



IN THE NAME OF GOD



# APPROACH TO ANOVULATION



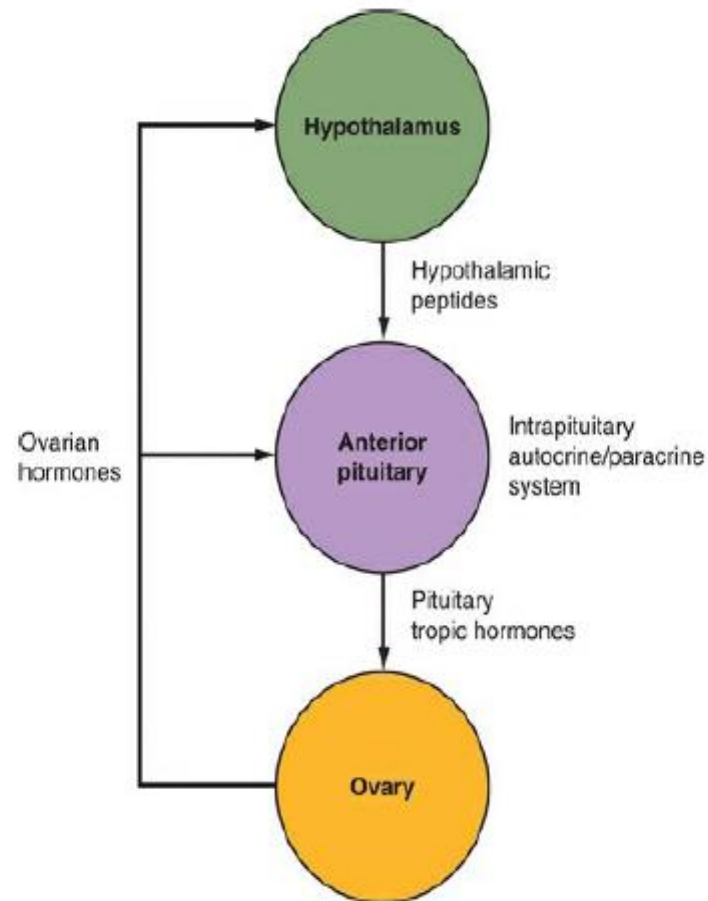
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# CAUSES OF ANOVULATION



# Central Defects as a Cause of Anovulation




The onset of puberty in girls results from **decreasing central inhibition of GnRH neuronal activity** and increasing pulsatile GnRH secretion

which stimulates a progressive increase in **pituitary gonadotropin release**

**ovarian follicular growth , menstrual cycle and secondary characteristics in adolescent girls**

until the HPO axis matures and the positive feedback relationship between estradiol LH surge and **ovulation** becomes established.

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- Factors that reactivate central inhibitory mechanisms
  - Emotional
  - Nutritional (weight loss, eating disorders),  
Pharmacologic (opiates or dopaminergic agonists)
  - Physical stress (excessive exercise)  
can suppress GnRH neuronal activity, leading to :  
dysfunctional patterns of gonadotropin secretion that  
fail to promote progressive follicular development,  
resulting in anovulation.

# Pituitary Tumors



- Pituitary tumors can cause anovulation by inhibiting gonadotropin secretion.

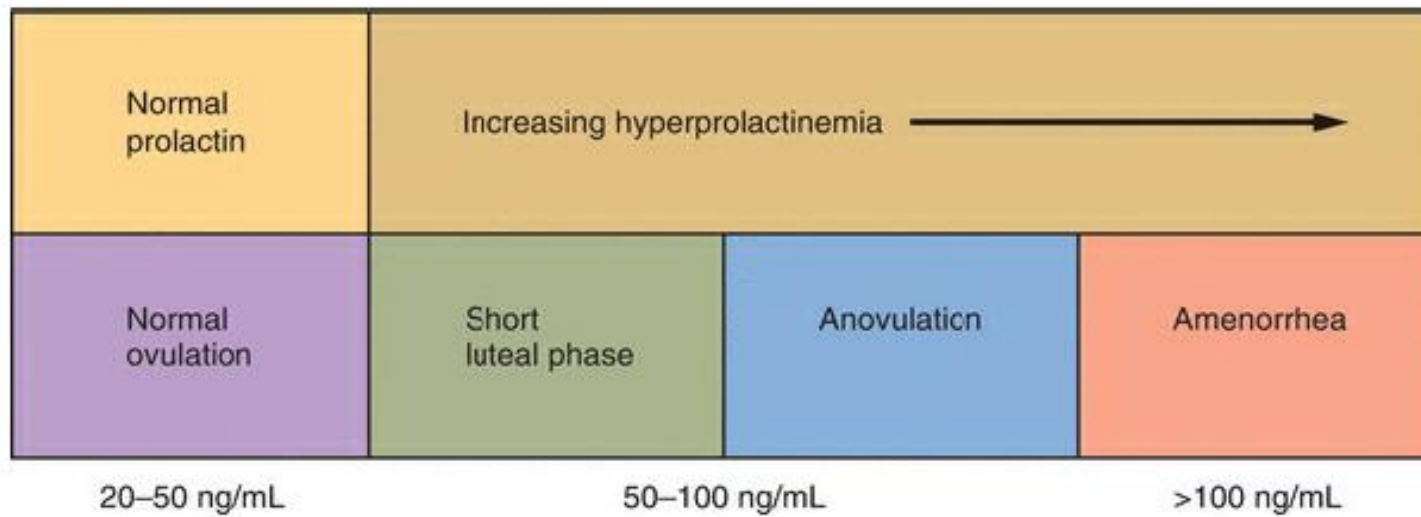
# Hyperprolactinemia





- The mechanism involves disruption or inhibition of the normal GnRH pulse rhythm, resulting in ineffective or frankly low levels of pituitary gonadotropin Secretion.

