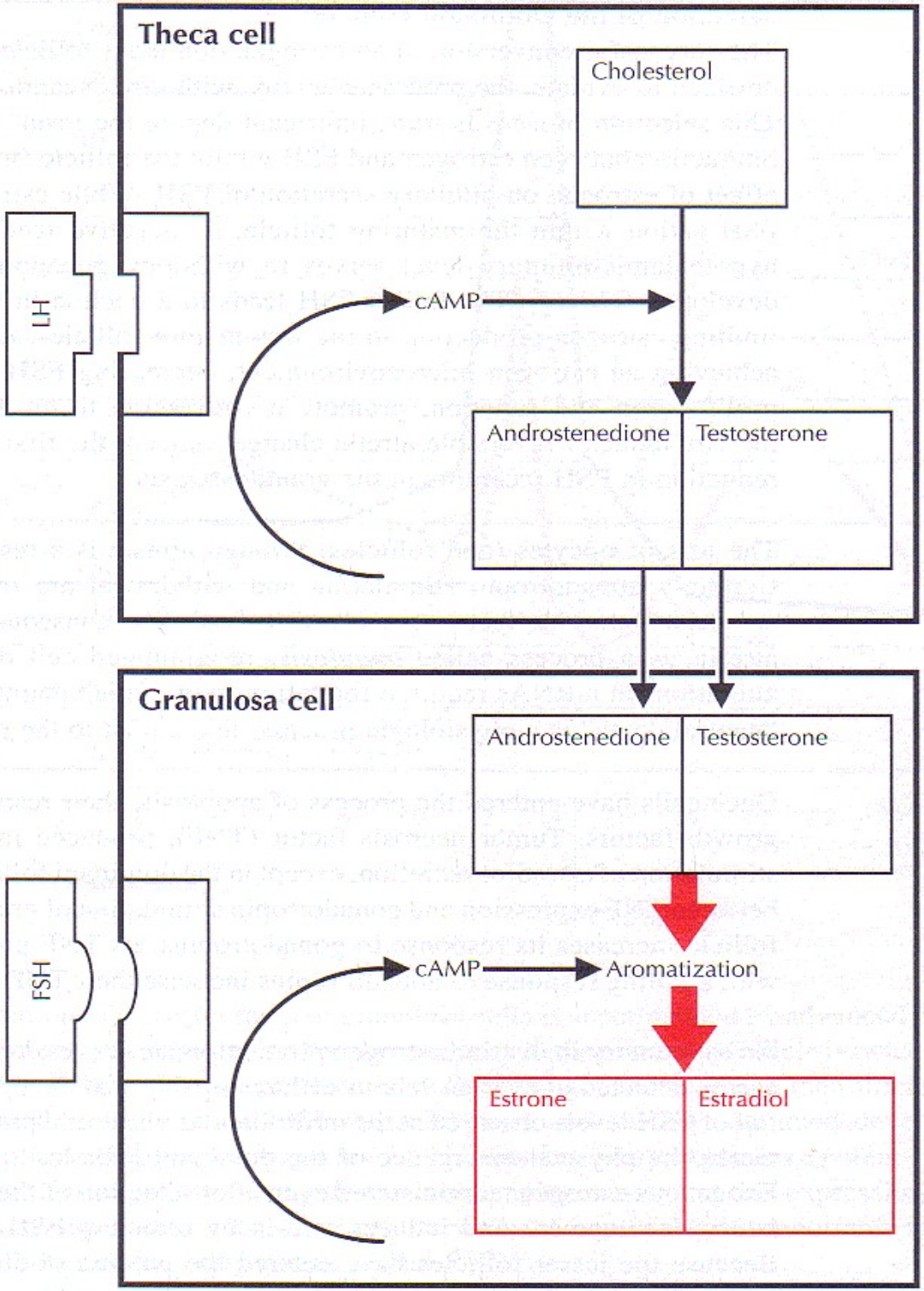
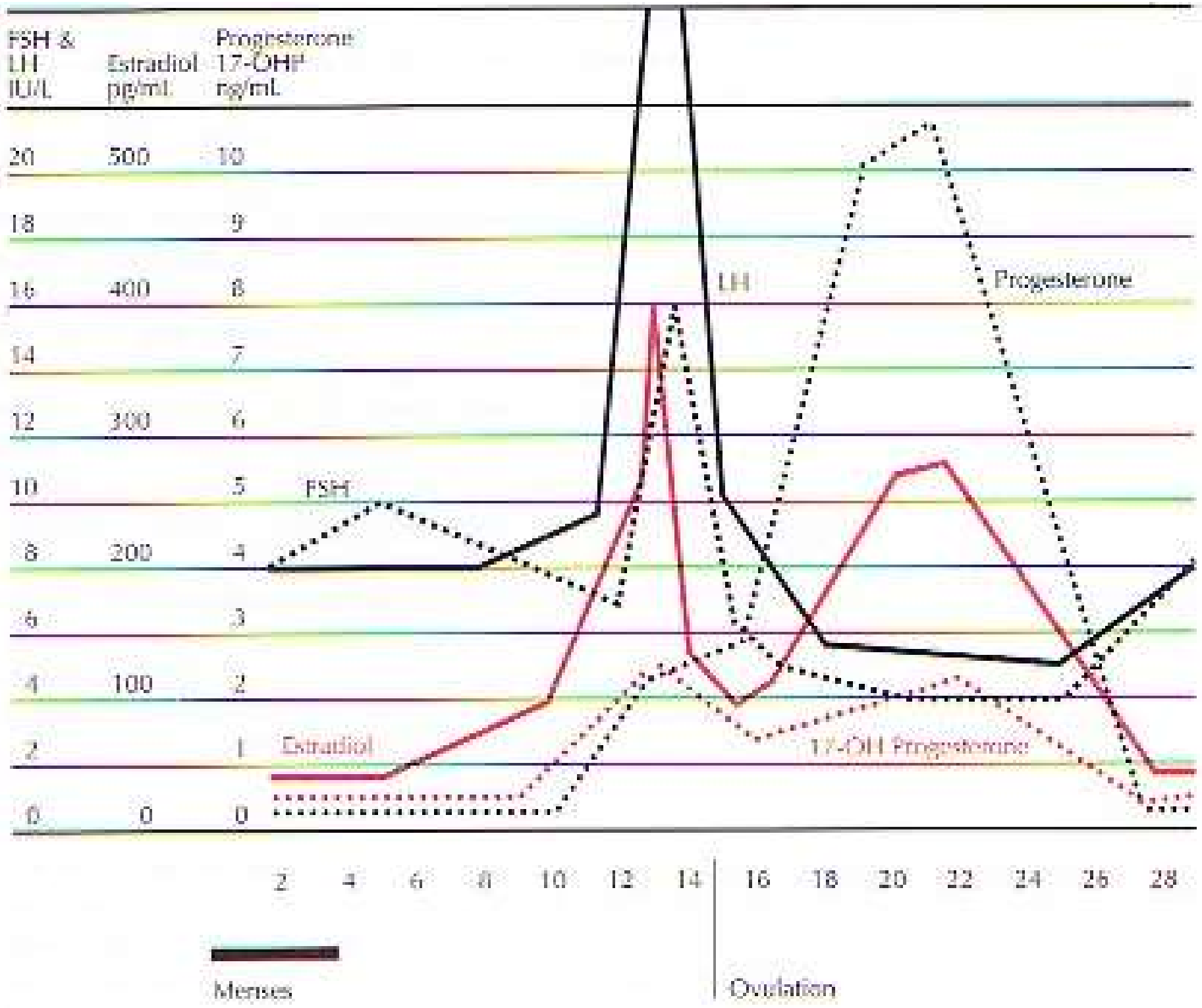
PCO-S
Pathophysiology and treatment

Michel Abou Abdallah , M.D.

