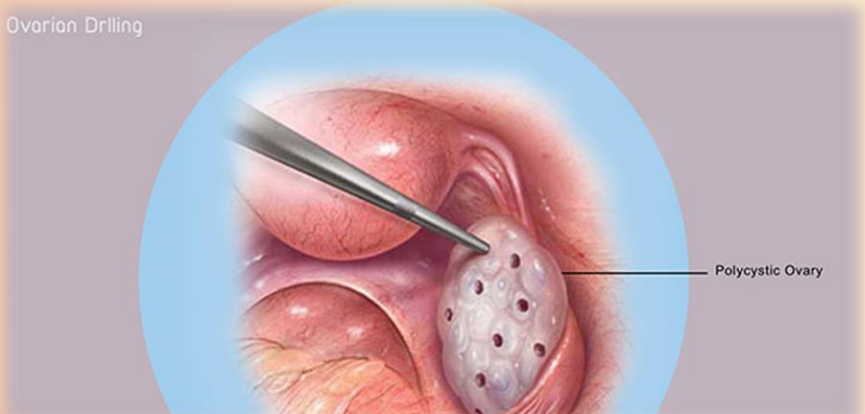

IN THE NAME OF GOD

Polycystic Ovary Syndrome (PCOS)

Niayesh Mohebbi
Department of Clinical Pharmacy
TUMS



PCOS; Points to Cover Today

- Epidemiology
- Pathophysiology
- Clinical Features
- Diagnosis
- Treatment

Epidemiology

- PCOS recognized as one of the most common endocrine/metabolic disorders of reproductive-age women, with a prevalence of approximately 6% to 15%, or approximately 1 in 10 women.
- PCOS is the leading cause of **anovulatory** infertility.

Diagnosis

- According to the Rotterdam criteria, the presence of two of these three features, after exclusion of related disorders, confirmed diagnosis of PCOS:

A. Oligo-ovulation or anovulation

B. Clinical or biochemical signs of hyperandrogenism

C. Polycystic ovaries (by ultrasound)

Clinical Features

Ovulatory dysfunction in PCOS presented clinically as a woman with irregular menstrual cycles:

Oligomenorrhea or amenorrhea (95%)

Common clinical signs of **hyperandrogenism** in PCOS include:

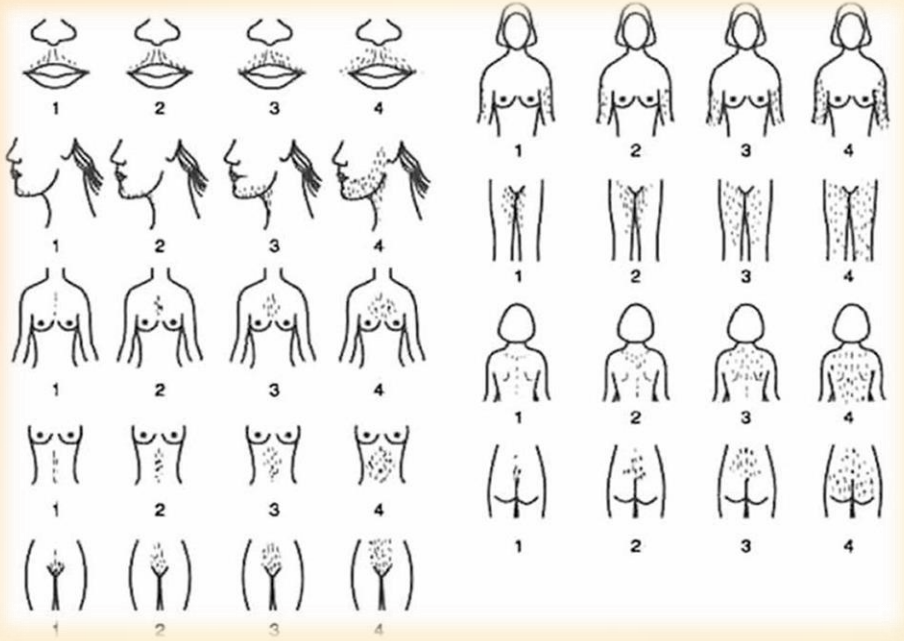
Hirsutism (60% to 75%)

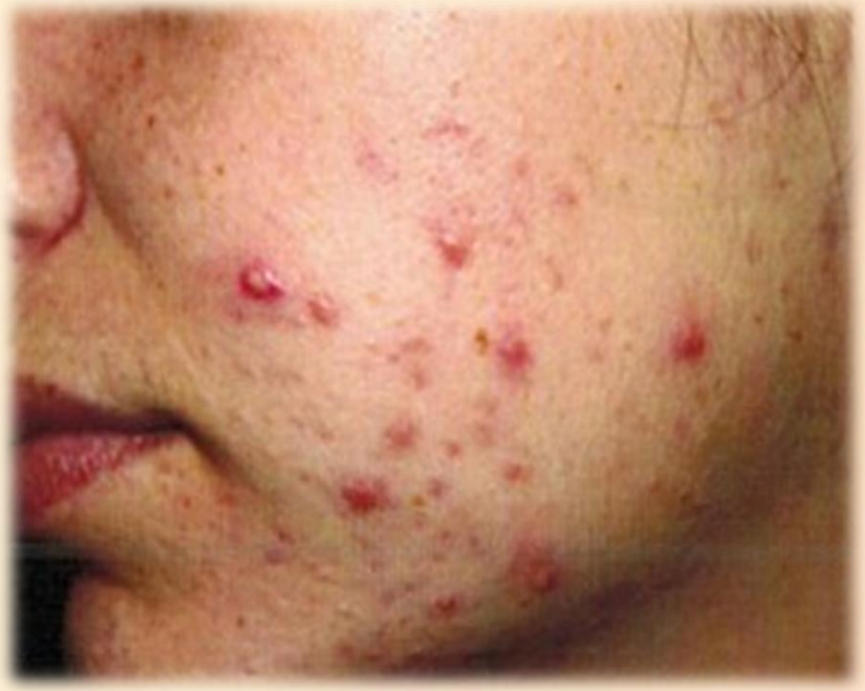
Acne (15% to 25%)

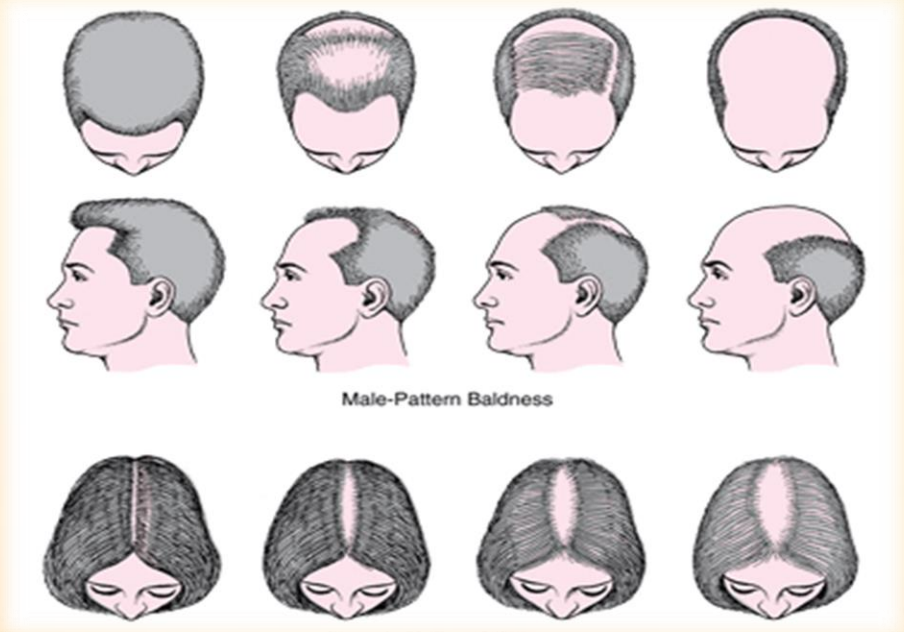
Alopecia: Male pattern hair loss (5% to 50%)

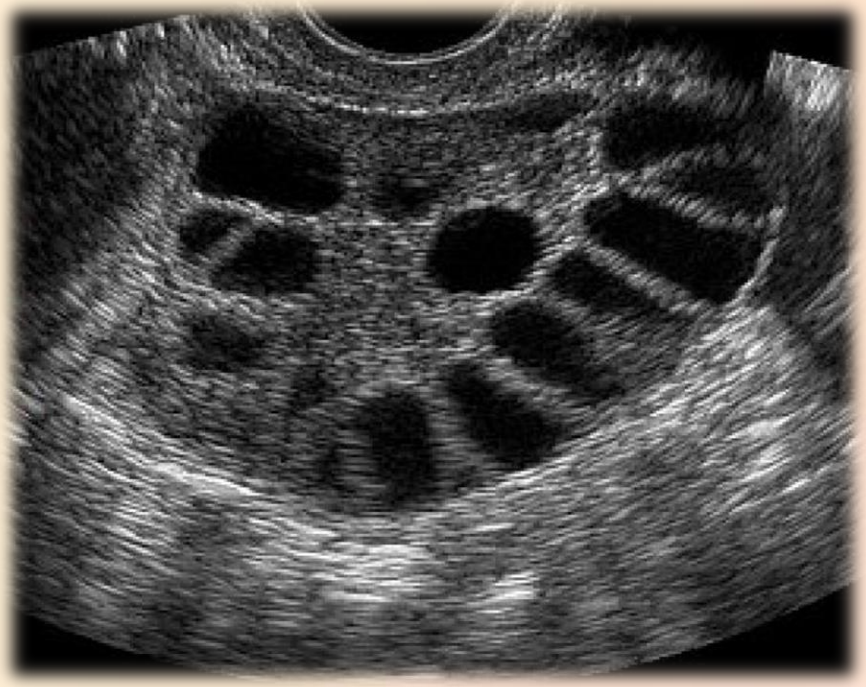
Elevated serum androgen concentrations

Obesity (BMI ≥30 kg/m2) (61% to 76%)






Male-Pattern Baldness



Differential Diagnosis

- Nonclassic Congenital Adrenal Hyperplasia (NCCAH)
- Thyroid disorders
- Hyperprolactinemia
- Androgen-secreting ovarian and adrenal tumors
- Ovarian hyperthecosis

Pathophysiology

The primary defect in PCOS is unknown, but at least three potential mechanisms, acting alone or synergistically, appear to create the characteristic clinical presentation:

