بسم الله الرحمن الرحيم

Polycystic Ovary Syndrome

A-Z

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PCOS

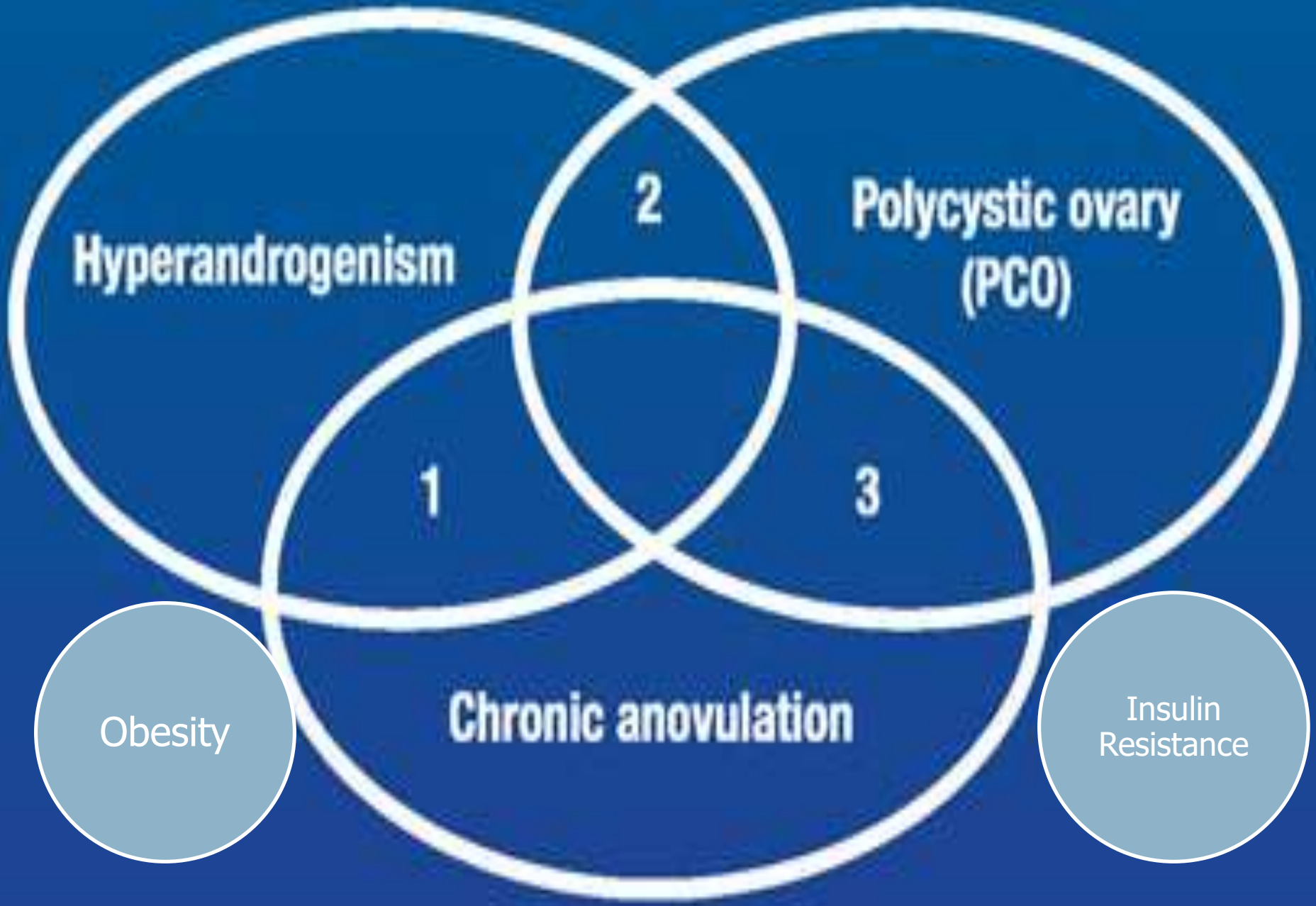

Hyperandrogenism
2
Polycystic ovary
(PCO)
1
3
Chronic anovulation
Obesity
Insulin
Resistance

Table 1. Diagnostic Criteria for the Polycystic Ovary Syndrome.

Variable	National Institutes of Health	Rotterdam	Androgen Excess and PCOS Society
Hyperandrogenism*	Hyperandrogenism required	Any two of the three features (hyperandrogenism, ovulatory dysfunction, polycystic ovarian morphologic features) required	Hyperandrogenism required
Oligo-ovulation or anovulation†	Ovulatory dysfunction required	Any two of the three features (hyperandrogenism, ovulatory dysfunction, polycystic ovarian morphologic features) required	Either ovulatory dysfunction or polycystic ovarian morphologic features required
Polycystic ovarian morphologic features‡	Not applicable	Any two of the three features (hyperandrogenism, ovulatory dysfunction, polycystic ovarian morphologic features) required	Either ovulatory dysfunction or polycystic ovarian morphologic features required
No. of combinations that meet criteria for the polycystic ovary syndrome	Two (hyperandrogenism plus ovulatory dysfunction; hyperandrogenism plus ovulatory dysfunction plus polycystic ovarian morphologic features)	Four (hyperandrogenism plus ovulatory dysfunction plus polycystic ovarian morphologic features; hyperandrogenism plus ovulatory dysfunction; hyperandrogenism plus polycystic ovarian morphologic features; ovulatory dysfunction plus polycystic ovarian morphologic features)	Three (hyperandrogenism plus ovulatory dysfunction plus polycystic ovarian morphologic features; hyperandrogenism plus ovulatory dysfunction; hyperandrogenism plus polycystic ovarian morphologic features)

Diagnosis in adolescent requires special considerations

- Diagnosis in adolescents is controversial as it is complicated by several factors
- Many features of polycystic ovary syndrome, including acne, menstrual irregularities, and hyperinsulinemia, are common in normal puberty
- Menstrual irregularities with anovulatory cycles and varied cycle length are common in adolescents for approximately 2 years after menarche owing to immaturity of hypothalamic-pituitary-ovarian axis
- Multicystic ovaries are a common normal finding in adolescents owing to natural history of ovarian development at menarche