Regulation of the Menstrual Cycle



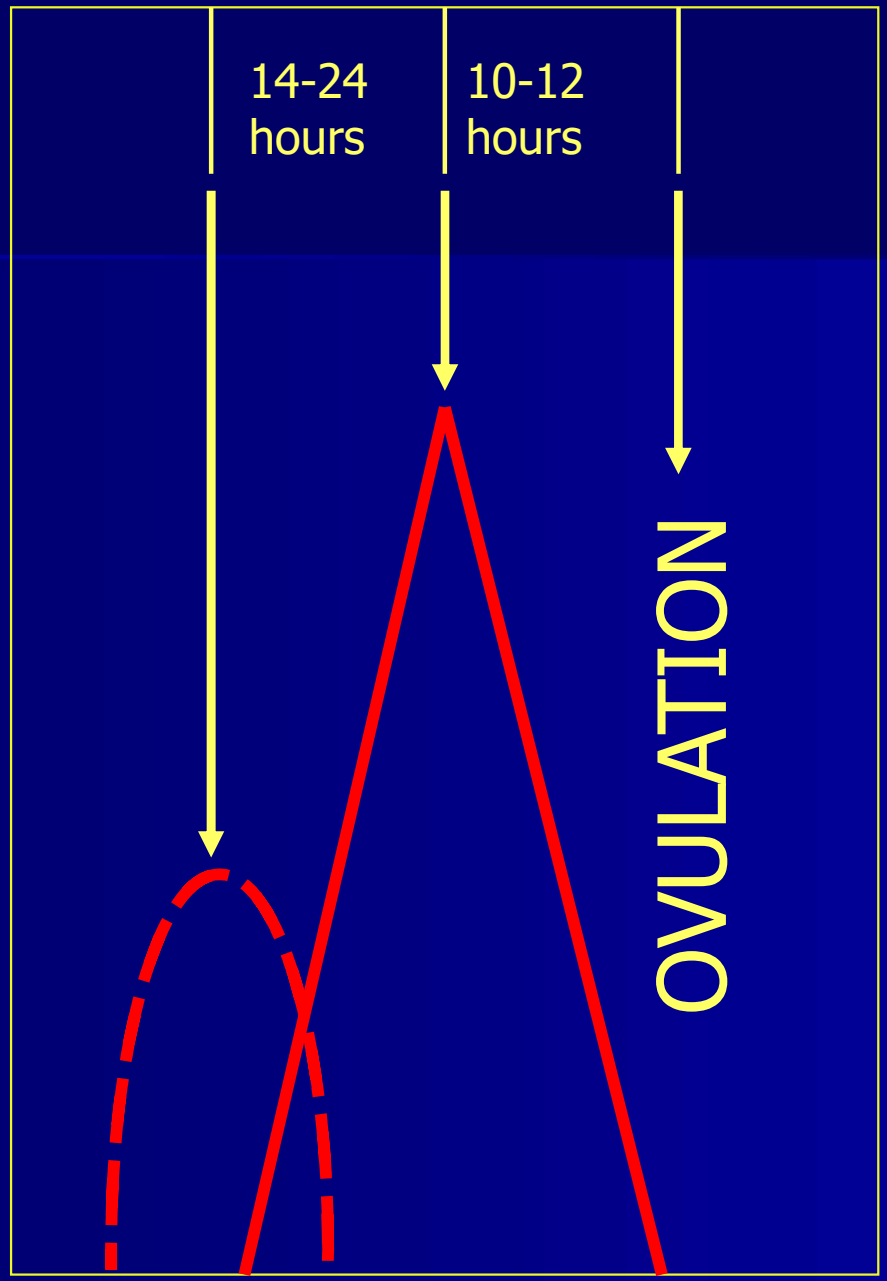

FSH & LH IU/L
Estradiol pg/mL
Progesterone 17-OHP ng/mL
20
18
16
14
12
10
8
6
4
2
0
500
400
300
200
100
0
10
9
8
7
6
5
4
3
2
1
0
FSH
LH
Progesterone
Estradiol
17-OH Progesterone
2
4
6
8
10
12
14
16
18
20
22
24
26
28
Menses
Ovulation

- LH Pulse Frequency:

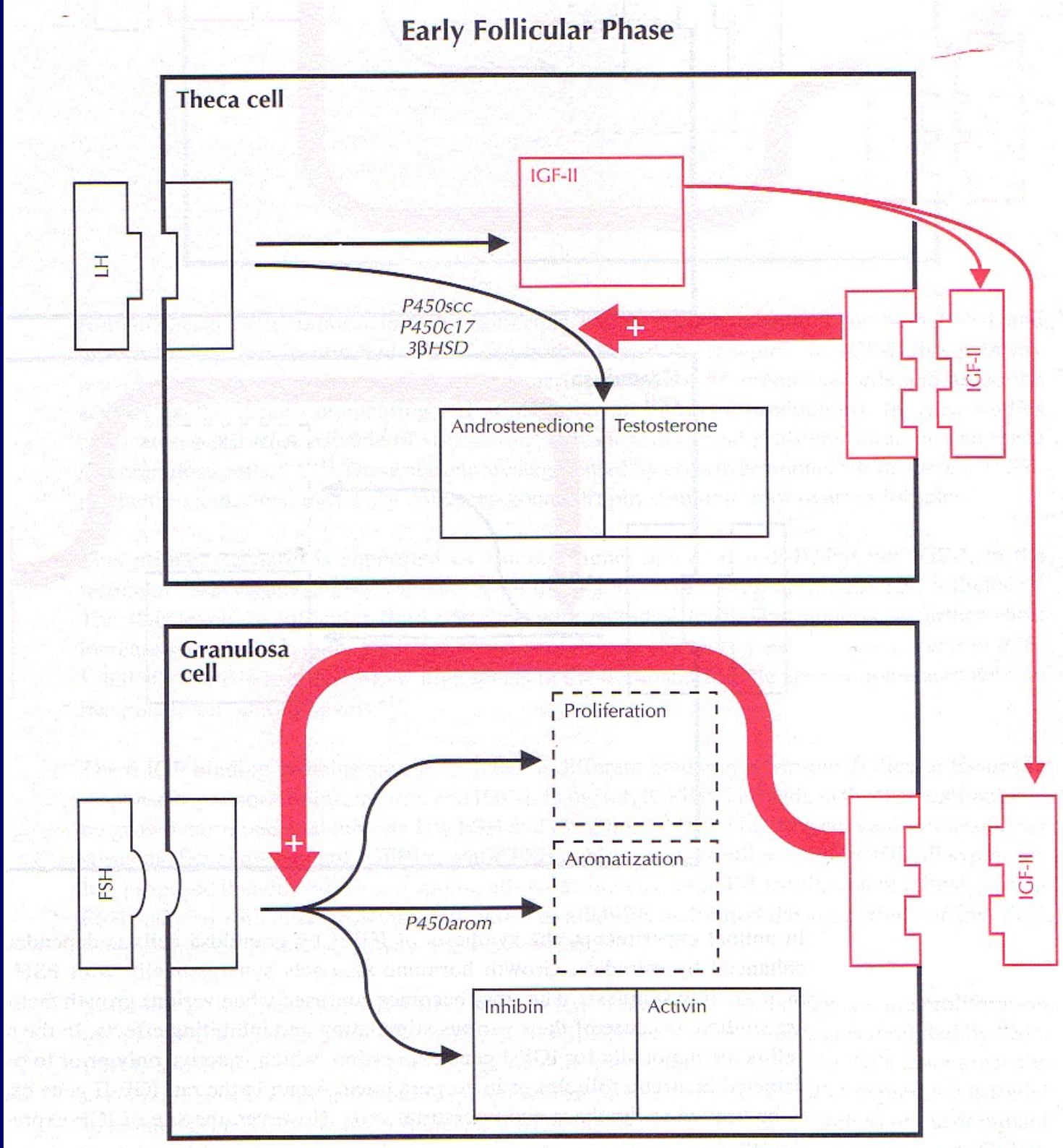
Early follicular phase – 90 minutes.
Late follicular phase – 60-70 minutes.
Early luteal phase – 100 minutes.
Late luteal phase – 200 minutes.

- LH Pulse Amplitude:

Early follicular phase – 6.5 IU/L.
Midfollicular phase – 5.0 IU/L.
Late follicular phase – 7.2 IU/L.
Early luteal phase – 15.0 IU/L.
Midluteal phase – 12.2 IU/L.
Late luteal phase – 8.0 IU/L.