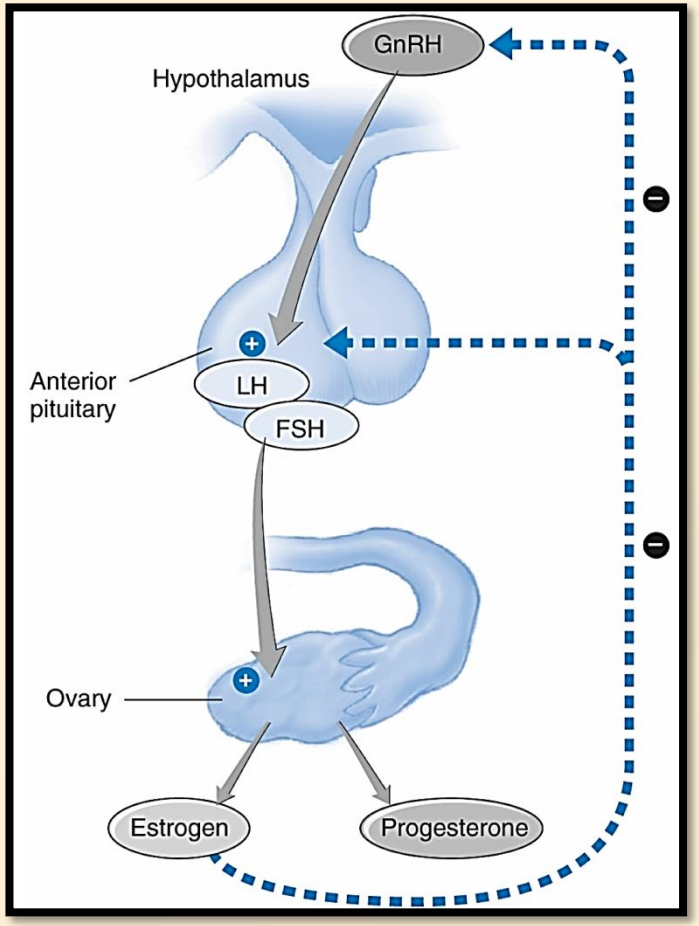
- Inappropriate **gonadotropin** secretion
- Excessive **androgen** production
- Insulin resistance with **hyperinsulinemia**

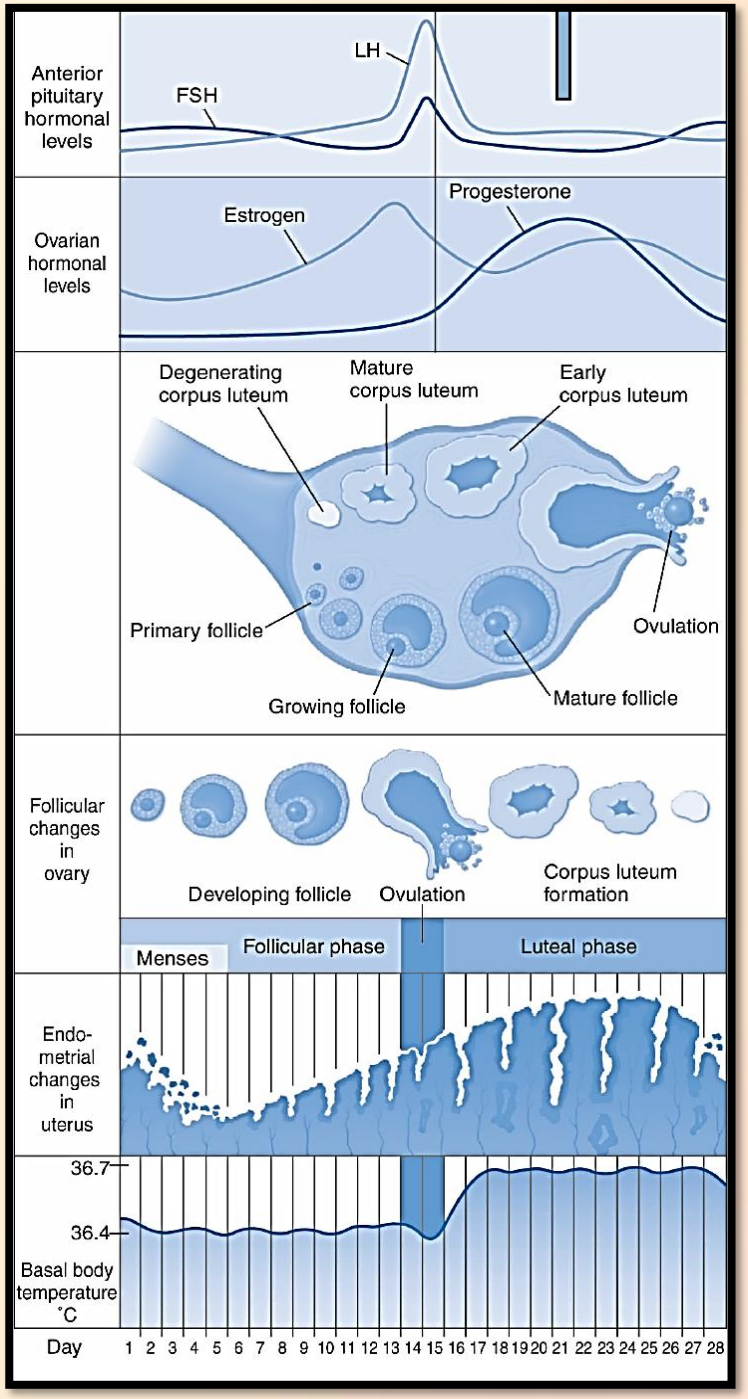
A **genetic** basis for PCOS has been postulated, but its mode of transmission is unclear

GONADOTROPIN SECRETION

- In PCOS, there is an increased frequency of GnRH stimulation, leading to an increase in LH pulse frequency and amplitude, whereas FSH secretion remains normal.
- The development of a dominant follicle does not occur because LH secretion occurs too early in the menstrual cycle. Therefore, a woman is left with several immature follicles and usually will not ovulate.

Menstrual Cycle Physiology





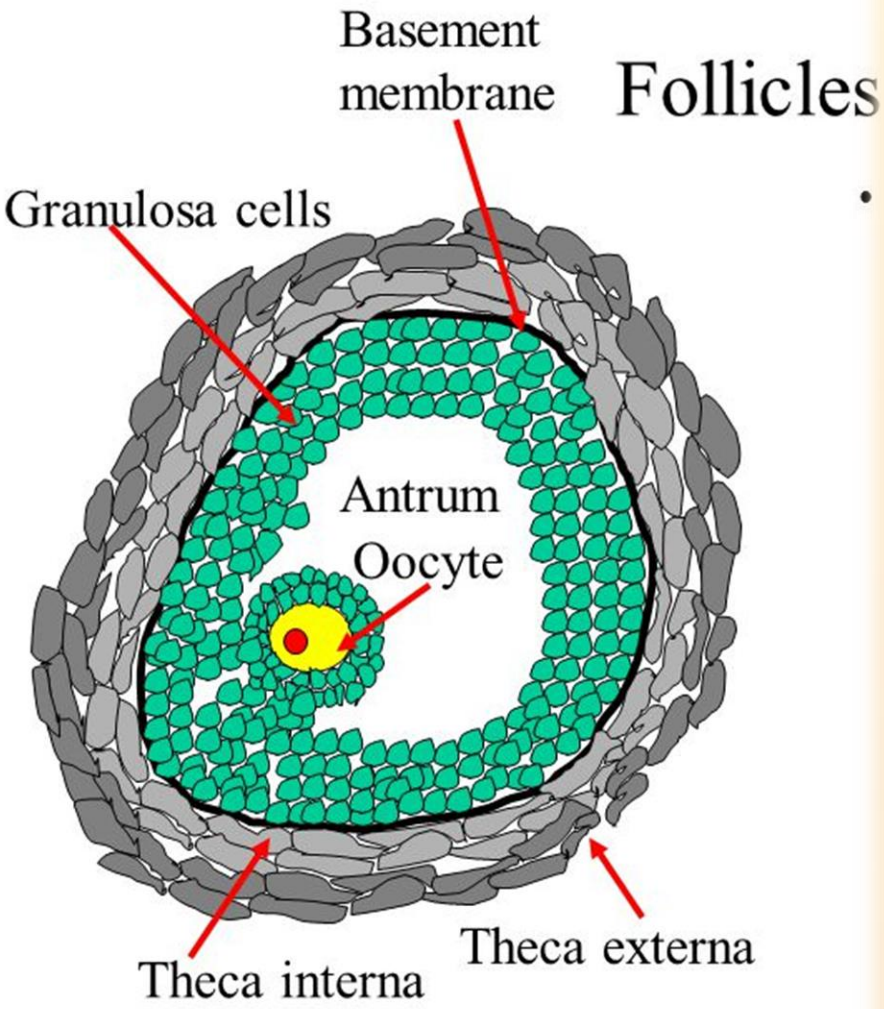
GONADOTROPIN SECRETION

- A woman with this abnormality does not enter the luteal phase of her menstrual cycle, leaving estrogen unopposed.

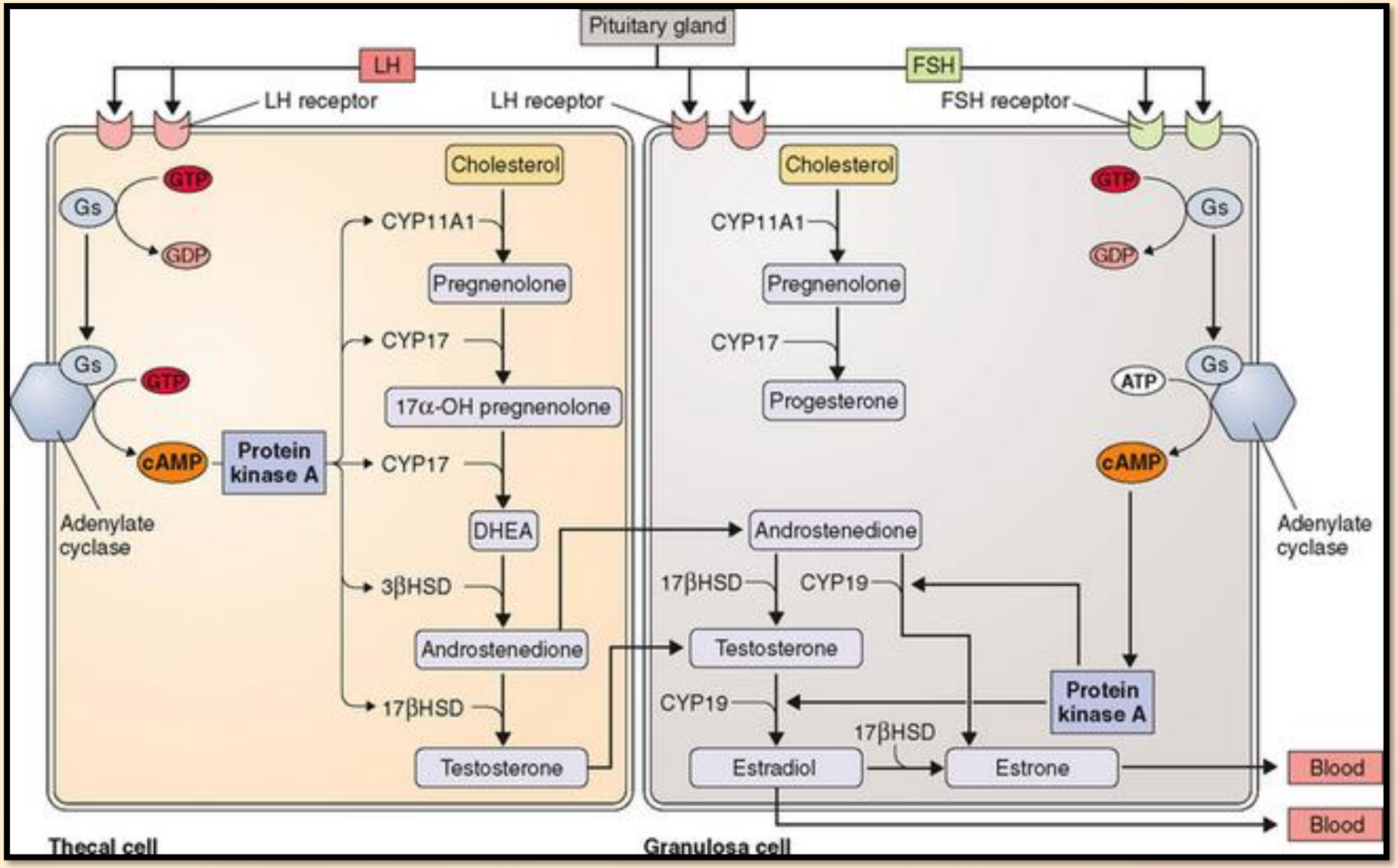
- Unopposed estrogen leads to endometrial hyperplasia and increases the risk for endometrial cancer.

