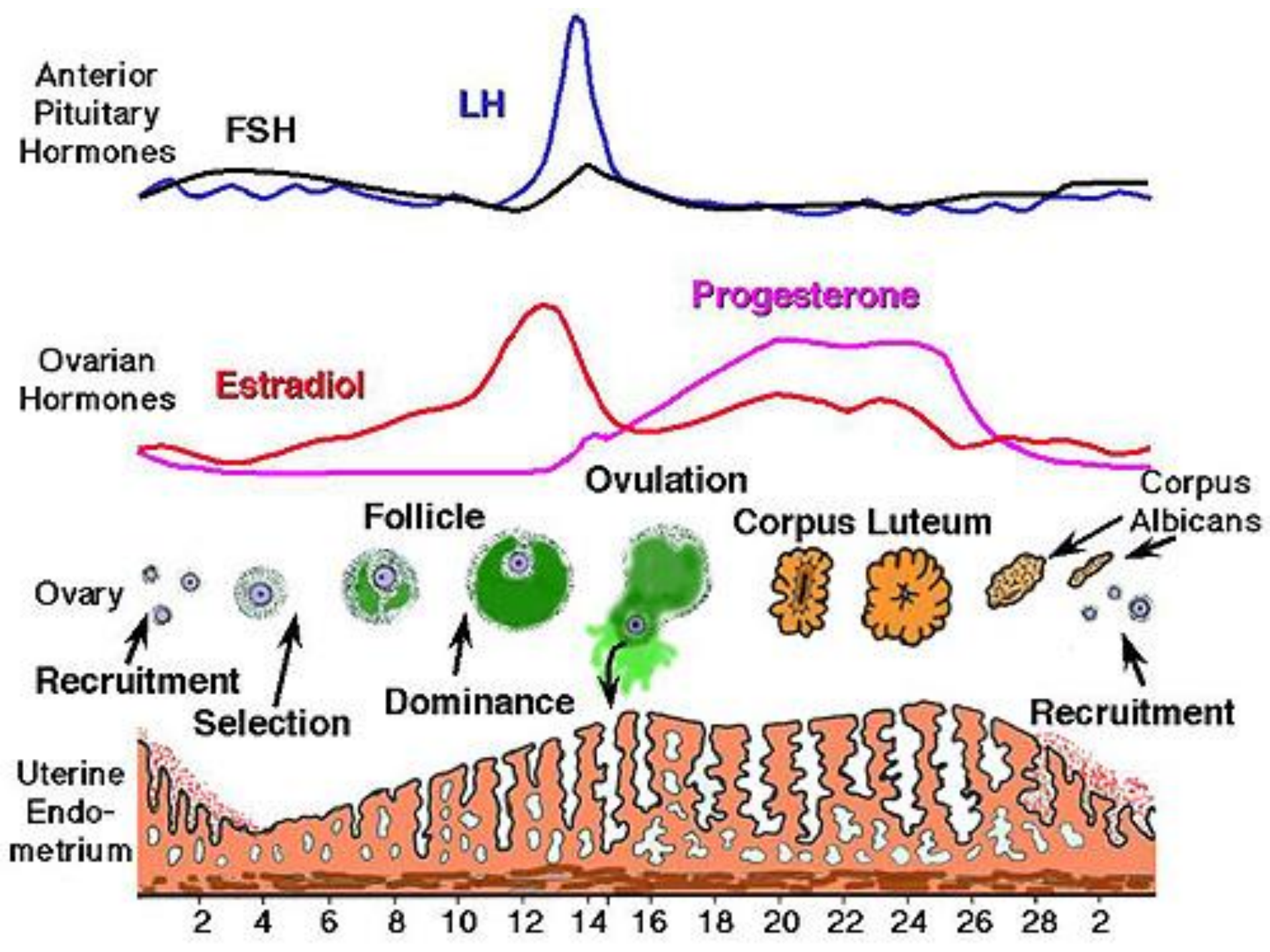
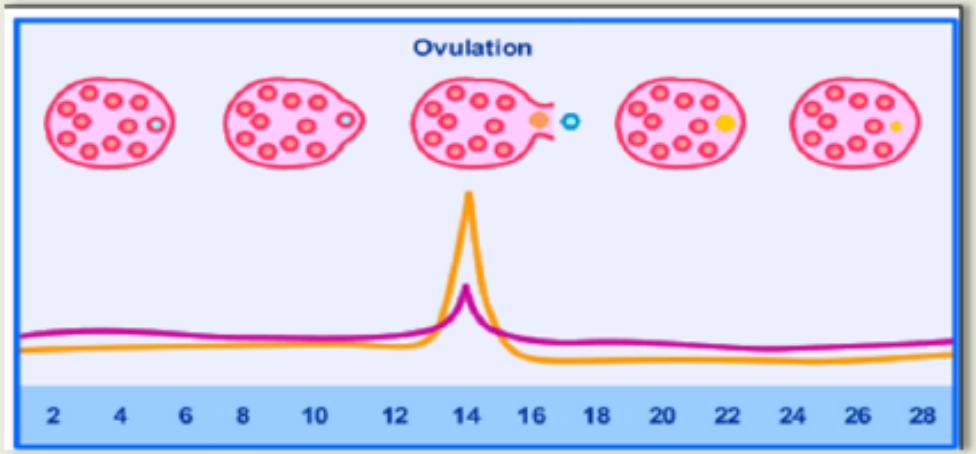
In the Name of God

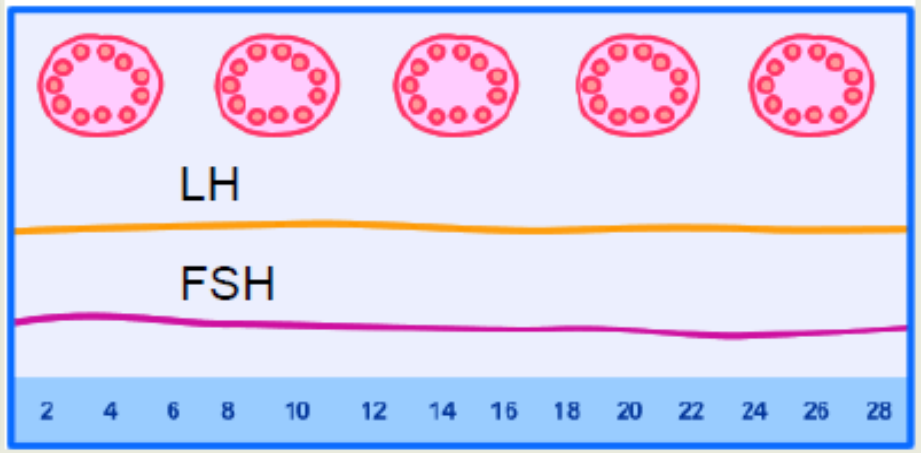

Anterior Pituitary Hormones
FSH
LH
Ovarian Hormones
Estradiol
Progesterone
Ovulation
Follicle
Corpus Luteum
Corpus Albicans
Ovary
Recruitment
Selection
Dominance
Recruitment
Uterine Endo-metrium
2 4 6 8 10 12 14 16 18 20 22 24 26 28 2