**Elevated prolactin levels** can result in a spectrum of ovulatory dysfunction, ranging from :

- Short luteal phase
- Anovulatory cycles
- Amenorrhea and Hypogonadotropic Hypogonadism.





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- A **breast examination with gentle compression** looking for evidence of galactorrhea and measurement of the **serum prolactin concentration** are important parts of the evaluation of all anovulatory women.

# Abnormal Gonadotropin Secretory Dynamics


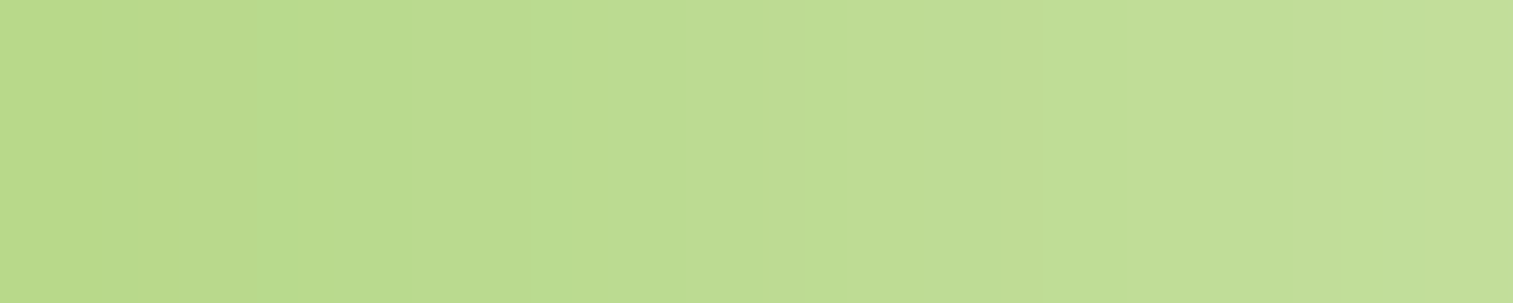


- The most common abnormality involving the gonadotropins is an increase in mean serum LH levels due to an increase in both LH pulse frequency and amplitude.
- Serum concentrations of FSH typically are normal or low.



The pattern could result from :

1. a decrease in hypothalamic dopamine or opioid inhibition of pulsatile GnRH secretion
2. From abnormalities in steroid hormone feedback including the lack of progesterone (due to anovulation)
3. Increased circulating androgen levels.



The increased prevalence of chronic anovulation and polycystic-appearing ovaries in women with **epilepsy** offers another example of how central nervous system dysfunction can disrupt the HPO axis and result in anovulation.

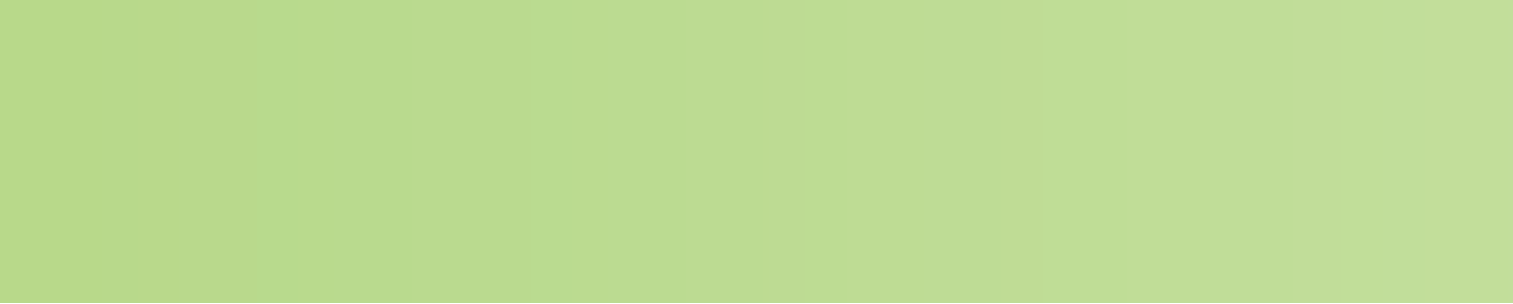





# Chronically Elevated Estrogen Concentrations



Sustained high levels of estrogen caused by increased production or decreased clearance and metabolism can through negative feedback prevent any significant increase in FSH levels resulting :

chronic anovulatory state.

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- Pregnancy is the most common and obvious example of anovulation resulting from **sustained high levels of estrogen production.**
  - Rare estrogen-producing ovarian tumors (e.g., granulosa cell tumors) can have the same effect.
  - **Adipose tissue has significant aromatase activity,** which converts androgens to estrogens, thereby providing at least one mechanism for the well-known association between obesity and chronic anovulation.