- Increased LH stimulation leads to increased steroidogenesis in the ovary, leading to excess androgen production.

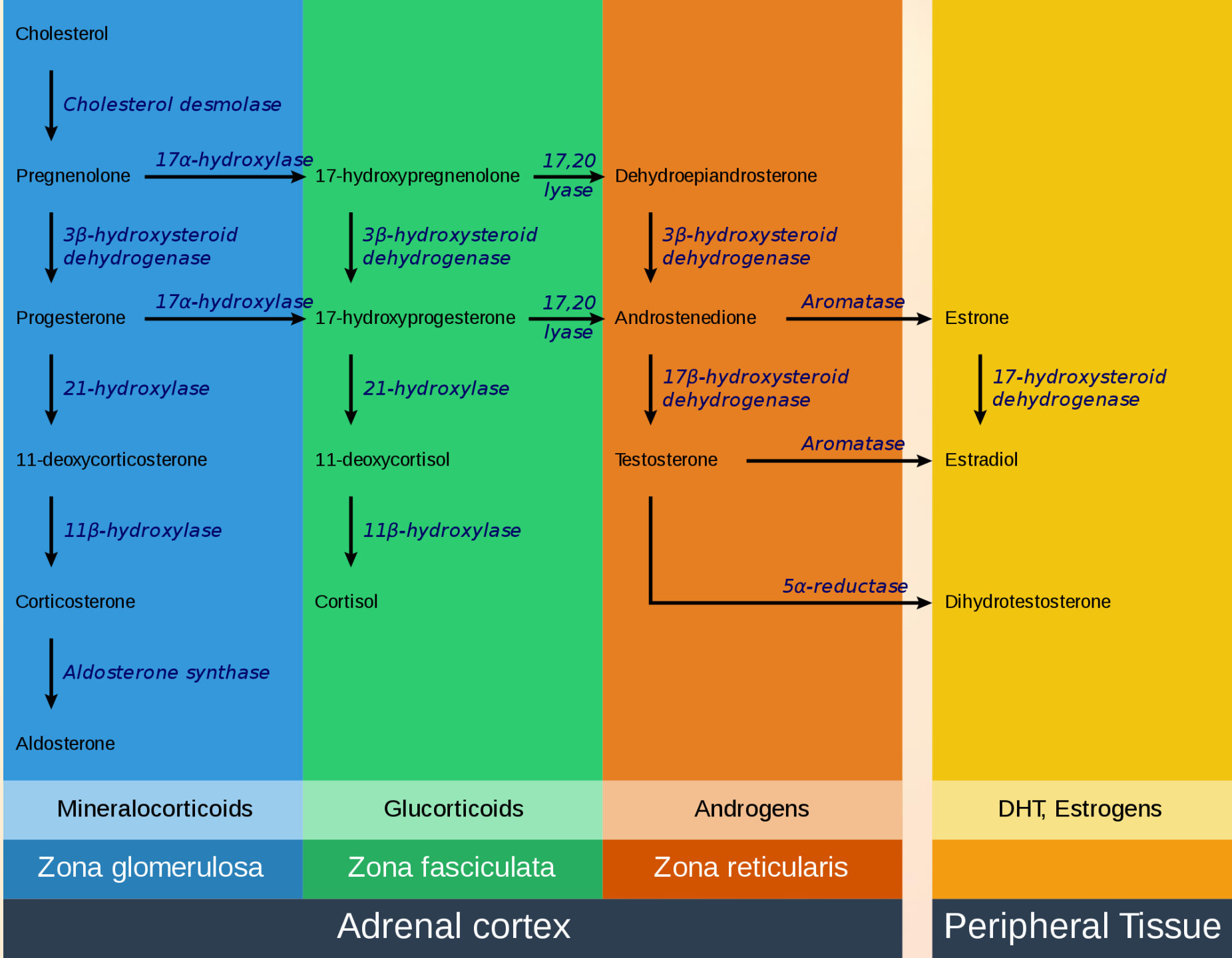
Follicles


Basement membrane
Granulosa cells
Antrum
Oocyte
Theca interna
Theca externa

Biosynthesis of Ovarian Hormones



Steroid Pathway in Adrenal Cortex



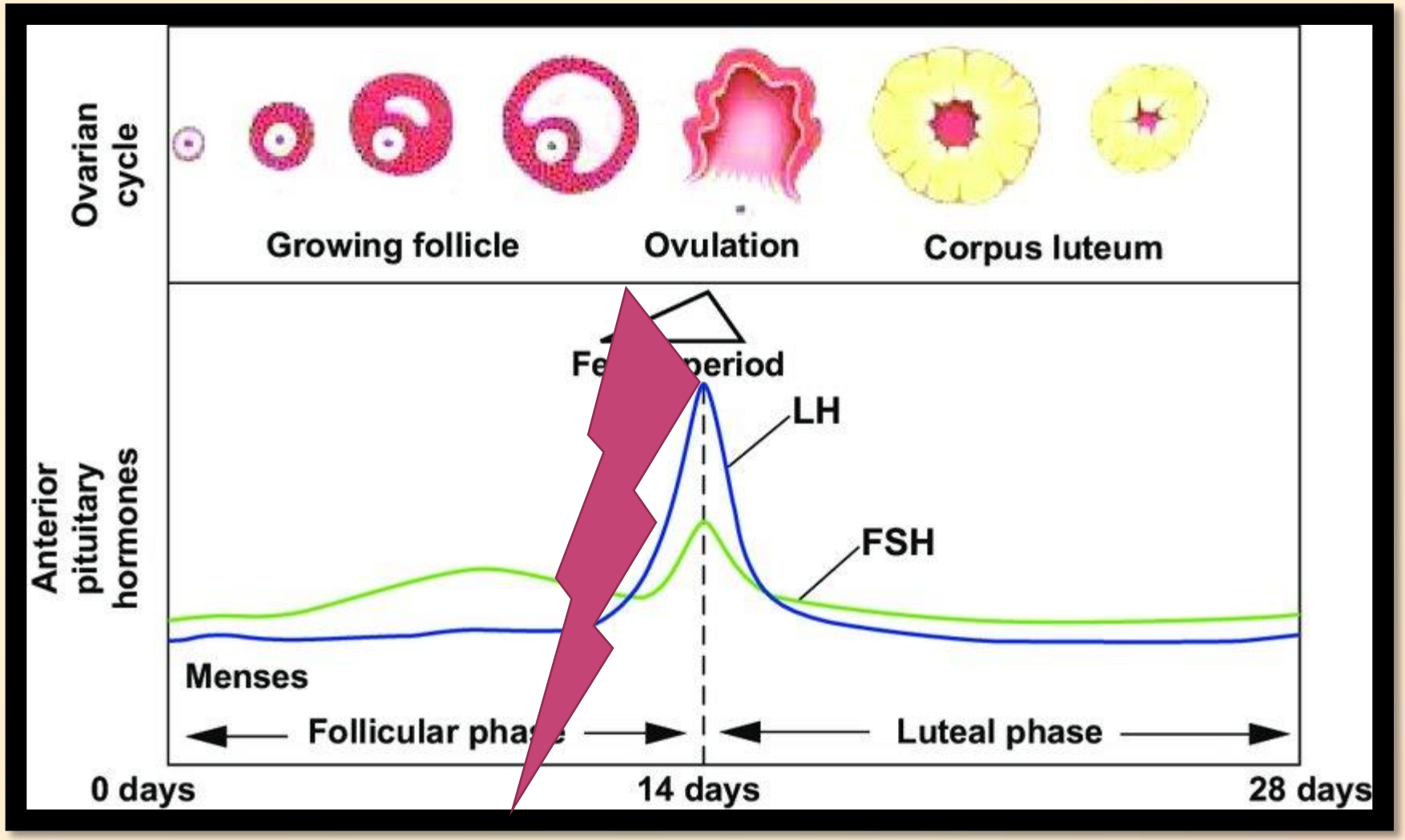
EXCESS ANDROGEN PRODUCTION

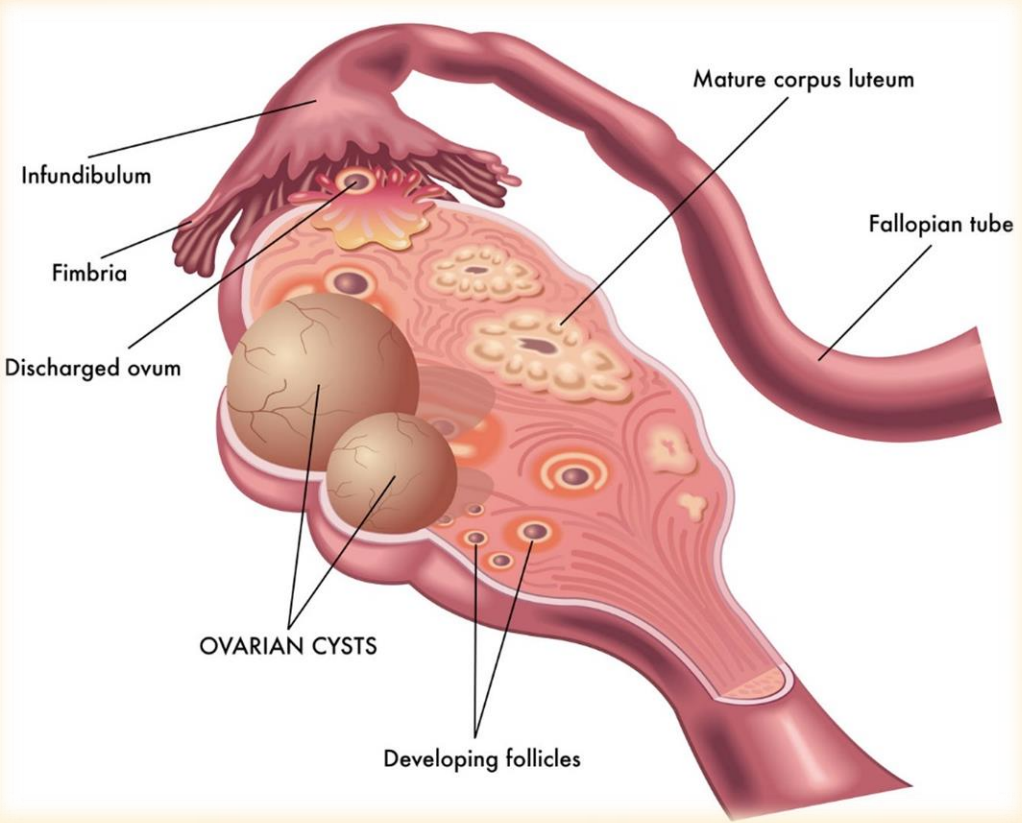
In women with PCOS, hypersecretion of LH and insulin increases the production of androgens, causing abnormal sex steroid synthesis, hyperandrogenism, and hyperandrogenemia.