Normal Menstrual Cycle



Cycle day

PCOS



Cycle day

Pathophysiology

- High variability in the clinical presentation
- Factors contribute to the clinical features
  - Intrinsic abnormality of theca cell function
  - Androgen excess
  - Hypersecretion of LH
  - Abnormal dynamics of FSH secretion
  - Insulin resistance (IR)

Androgen Excess

- Elevated testosterone and/or androstenedione is the most consistent biochemical abnormality
- Ovary as the major source of hyperandrogenemia
- Adrenal androgen excess in a minority of patients

Hypersecretion of LH

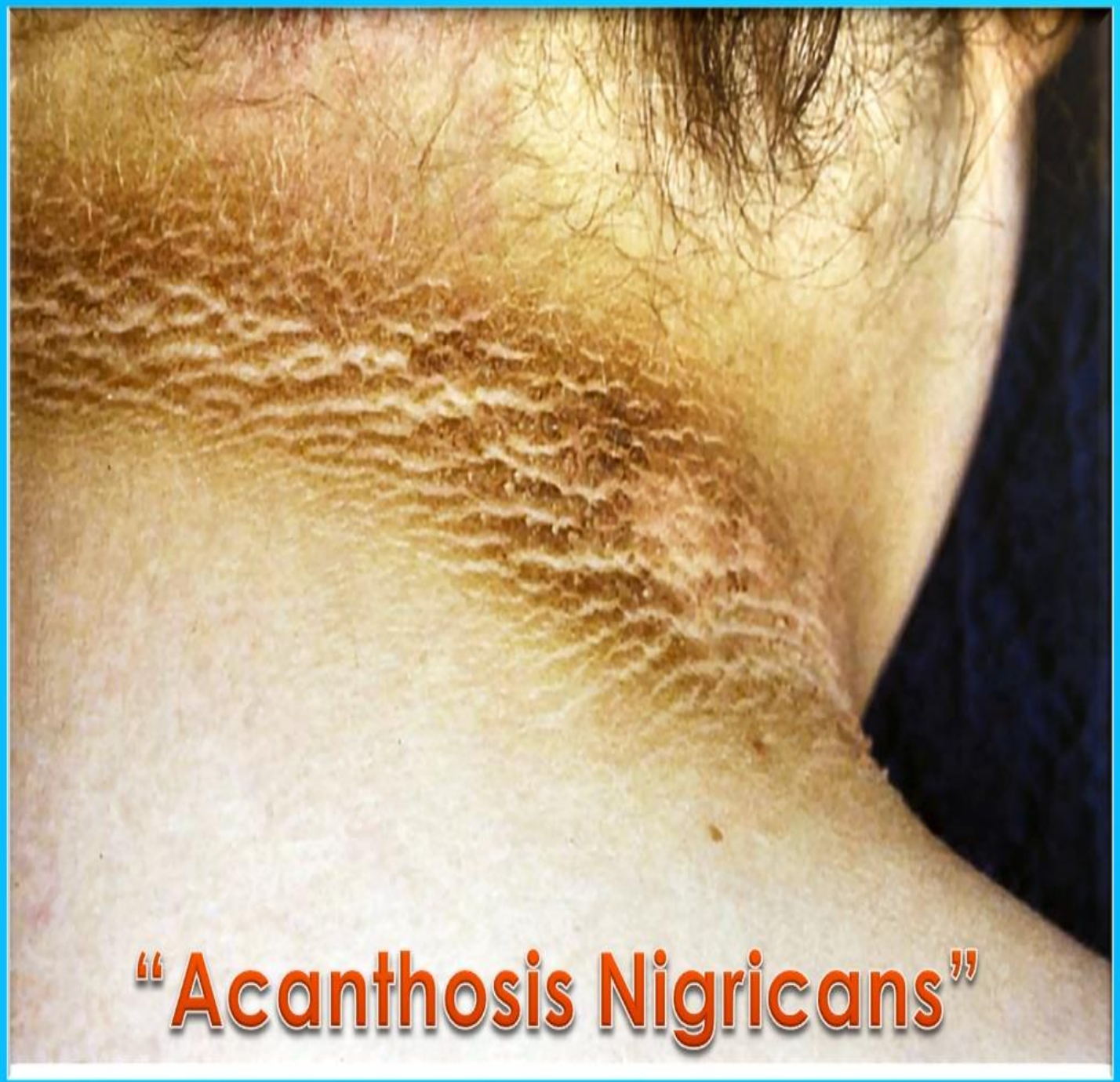
- Abnormal LH dynamics
  - Increase in both
    - LH pulse frequency
    - LH pulse amplitude
      - Stimulation of ovarian theca cells
        - Androgen excess
    - Impaired progesterone-mediated negative feedback