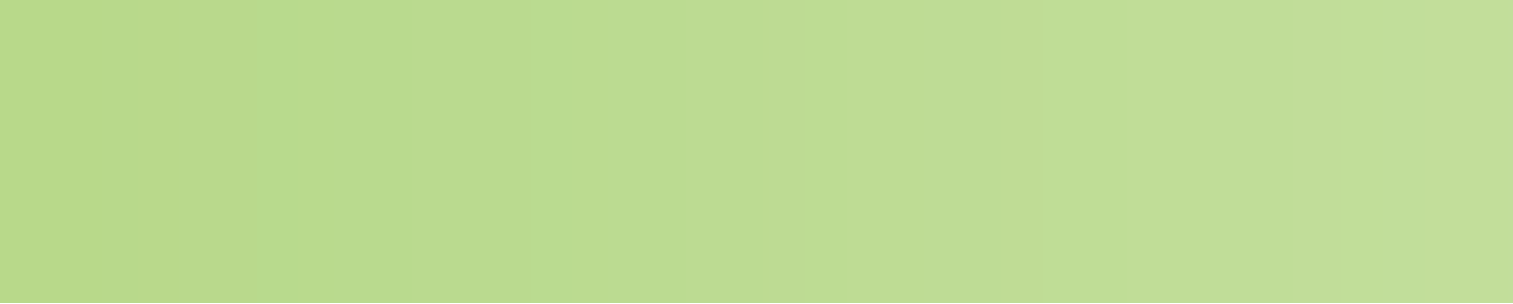

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- The clearance and metabolism of estrogen can be impaired in a variety of conditions, such as thyroid or hepatic disease.
  - Hypothyroidism can be associated with elevated prolactin levels  
providing the rationale for measuring TSH  
in the evaluation of anovulatory and amenorrheic women.

# Failure of the LH Surge



- The **rising estradiol levels** arising from the preovulatory follicle in the late follicular phase induce **the midcycle LH surge** through a positive feedback effect and this stimulates ovulation.



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- Quite obviously, women with gonadal dysgenesis or ovarian failure are anovulatory because they have no remaining functional ovarian follicles and no significant estrogen production.
  - Anovulatory cycles are common at extremes of reproductive ages such as in the months following menarche and in the perimenopausal period.

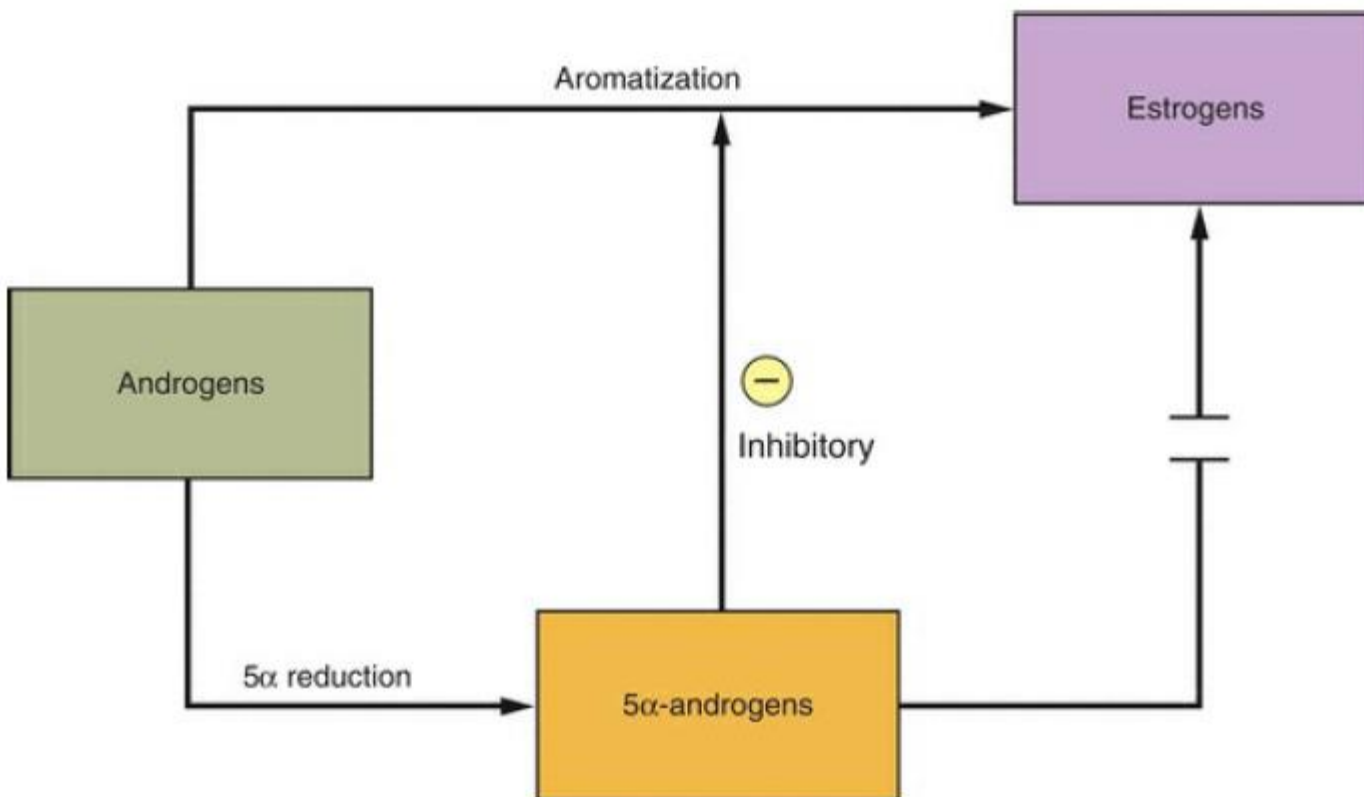
# Local Ovarian Conditions



- The “two-cell, two-gonadotropin” concept of ovarian follicular development emphasizes the critical importance of local androgen concentrations within the ovary.
- At low levels, ovarian androgens serve as substrate for FSH-induced aromatization and estrogen production.
- At higher concentrations however, intraovarian androgens are converted alternatively to more potent  $5\alpha$ -reduced androgens, which cannot be converted to estrogen and also inhibit aromatase activity and FSH induction of LH receptors on granulosa cells.