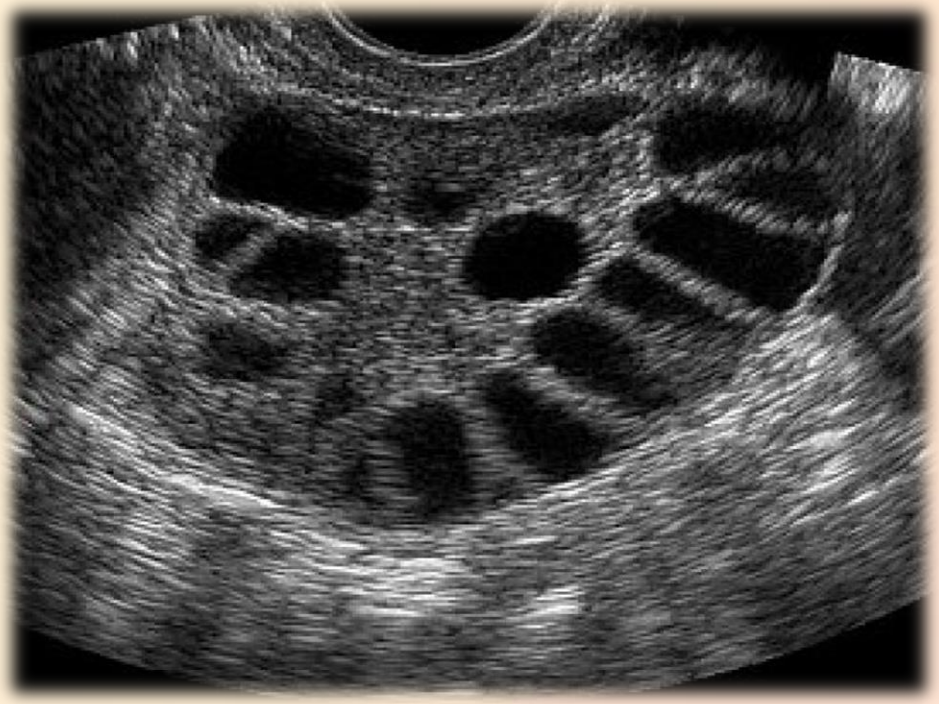
Elevated androgen levels are seen in approximately 60% to 80% of women with PCOS, mostly as increased free testosterone concentrations.

Polycystic ovaries

- During a woman’s menstrual cycle, an egg grows in a sac called a follicle. This sac is located inside the ovaries. In most cases, this follicle or sac breaks open and releases an egg. But if the follicle doesn’t break open, the fluid inside the follicle can form a cyst on the ovary.
- The follicles keep growing and form multiple "cysts.“
- These may be described as appearing like a "string of pearls" in an ultrasound image.


Ovarian cycle
Growing follicle
Ovulation
Corpus luteum
Anterior pituitary hormones
LH
FSH
Menses
Follicular phase
Luteal phase
0 days
14 days
28 days


Mature corpus luteum
Infundibulum
Fallopian tube
Fimbria
Discharged ovum
OVARIAN CYSTS
Developing follicles



Insulin Resistance

- The cellular and molecular mechanisms for insulin resistance are different from those seen with obesity and type 2 diabetes.
- Insulin resistance is associated with reproductive and metabolic abnormalities in women with PCOS and can occur in both obese and nonobese women.

Mechanism

- Hyperinsulinemia results because of the compensatory increase in insulin secretion secondary to insulin resistance.
- The insulin resistance in PCOS has been shown to be a selective, tissue-specific process where insulin sensitivity is increased in the ovarian androgenic pathway (causing hyperandrogenism), but insulin resistance is seen in other tissues involved with carbohydrate metabolism, specifically in the fat and muscle.

Insulin & PCOS

Insulin has both direct and indirect roles in PCOS.

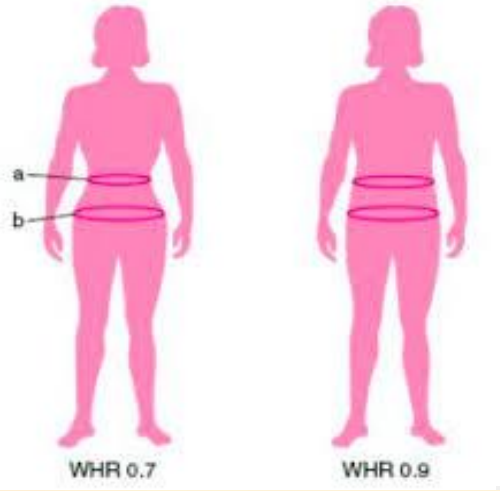
- In the **ovary**, insulin acts alone or synergistically with LH to increase androgen production in theca cells.
- In the **liver**, insulin inhibits synthesis of SHBG, a key protein that binds to testosterone, and thus increases the free fraction of androgens available for biologic activity.

Therefore, hyperinsulinemia is a major contributor to hyperandrogenemia in PCOS.

Directly, insulin may enhance the amplitude of LH pulses, further exacerbating the gonadotropin secretion defect in PCOS.

IMPAIRED GLUCOSE TOLERANCE AND DIABETES

- Women with PCOS have a higher prevalence of IGT, gestational diabetes, diabetes, and insulin resistance.
- A family history increases the risk of these conditions further.
- Waist–hip ratio and BMI appeared to be the most clinically important predictors of glucose intolerance.



Health risk	Women	Men
Low	0.80 or lower	0.95 or lower
Moderate	0.81–0.85	0.96–1.0
High	0.86 or higher	1.0 or higher

- ❖ According to the WHO, a healthy WHR is:
- ✓ 0.9 or less in men
- ✓ 0.85 or less for women

IGT

- Women with PCOS who have IGT appear to exhibit DM2 at higher rates than the general population.
- Therefore, screening and diagnosis of these conditions is important for women with PCOS.
- Glucose tolerance should be assessed in all women with PCOS using a **fasting** and **2-hour** oral (75 g) glucose tolerance test.
- **Insulin concentrations** are typically not obtained in clinical settings because they are **inaccurate**.

METABOLIC SYNDROME AND CARDIOVASCULAR RISK

- Approximately 1/3 to 1/2 of women with PCOS have metabolic syndrome.

❖ Metabolic syndrome is present when the patient exhibits any three of these symptoms:

✓ abdominal obesity (>101 cm in men and >89 cm in women)

✓ TG ≥ 150 mg/dL, low HDL cholesterol (<40 mg/dL in men and <50 mg/dL in women)

✓ BP ≥ 130/85 mm Hg,

✓ FBS ≥ 110 mg/dL

METABOLIC SYNDROME

- It is believed that **insulin resistance** and **hyperandrogenism** are contributing factors to metabolic syndrome in women with PCOS.

- Insulin resistance in the metabolic syndrome has been associated with a 2-fold increased risk of CVD and a 5-fold increased risk of DM2.

- With increasing age, and especially as women with PCOS become postmenopausal, the risk of HTN increases 2-fold.

METABOLIC SYNDROME AND CARDIOVASCULAR RISK

- Dyslipidemia in women with PCOS:

↓ HDL-C, ↑ TG, ↑ LDL-C, and higher LDL–HDL ratios

- Women with PCOS are considered to be at risk for CVD when any of these risk factors are present:

◉Obesity, ◉cigarette smoking ◉HTN ◉dyslipidemia

◉subclinical vascular disease ◉IGT ◉FH of premature CVD

OBSTRUCTIVE SLEEP APNEA

- OSA is cessation of breathing that occurs during sleep.
- Patients may not be aware that they are having the symptoms of sleep apnea, which include snoring and a gasping or snorting when breathing resumes.
- **Insulin resistance** appears to be a strong predictor of sleep apnea—more so than age, BMI, or the circulating testosterone concentration.
- This can be treated with continuous positive airway pressure (CPAP).