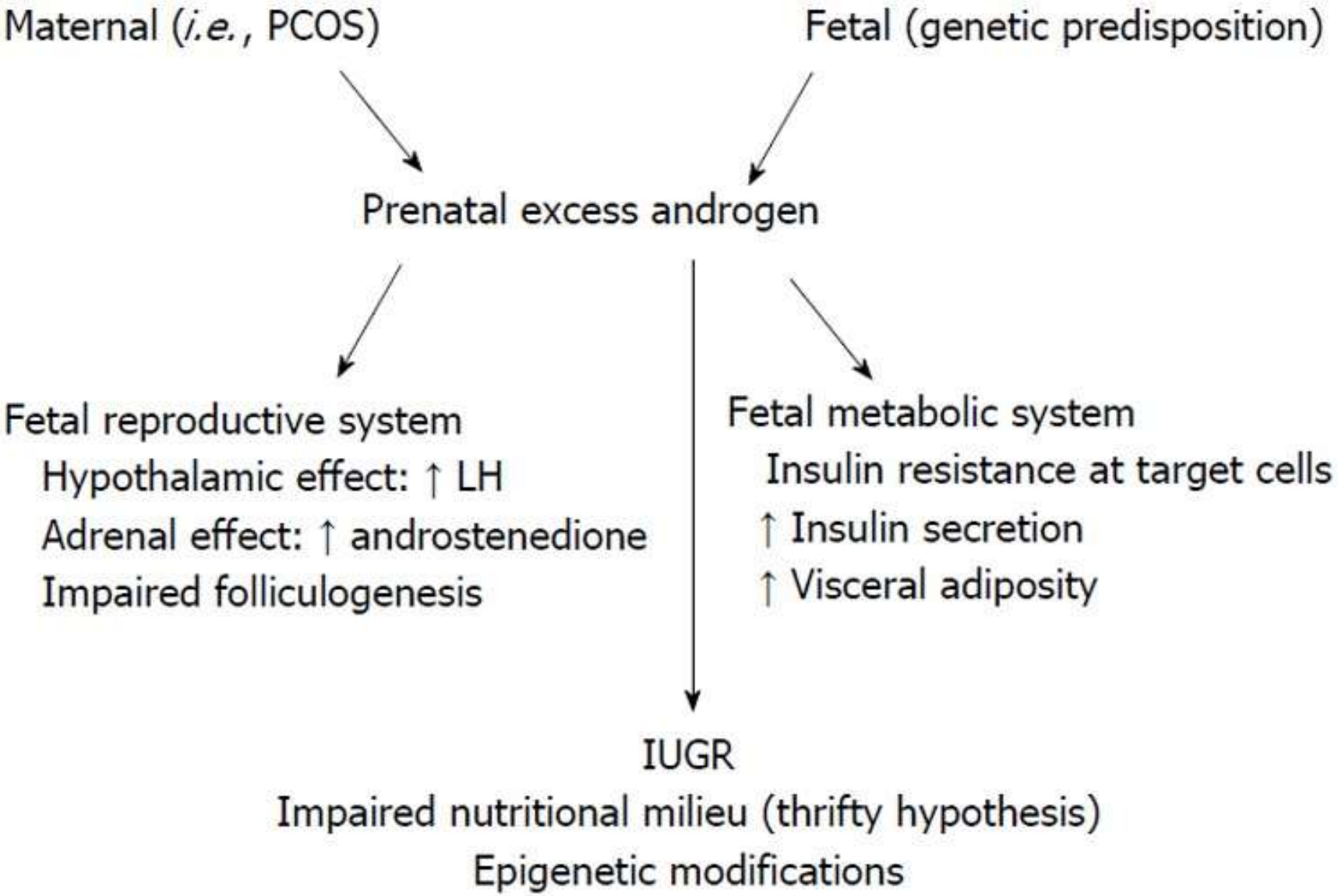
Proposed criteria for diagnosis in adolescents include the otherwise unexplained combination of:

- Abnormal uterine bleeding pattern, meeting both of the following requirements:
- Abnormal for gynecologic age (eg, ovulatory dysfunction that persists more than 2 years after menarche)
- Cycles shorter than 19 days or longer than 90 days are abnormal at any stage
- 75% of menstrual cycles range from 21 to 45 days during first postmenarcheal (gynecologic) year
- 95% of adolescents achieve 21- to 40-day adult menstrual cyclicity by fifth gynecologic year
- Persistent symptoms for 1 to 2 years
- In adolescent females, large, multicystic ovaries are a common finding; therefore, ultrasonography is not a recommended investigation in patients younger than 17 years

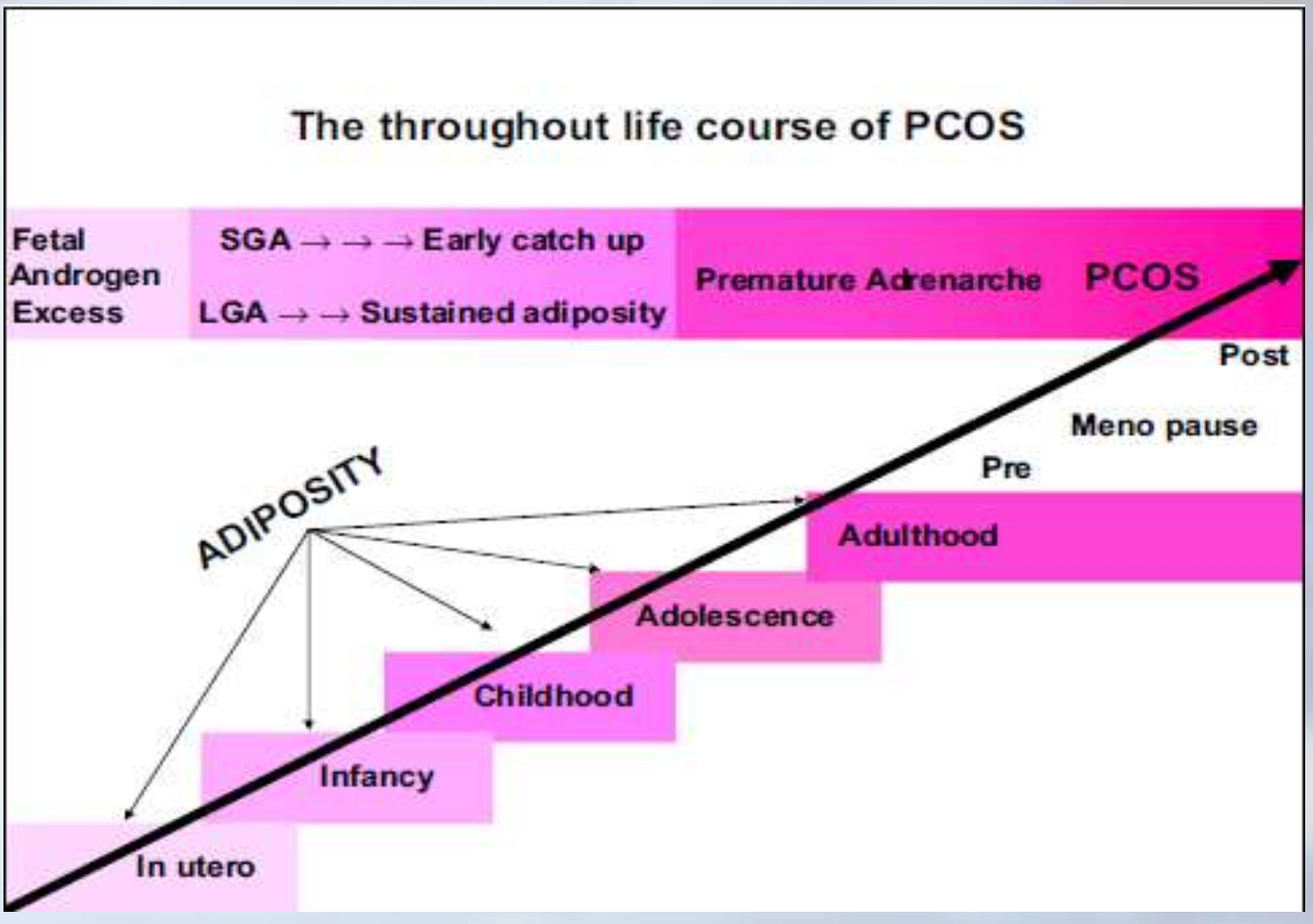
History

- The description of polycystic ovaries dates back as far as 1720.
- Stein and Leventhal, USA 1935.