- Consequently, abnormally high local androgen concentrations, from any cause
- impede follicular maturation
- promote follicular atresia
- and predispose to a chronic anovulatory state.









# Obesity



- **Obesity predisposes to chronic anovulation in at least three distinct ways:**
  1. Increased peripheral aromatization of androgens, resulting in chronically elevated estrogen concentrations.
  2. Decreased levels of hepatic sex hormone binding globulin (SHBG) production, resulting in increased circulating concentrations of free estradiol and testosterone.
  3. Insulin resistance, leading to a compensatory increase in insulin levels that stimulates androgen production in the ovarian stroma, resulting in high local androgen concentrations that impair ovarian follicular development.

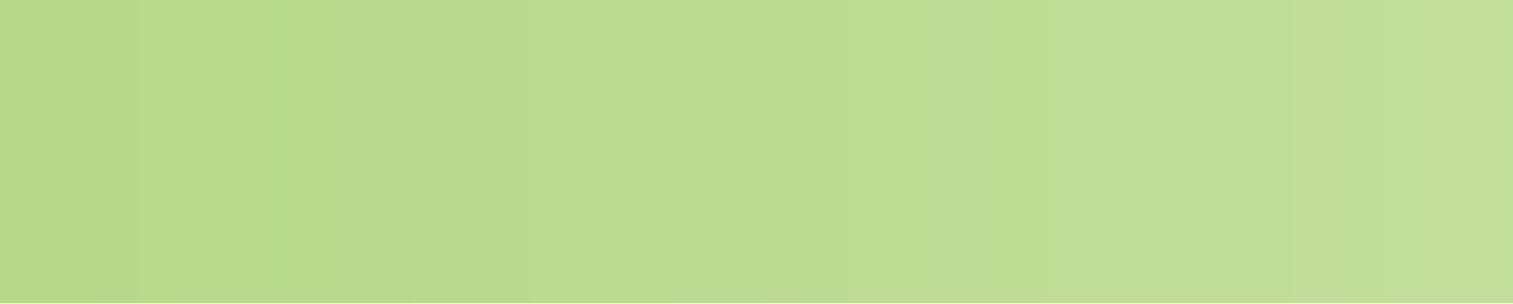

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- Importantly, mild insulin resistance as well as some degrees of hyperandrogenemia are often encountered as a physiologic phenomenon at puberty.
  - However, both these states get exacerbated in the setting of childhood obesity.
  - These two features—persistent insulin resistance and elevated androgens—ultimately predispose to a PCOS phenotype in obese adolescents.

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- Even modest weight loss(2-5%), which results in decreased circulating insulin and androgen concentrations, frequently restores ovulatory function and normal menstrual Cyclicity.
  - Therefore, in obese girls and women who are experiencing menstrual irregularity, weight reduction must be considered as a first-line management approach.



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		Elevated prolactin
Antianxiety/antidepressant		Elevated testosterone depending on the type of formulation
Androgens		
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)



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- PCOS is the most obvious and common condition associated with chronic anovulation,
  - Affecting 4–6% of reproductive-age women, although given changes in diagnostic criteria, the prevalence has doubled.
  - It is inaccurate to state that PCOS is the most common “cause” of anovulation, because PCOS does not cause anovulation; rather, anovulation is commonly encountered in women with PCOS.

# POLYCYSTIC OVARY SYNDROME



- Multicystic or “sclerocystic” ovaries were recognized as early as the mid-18th century but associated primarily with pelvic pain or menorrhagia.
- In 1935, Irving F. Stein and Michael L. Leventhal first described a symptom complex associated with anovulation.

# Diagnostic Criteria for PCOS

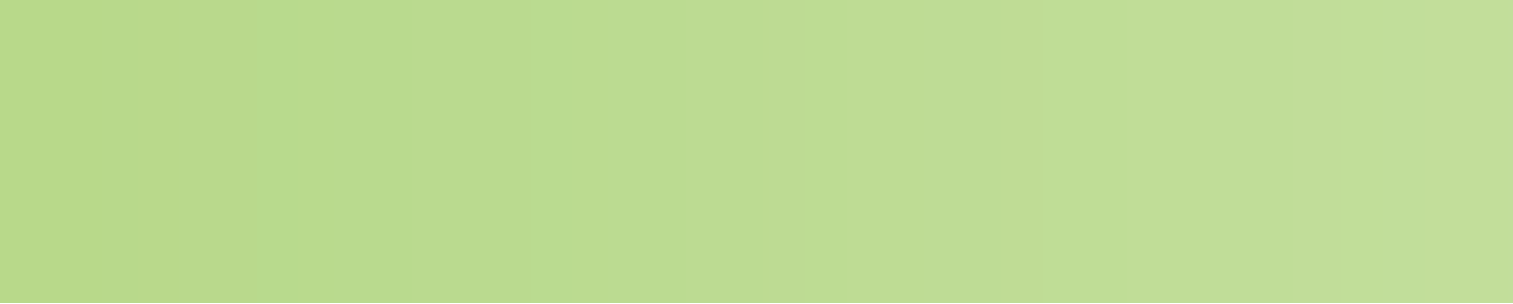



- European Society of Human Reproduction and Embryology (**ESHRE**) and the American Society for Reproductive Medicine (**ASRM**) , convened in Rotterdam, the Netherlands, **in 2003**, concluding that diagnosis of PCOS
- **Should be based on at least two of the three major criteria:**
  - (1) oligomenorrhea or amenorrhea
  - (2) clinical or biochemical signs of hyperandrogenism,
  - (3) polycystic-appearing ovary(ies) (assessed by ultrasonography, described as an ovarian volume of more than 10 mL and/or more than 12 follicles measuring between 2 and 9 mm in size in at least one ovary.