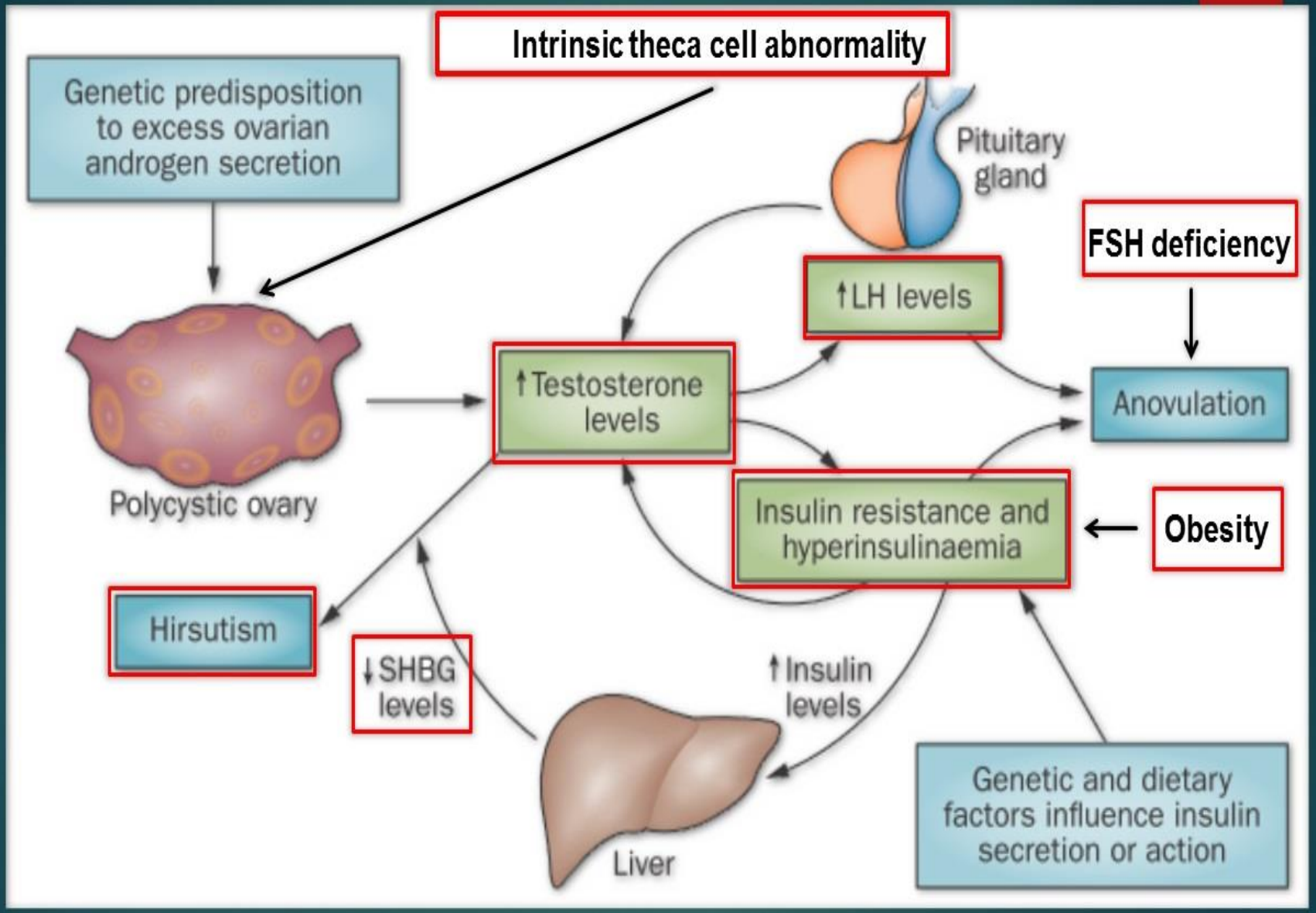
Abnormal dynamics of FSH secretion

- FSH levels are usually within the normal range
  - Typically lower than in the early follicular phase of women with normal menstrual cycles
- Suboptimal levels of FSH
  - Arrest in follicular development
  - Anovulation

Insulin Resistance(IR)

- Many, but not all, patients have IR
- Obesity exacerbates IR
  - Abdominal adiposity is important determinant
  - Even lean women have increased abdominal adiposity
- Fetal programming
  - Androgen exposure may program the fetus to express features characteristic of PCOS in adult (CAH & virilizing tumors)
  - Deposition of fetal abdominal fat
  - IUGR and SGA are at risk for developing IR and PCOS
  - Human evidence is inconclusive
- IR is tissue-selective
  - Affecting adipose tissue and muscle
  - Sparing the ovary


“Acanthosis Nigricans”



Pathogenesis

Clinical Presentation of Women with PCOS

Adolescent Period	Reproductive Period	Menopausal

- Menstrual Irregularity
- Cosmetic concerns
  - Acne
  - Hirsutism
  - Hair Loss