14-24
hours
10-12
hours
OVULATION

Regulation of the Menstrual Cycle



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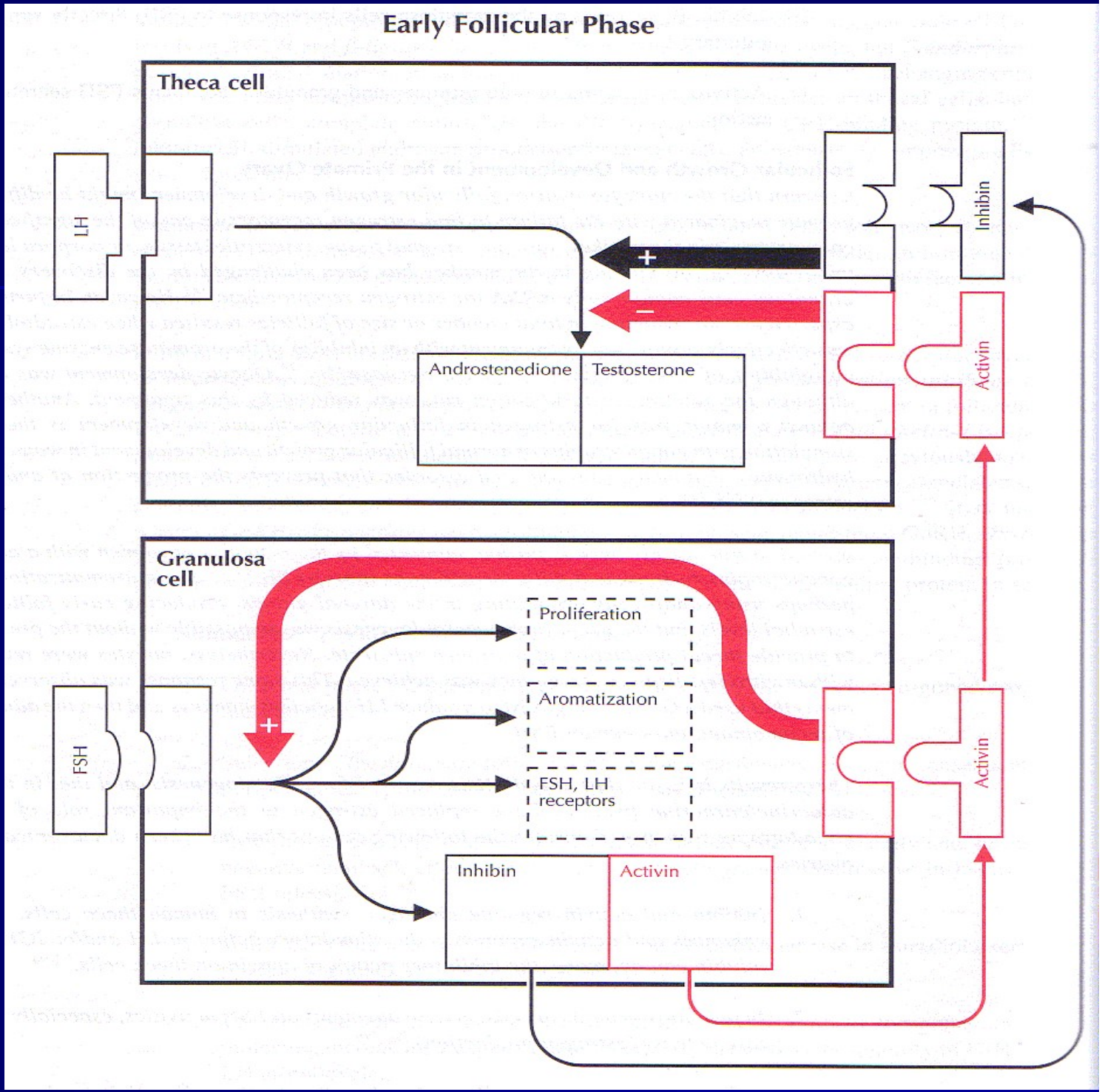
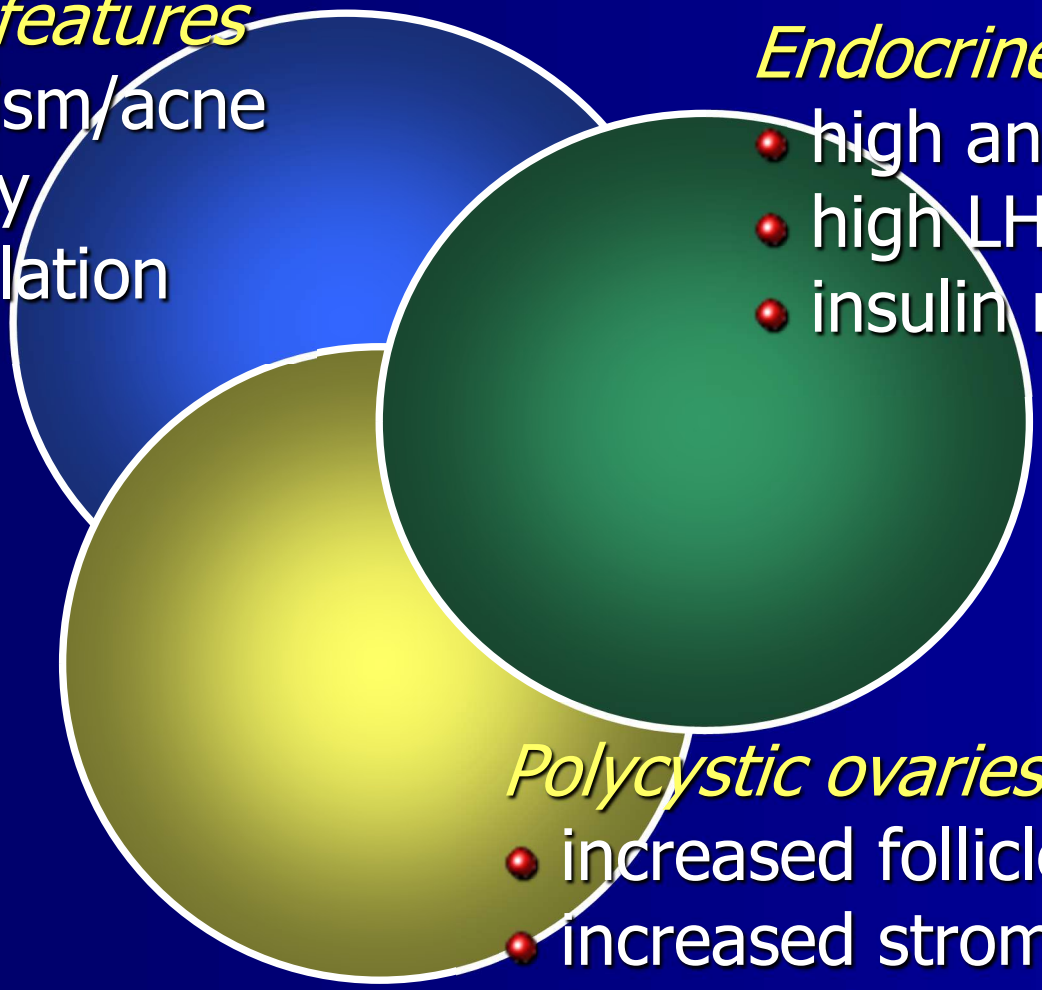


PCOS
- diagnostic dillema's -



Clinical features
- hirsutism/acne
- obesity
- anovulation

Endocrine features
- high androgens
- high LH
- insulin resistance

Polycystic ovaries
- increased follicle #
- increased stroma
- increased ovarian volume

Applied criteria for PCOS diagnosis in the literature

- Elevated LH — *Yen, Schoemaker*
- Elevated androgens — *Lobo, Barbieri, NIH*
- Ultrasound — *Jacobs, Franks, Balen*
- LH + US — *Conway, Risma*
- Androgens + US — *Fauser, Norman*
- LH + Androgens — *Shelly, Ardeans*
- LH + Andr + US — *Eden, Pache*
- Insulin resistance — *Nestler, Dunaif*

PCOS

- phenotype expression during adult life -

- Oligo- amenorrhea
- Infertility
- Obesity
- Hirsutism
- Type 2 diabetes
- Other

- Gynecologist
- gynecologist
- Internist
- Dermatologist
- Internist

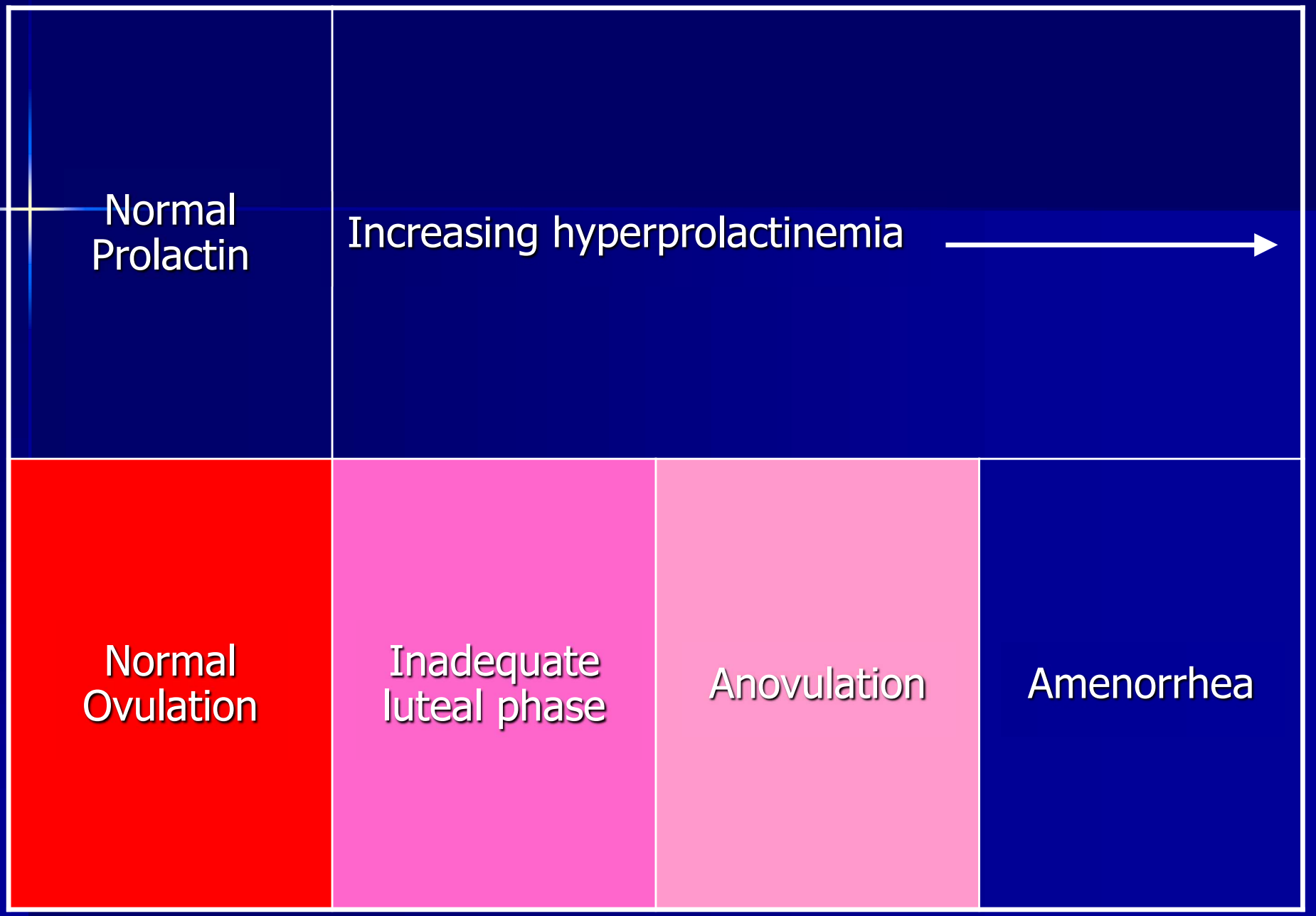
PCOS diagnostic criteria - 1990 NIH 'concensus' -