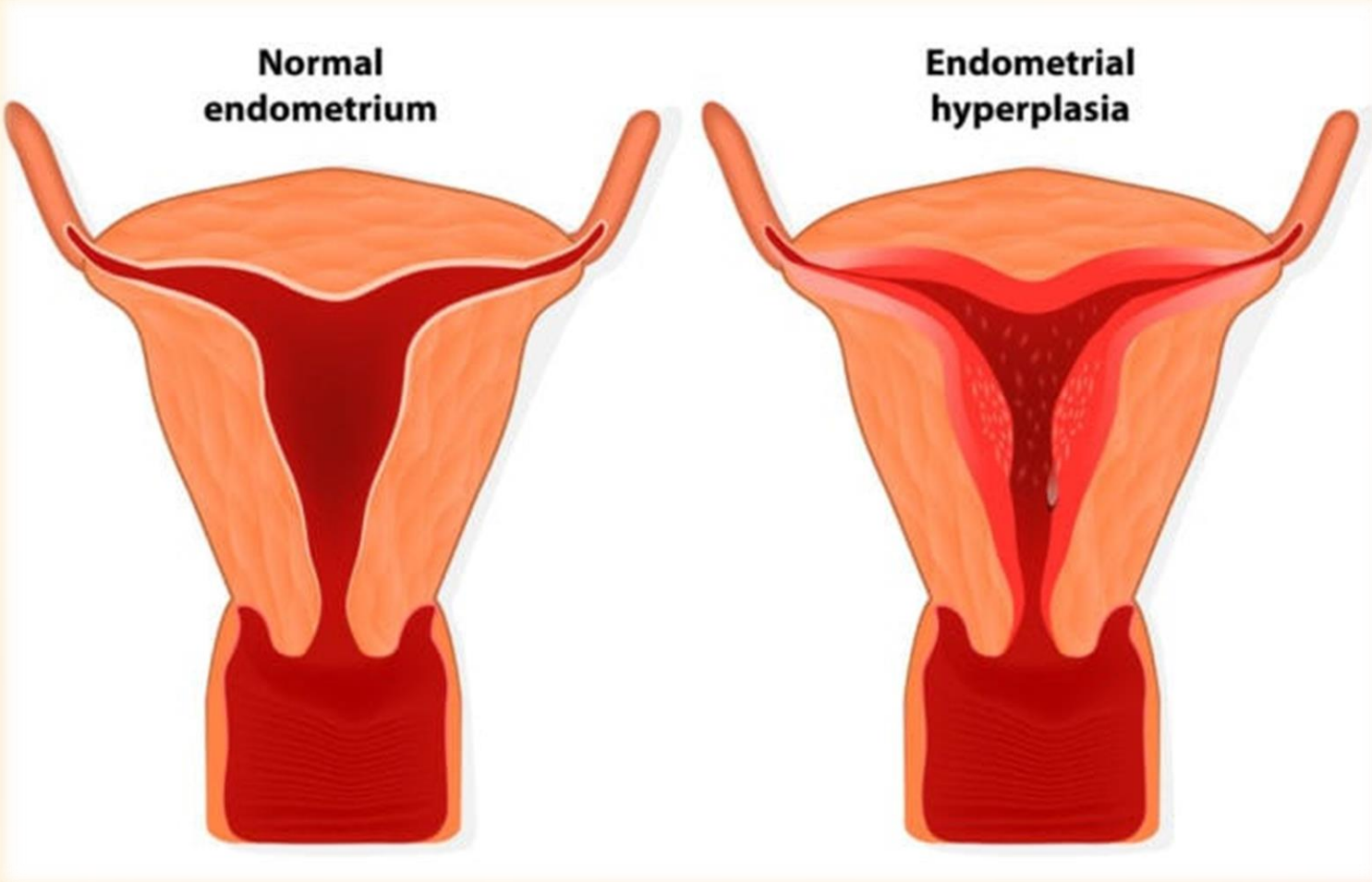
ENDOMETRIAL HYPERPLASIA AND CANCER

- Chronic anovulation in women with PCOS results in an endometrium that is exposed to the prolonged effects of estrogen unopposed by progesterone ➲ **PCOS is a risk factor for endometrial hyperplasia**

- It is considered prudent management to induce artificial withdrawal bleeding by administering a course of progestin at least every 3 months to prevent endometrial hyperplasia in women with PCOS who experience either amenorrhea or oligomenorrhea.

- Alternatively, **ultrasound** scans can also be used to measure endometrial thickness and morphology every 6 to 12 months.

PCOS Long Term Complication



PSYCHOSOCIAL ISSUES

❖**Mood disorders**

- There is evidence that women with PCOS may be more likely to have mood disorders (depression and anxiety) when compared with women without PCOS.

- The Androgen Excess and PCOS Society suggests **screening for depression and anxiety at the time of diagnosis.**

- Diagnosis?!
- Treatment?!

The overall goals of therapy of women with PCOS include:

- Amelioration of hyperandrogenic features (hirsutism, acne, scalp hair loss).
- Management of underlying metabolic abnormalities and reduction of risk factors for DM2 and CVD.
- Contraception for those not pursuing pregnancy, as women with oligomenorrhea ovulate intermittently and unwanted pregnancy may occur.
- Ovulation induction for those pursuing pregnancy.
- Prevention of endometrial hyperplasia and carcinoma which may occur as a result of chronic anovulation.

NONPHARMACOLOGIC TREATMENT

- A 5% to 10% **weight reduction** program
- **Diet** modification ➲ ↓ free testosterone concentrations
- **Exercise** (150 minutes/week of moderate exercise or 75 minutes/week of vigorous exercise)

DIET COMPOSITION

- Low in saturated fat, high in fiber and low-glycemic-index carbohydrate foods
- Glycemic index is a classification of carbohydrates based on the blood glucose response during 2 hours.
- Low-glycemic index foods include bran cereals, mixed grain breads, broccoli, peppers, lentils, and soy.
- High-glycemic index foods, or those that should be minimized, include white rice and bread, potatoes, chips, and foods containing simple sugars (e.g., juice).

PHARMACOLOGIC TREATMENT

- Combined oral contraceptive (COC) pills
- Insulin sensitizing agents
- Antiandrogen medications

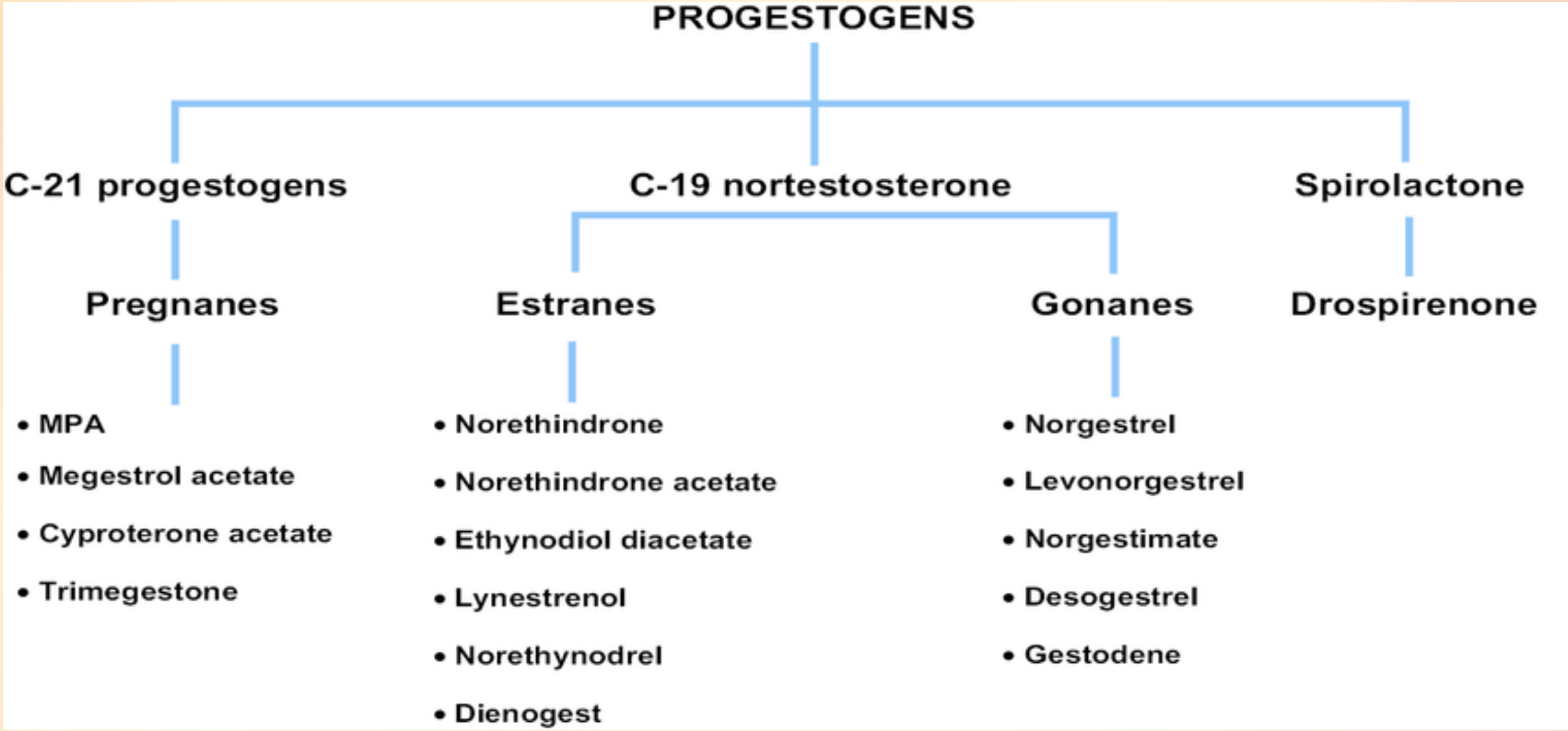
COMBINED ORAL CONTRACEPTIVES

- Estrogen–progestin combination therapy with a COC is the treatment of choice for women seeking regularity in menstrual cycles and relief from hyperandrogenic symptoms.

- The estrogen component suppresses LH, resulting in a reduction of androgen production, and increases hepatic production of SHBG, thereby reducing free testosterone.

- COC therapy in PCOS should be initiated with a formulation that contains a low dose or very low dose of estrogen (≤35 mcg of ethinyl estradiol) and a progestin with low androgenic or antiandrogen properties. Desogestrel and norgestimate are progestins with low androgen potential, and drospirenone is an antiandrogen.

Sl. No.	Kind of Progestin	Generation	Effects
1.	Northindrone	1st	Low progestational and slight oestrogenic effect. In low dose improve lipid profile by raising HDL and lowering LDL.
2.	Northindrone Acetate	1st	Low progestational and slight oestrogenic effect.
3.	Ethynodiol Diacetate	1st	Medium progestational effect, minor oestrogenic effect and little androgenic effect. Associated with mid-cycle BTB and spotting but with higher dose of oestrogen, no such side effects.
4.	Levonogestrel	2nd	High progestational and androgenic effect. Negatively affect serum lipoprotein.
5.	Norgestrel Mixture of inactive (dextro-norgestrel) & active levonogestrel.	2nd	High progestetational and strong antioestrogenic effect as well as high androgenic effect. May cause LDL cholesterol to be increased and allowing HDL cholesterol to be lower.
6.	Desogestrel	3rd	High progestational selectivity, minimizing androgenic effects and oestrogenic activity.
7.	Norgestimate	3rd	High progestational and slight oestrogenic effect. Minimal effect on serum lipoprotein and on carbohydrate metabolism. Helpful in lowering side-effects such as nausea and vomiting.
8.	Drospirenone (Progestin derived from 17a-Spirolactoneis)	4th	Potent progestogenic, low androgenic activity helps to suppress the secretion of the hormone that regulates the body's water and electrolyte. Causes higher K level, so women with kidney, liver or adrenal disease shouldn't use.