- Infertility
- Early Pregnancy loss
- During pregnancy
  - PIH
  - GDM

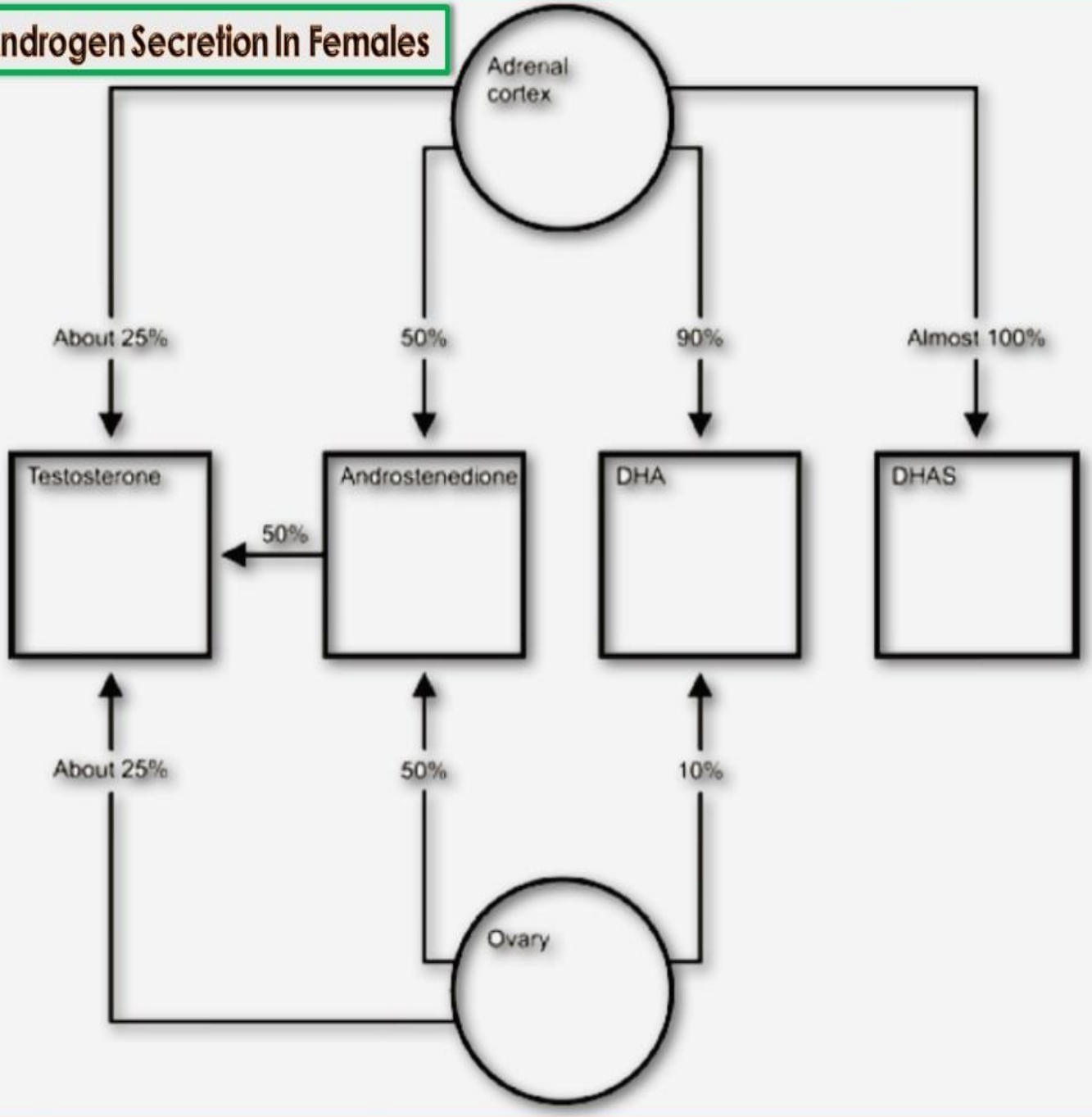
- Metabolic Syndrome
- Ca Endometrium

Obesity

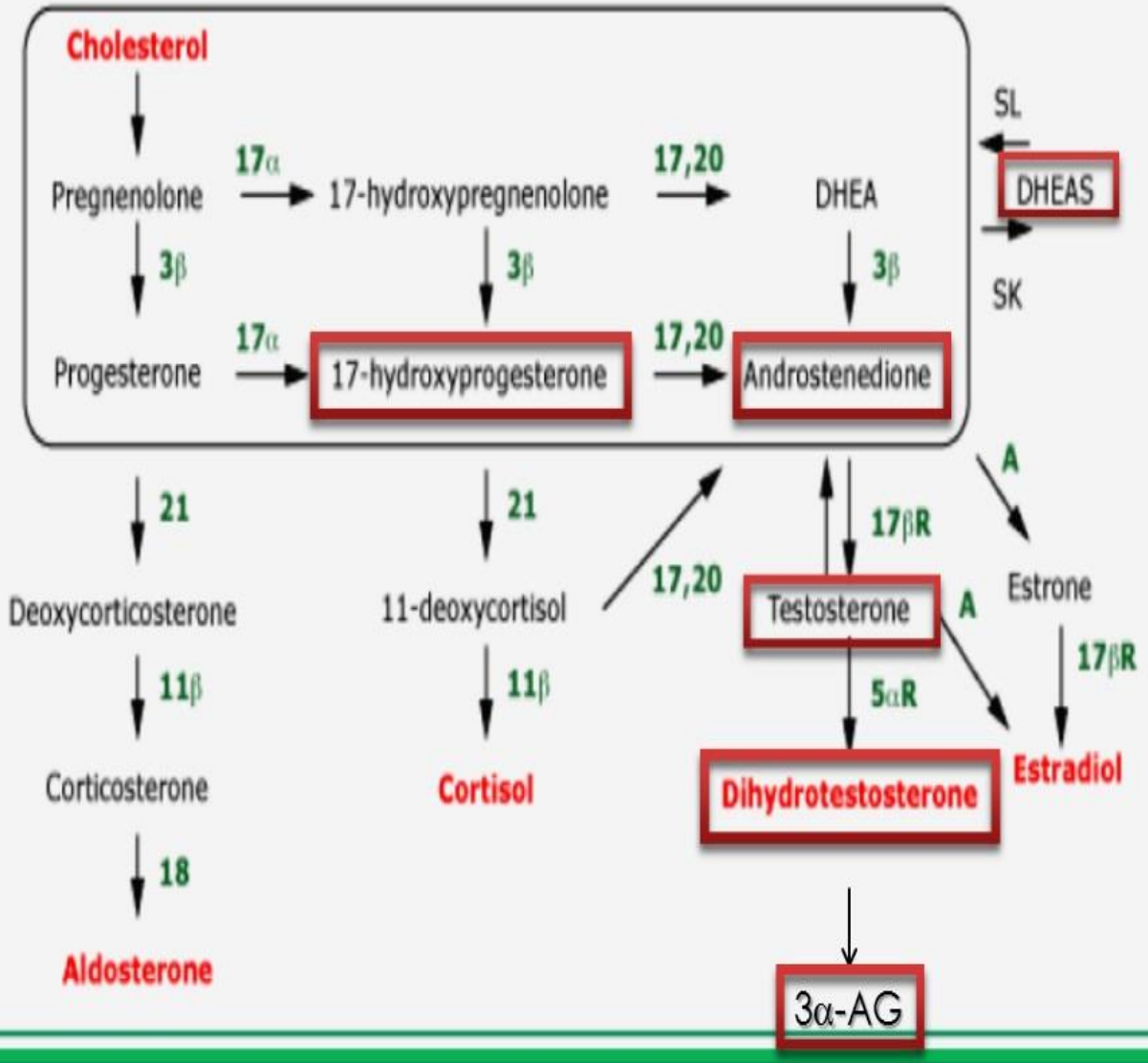
Clinical hyperandrogenism

- Hirsutism
- Acne
- Oily skin
- Alopecia androgenetica

Androgen Secretion In Females



Synthetic pathways for adrenal steroid synthesis