- Chronic anovulation
- Hyperandrogenism (clinical or biochemical)

exclusion of other etiologies

(both criteria)

Dunaif. PCOS. 1992. Blackwell Scientific


Normal Prolactin
Increasing hyperprolactinemia
Normal Ovulation
Inadequate luteal phase
Anovulation
Amenorrhea

Abnormal Feedback Signals

Estradiol levels must rise and fall in synchrony with morphologic events,

1) Estradiol levels may not fall low enough to allow sufficient FSH response for the initial growth stimulus
2) Levels of estradiol may be inadequate to produce the positive stimulatory effects necessary to induce the ovulatory surge of LH.

A. Loss of FSH Stimulation

B. Persistent Estrogen Secretion

- Pregnancy
- Ovarian or adrenal tumor

C. Abnormal Estrogen clearance & metabolism

- Hepatic Disease
- Thyroid

Hyperthyroidism & Hypothyroidism can cause persistent anovulation by altering:

1. Metabolic clearance
2. Peripheral conversion rates among the various steroids.

D. Extraglandular Estrogen Production

The *Adrenal gland does not secrete E2 but:*

1. Contributes to the total estrogen level by the extragonadal peripheral conversion of C-19 androgenic precursors, androstenedione to estrogen
2. Psychological or physical stress may increase the adrenal contribution of estrogenic precursor.

E. Loss of LH Stimulation

- Gonadal dysgenesis
- Ovarian Failure

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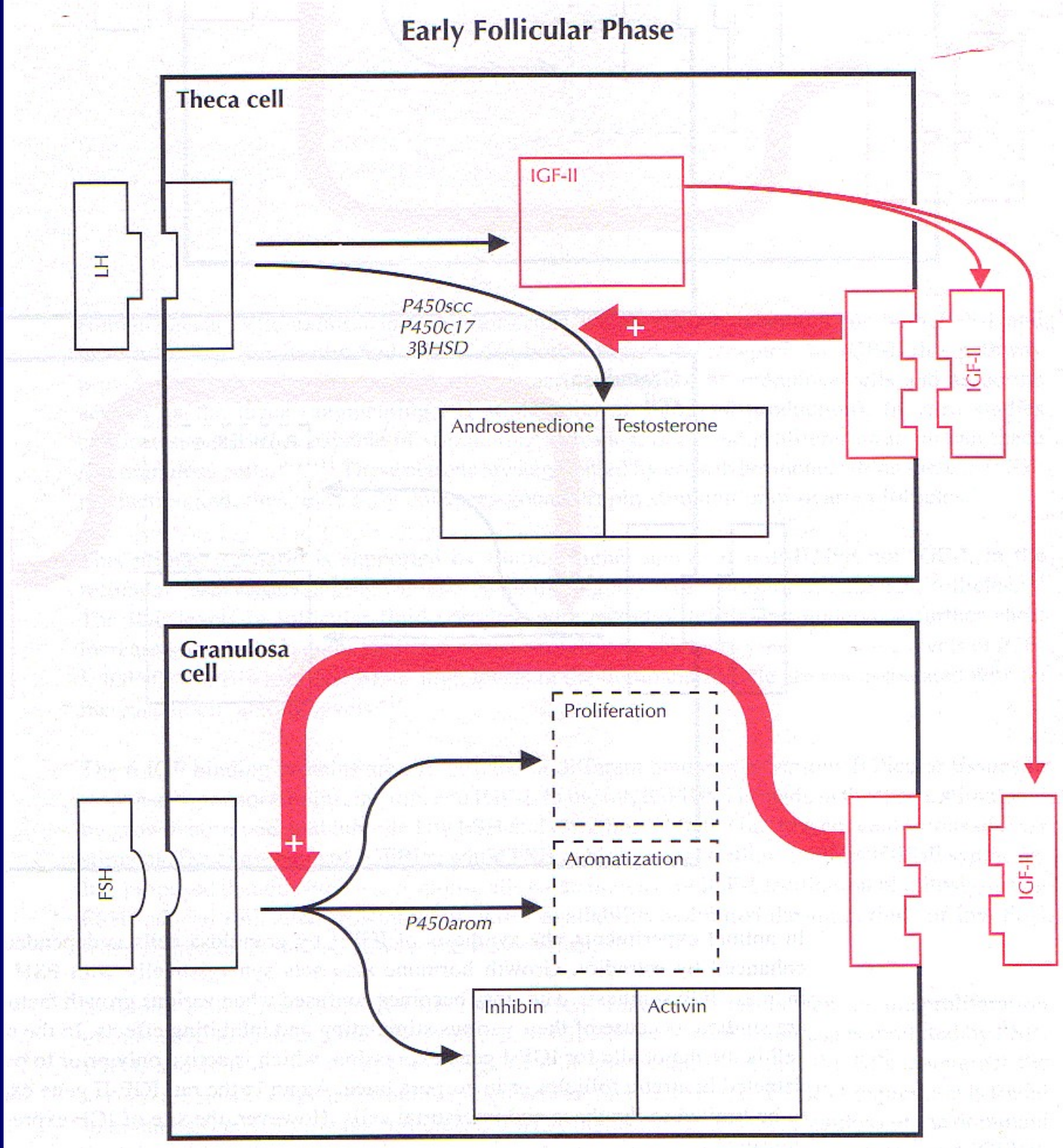

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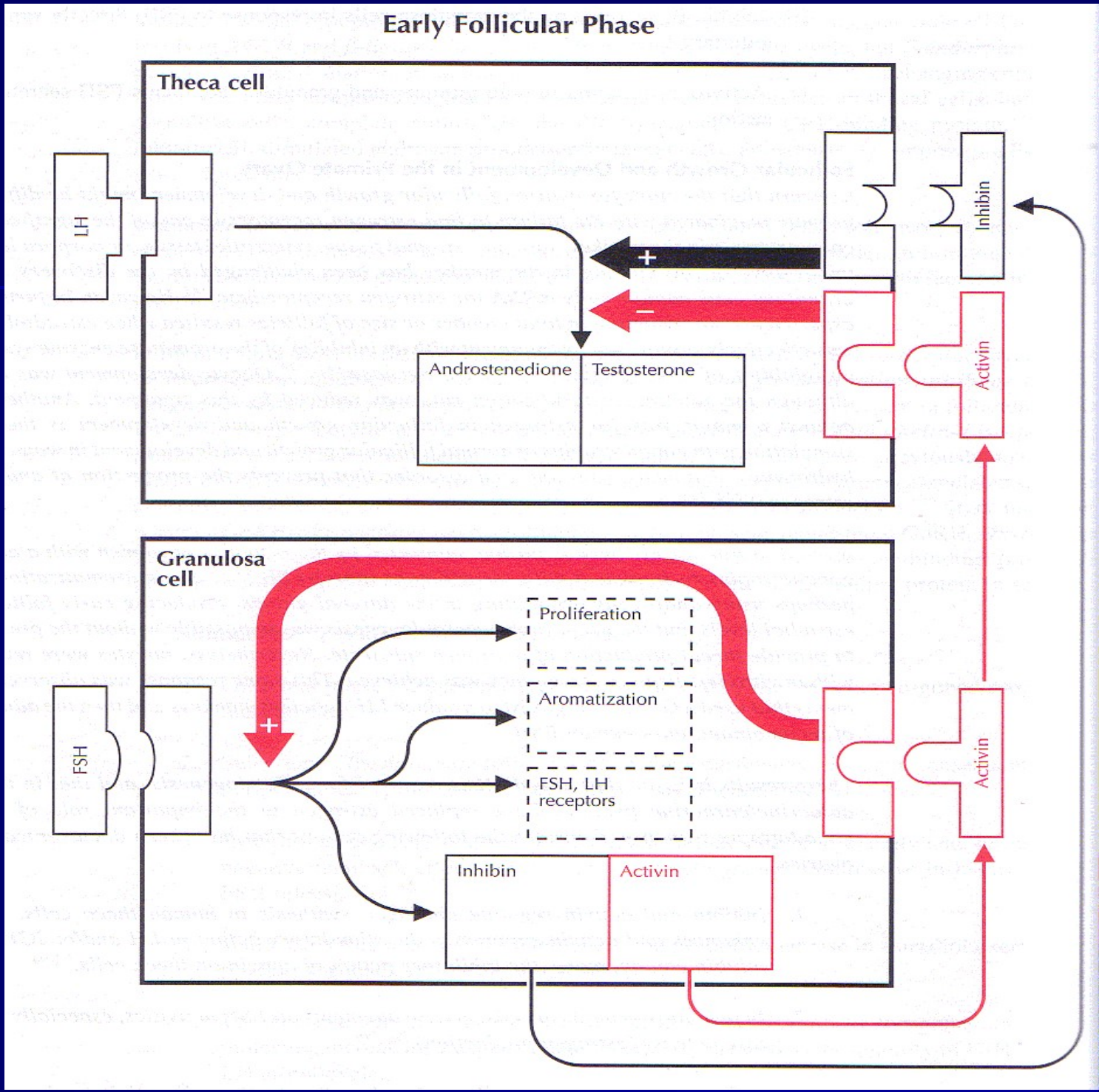