PROGESTOGENS
C-21 progestogens
C-19 nortestosterone
Spirolactone
Pregnanes
Estranes
Gonanes
Drospirenone
• MPA
• Megestrol acetate
• Cyproterone acetate
• Trimegestone
• Norethindrone
• Norethindrone acetate
• Ethynodiol diacetate
• Lynestrenol
• Norethynodrel
• Dienogest
• Norgestrel
• Levonorgestrel
• Norgestimate
• Desogestrel
• Gestodene

کنتراسپتیو ال دی : LD contraceptiveیا کنتراسپتیوهای با دز پایین LD = LOW DOSE

- این قرص شاید قدیمی ترین، مشهورترین و پرمصرف ترین کنتراسپتیو ایران باشد. قرص های زرد یا نخودی رنگ در بسته بندی ۲۱ عددی

- levonorgestrel : 0.15 mg
- Ethinylestradiol : 0.03 mg

کنتراسپتیو اچ دی : HD contraceptiveیا کنتراسپتیوهای با دز بالا HD = HIGH DOSE

- قرصهای سفید رنگ در بسته بندی ۲۱ عددی

- levonorgestrel : 0.25 mg
- Ethinylestradiol : 0.05 mg

کنتراسپتیو تری فازیک triphasic contraceptiveیا قرص های سه رنگ:

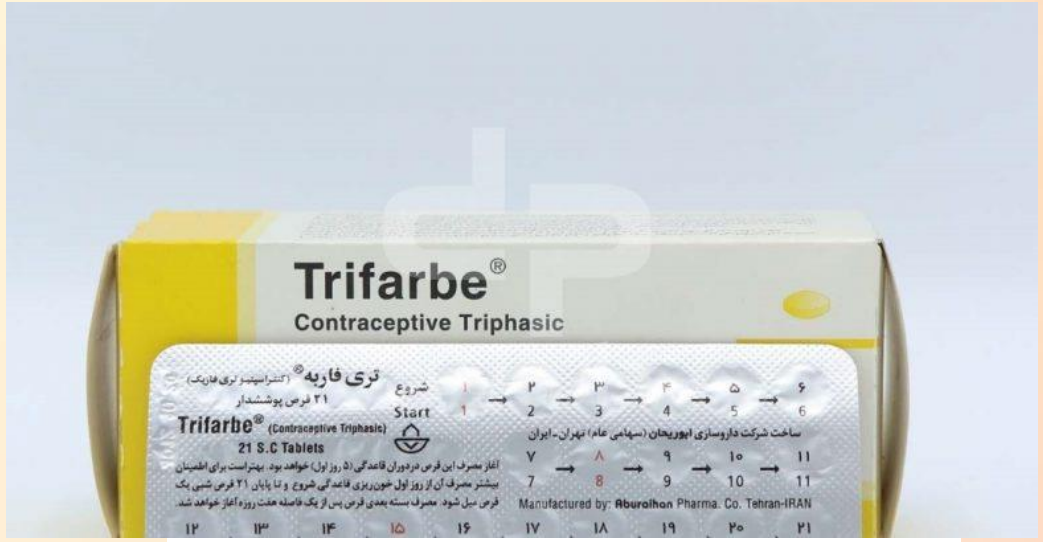
- این قرصها بر اساس میزان هورمونهای طبیعی بدن در طی دوره های سیکل ماهیانه ساخته شده اند و میزان هورمونهای آنها متغیر است وهمانگونه که از اسمشون پیداست دارای سه فاز هستند (TP)
- این قرصها برای مصرف راحتتر و مشخص شدن سه فاز مصرفی آن دارای سه نوع قرص (با سه رنگ) در یک بسته (بلیستر) ۲۱ عددی هستند، به ترتیب زیر:
- ۶ قرص نارنجی
- ۵ قرص زرد
- ۱۰ قرص سفید

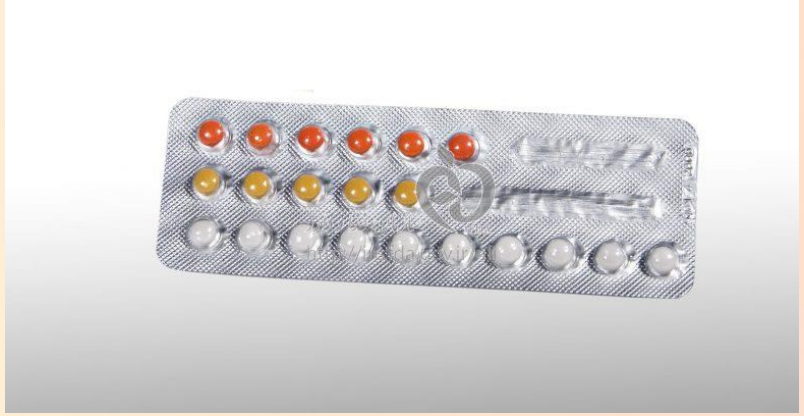
که باید به همان ترتیب ذکر شده از روز اول قاعدگی مصرف شوند.

levonorgestrel : 0.03 mg
Ethinylestradiol : 0.05 mg

levonorgestrel : 0.04 mg
Ethinylestradiol : 0.075 mg

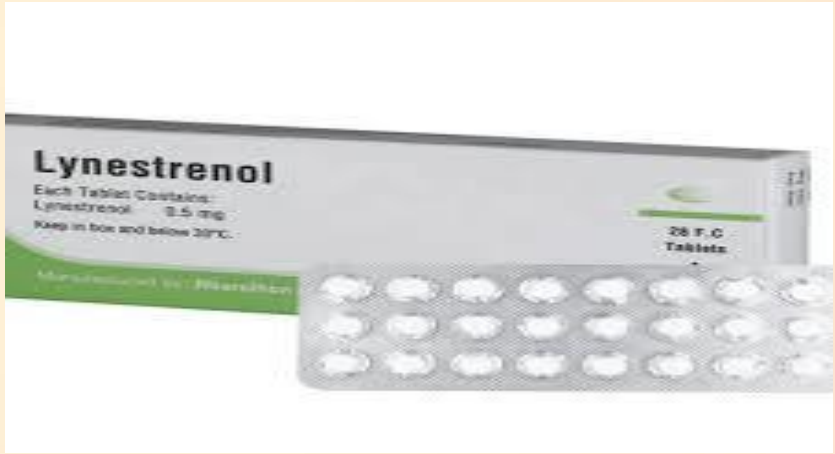
levonorgestrel : 0.03 mg
Ethinylestradiol : 0.025 mg





قرص شیردهی یا لاینسترنول Lynestrenol

- قرصهای سفید رنگ در بلیسترهای ۲۸ عددی هستند (۷ قرص بیشتر از قرصهای ذکر شده در بالا) – این قرصها دارای جزء استروژنی نیستند چون استروژن ترشح شیر را کم می کند و ممکن است اثرات سویی بر شیرخوار داشته باشد. به این نوع داروها مینی پیل pill-miniهم گفته می شود.



داروهای نسل جدید در بازار ایران:

- تفاوت آنها استفاده از پروژستینهای جدیدتر و با عوارض کمتر، استفاده از آنها در برخی حالت ها یا بیماریهای زمینه ای (ماتند آکنه و ...) است؛ وگرنه مکانیسم عمل، درصد شکست آنها با گروه کلاسیک تقریبا یکسان است.
- داروهای این گروه شامل روکین، مارولون، مارولین،کنتراسمین، دزوسپتیو، یاسمین، یاز می باشد.
- از داروهای فوق دزوسپتیو و مارولون و مارولین یکی هستند و همان کنتراسپتیو DEمی باشند.

- Desogestrel:0.15 mg
- Ethinylestradiol: 0.03 mg


MSD
Marvelon®
Marvelon®
Marvelon®


دزوسپتیو®
کنتراسپتیو دی ای
۲۱
قرص روکشدار
هر قرص روکشدار حاوی:
۰/۱۵ میلی گرم
دزوژسترل
۰/۰۳ میلی گرم
اتینیل استرادیول
دستور پزشک
ساخت شرکت ایران هورمون - تهران - ایران


Marolin®
Contraceptive DE
21 Tablets
Each tablet contains:
Desogestrel 0.15mg
Ethinyl Estradiol 0.03mg
Manufactured by:
Marolin®
مارلین
Marolin®

- داروی روکین و کنتراسمین و یاسمین ترکیب مشابهی هستند.

- Drospirenone: 3 mg
- Ethinylestradiol: 0.03 mg

- مکانیسم اثر این دارو هم مانند سایر داروهای این دسته مهار تخمک گذاری از طریق سرکوب LHو FSHاست.
- طرز مصرف آن در رژیمهای ۲۱ روزه که با شروع اولین روز قاعدگی مصرف قرصها ترجیحا بعد از شام و یا موقع خواب شروع شده و تا ۲۱ روز ادامه می یابد .
- مهمترین حسن این دارو نداشتن فعالیت آندروژنی است بنابراین در خانمهای دارای آکنه یا مشکلاتی مانند هیرسوتیسم (افزایش و یا وجود موهای غیرطبیعی و زاید) استفاده از روکین توصیه می گردد (که هم نوعی درمان می باشد و هم خود این داروی هورمونی باعث افزایش آکنه یا موهای زاید نمی گردد).
- چند مزیت دیگر آن عبارتند از:استفاده از آن در درمان آکنه و هیرسوتیسم و نیز PMSیا سندرم پیش قاعدگی - احتمال حاملگی با مصرف صحیح این دارو کمتر از ۱ درصد است.

قرص یاز :

- yazقرص یاز ۲۸ قرص در هر بسته دارد که ۲۴ تای آن صورتی کمرنگ و ۴ تای ان سفید رنگ است برای شروع قرص در روز اول سیکل اولین قرص صورتی کمرنگ را بخورید- به کلمه STARTپشت بسته قرص توجه کنید.- ترجیحا در ساعتی معین- و سپس مصرف قرصها را به صورت شبی یکی ادامه دهید.
- پس از تمام شدن قرصهای صورتی قرصهای سفید را بخورید تا بسته قرص تمام شود حتی اگر در طی این مدت پریود بشوید یا نه باید شروع بسته جدید را آغاز کنید. این قرص می تواند PMDDرا کاهش دهد.

- Drospirenone: 3 mg
- Ethinylestradiol: 0.02 mg

قرص بلارا:

- بسته بلارا حاوی ۲۱ قرص می باشد. مصرف بلارا، را باید از روز اول سیکل آغاز کرد .برای افزایش کارایی، قرص ها باید به طور منظم در هر ۲۴ ساعت مصرف شود. پس از مصرف آخرین قرص، برای یک دوره هفت روزه، نباید قرص ها مصرف شود.که ۴ – ۲ روز پس از مصرف آخرین قرص، خونریزی اتفاق می افتد. پس از ۷ روز، مصرف قرص را باید ادامه داد.

- Chlormadinone acetate: 2 mg
- Ethinylestradiol: 0.03 mg

anti-estrogenic effect

moderate anti-androgenic

- Cyproterone Acetate: 2 mg
- Ethinylestradiol: 0.035 mg

Long Term Advantage

Regardless of the COC selected, one of the long-term benefits is that the risk for endometrial cancer would be reduced by 50%, even up to two decades after discontinuation.

Side Effects

Breast tenderness

Mood swings

Breakthrough bleeding

Libido changes

Drug Class (Example)	Purpose of Therapy	Mechanism of Action	Effective Dose	Side Effects
Combined oral contraceptive (estrogen and progestin)	Menstrual cyclicity, hirsutism, acne	Suppresses LH (and FSH) and thus ovarian androgen production; increases sex hormone–binding globulin, which decreases free testosterone	One tablet orally daily for 21 (or 24) days, then 7-day (or 4-day) pill-free interval	Breast tenderness, breakthrough bleeding, mood swings, libido changes
Progestins (medroxyprogesterone)	Menstrual cyclicity	Creates withdrawal bleeding by transforming proliferative endometrium into secretory endometrium	5–10 mg orally daily for 10–14 days every 1–2 months	Breakthrough bleeding, spotting, mood swings

Insulin Sensitizing Agents

- Metformin inhibits hepatic glucose output, providing lower insulin concentrations and reducing androgen production in the ovary.
- It also appears to influence ovarian steroidogenesis directly.
- The most effective dose of metformin in PCOS is 500 mg orally 3 TID. It should be titrated slowly to this effective dose; doses up to 2,000 mg daily or 2,550 mg daily may be necessary for individual circumstances.
- An eGFR should be calculated at least annually in women using metformin because it is contraindicated if eGFR is <30 ml/min/1.73 m2.