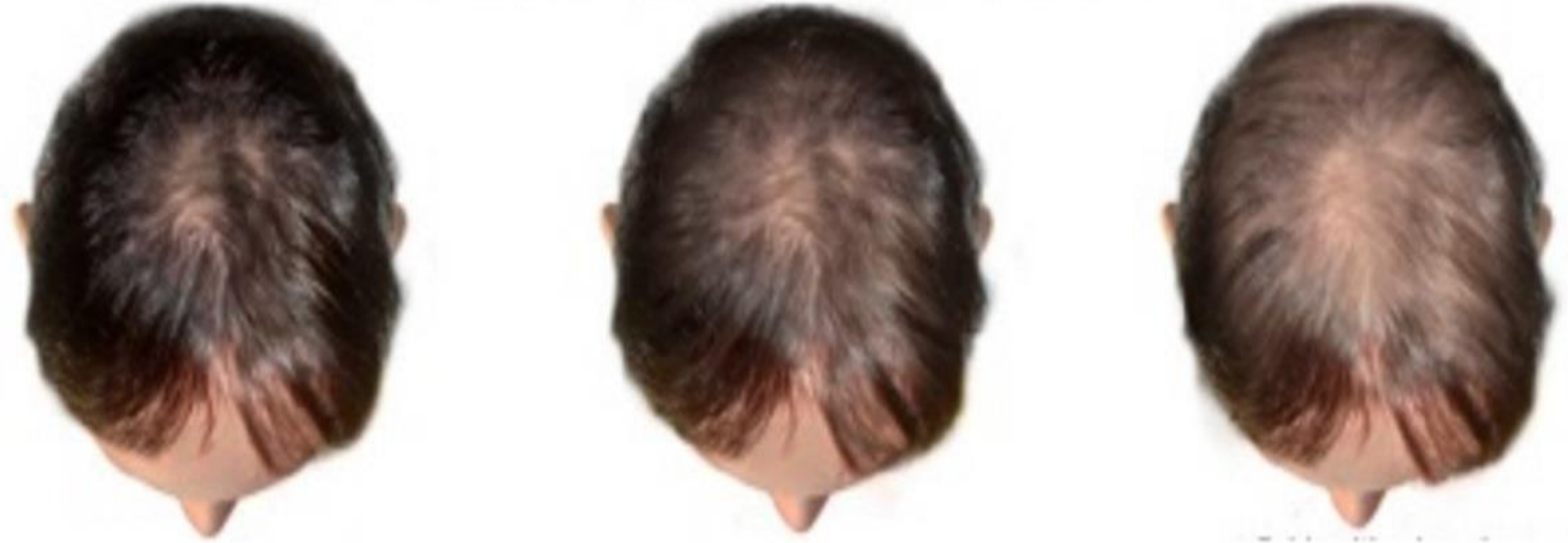
PCOS & Metabolic Syndrome

Metabolic Syndrome:

- Cluster of Cardiovascular risk factors related to Insulin Resistance:
  - Obesity
  - Hyperinsulinemia
  - Hypertension
  - Atherogenic Dyslipidemia
  - Atherosclerosis
  - Hyperglycemia
- Major Risk Factors:
  - Physical inactivity
  - Atherogenic diet
  - Adiposity / abdominal obesity

