyperandrogenism is not necessary.

Clinical Hyperandrogenism

- Hirsutism ,acne, and androgenic alopecia
- All of effects of androgens on the pilo sebaceous unit
- Hirsutism is the growth of terminal hairs on the face or body in a male pattern symptom of PCOS.

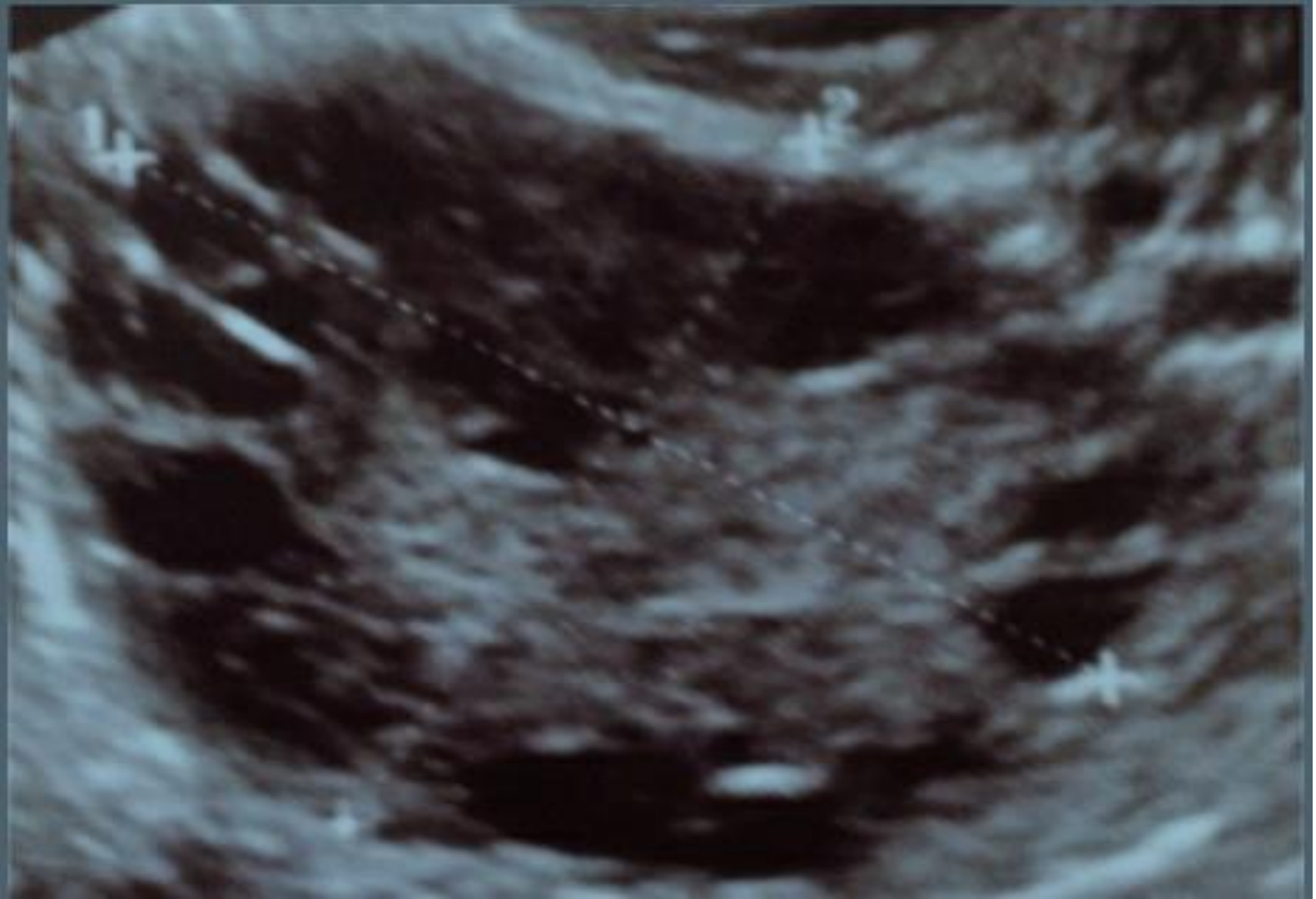




- Normal cyclic menses result from normal ovulatory function .
- The normal menstrual interval ranges between 21 and 35 days.
- Oligomenorrhea is defined as less than eight menstrual cycles per year.