The 2003 ESHRE/ASRM (“Rotterdam”) criteria sought to recognize and accommodate a broader spectrum of the disorder.

Given that women need only fulfill two of the three diagnostic criteria, it allows for inclusion of women with regular menstrual cycles and/or women having neither hyperandrogenemia nor hirsutism.

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- AMH is produced by granulosa cells, and expression is greatest in the granulosa cells of follicles measuring less than 4 mm (preantral 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 stages



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- AMH has been proposed as an inclusion criterion for the diagnosis of PCOS, likely replacing (or serving as a surrogate for) PCO morphology
  - studies have demonstrated that an AMH of 5 ng/mL has a high specificity (97%) and greater sensitivity than the current criteria for PCO morphology.



- A threshold of  $\text{AMH} \geq 5 \text{ ng/mL}$  may be used as a further suggestion of PCOS
- much like the utility of a reversed FSH/LH ratio in serving to suggest ovulatory dysfunction.

# Pathophysiology of Polycystic Ovary Syndrome



An altered pattern of GnRH release that leads to an increased LH pulse frequency offers a unifying mechanism for both ovarian androgen excess (due to LH-mediated stimulation of androgen production by ovarian stroma)

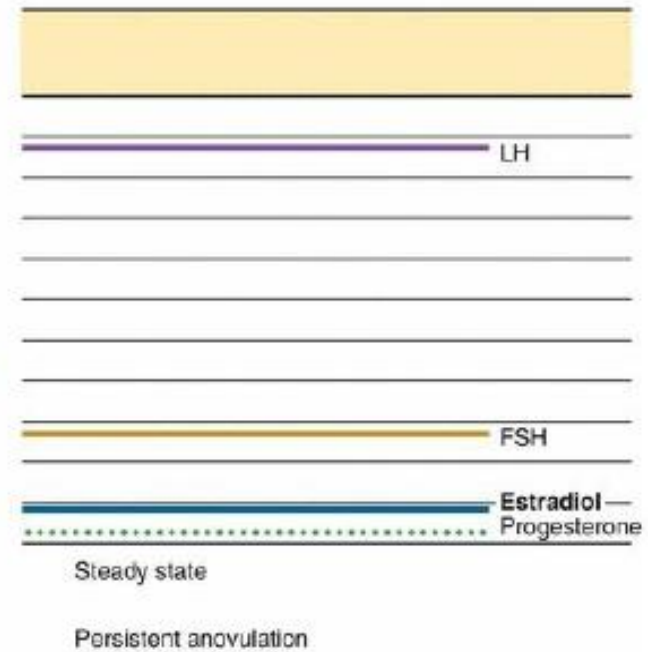
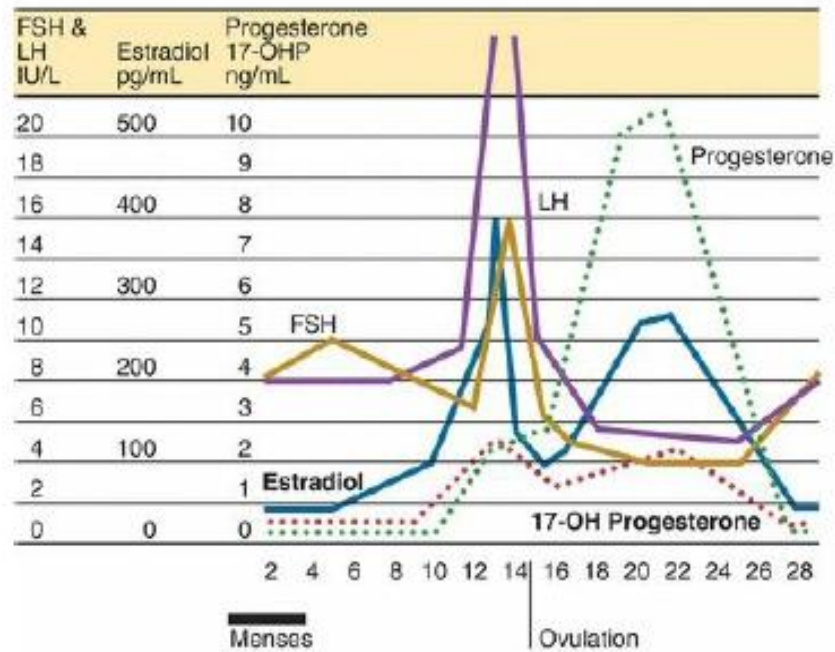
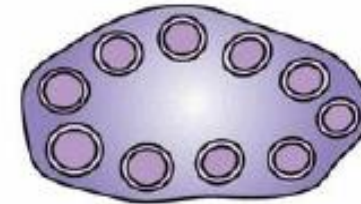
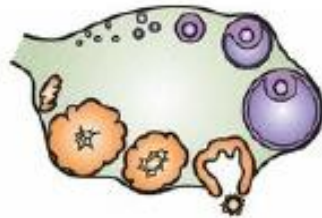
and impaired follicle development that results in chronic anovulation (due to the relatively low FSH levels that occur secondary to altered GnRH release pattern).