Local OvarianConditions

1. Selection of the dominant follicle is established during days 5-7, and consequently, peripheral levels of E_2 begin to rise significantly by cycle day 7.

2. Derived from the dominant follicle, E_2 levels increase steadily and, through negative feedback effects, exert a progressively greater suppressive influence on FSH release.

3. Insulin- like growth factor-II (IGF-II) is produced in theca cells in response to gonadotropin stimulation, and this response is enhanced by estradiol and growth hormone. In an autocrine action, IGF-II increases LH stimulation of androgen production in thecal cells.

4. IGF-II stimulates granulosa cell proliferation, aromatase activity, and progesterone synthesis.

5. FSH inhibits IGF binding protein synthesis and thus maximizes growth factor availability.

6. FSH stimulates inhibin and activin production by granulosa cells.

7. Activin augments FSH activities: FS receptor expression, aromatization, inhibin/activin production, and LH receptor expression.

8. Inhibin enhances LH stimulation of androgen synthesis in the theca to provide substrate for aromatization to estrogen in the granulosa.

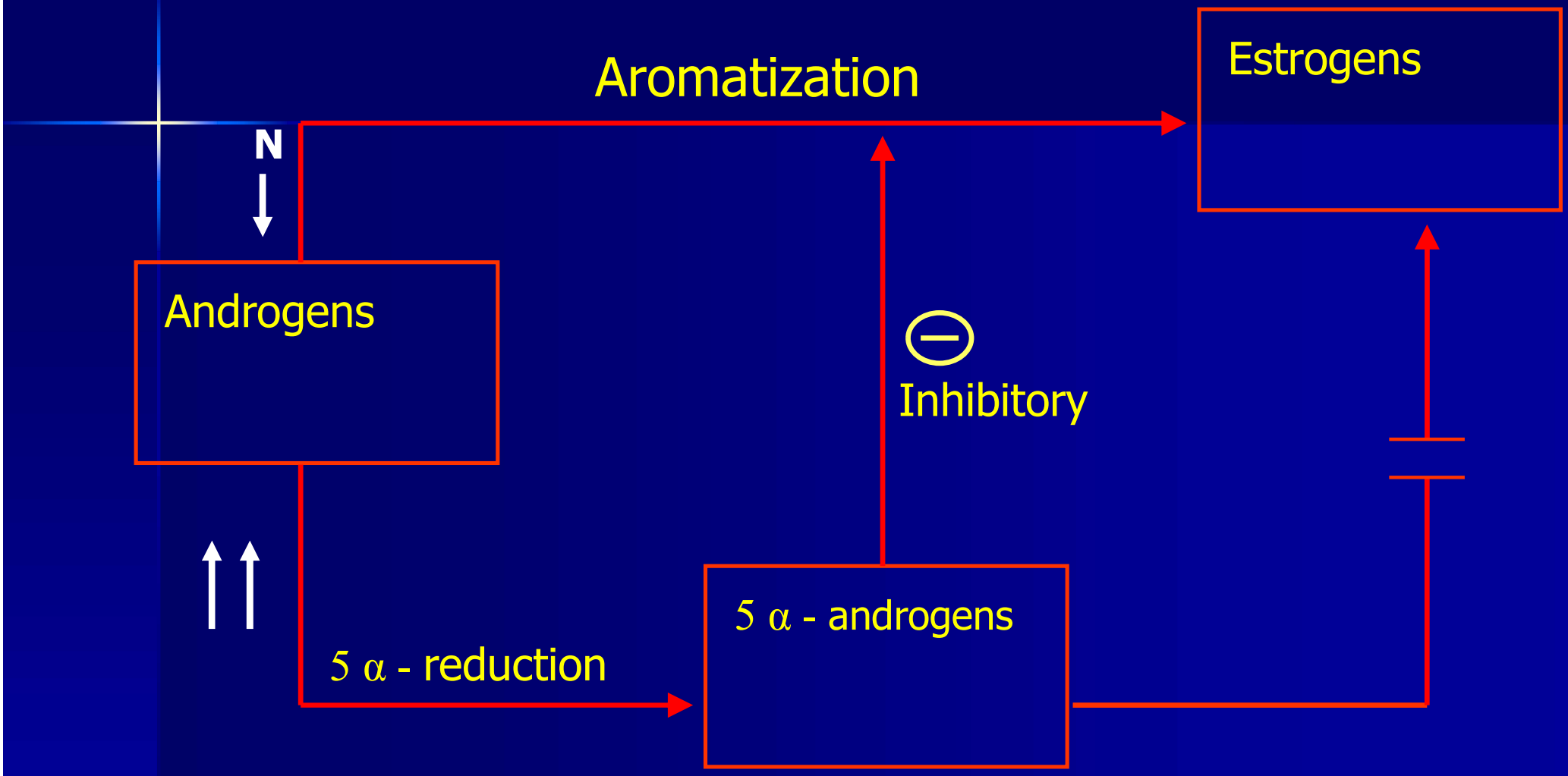
9. While directing a decline in FSH levels, the midfollicular risein estradiol exerts a positive feedback influence on LH secretion. LH levels rise steadily during the late follicular phase, stimulating androgen productionin the theca.

10. The positive action of estrogen also includes modification of the gonadotropin molecule, increasing the quality (the bioactivity) as well as the quantity of LH at midcycle..

11. Inhibin and, less importantly, follistatin, secreted by the granulosa cells in response to FSH, directly suppress pituitary FSH secretion.