Disease evolution!!!! **Thrifty phenotype hypothesis????**


Maternal (*i.e.*, PCOS)
Fetal (genetic predisposition)
Prenatal excess androgen
Fetal reproductive system
Hypothalamic effect: ↑ LH
Adrenal effect: ↑ androstenedione
Impaired folliculogenesis
Fetal metabolic system
Insulin resistance at target cells
↑ Insulin secretion
↑ Visceral adiposity
IUGR
Impaired nutritional milieu (thrifty hypothesis)
Epigenetic modifications

Natural history
(E. Diamanti-Kandarakis, 2010)



Prevalence

- The UK and US------6–7%.
- The prevalence tends to vary depending on ethnicity and the criteria used to define PCOS.
- PCOS is higher in those with:
  - gestational diabetes.
  - premature adrenarche
  - in those with first-degree relatives who have PCOS.
  - DENND1A over-expression

Genetics

- Clusters in families and both female and male relatives can show stigmata of the syndrome
- Complex, polygenic disorder with multiple alleles associated with a small degree of risk
- Genome-wide association studies implicate many genes, including:
  - LHCGR (luteinizing hormone/choriogonadotropin receptor)
  - FSHR (follicle stimulating hormone receptor)
  - INSR (insulin receptor)
  - DENND1A (DENN domain containing 1A)
  - THADA (THADA armadillo repeat containing)

Ethnicity/race

- **Ethnic variations affect phenotypic expression**
  - Patients of European ancestry display greater midline hirsutism than those of East Asian ancestry
  - Patients of African ancestry have higher rates of hypertension and cardiovascular risk factors
  - Patients of Mediterranean ancestry have greater quantities of body hair compared with most patients of Asian ancestry, who have relatively little body hair
- **Other risk factors/associations**
  - Associated with several cardiometabolic diseases or conditions that should be assessed and monitored
  - Obesity (about 75% of patients)
  - Type 2 diabetes mellitus (about 10% of patients)
  - Dyslipidemia (about 70% of patients)
  - Obstructive sleep apnea
  - Nonalcoholic steatohepatitis
  - Subclinical vascular disease

Long term effects

- Obesity: the best waist circumference >78 cm
- Poor Quality of life
- Depression (Rasgon NL, 2003)
- DM------20%-
- HT-------40 % (Enrico Carmina, 1998)
- Higher rate of TAH
- Cardiovascular diseases. **(L. W. Cho, 2011)**
- Ca endometrium & ovary------2-3 fold (E Carmina, 1997)
- PCOS and pregnancy.
- Non-alchoholic fatty liver disease (NAFLD)- 4 folds increase.
- Infertility.
- Sleep apnea
- IBS

Metabolic dysfunction

- Insulin resistance, glucose intolerance, and type 2 diabetes are common comorbidities
- More than 50% of patients are insulin resistant, even those whose weight falls within reference range
- Impaired glucose tolerance occurs in 35% of adult patients
- Approximately 25% of adolescent patients have metabolic syndrome
- Type 2 diabetes occurs in 10% of patients (also influenced by age, adiposity, and family history)
- Screen for impaired glucose tolerance and type 2 diabetes with a 2-hour oral glucose tolerance test, repeated every 3 to 5 years depending on various factors such as degree of overweight or obesity, presence of central adiposity, and interval weight gain

Depression

- Increased incidence and prevalence over lifetime
- Screen for depression and anxiety at diagnosis, then periodically

Endometrial cancer

- Health professionals and women with PCOS should be aware of a 2- to 6-fold increased risk of endometrial cancer, which often presents before menopause; however absolute risk of endometrial cancer remains relatively low
- Health professionals require a low threshold for investigation of endometrial cancer in women with PCOS or a history of PCOS, with investigation by transvaginal ultrasound and/or endometrial biopsy recommended with persistent thickened endometrium and/or risk factors including prolonged amenorrhea, abnormal vaginal bleeding or excess weight. However, routine ultrasound screening of endometrial thickness in PCOS is not recommended.
- Optimal prevention for endometrial hyperplasia and endometrial cancer is not known. A pragmatic approach could include COCP or progestin therapy in those with cycles longer than 90 days

Hypertension

- At menopause, women with polycystic ovary syndrome have risk of developing hypertension that is 2.5-fold higher than that of age-matched controls; hypertension may accelerate atherosclerotic cardiovascular disease
- Screen with blood pressure measurement at each visit

Obstructive sleep apnea

- Prevalence of sleep apnea is 5- to 30-fold higher for patients with polycystic ovary syndrome, even after adjustment for age and BMI
- Screen with symptom assessment, and if apparent apnea/hypopnea is identified, obtain polysomnography
- Successful treatment of obstructive sleep apnea with CPAP improves insulin sensitivity and reduces diastolic blood pressure

Dyslipidemia

- Approximately 70% of patients with newly diagnosed disease have abnormal lipid levels, including increased total cholesterol level, high triglyceride levels, high LDL-C level, and decreased HDL-C level
- Screen with semiannual measurement of blood lipid levels, or more frequently if there has been interval weight gain
- Treatment or primary prevention of atherosclerotic cardiovascular disease depends on several factors, including LDL-C level, age, presence of diabetes, and estimated risk of cardiac event within 10 years following guidance established for the general population

Irregular cycles and ovulatory dysfunction

- Irregular menstrual cycles are defined as:
  - Normal in the first year post menarche as part of the pubertal transition
  - 1 to <3 years post menarche: <21 or >45 days.
  - 3 years post menarche to perimenopause: <21 or >35 d or <8 cycles per year.
  - 1 year post menarche >90 days for any one cycle.
  - Primary amenorrhea by age 15 or >3 years post thelarche (breast development)