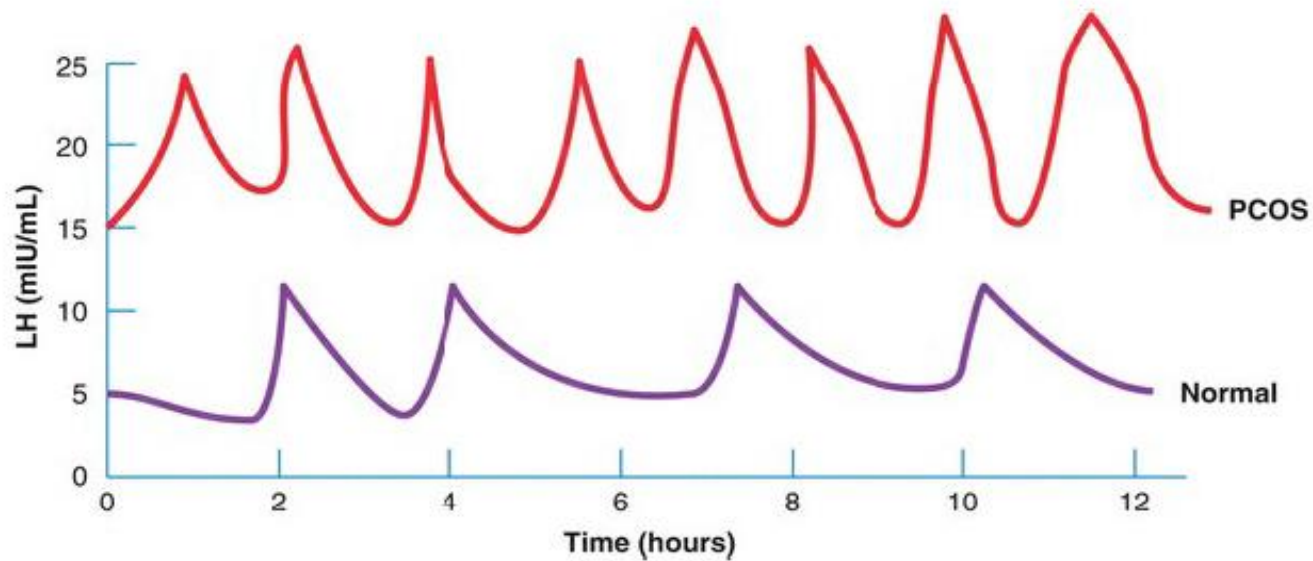
A vicious cascade of events is thus created with insulin excess worsening hyperandrogenism through