12. FSH induces the appearance of LH receptors on granulosa cells.

Critical Role for the Concentration of A in the Ovarian Follicle

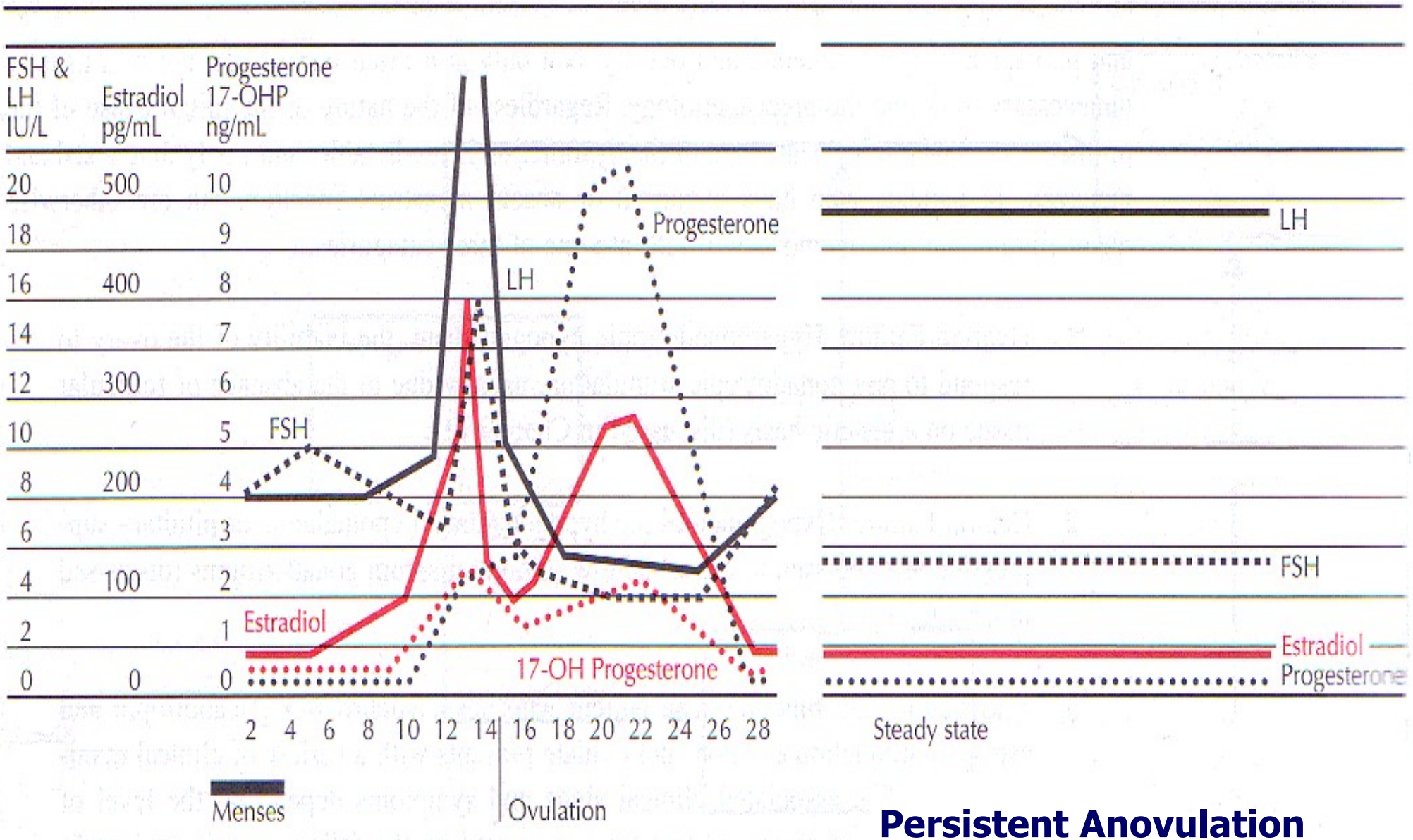


Excess Body Weight

The frequency of obesity → 35% to 60%

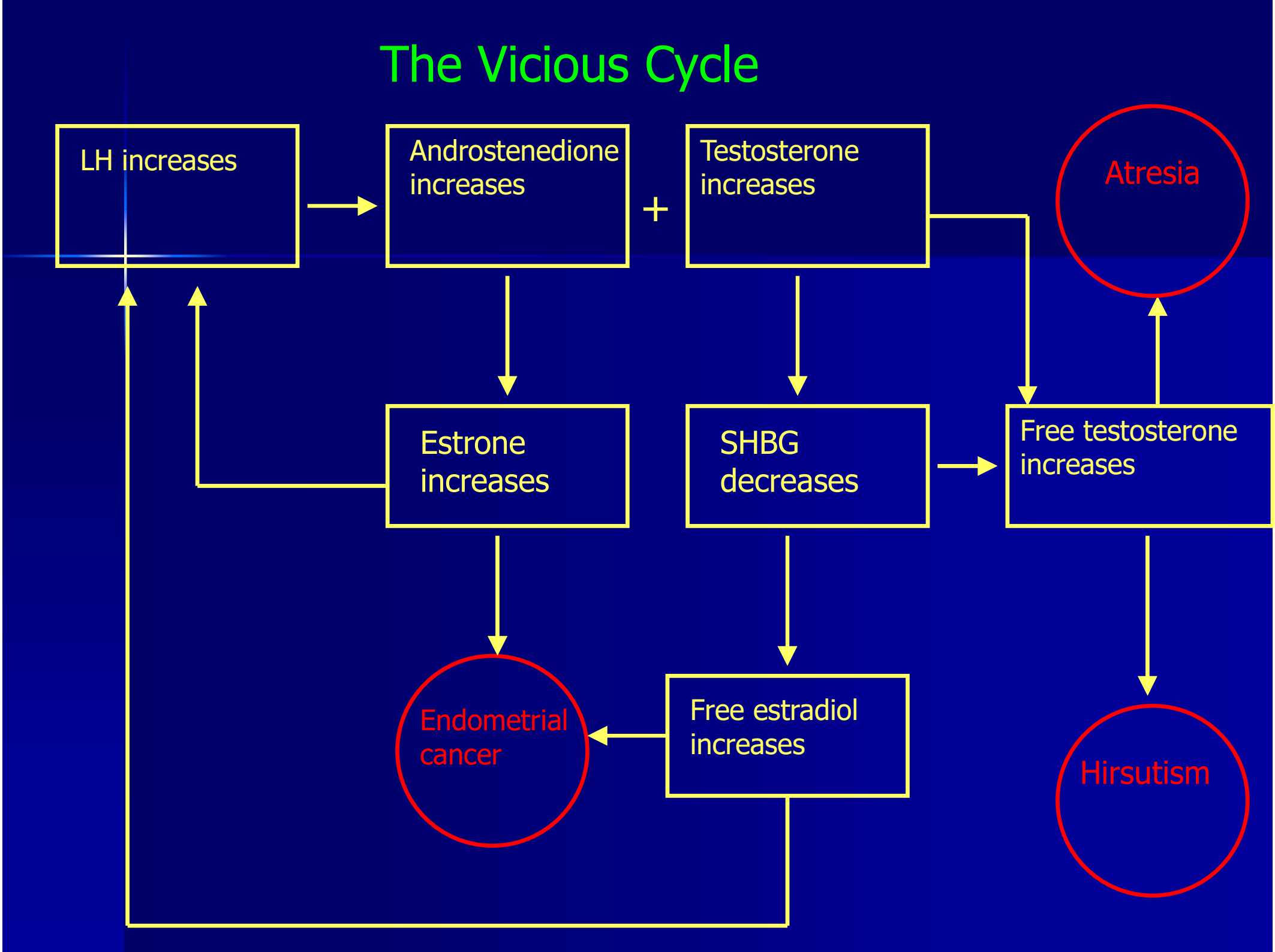
1. Increased peripheral aromatization of androgens to estrogens.
2. Decreased levels of sex hormone-binding globulin (SHBG), resulting in increased levels of free estradiol and testosterone.
3. Increased insulin levels that can stimulate ovarian stomal tissue production of androgens.

Normal Coordination



Persistent Anovulation

The Vicious Cycle



The characteristics of the ovary reflect this dysfunctional state.

1. The surface area is doubled, giving an average volume increase of 2.8 times

2. The same number of primordial follicles is present, but the number of growing and atretic follicles is doubled. Each ovary may contain 20-100 cystic follicles.

3. The thickness of the tunica (outermost layer) is increased by 50%.

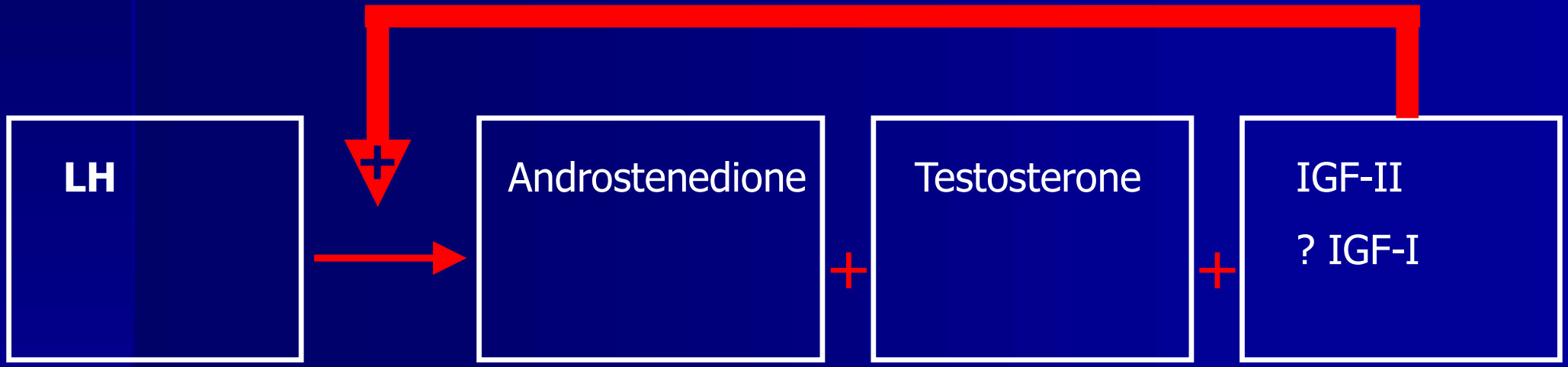
4. There are 4 times more ovarian hilus cell nests (hyperplasia).