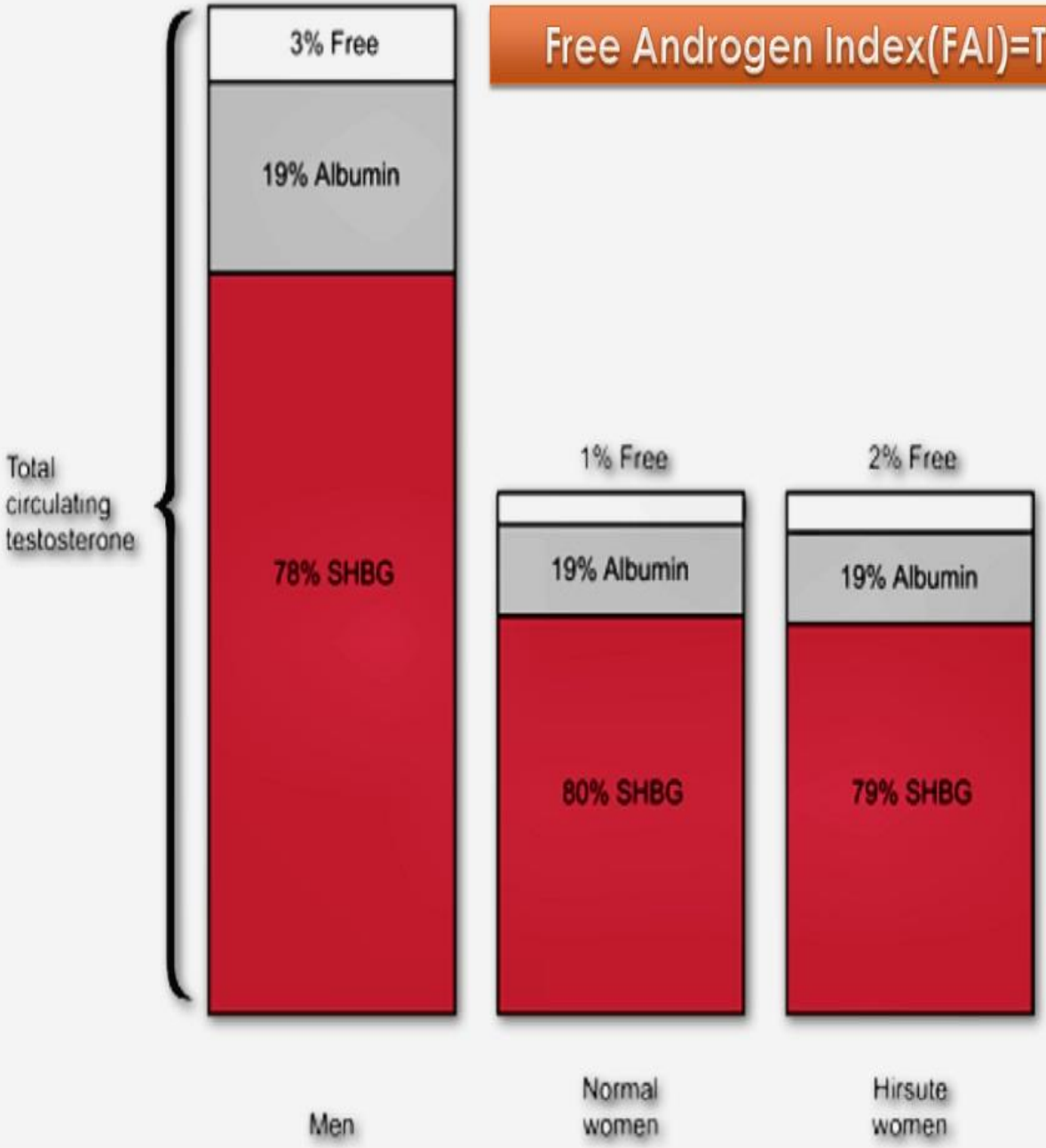
Male-pattern hair loss

Female-pattern hair loss

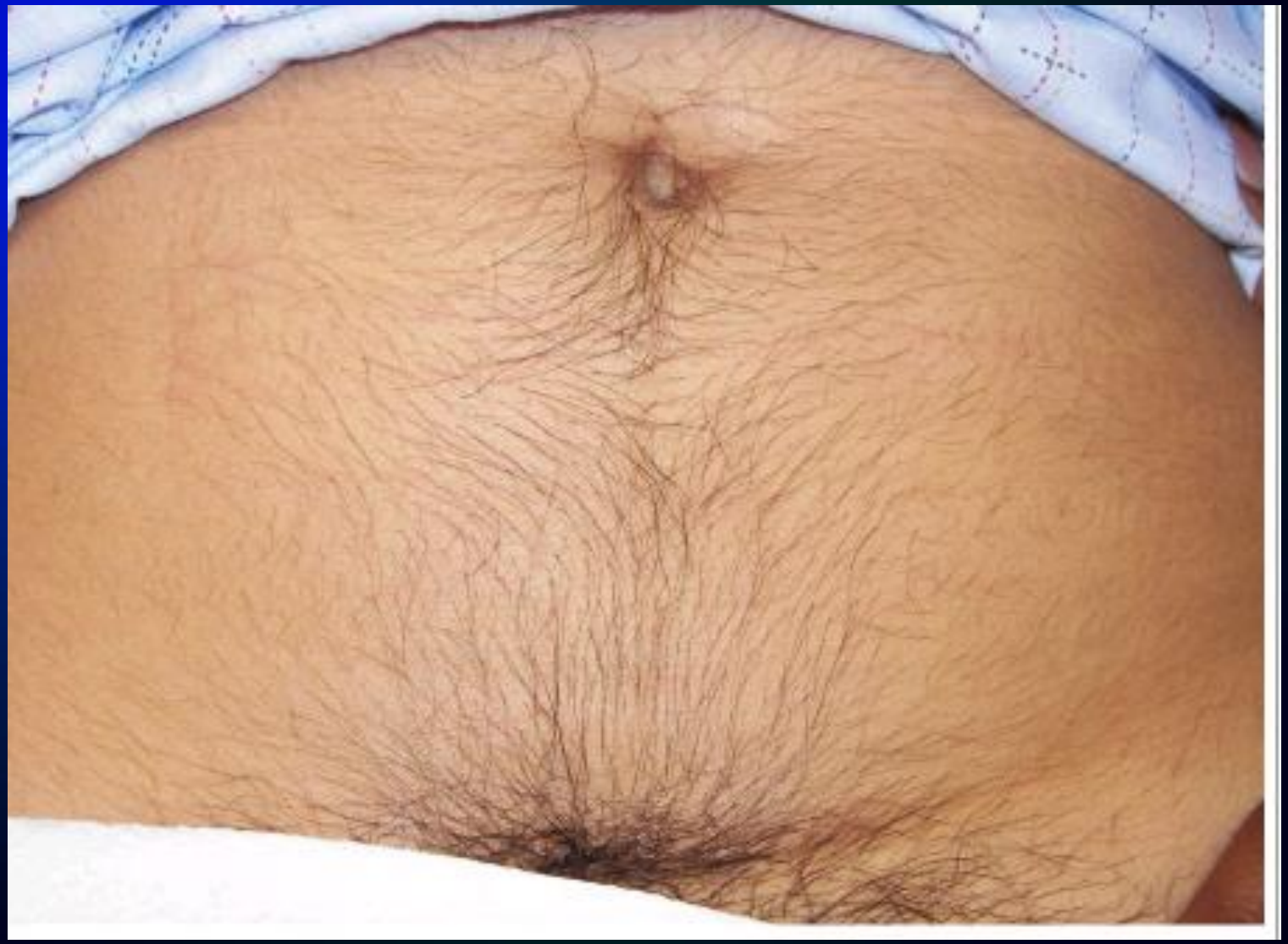


Female Pattern Hair Loss

Free Androgen Index(FAI)=TT/SHBG



Male Type Hair Growth on Abdomen- PCOS

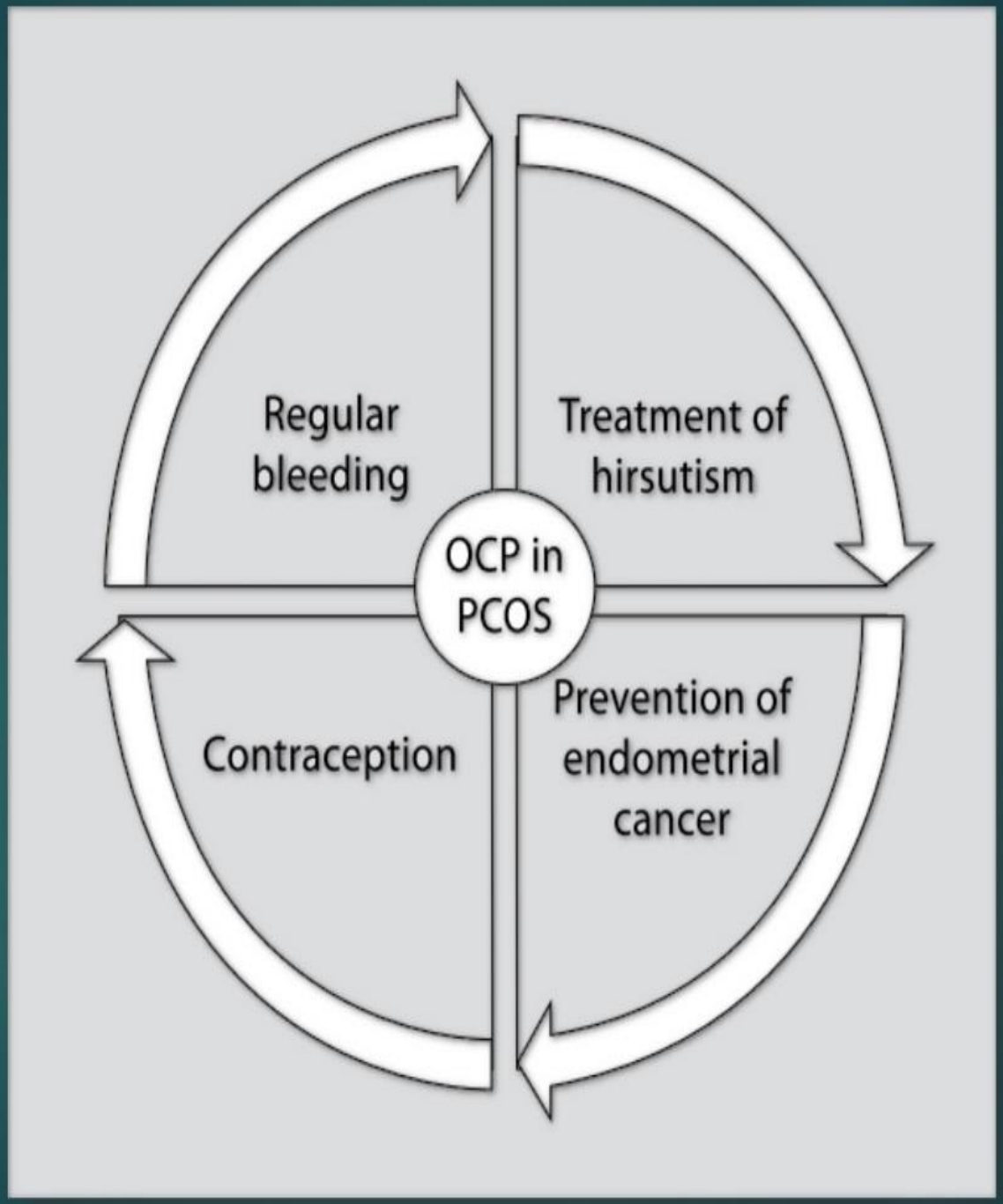


Factors Influencing SHBG Levels

- Increased
  - Estrogens (ERT, HRT, OCPs)
  - Pregnancy
  - Hyperthyroidism
- Decreased
  - Androgens
  - Glucocorticoids
  - Hypothyroidism
  - Insulin Resistance
    - Obesity
    - PCOS

Management

- The most important consideration of management is to tailor treatment choices to the specific needs of the patient(individualized therapy)
  - Cost / availability
  - Patient preference
  - Adverse effects of interventions
- Hyperandrogenism
- Menstrual irregularity / Dysmenorrhea
- Endometrium protection
- Cardiometabolic risk
- Depression
- Sleep apnea
- NAFLD
- Anovulatory infertility


Regular bleeding
Treatment of hirsutism
OCP in PCOS
Contraception
Prevention of endometrial cancer

Benefits of exercise:

↑ BMR (basal metabolic rate)

↓ Weight (results in ↑ sex hormone binding globulin → ↓ testosterone → ↓ hair growth and ↓ acne)

Fig. 5 **The benefits of weight loss in PCOS.**

Oral Contraceptives(OCPs)

- Endocrine Society recommends OCPs as the preferred option
- If OCPs are ineffective at treating hirsutism