CCR

Hyperandrogenism

- Reliable assessment of biochemical hyperandrogenism is not possible in women on hormonal contraception, due to effects on sex hormone-binding globulin and altered gonadotrophin-dependent androgen production CPP.
- Where androgen levels are markedly above laboratory reference ranges, other causes of biochemical hyperandrogenism need to be considered. CPP
- Modified Ferriman Gallwey score (mFG) with a level ≥4-6 indicating hirsutism, depending on ethnicity.
- The Ludwig visual score is preferred for assessing the degree and distribution of alopecia

Ultrasound in PCOS

- Ultrasound should not be used for the diagnosis of PCOS in those with a gynecological age of <8 years (<8 years after menarche), due to the high incidence of multi-follicular ovaries in this life stage.
- In patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for PCOS diagnosis; however, ultrasound will identify the complete PCOS phenotype.
- In transabdominal ultrasound reporting is best focused on ovarian volume with a threshold of ≥10 ml, given the difficulty of reliably assessing follicle number with this approach.
- Reporting of endometrial thickness and appearance is referred; three-layer endometrial assessment may be useful to screen for endometrial pathology.
-

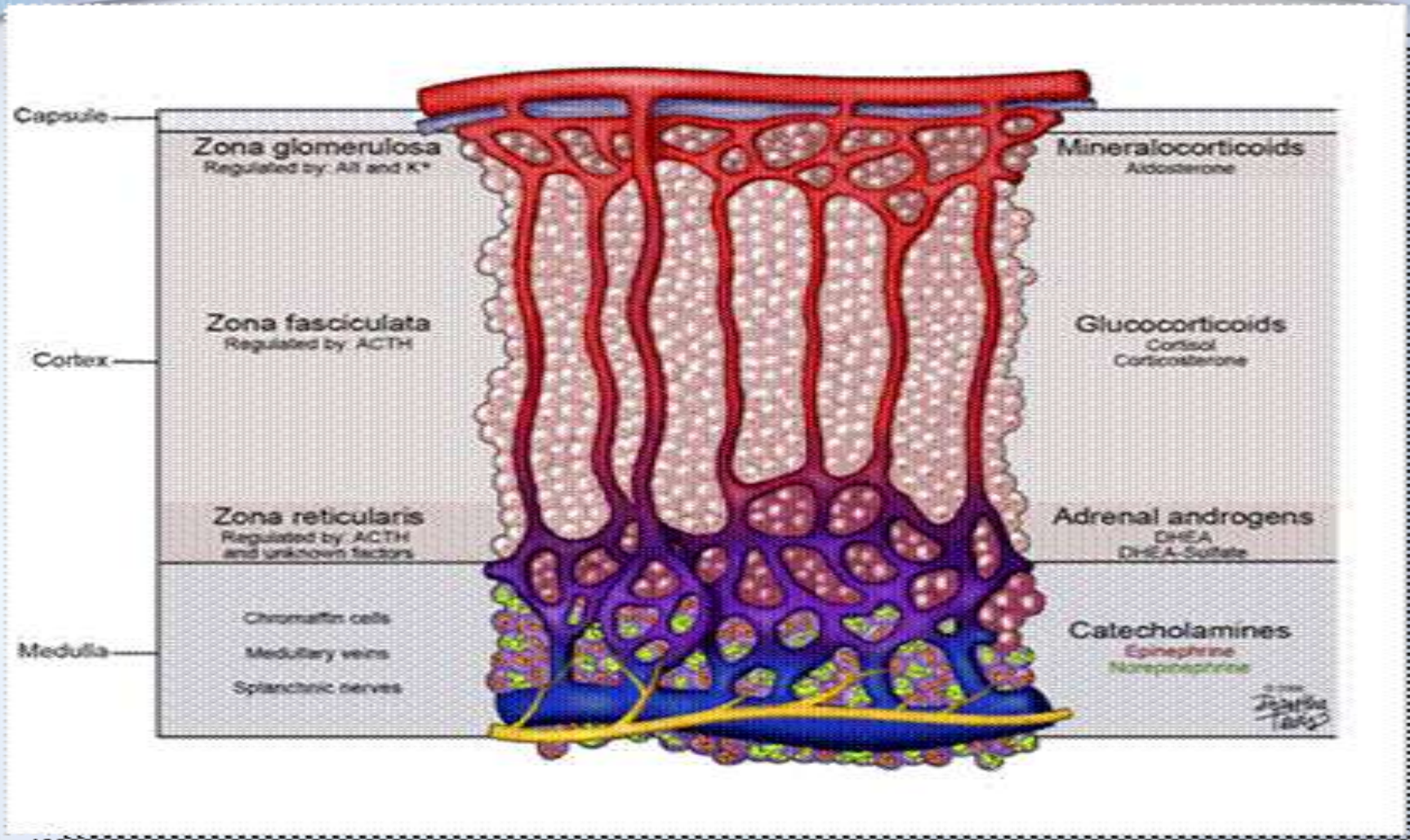
WHO classes of anovulation

- Class 1: Hypogonadotrophic hypogonadal anovulation
- Class 2: Normogonadotrophic normooestrogenic anovulation