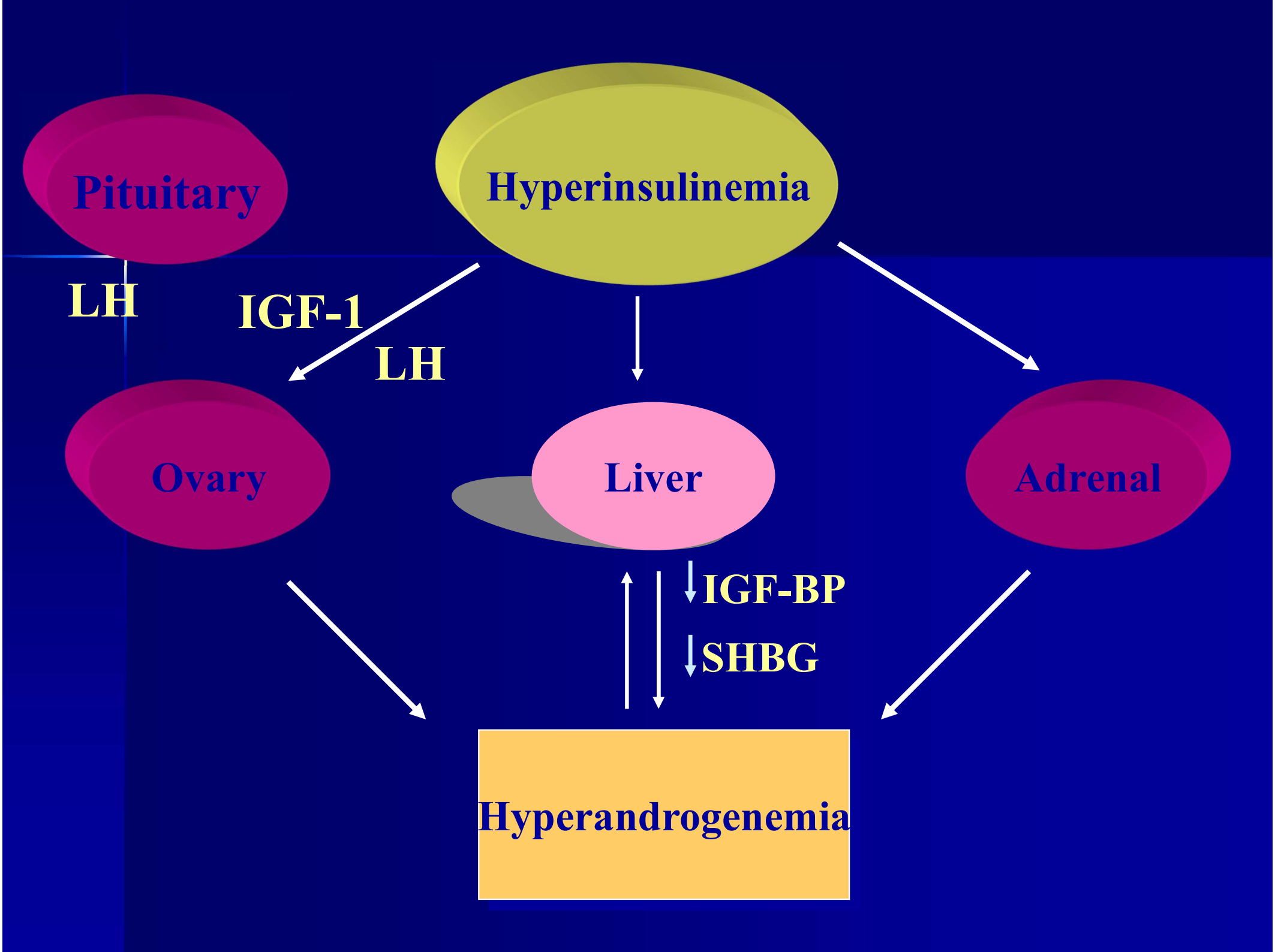
Hyperthecosis

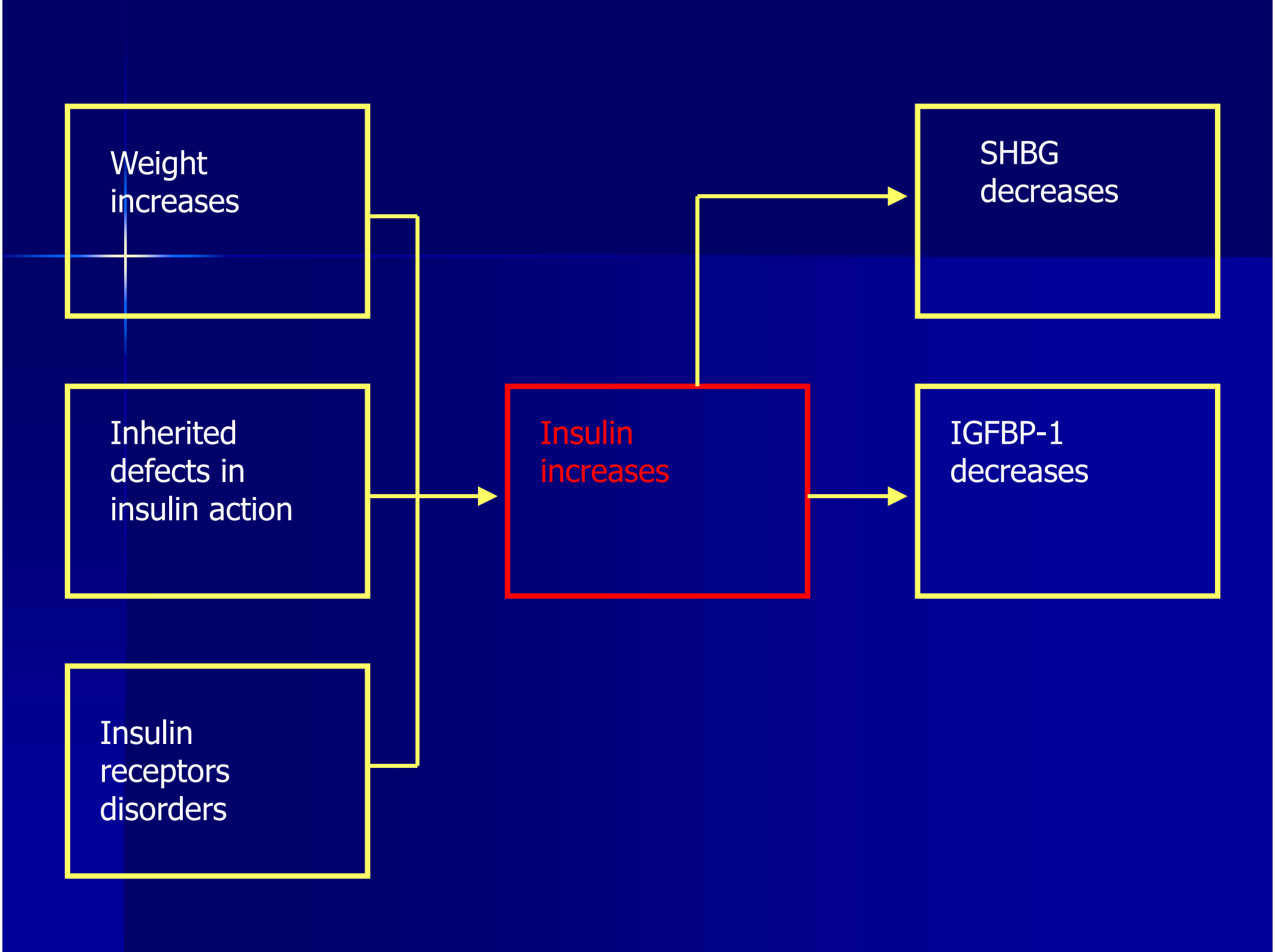
Patches of luiteinized theca-like cells scattered throughout the ovarian stroma