Side Effects

The gastrointestinal (GI) side effects of diarrhea, nausea, vomiting, and abdominal bloating are usually **transient** and **dose-related**, and can be minimized by taking with food instead.

Antiandrogen Medications

- Although frequently used, **antiandrogens do not have FDA-approved** uses for the treatment of female hirsutism or acne in the United States.
- Commonly prescribed agents for hirsutism include:

◉ Spironolactone ◉ Drospirenone (a derivative of spironolactone)

◉ Finasteride ◉ Flutamide ◉ Eflornithine

- Cosmetic approaches: Electrolysis and laser therapy

Spironolactone

- Spironolactone acts by competitively inhibiting DHT from interacting with its androgen receptor. This causes a decrease in activity of ovarian produced testosterone.
- Spironolactone reduces hair growth by 40% to 88%; however, it takes 6 to 9 months for improvement.
- Spironolactone may be associated with possible teratogenicity (feminization of the male fetus), so it is prudent to advise women to avoid pregnancy for at least 4 months after the discontinuation of spironolactone.
- The usual effective dose is 50 to 100 mg orally twice daily for 6 to 12 months.

Side Effects

GI Hyperkalemia Menstrual disturbance Headache Fatigue

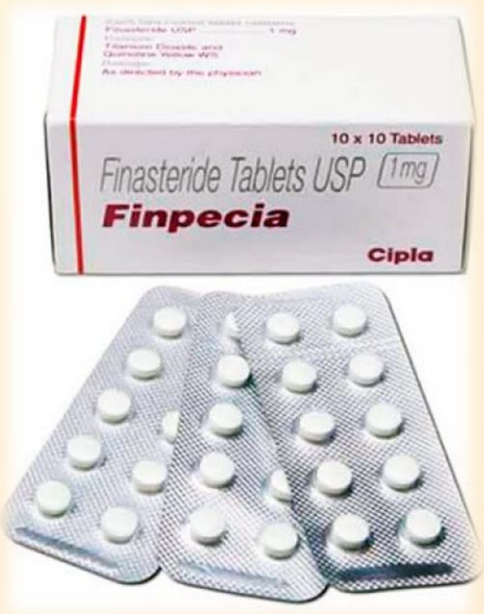
- Monitoring: Serum potassium and renal function should be monitored
- Attention: spironolactone should not be used with a COC containing drospirenone because of a potential risk for hyperkalemia.

Finasteride

- Finasteride is a type II 5α-reductase inhibitor, which decreases the conversion of testosterone to DHT.
- It provides an approximate 30% reduction from baseline for hirsutism.
- Compared with spironolactone, finasteride is as or less effective in women with hirsutism.
- The dose of 2.5 to 5 mg orally daily typically takes 6 months for clinical improvement.
- It is critical to avoid pregnancy while taking this drug owing to the potential teratogenic effect of abnormal genitalia in the male fetus. Finasteride should not be touched or handled by women who are or may be pregnant.

Attention

Most physicians advise women to wait 1-2 months after stopping finasteride before trying to conceive. The drug does have a short half life (6-8 hours) and is mostly cleared out of the body in a few days.



Flutamide

- Flutamide is a nonsteroidal antiandrogen (NSAA) acts as a selective antagonist of the androgen receptor (AR), competing with androgens like testosterone and dihydrotestosterone (DHT) for binding to ARs in tissues.
- Flutamide is effective for hirsutism, but it is not used because of hepatotoxicity.

Eflornithine HCl

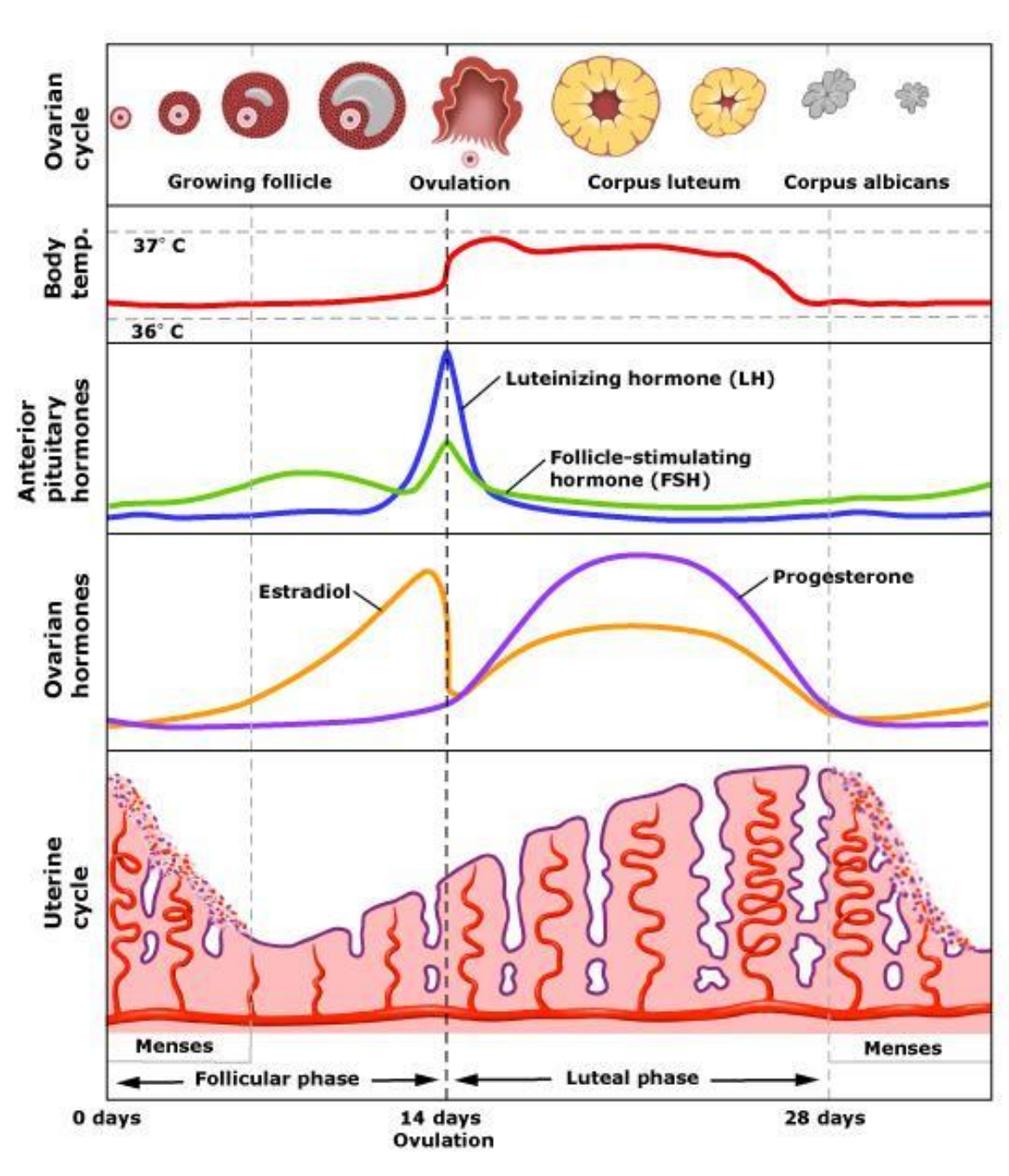
- Eflornithine is a specific irreversible inhibitor of the enzyme ornithine decarboxylase (ODC). Topical eflornithine inhibits skin ODC activity, resulting in a reduction in the rate of hair growth.
- Eflornithine has been approved for topical use in treating facial hirsutism, but has not been well studied in women with PCOS.
- Apply a thin layer twice daily, at least 8 hours apart, to affected facial area(s). Rub the cream into the skin thoroughly. Do not wash the treated area for at least 4 hours. The onset of action may take 4—8 weeks using the topical cream for facial hirsutism.

Menstrual Disturbance

- Irregular menstrual cycle
- Amenorrhea & oligomenorrhea
- Menorrhagia

Treatment?

- First generation progesterone



NONPHARMACOLOGIC TREATMENT

- Diet
- Exercise
- Weight reduction

PHARMACOLOGIC TREATMENT

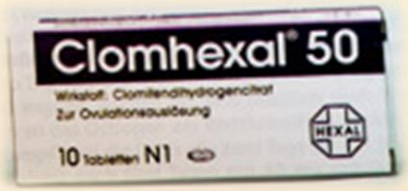
AGENTS FOR OVULATION INDUCTION INCLUDED:

- Clomiphene Citrate
- Aromatase Inhibitors
- Gonadotropin Therapy

Clomiphene Citrate

- Clomiphene citrate induces ovulation via an antiestrogenic effect on the hypothalamus. GnRH secretion is increased, which increases FSH production. The increase in FSH concentrations causes appropriate follicle development and estrogen secretion, which produces a positive feedback on the hypothalamic–pituitary system to create a LH surge for ovulation.
- The usual initial dose of clomiphene citrate is 50 mg orally daily for 5 days, started on day 5 after a spontaneous or progestin-induced menses.
- The clinician must determine whether ovulation occurs with each cycle.
- If ovulation does not occur, the dose can be increased by 50 mg orally daily up to 150 mg orally daily; however, doses greater than 100 mg orally daily for 5 days are not recommended by the manufacturers.

- If conception does not occur, women can use clomiphene for three to four cycles before considering another regimen.
- Most women respond to clomiphene citrate within three to four ovulatory cycles, but 5% to 10% have demonstrated clomiphene resistance and need to consider other options.
- For women who are clomiphene citrate-resistant, dexamethasone can be used in conjunction with clomiphene or an aromatase inhibitor can be used.
- Long-term cyclic therapy is not recommended beyond a total of six cycles because of potential ovarian cancer risk (OHSS)



Side effects

Ovarian enlargement presenting as abdominal or pelvic pain, tenderness, pressure, or swelling

Breast tenderness or discomfort

Increased likelihood of multiple births

Flushing, night sweats

Headache

Abnormal uterine bleeding

Ovarian hyperstimulation syndrome (OHSS)

Nausea, vomiting, or diarrhea

Blurred vision or other visual disturbances

Aromatase Inhibitors

- Letrozole is an aromatase inhibitor which blocks estrogen synthesis to directly affect hypothalamic–pituitary–ovarian function and increase pregnancy rates.
- Ovulation induction and live birth occur in approximately 48% and 27% of women with PCOS, respectively, using letrozole.

Potential Advantages of Letrozole over Clomiphene

- A high rate of mono-follicular development, which should theoretically reduce the risk of multiple pregnancies.
- No direct antiestrogenic ADR on the endometrium, due to an absence of peripheral estrogen receptor blockade.
- A shorter half life (48 hours vs 2 weeks of clomiphene), which would predict a lower risk of teratogenicity.
- Better side effects profile.
- Lower serum estradiol levels.

Dose

The starting dose is 2.5 mg/day, cycle days 3 to 7, following a spontaneous menses or progestin-induced bleed.