Further ovarian androgen production

Lowering of hepatic SHBG production







Treatment with a progestin slows LH pulse frequency

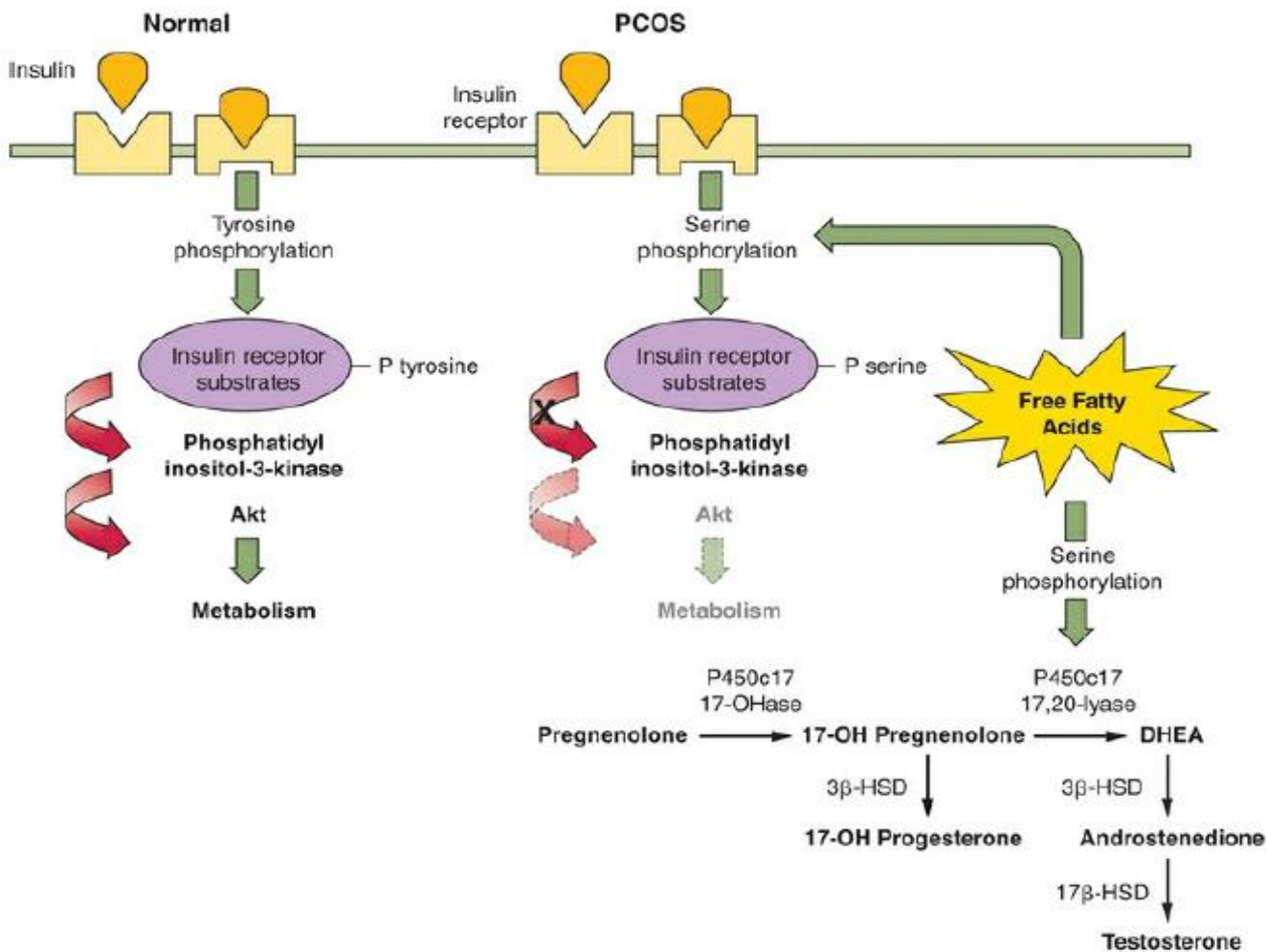
# Insulin Secretion and Action



- **Insulin resistance** is a common feature in obese and, to a lesser extent, lean women with PCOS; the overall prevalence ranges **between 50% and 75%**.
- **In obese PCOS women, 70–80% are insulin-resistant, while 20–25% of lean women with PCOS are insulin-resistant.**
- **Up to 35% of women with PCOS exhibit impaired glucose tolerance, and 7–10% meet the criteria for type 2 diabetes Mellitus.**
- **women with type 2 diabetes are sixfold more likely than** nondiabetic women of similar age and weight to have PCOS.



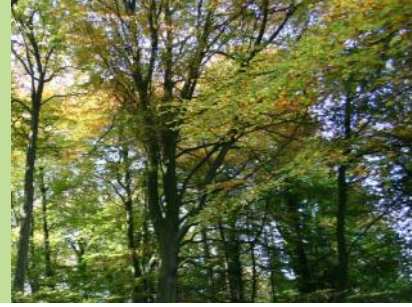
- The combined actions of insulin and androgens lower SHBG concentrations
  - increased free androgen levels
  - which aggravate the underlying insulin resistance.
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- Ultimately, these conditions foster a self-propagating positive feedback loop that can increase in severity over time.





- Insulin resistance and hyperinsulinemia are the cause, not the result, of hyperandrogenism in PCOS.

# Obesity, Weight, and Energy Regulation



- Obesity, by itself, is associated with insulin resistance and compensatory hyperinsulinemia.
- Obesity in women with PCOS typically is distributed centrally, with a greater increase in visceral than in subcutaneous fat.
- However, even lean women with PCOS have an 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.





Adrenal androgen production (**androstenedione**, **DHEA**, **DHEA-S**) also is increased in women with PCOS  
**over half** exhibit moderately increased circulating DHEA-S levels.

# Ovulatory and Menstrual Dysfunction





- The majority of women with PCOS, approximately 60–85%, exhibit obvious menstrual dysfunction.
- The most common menstrual abnormalities in women with PCOS are oligomenorrhea and amenorrhea.
- Polymenorrhea (regular cycles occurring at intervals <21 days) is quite uncommon, observed in less than 2% of the PCOS population.

# Abnormal Gonadotropin Secretion



- Altered LH/FSH ratios are **more often encountered in the lean than in obese women** with PCOS. In the past, an increased LH/FSH ratio (e.g.,  $>2:1$ ) has been regarded as a marker of PCOS.
- Consequently, gonadotropin levels or ratios are not a reliable diagnostic criterion; **they neither make, nor exclude**, the diagnosis of PCOS.

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- The **fasting serum insulin concentration** is easy to obtain ; in euglycemic white women with PCOS, values greater than **20–30 mu/ml** suggest insulin resistance.
  - The **fasting glucose/insulin ratio** has been used widely  
a **ratio less than 4.5** has reasonable sensitivity and specificity for insulin Resistance.



Specific screening for insulin resistance also is recommended for women with markedly elevated serum androgen levels ( $\geq 150$  ng/dl) to differentiate the severe insulin resistance syndromes from androgen-secreting tumors.

# Dyslipidemia



- Dyslipidemia is perhaps the most common metabolic abnormality observed in women with PCOS.
- Insulin resistance and hyperinsulinemia are associated with **decreased HDL and elevated TG levels**, and numerous studies have observed such abnormalities in women with PCOS.
- Some also have observed **elevated LDL** concentrations.



# Inflammation



- PCOS is a pro-inflammatory state.
- As increased central adiposity is present in PCOS patients regardless of BMI, this may explain the inflammatory state of PCOS.
- C-reactive protein (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

# Cancer Risk



- Chronic anovulation, obesity, and hyperinsulinemia provide an environment that is conducive to risk for proliferative endometrial pathologies such as endometrial hyperplasia and even endometrial cancer in women with PCOS.
- The risk for endometrial cancer may be as high as threefold greater in anovulatory women with PCOS compared to women with normal reproductive physiology.

# Exclusion of Other Disorders



- PCOS is a diagnosis of exclusion, after considering and eliminating other causes of chronic anovulation (primarily thyroid disorders and hyperprolactinemia) and of androgen excess.
- Together, CAH, androgen-secreting tumors, severe insulin resistance syndromes, Cushing syndrome, and idiopathic hirsutism account for about 10–30% of hyperandrogenism in women.