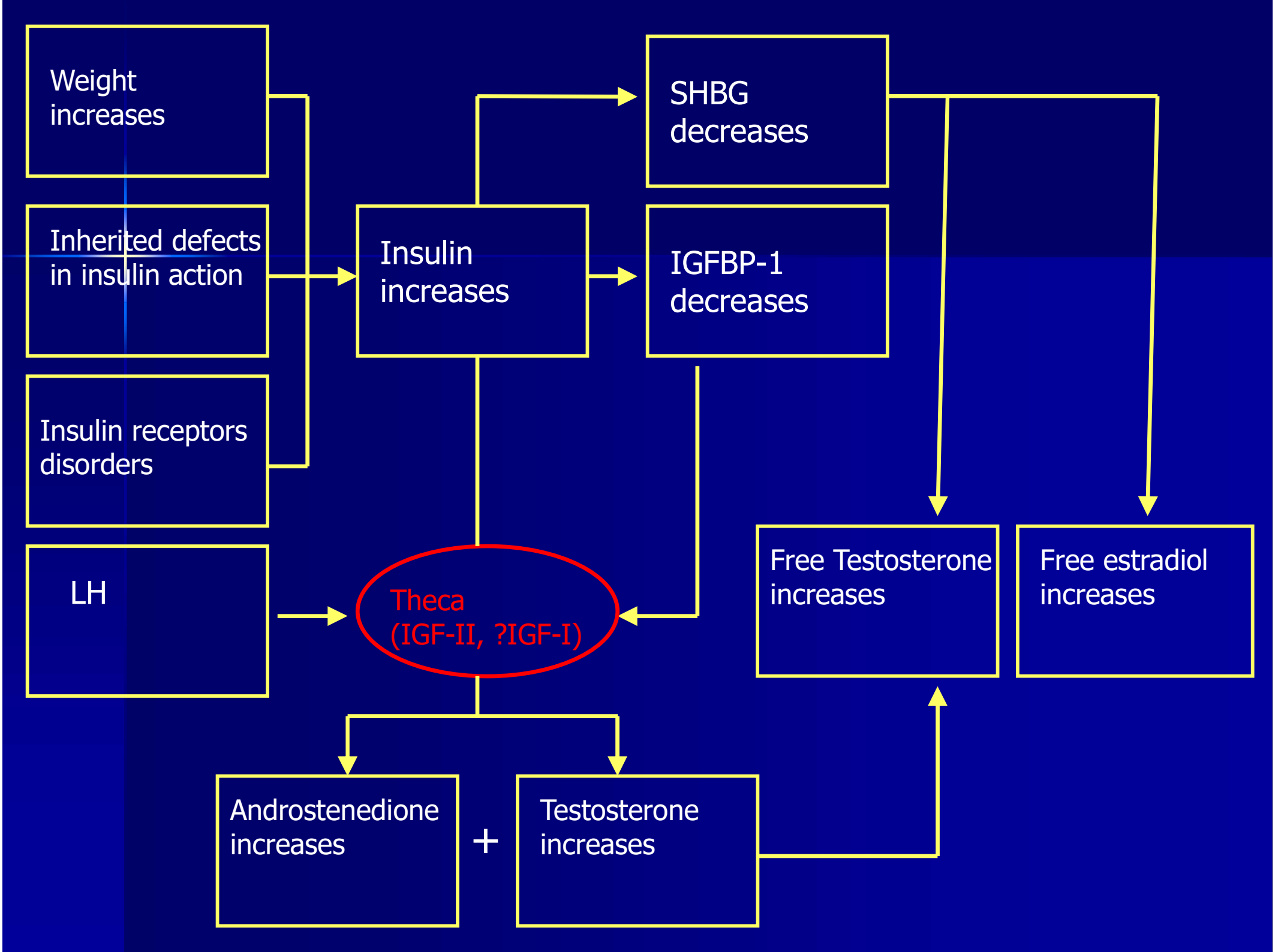
- Same histologic findings
- Intense androgenization
- Lower LH levels

How Does Hyperinsulinemia Produce Hyperandrogenism?



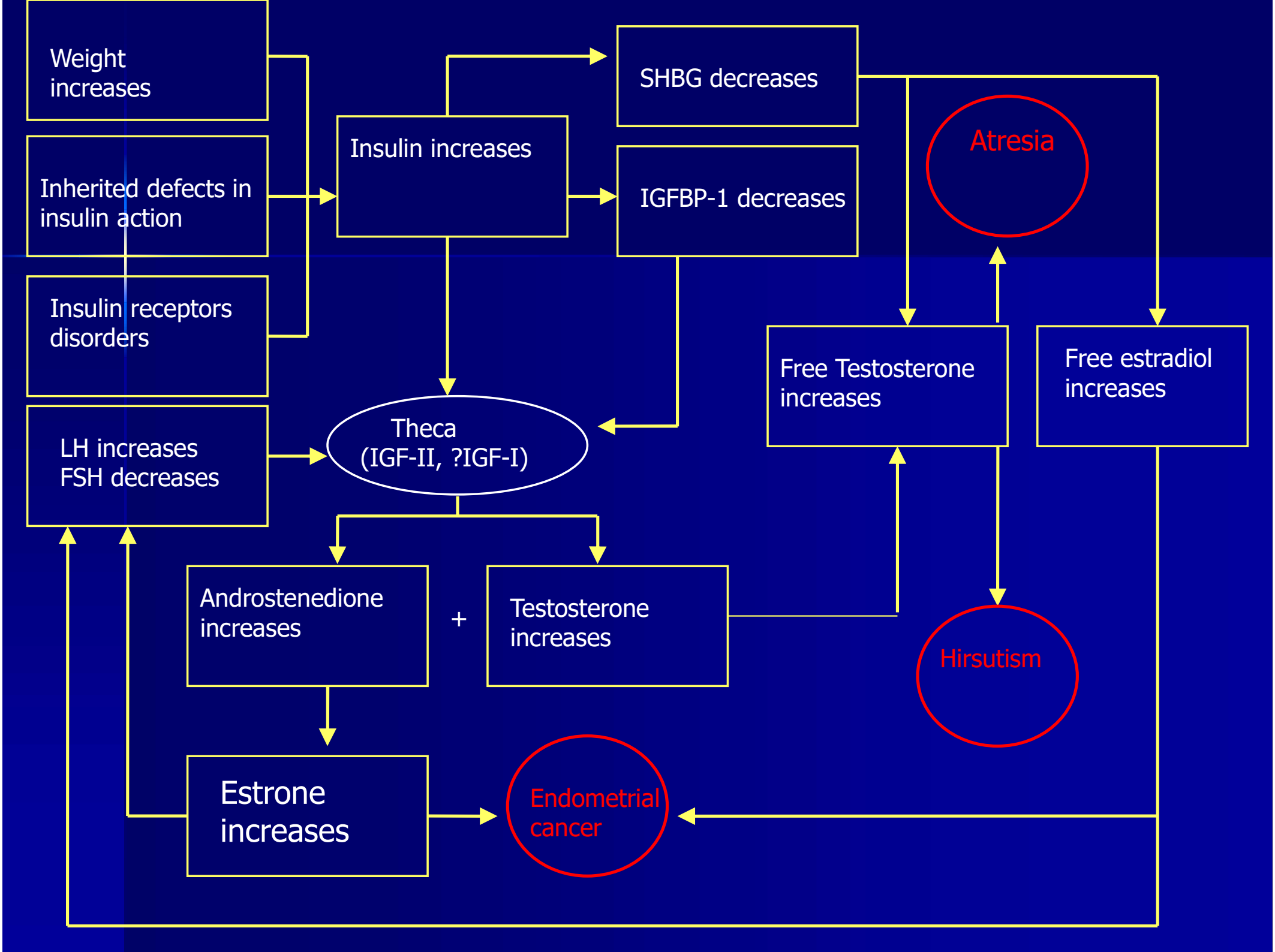

Pituitary
Hyperinsulinemia
LH
IGF-1
LH
Ovary
Liver
Adrenal
IGF-BP
SHBG
Hyperandrogenemia


Weight increases
Inherited defects in insulin action
Insulin receptors disorders
Insulin increases
SHBG decreases
IGFBP-1 decreases


Weight increases
Inherited defects in insulin action
Insulin receptors disorders
LH
Insulin increases
SHBG decreases
IGFBP-1 decreases
Theca (IGF-II, ?IGF-I)
Androstenedione increases
+
Testosterone increases
Free Testosterone increases
Free estradiol increases

The Clinical Consequences of Persistent Anovulation

1. Infertility.
2. Menstrual bleeding problems, ranging from amenorrhea to dysfunctional uterine bleeding.
3. Hirsutism, alopecia, and acne.
4. An increased risk of endometrial cancer and, perhaps, breast cancer.
5. An increased risk of cardiovascular disease
6. An increased risk of diabetes mellitus in patients with insulin resistance.


Weight increases
Inherited defects in insulin action
Insulin receptors disorders
LH increases
FSH decreases
Insulin increases
SHBG decreases
IGFBP-1 decreases
Atresia
Free Testosterone increases
Free estradiol increases
Theca (IGF-II, ?IGF-I)
Androstenedione increases
+
Testosterone increases
Hirsutism
Estrone increases
Endometrial cancer

Overall Goals of Treatment

1. Reduce the production and circulating levels of androgens.
2. Protect the endometrium against the effects of unopposed estrogen.
3. Support lifestyle changes to achieve normal body weight.
4. Lower the risk for cardivascular disease.
5. Avoid the effects of hyperinsulinemia on the risks of cardiovascular disease and diabetes mellitus.
6. Induction of ovulation to achieve pregnancy.

Cervical score scheme according to INSLER

Cervical Factor	Score			
	0	1	2	3
Amount of cervical secretion	0 = no secretion	1 = little secretion. A small amount of cervical secretion can be detected in the cervical canal	2= 1 drop of secretion. A shiny drop of secretion projects from the cervical orifice. The secretion can easily be removed from the cervical canal.	3= copious secretion, which flows spontaneously from the cervical canal.
Spinnbarkeit	0=none	1=slight Spinnbarkeit". A mucus thread can be drawn about ¼ of the distance from the cervical orifice to the vulva without breaking.	2=good "Spinnbarkeit" A mucus thread can be drawn about half the distance from the cervical orifice to the vulva without breaking.	3= extremely good "Spinnbarkeit" A mucus thread can be drawn the entire distance from the cervical orifice to the vulva without breaking.
Fern phenomenon	0= no secretion or amorphous secretion	1= linear . Slight linear crystallization is seen only in several sites. Without lateral branching.	2= partial Good "fern" crystallization with lateral branching in some sites but only linear crystallization in other areas, and also the presence of amorphous areas.	3= complete the fern phenomenon is fully expressed throughout the smear.
Cervix	O= closed Pale pink mucosa. External os barely accessible with narrow probe.		2= partially open , Pink mucosa. Probe readily enters the cervical canal.	3= wide open Hyperemic mucosa. External os wide open.