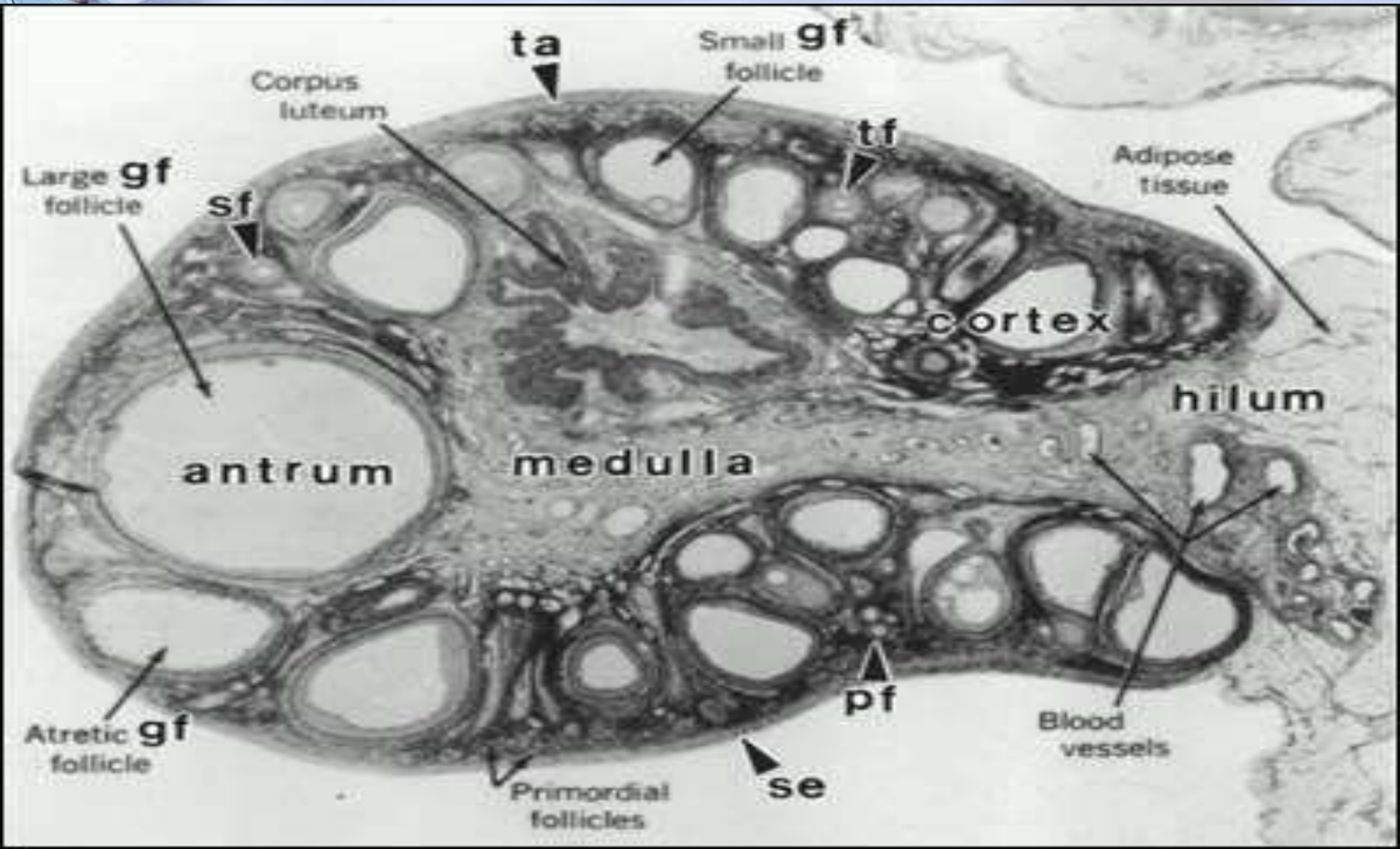
  This group accounts for 85% of ovulatory disorders. Women may secrete normal gonadotrophins and oestrogens but FSH secretion during the follicular phase is subnormal. This subgroup includes women with PCOS.
- Class 3: Hypergonadotrophic hypogonadism

- Hyperprolactinaemic anovulation

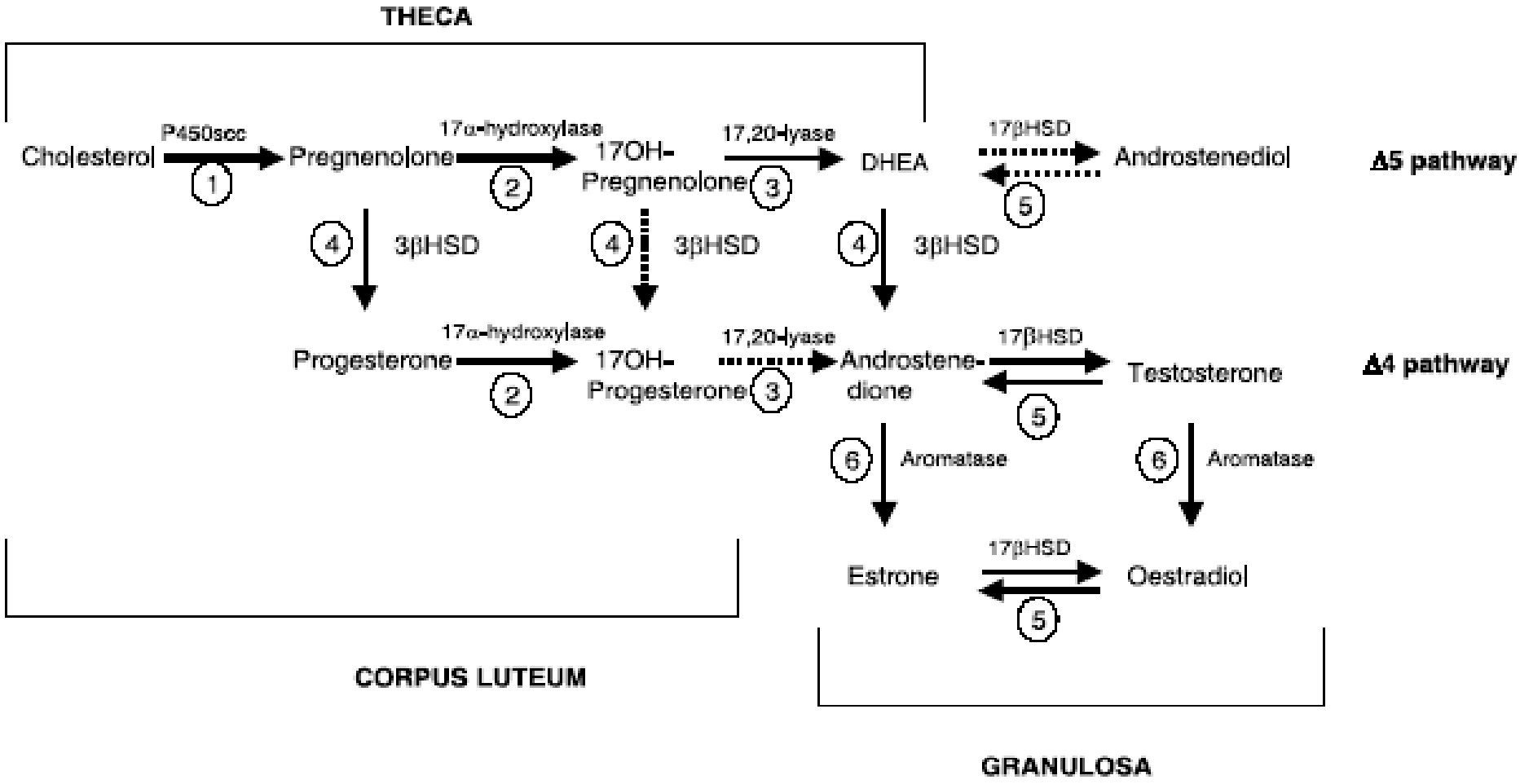
Schematic presentation of the adrenal zones and the main product



The adult ovary can be subdivided into three regions: the cortex, medulla, and hilum regions