- The majority of women with PCOS
- 60–85% menstrual dysfunction
- The most common menstrual abnormalities in women with PCOS are oligomenorrhea and amenorrhea.
- Polymenorrhea (<21 days) is quite uncommon, observed in less than 2%

- PCOS also increased size and stromal volume
- Many small follicles are displaced peripherally and surround the dense central stroma of a polycystic ovary
- The Rotterdam criteria for an ovary to be considered
- polycystic weighs ovarian volume (>10 mL3)
- Total number of small follicles measuring between 2 and 9 mm in size (≥12)



- 30% of regularly menstruating normal women without PCOS
- 14% of women using oral contraceptives
- Meet the ultrasonographic criteria for PCO.

- The important point is that PCOS is a functional disorder in which PCO result from chronic anovulation.

Metabolic Abnormality	Health Implications	Screening	Management Considerations
Abnormalities in glucose homeostasis	Type II diabetes Risk for CVD Risk for endometrial hyperplasia	OGTT HbA1c Fasting or OGTT provoked insulin levels	Weight reduction Exercise and dietary modifications Insulin sensitizers Incretins Insulin
Lipid abnormalities	Risk for CVD Stroke risk	Fasting lipid profile	Weight reduction Dietary modifications Exercise Lipid-lowering agents Low-dose aspirin
Inflammation	Risk for CVD	Cardio CRP	Weight reduction Dietary modifications Exercise Lipid-lowering agents Low-dose aspirin
Metabolic syndrome	Exaggerated risk for CVD, all-cause mortality, and cancer risk	Fasting lipids HbA1c Fasting glucose Blood Pressure monitoring Waist circumference	Aggressive approach to risk reduction through combination of lifestyle modifications aimed at weight reduction, plus the use of antihypertensive, lipid-lowering and glucose-lowering agents

Insulin Resistance

- The insulin resistance among women with PCOS is between **30% and 35%** and is greater in the obese than in lean PCOS population.
- A baseline 2-hour OGTT is recommended for all women with PCOS,
- 35% impaired glucose tolerance and 10% have diabetes mellitus.

- Screening for glucose intolerance also is recommended for girls with premature adrenarche or menstrual irregularity that persists for more than 2 years after menarche
- Hyperinsulinemia often is a RESULT ,dysfunction of the HPO axis and they are at high risk for developing diabetes and sever hyperandrogenism.

Timing	Glucose (mg/dL)	Insulin (mU/mL)	Interpretation
Fasting (0 min)	<100	<20	**Impaired fasting glucose (IFG)** is between 100 and 125.99 mg/dL **Diabetes mellitus** if fasting glucose level is ≥126 **Insulin-resistant** if fasting insulin level is >20
30–90 min	<200	<80–100 Level peaks at 30 min and should decline over time and remain <80–100	**Insulin-resistant** if insulin level is ≥80–100 at any time **Severe insulin resistance** if insulin level is >300
120 min	<140	Level should be less than at 90-min interval <80	**Impaired glucose tolerance (IGT)** if glucose level is between 140 and 199.9 mg/dL **Diabetes mellitus (DM)** if glucose level is ≥200 mg/dL **Insulin-resistant** if insulin level is >55 **Severe insulin resistance** if insulin level is >100

PCO

- Dyslipidemia:70% TG↑ HDL↓
- Cancer Risk for endometrial may be as high as threefold greater in anovulatory women with PCOS compared to women with normal reproductive physiology.

Inflammation

- PCOS compared to non-PCOS women, it was found (CRP) was elevated in PCOS.
- CRP is a marker of chronic inflammation and is correlated with insulin resistance, body weight, and adipose mass.
- Treatment with metformin lowers CRP levels.