If the cycle is ovulatory but pregnancy has not occurred, the same dose should be used in the next cycle.

If ovulation does not occur, the dose should be increased to 5 mg/day, cycle days 3 to 7, with a maximal dose of 7.5 mg/day.

Up to 5 treatment cycle may be administered.

Higher doses (7.5 mg) appear to be associated with a thinning of the endometrium similar to that seen with clomiphene citrate.

Side Effects

- **Dizziness, drowsiness, weakness, fatigue**
- Flushing
- Headache
- Nausea, constipation
- **Bone pain, muscle or joint pain**
- **Numbness, tingling, weakness, or stiffness in your hand or fingers**

Attention

- The American College of Obstetrics and Gynecology (ACOG) has published revised recommendations for the choice of ovulation induction agents in women with PCOS.
- While they previously suggested letrozole as first-line therapy (over clomiphene citrate) only for women with a BMI >30 kg/m2 , they now recommend it for all women with PCOS, regardless of BMI.
- In addition, they recommend lifestyle changes and weight loss for all obese women with PCOS to try to restore ovulatory cycles without the use of ovulation induction agents.

Gonadotropin Therapy

Preparations:

- hMG and FSH
- Ovulatory triggers

hMG and FSH

Gonadotropins extracted from the urine of postmenopausal women (human menopausal gonadotropins [hMG]), in which the ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH) bioactivity is 1:1, have assumed a central role in ovulation induction.

Refinement of the initially crude preparation resulted in the availability of purified and highly purified urinary FSH (uFSH).

Since 1996, recombinant human FSH (rhFSH, >99 percent purity) has been available. Recombinant preparations are appealing due to their ease of administration (subcutaneous rather than intramuscular), purity, and batch-to-batch consistency.


Merional®
IBSA
75 I.U. s.c., i.m.
Highly purified lyophilized human Menopausal Gonadotropin (hMG)
Gonadotrophine humaine de la ménopause (hMG) lyophilisée, hautement purifiée
1 lyophilized vial + 1 ampoule of solvent
1 flacon de lyophilisat + 1 ampoule de solvant
Merional
75 I.U.
Menotropinum (HMG)
Solvens


FERRING
PHARMACEUTICALS
Menogon® 75 IU
Liyofilize Toz İçeren Ampul
5
Ampul
Menotropin (75 IU FSH + 75 IU LH)


IBSA
Fostimon®
75 I.U. s.c., i.m.
Highly purified lyophilized Urofollitropin (FSH)
Urofollitrophine (FSH) lyophilisée, hautement purifiée
1 lyophilized vial + 1 ampoule of solvent
1 flacon de lyophilisat + 1 ampoule de solvant
Fostimon
75 I.U.
Solvens


LG Life Sciences
HMG
IVF-M Inj.
Menotropin
(Human Menopausal Gonadotropin)
75 IU×1Vial
IVF-M
Chloride


Menopur®
75IU FSH + 75IU LH
5 fiolek + 5 ampułek
Menotropinum


NDC 55566-8505-6
Bravelle® 75 IU
(urofollitropin for injection, purified)
5 single dose vials of urofollitropin for injection, purified
5 single dose vials of 0.9% Sodium Chloride Injection, USP, 2 mL
5 Q-Cap® Vial Adapters
FOR SUBCUTANEOUS OR INTRAMUSCULAR INJECTION ONLY
Rx only
Q-Cap
Vial Adapters for Needle-Free Reconstitution
For exclusive use with Ferring reproductive health products
FERRING
PHARMACEUTICALS
Bravelle


GONAL-f® RFF 75 IU
(follitropin alfa for injection)
For subcutaneous injection
Rx only
1 vial Gonal-f® RFF
1 pre-filled syringe Sterile Water for Injection, USP
1 18-gauge needle for reconstitution
1 29-gauge needle for administration
* revised formulation female
EMD Serono
NDC 44087-9005-1


Puregon® 300 IU/
solution for injection
follitropin beta
Puregon® 600 IU/0.72 ml
solution for injection
follitropin beta


LG Life Sciences
Follitrope™ Inj. Prefilled syringe
(Follitropin)
75
75 IU/0.15mL X1Syr.


GONAL-f 300 IU/0.5 mL
(22 micrograms/0.5 mL)
solution for injection in pre-filled pen
Follitropin alfa
GONAL-f 450 IU/0.75 mL
(33 micrograms/0.75 mL)
solution for injection in pre-filled pen
Follitropin alfa
GONAL-f 900 IU/1.5 mL
(66 micrograms/1.5 mL)
solution for injection in pre-filled pen
Follitropin alfa


Cinnal-f
Follitropin Alfa
Follitropin alfa 5.5 µg 75 IU
for SC injection
Store between 2-8°C

Which one is better?

The degree to which the type of FSH compound employed may influence outcome of ovulation induction has been controversial.

In a meta-analysis of 14 trials in 1726 women (comparing rhFSH and urinary gonadotropins [FSH-highly purified (HP) or human menopausal gonadotropins (hMG)] and four trials comparing FSH-purified [P] and hMG or HP-hMG), the following results were seen:

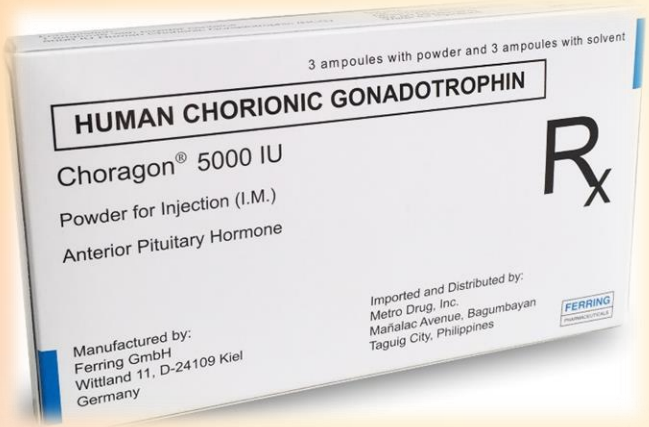
- There were no differences in clinical pregnancy or live-birth rates for rhFSH and urinary-derived gonadotropins.
- There also were no differences between hMG preparations and urinary FSH-P.
- After pooling the data, there were no differences in the rates of OHSS between rhFSH and urinary-derived gonadotropins.

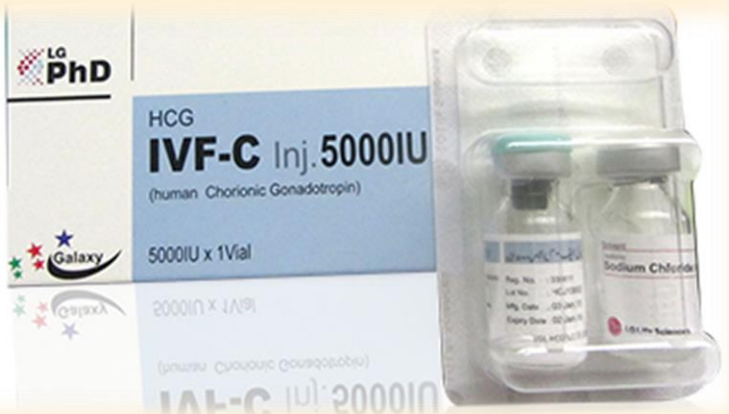
Side Effects

- CNS: headache (34%), dizziness & malaise (1-10%)
- GI: abdominal pain (18%), nausea (12%), vomiting, diarrhea, constipation
- Endocrine & metabolic: hot flash, OHSS (13%, dose related)
- Local: injection site reactions (4-12%)
- GU: ectopic pregnancy, vaginal bleeding
- Respiratory: cough, flu-like symptoms

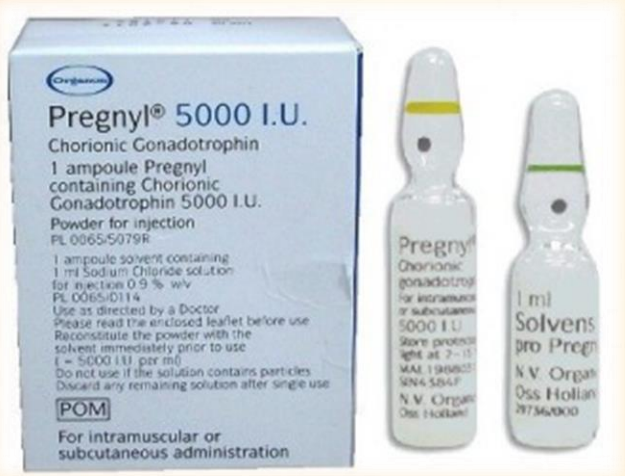
Ovulatory Triggers

- Human chorionic gonadotropin (hCG) is used to trigger and initiate the ovulatory cascade when the ovarian follicles are mature with a mean diameter of 18 mm or more.
- Both urinary and recombinant hCG preparations are available. A meta-analysis found no differences in clinical outcomes between recombinant and urinary hCG for induction of final follicular maturation.
- A dose of 250 mcg of recombinant hCG appears to be equivalent to the standard doses of urinary hCG (5000 to 10,000 units).


3 ampoules with powder and 3 ampoules with solvent
HUMAN CHORIONIC GONADOTROPHIN
Choragon® 5000 IU
Powder for Injection (I.M.)
Anterior Pituitary Hormone
Rx
Manufactured by:
Ferring GmbH
Wittland 11, D-24109 Kiel
Germany
Imported and Distributed by:
Metro Drug, Inc.
Mañalac Avenue, Bagumbayan
Taguig City, Philippines
FERRING


LG PhD
HCG
IVF-C Inj.5000IU
(human Chorionic Gonadotropin)
Galaxy
5000IU x 1Vial
Sodium Chloride


OVITRELLE® 250 µg/0.5 ml
Kullanıma hazır şırıngada enjeksiyonluk çözelti
Koriogonadotropin alfa
Deri altı kullanım içindir
1 kullanıma hazır şırınga
MerckSerono


Pregnyl® 5000 I.U.
Chorionic Gonadotrophin
1 ampoule Pregnyl containing Chorionic Gonadotrophin 5000 I.U.
Powder for injection
PL 0065/5079R
1 ampoule solvent containing 1 ml Sodium Chloride solution for injection 0.9 % w/v
PL 0065/0114
Use as directed by a Doctor
Please read the enclosed leaflet before use
Reconstitute the powder with the solvent immediately prior to use
1 = 5000 I.U. per ml
Do not use if the solution contains particles
Discard any remaining solution after single use
POM
For intramuscular or subcutaneous administration
Pregnyl
5000 I.U.
1 ml
Solvens
pro Pregn


Choriomon®
5000 IU i.m. /s.c.
Enjeksiyon İçin Liyofilize Toz İçeren Fl
Choriomon
5000 I.U.
Exp.:
SA, Lugano

Side Effects

- CNS: fatigue, headache, irritability
- Endocrine & metabolic: OHSS
- GU: rupture of ovarian cyst
- Local: pain at injection site
- Cardiovascular: edema, arterial thrombosis

THE END...