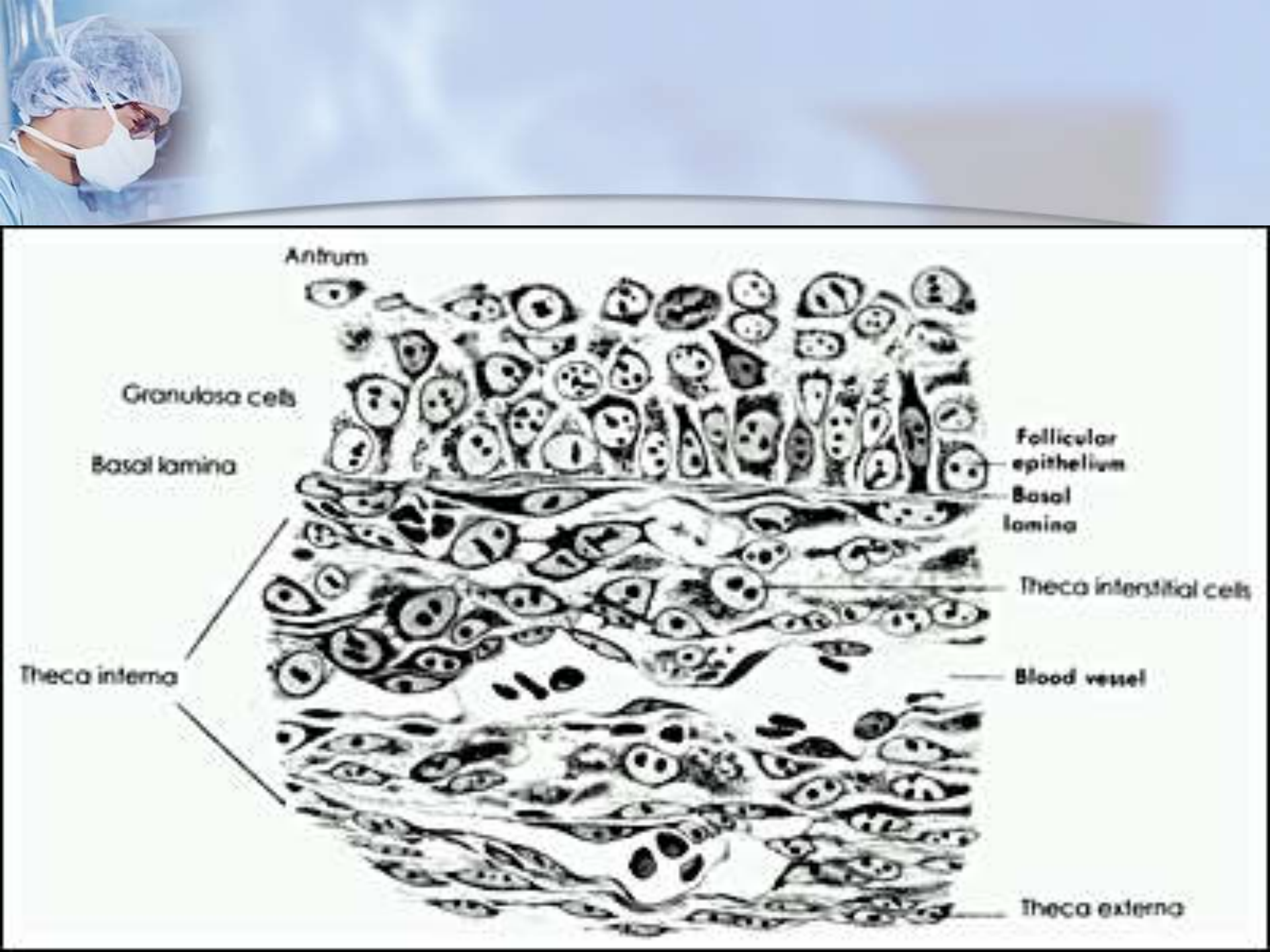


Ovarian steroidogenesis

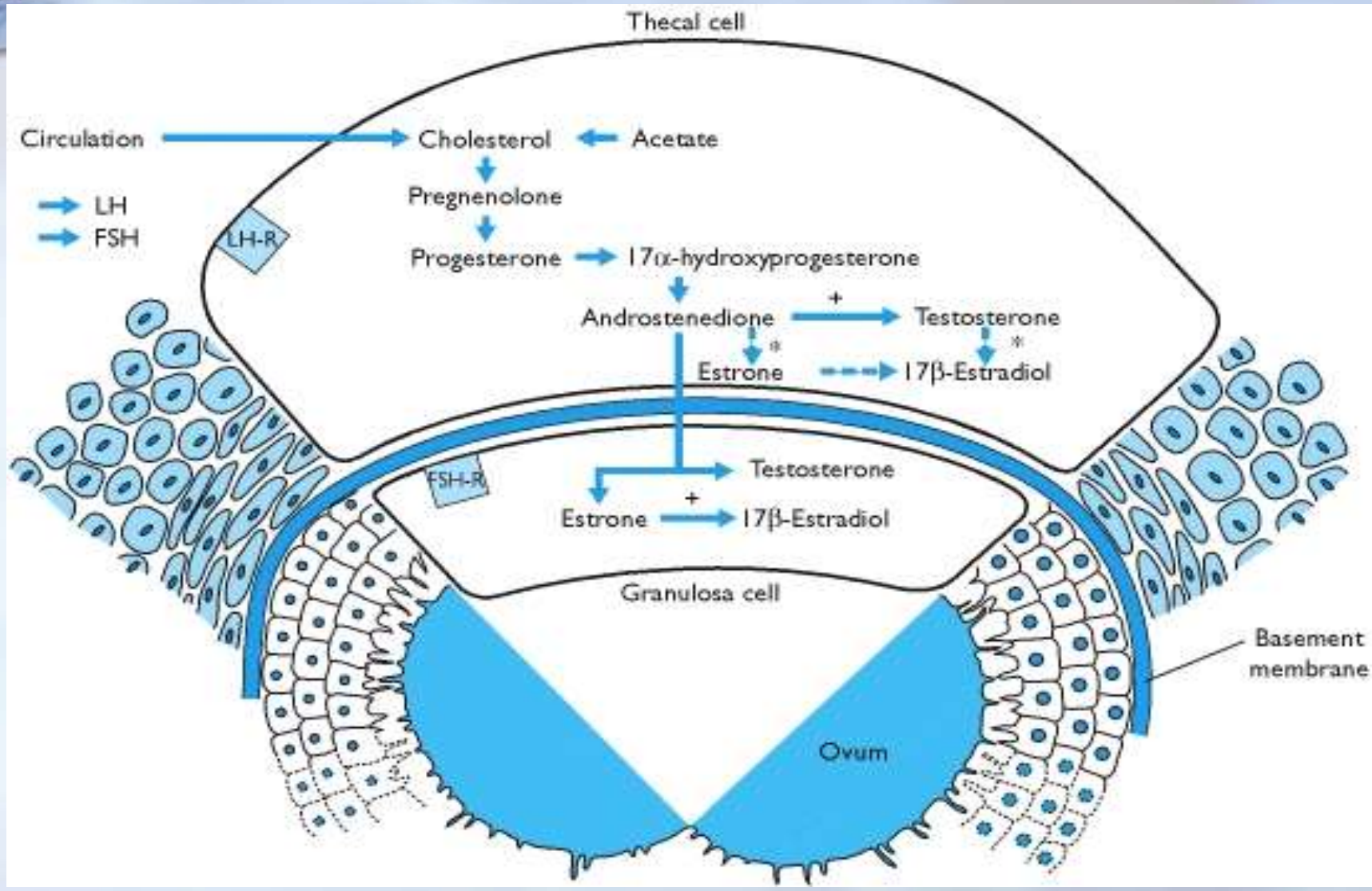


Ovarian Vs Adrenal steroidogenesis

- The ovary lacks the 21-hydroxylase and B-hydroxylase reactions.
- Hence, no glucocorticoids and mineralocorticoids in the ovary