  - Anti-androgen therapy can be added after 6 months of therapy with OCPs
    - Cyproterone acetate
    - Spironolactone
    - Flutamide
    - Finasteride

OCP Preparations

- POP = Progestin Only Pills / Minipills
- E + P
  - Monophasic
  - Biphasic
  - Multiphasic
    - No proven clinical advantage
- Continuous or extended-cycle
- Estrogen component
  - EE / E2 / E2V
- Dosage
  - Standard = 30-35 µg
  - Low dose = 10, 20, 25 µg
- Progestin component

Classification of Progestins

- Structurally related to testosterone
  - **Estranes**
    - Norethisterone
    - Norethisterone acetate
    - Norethynodrel
    - Levonorgestrel (LD & HD)
  - **Gonanes**
    - Desogestrel (Marvelon®)
    - Gestodene
    - Norgestimate
- Structurally related to progesterone
  - **Pregnanes**
    - Medroxyprogesterone acetate
    - Cyproterone acetate (Diane®)
  - **Norpregnanes**
    - Trimegestone
  - **Spironolactone derivative**
    - Drospirenone (Yasmin® & Yaz®)

Classification of Progestins

- First generation
  - Norethindrone acetate
  - Norethynodrel
- Second generation
  - Norgestrel
  - Levonorgestrel (LD & HD)
- Third generation
  - Desogestrel (Marvelon®)
  - Gestodene
  - Norgestimate
- Forth generation
  - Drospirenone (Yasmin® & Yaz®)
- Unclassified
  - Cyproterone acetate (Diane®)