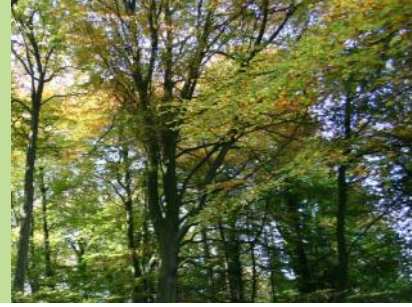
Condition	Features Shared with PCOS	Unique Features and Methods for Exclusion
Late-onset congenital adrenal hyperplasia	Oligoanovulation Hyperandrogenism Hyperandrogenemia	Autosomal recessive disorder Elevated 17-OHP levels in the commonest variant due to 21-hydroxylase deficiency
Androgen secreting tumor Ovarian Adrenal	Oligoanovulation Hyperandrogenism Hyperandrogenemia	Rapid progression of clinical symptoms of hyperandrogenism Signs of virilization Markedly elevated total testosterone levels Elevated DHEA-S levels
Cushing syndrome	Oligoanovulation Hyperandrogenism Hyperandrogenemia	Clinical stigmata including hypertension, moon facies, buffalo hump, skin plethora, hypertension Elevated 24-hour urine-free cortisol
Hyperprolactinemia	Oligoanovulation	Elevated prolactin levels
Hypothyroidism	Oligoanovulation Coarsening of hair Hair loss	Elevated TSH levels (primary hypothyroidism) Positive antithyroid antibodies (Hashimoto thyroiditis)
Iatrogenic Androgenic agents Antidepressants Antiseizure	Oligoanovulation Hyperandrogenism	Androgen exposure Suppressed FSH/LH levels Elevated total testosterone Antidepressants and antiseizure Hyperprolactinemia
Severe insulin resistance syndrome	Oligoanovulation Hyperandrogenism Hyperandrogenemia	Elevated fasting insulin levels Markedly elevated provoked insulin levels during OGTT Acanthosis nigricans

# Thyroid Disorders



- The overall high prevalence of thyroid dysfunction in women warrants specific testing to exclude the diagnosis **in all anovulatory women, including those with evidence of hyperandrogenism.**
- Serum **TSH** is considered as the gold standard first-line test for assessing primary thyroid disorders.

# Hyperprolactinemia



Hyperprolactinemia is highly associated with menstrual dysfunction and is one of the most common causes of secondary amenorrhea.


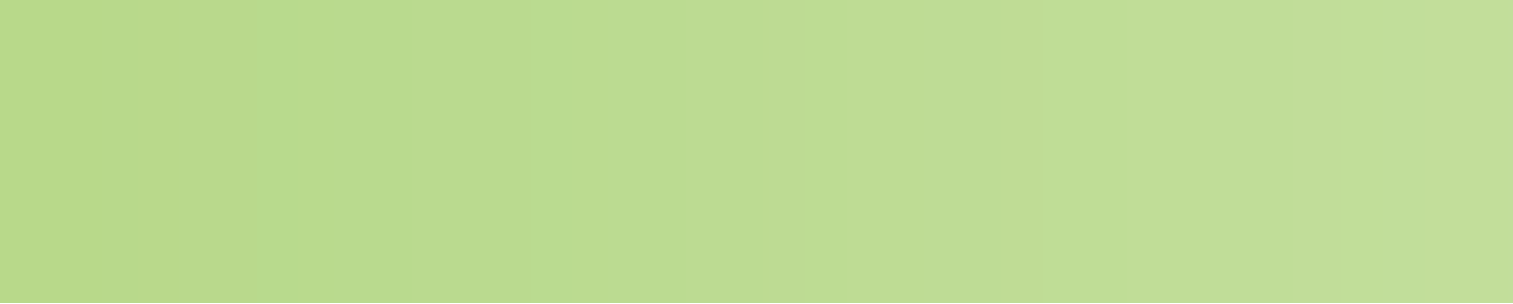


# Nonclassical Congenital Adrenal Hyperplasia



The most common cause is 21-hydroxylase deficiency; other enzyme defects (11 $\beta$ -hydroxylase, 3 $\beta$ -hydroxysteroid dehydrogenase) are relatively rare.

In all, the pathophysiology stems from decreased cortisol production, which stimulates a compensatory increase in pituitary ACTH secretion, causing adrenal hyperplasia; resulting in increased production of androgens.



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

# Androgen-Secreting Ovarian and Adrenal Tumors



- Androgen-secreting tumors almost always are accompanied by severe or rapidly progressive hirsutism or symptoms or signs of **virilization** (deepening of the voice, temporal or male pattern balding, breast atrophy, increased muscle mass, and clitoromegaly).
- The possibility of a tumor is excluded primarily by the clinical history and physical examination.
- A serum total testosterone concentration **greater than 150 ng/dl** identifies almost all women with a potential androgen-producing tumor.

# Cushing Syndrome



- The disorder has features commonly 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%**.
- Consequently, **routine screening is not justified** and should be limited to the very few patients who also have distinct signs and symptoms of hypercortisolism.

# Methods of screening for Cushing syndrome



- The overnight dexamethasone suppression test is the best single screening test because of its simplicity and ability to discriminate.
- The test is performed by administering 1.0 mg of dexamethasone between 11:00 P.M. and midnight and measuring the serum cortisol at 8:00 A.M. the next morning; values less than 1.8 mg/dl are normal.

# Idiopathic Hirsutism



- The prevalence of **idiopathic hirsutism** among hirsute women is approximately **5–7%**.
- It is generally assumed that idiopathic hirsutism results from **increased peripheral 5 $\alpha$ - reductase activity**, which amplifies the action of normal circulating testosterone concentrations via increased intracellular conversion to the more potent androgen, **DHT**.



# Severe Insulin Resistance Syndromes



The diagnosis can be substantiated by findings of markedly elevated levels of insulin, typically greater than **80 mu/ml** fasting or greater than **300 mu/ml** 2 hours after an oral glucose load.



*Thank you!*