Antrum
Granulosa cells
Basal lamina
Follicular epithelium
Basal lamina
Theca interstitial cells
Theca interna
Blood vessel
Theca externa

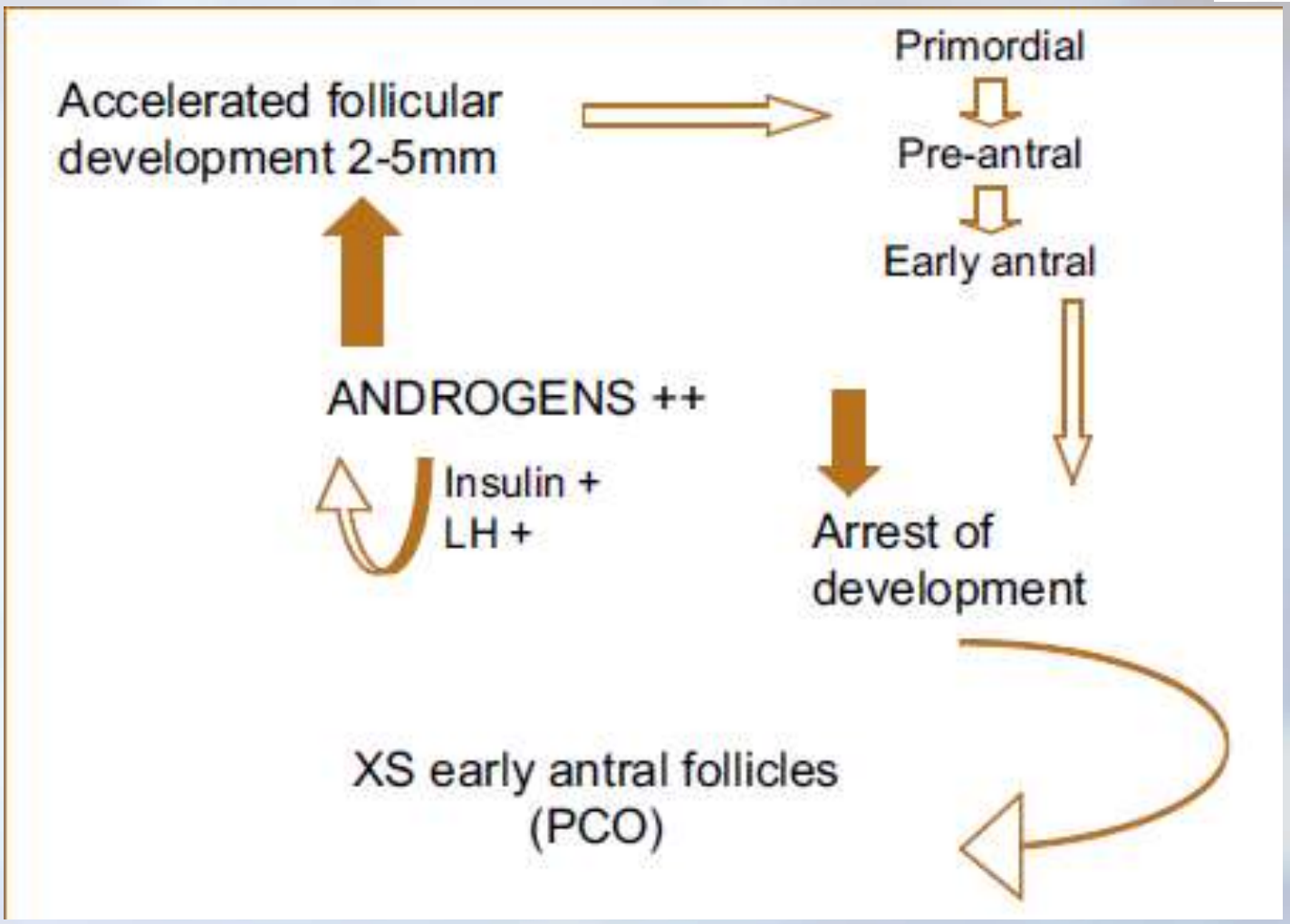
Two gonadotropin-two cell theory



Folliculo-genesis in PCOS

- PCOS: is the commonest cause of anovulatory infertility.
- Anovulation in PCOS is characterized by arrested growth of antral follicles.
- Although arrested antral follicle growth probably reflects the abnormal endocrine environment in PCOS (and, particularly the effect of hyperinsulinemia),
- There is increasing evidence of abnormalities of follicle development from the very earliest, gonadotropin-independent stages.
- The underlying molecular basis of this fundamental ovarian abnormality remains to be determined.