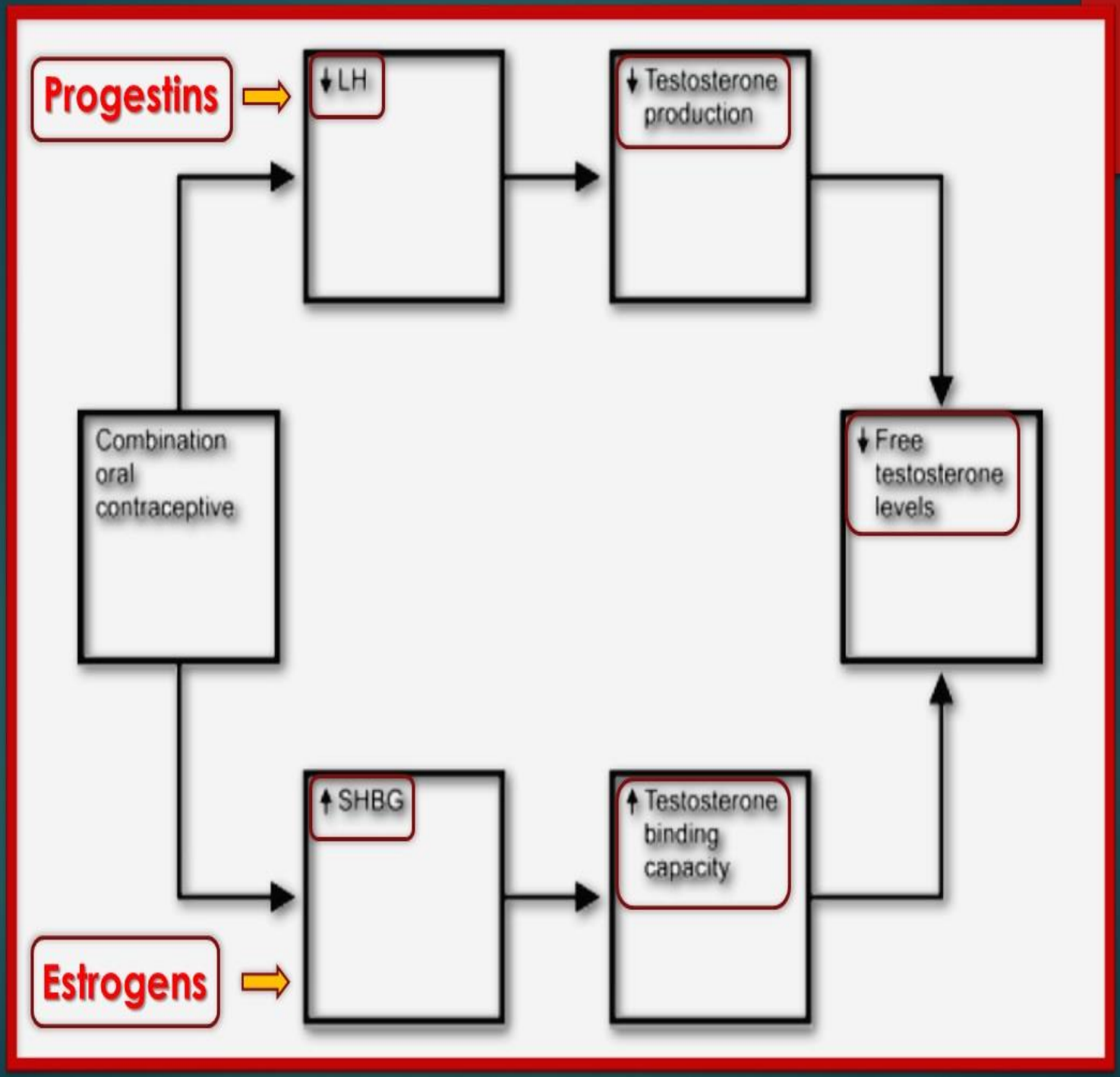
Androgenic Activity of Progestins

- **High**
  - Norgestrel
  - Levonorgestrel
- **Intermediate**
  - Norethindrone
  - Norethindrone acetate
- **Low**
  - Norgestimate
  - Desogestrel
  - Drospirenone

OCP Preparations

- LD
  - EE = 30 μg + Levonorgestrel = 15 mg
- HD
  - EE = 50 μg + Levonorgestrel = 25 mg
- Cyproterone compound / Diane®
  - EE = 35 μg + Cyproterone acetate = 2 mg
- Yasmin®
  - EE = 30 μg + Drospirenone = 3 mg
- Yaz®
  - EE = 20 μg + Drospirenone = 3 mg
- Marvelon®/ Desoceptive
  - EE = 30 μg + Desogestrel = 150 μg

- **Topical hair growth inhibitor**
  - Eflornithine hydrochloride
- **Suppression of circulating androgens**
  - Oral contraceptives (LD, HD, Triphasic, Cyproterone Compound / Diane®, Marvelon® / Desoceptive, Yasmin®, Yaz®,)
  - Insulin sensitizers (metformin, pioglitazone)
  - GnRH analogs (triptorelin)
  - Glucocorticoids (prednisolone, dexamethasone)
- **Peripheral androgen blockade**
  - Spironolactone
  - Cyproterone acetate
  - Drospirenone
  - Flutamide
  - Finasteride / Dutasteride


Progestins
LH
Testosterone production
Combination oral contraceptive
Free testosterone levels
SHBG
Testosterone binding capacity
Estrogens

Menstrual Irregularity

- A common presenting feature
- An index of oligo-anovulation
- Combined OCPs are a mainstay of treatment
- Metformin can ameliorate menstrual irregularity
  - Second line therapy
  - More beneficial for adolescents vs. adults
  - Beneficial effects on menstrual cycles persisted for 6 months after discontinuation

METFORMIN DOSING

- Target—1500-2550 mg per day
- Clinically significant responses not regularly observed at doses less than 1000 mg per day
- Extended release formulations—fewer side-effects. Entire dose should be given with dinner

Anovulatory infertility

- Clomiphene citrate
- Metformin
- Thiazolidinediones
- Aromatase inhibitors
- Gonadotropins
- Laparoscopic ovarian diathermy
- IVF

Endometrium Protection

- PCOS share many of the risk factors associated with the development of endometrial cancer
  - Obesity
  - Hyperinsulinism
  - Diabetes mellitus
- Increased risk of developing endometrial cancer (3X)

Depression / Anxiety / Eating Disorders

- Increased prevalence of depression in PCOS
  - Independent of obesity, androgens, hirsutism, acne, and infertility
- Higher rates of anxiety and panic disorders
- Eating disorders are more common in PCOS
- First choice = Fluoxetine
- Second Choice = Citalopram

Obesity

- If lifestyle intervention is unsuccessful, other treatment options can be considered
  - Orlistat
  - Liraglutide
  - Sandostatin LAR
  - Lorcaserin (Belviq®)
  - Phentermine / Topiramate CR (Qsymia®)
  - Naltrexone SR / Bupropion SR (Contrave®)
  - Bariatric surgery

Oral Contraceptives(OCPs) Endocrine Society Guideline(ES)

- First-line management for the
  - Menstrual abnormalities
  - Hyperandrogenemia (hirsutism/acne)
  - ES do not suggest one OCP formulation over another
- Extended-cycle OCPs
  - Greater hormonal suppression
  - Prevention of rebound ovarian function during the pill-free interval
- Risk-benefit ratios may vary among preparations and with different progestins
  - Residual androgenic activity
- Screening for contraindications to OCPs use

Increased Binding Proteins

- Oral estrogens raise
  - Thyroxine-binding globulin (TBG)
  - Cortisol-binding globulin (CBG)
  - Sex hormone-binding globulin (SHBG)
- Total T4, T3, cortisol, estradiol, and testosterone increase
- Free T4, T3, cortisol, and testosterone do not change