Thyroid Disorders

- Thyroid dysfunction in women diagnosis in all anovulatory women, and hyperandrogenism.
- Serum TSH is considered as the gold standard first-line test for assessing primary thyroid disorders.

Hyper prolactinemia

- The high prevalence of hyper prolactinemia among women with menstrual dysfunction justifies specific in all women with menstrual abnormalities and ovulatory dysfunction.

Congenital Adrenal Hyperplasia(Non classical)

- Hyper androgenism having an early onset of hirsutism (including girls premature adrenarche)
- Women with a family history of the disorder
- High-risk ethnic groups (Hispanic,Mediterranean, Slavic, Ashkenazi Jewish, or Yupik Eskimo heritage)

- In chronically anovulatory women with hyperandrogenism,
- Follicular phase morning serum 17-OHP concentration less than 200 ng/dL excludes
- Level greater than 800 ng/dL all but establishes the diagnosis of late-onset CAH due to 21-hydroxylase deficiency.

DDX PCO

- Androgen-Secreting Ovarian and Adrenal Tumors serum total testosterone concentration greater than 150 ng/dL
- Cushing Syndrome: the over night dexamethasone suppression test is the best single screening test
- Idiopathic Hirsutism is defined classically as hirsutism by normal ovulatory and menstrual function and with normal circulating androgen levels.
- Severe Insulin Resistance Syndromes

Cushing Syndrome

- The disorder has features observed in women with PCOS, including menstrual dysfunction and
- central obesity.
- However, the prevalence of Cushing syndrome in women presenting with hyperandrogenism is extremely low, well below 1%.

- Symptoms of severe fatigue and muscle weakness
- atrophy of the skin and subcutaneous tissue (easy bruising purple striae on the abdomen and flanks); hyperpigmentation in areas most exposed to light or chronic mild trauma, friction, or pressure (the elbows, knees, knuckles, and shoulders); hypertension; diabetes; and features of cognitive impairment in anovulatory woman should raise concerns for Cushing syndrome.

Key Points: Severe Insulin Resistance Syndromes

- Polycystic ovary syndrome is not a specific endocrine disease but is a syndrome represented by a collection of signs and symptoms, and no one sign, symptom, or test is diagnostic.
- Diagnosis of polycystic ovary syndrome is based primarily on the clinical history and physical examination. The major clinical features of polycystic ovary syndrome are chronicity of hyperandrogenism and menstrual dysfunction.
- Although present in most women with chronic hyperandrogenic anovulation, polycystic-appearing ovaries alone do not establish and are not required for diagnosis of polycystic ovary syndrome.
- Gonadotropin levels or ratios are not a reliable criterion for diagnosis of polycystic ovary syndrome.
- Knowing and understanding the health implications and consequences of chronic anovulation and timely initiation of appropriate management strategies are far more important than simply assigning a diagnostic label of PCOS.
- Laboratory evaluation of women with suspected polycystic ovary syndrome should include:
    - **Tests for ruling out common conditions that can mimic PCOS:**
        - Serum thyroid-stimulating hormone (TSH)

- Serum prolactin
- Serum 17-hydroxyprogesterone (especially in women with a pre- or perimenarcheal onset of hirsutism, a family history of congenital adrenal hyperplasia, or high-risk ethnicity time blood draw in morning in follicular phase)
- 24-hour urine-free cortisol if suspecting Cushing syndrome in differential diagnosis

- **Tests that quantify presence, severity, and source of hyperandrogenemia:**
  - Serum total and free testosterone (in women with moderate to severe hirsutism and/or acne or alopecia
  - Serum DHEA-S (to determine adrenal contribution to signs/symptoms of androgen excess)
- **Tests that allow risk assessment:**
  - Oral glucose tolerance test (2-hour, 75-g glucose load) with frequent sampling for glucose (can consider additionally testing insulin levels)
  - Fasting lipid profile
  - Comprehensive metabolic panel
  - Endometrial sampling to rule out endometrial hyperplasia/cancer (consider in obese women and in those with history of prolonged periods of oligomenorrhea/amenorrhea that indicate long-term


Thank you for your
attention