Ovarian follicular defect

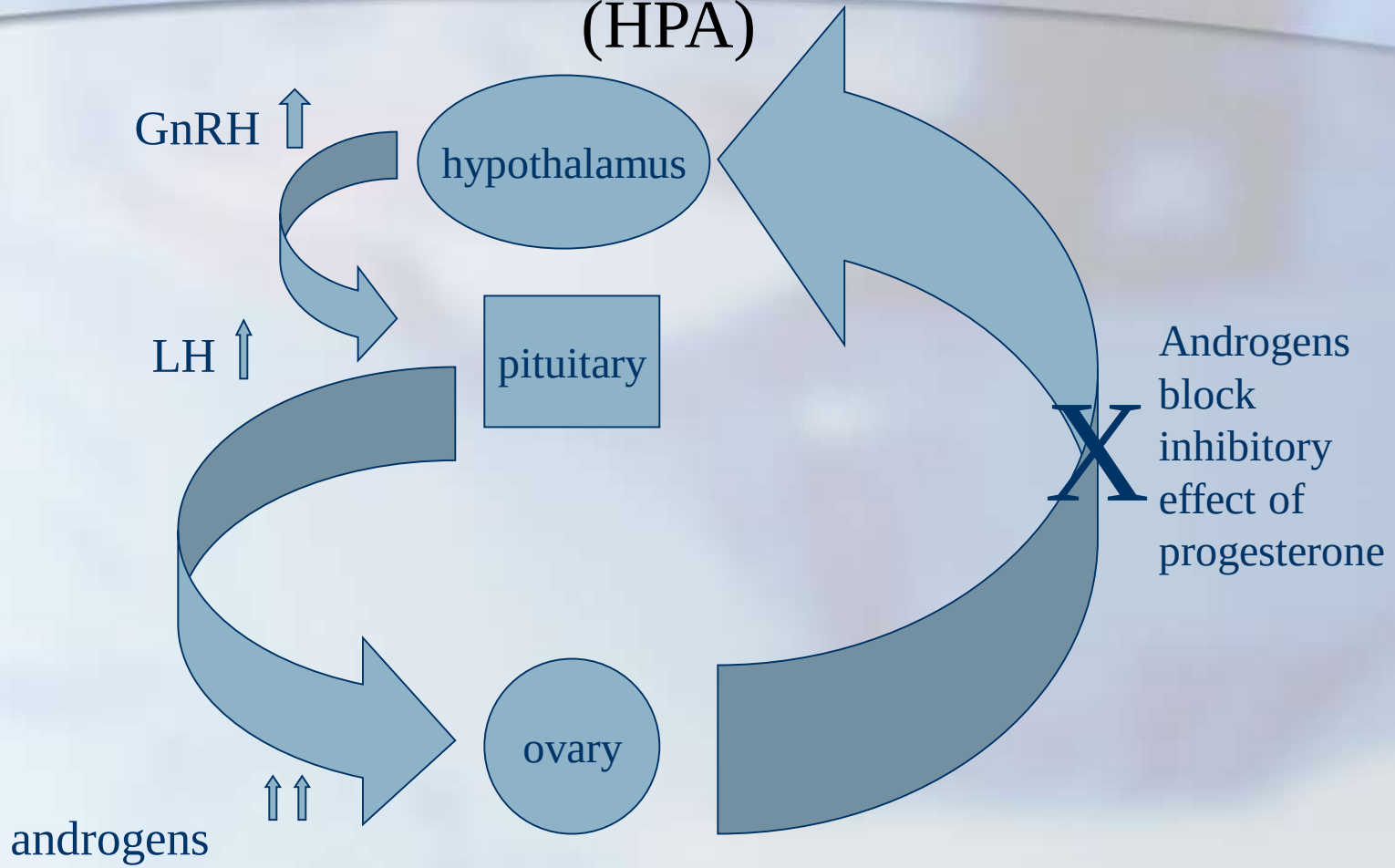


Anti-Mullerian Hormone (AMH)

- AMH is a polypeptide of the transforming growth factor beta (TGFβ) family, solely secreted by granulosa cells of the pre-antral and small antral ovarian follicles
- Serum AMH levels are elevated in normoandrogenic women with PCO and are further increased in hyperandrogenic women with PCO, independent of antral follicle number.
- Serum AMH levels in PCOS patients are elevated two to threefold, are positively correlated with antral follicle number and serum androgen levels, and are reduced in parallel with antral follicle number by metformin therapy
- In women, AMH inhibits the recruitment of primordial follicles out of the resting oocyte pool and may suppress follicle-stimulating hormone (FSH) action contributing to ovulatory disturbances[33]

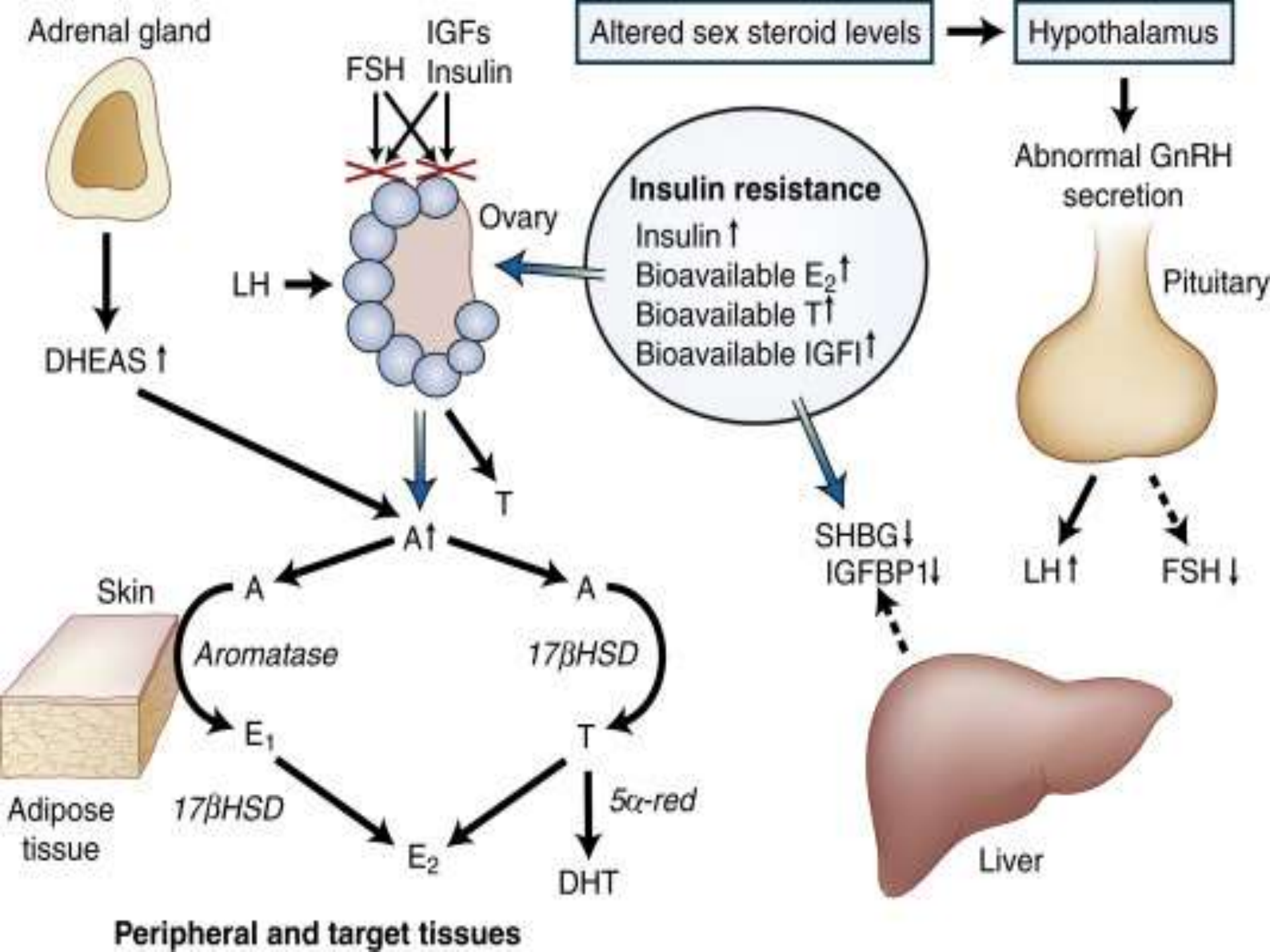
Pathophysiology:

Abnormalities in the hypothalamic pituitary axis (HPA)

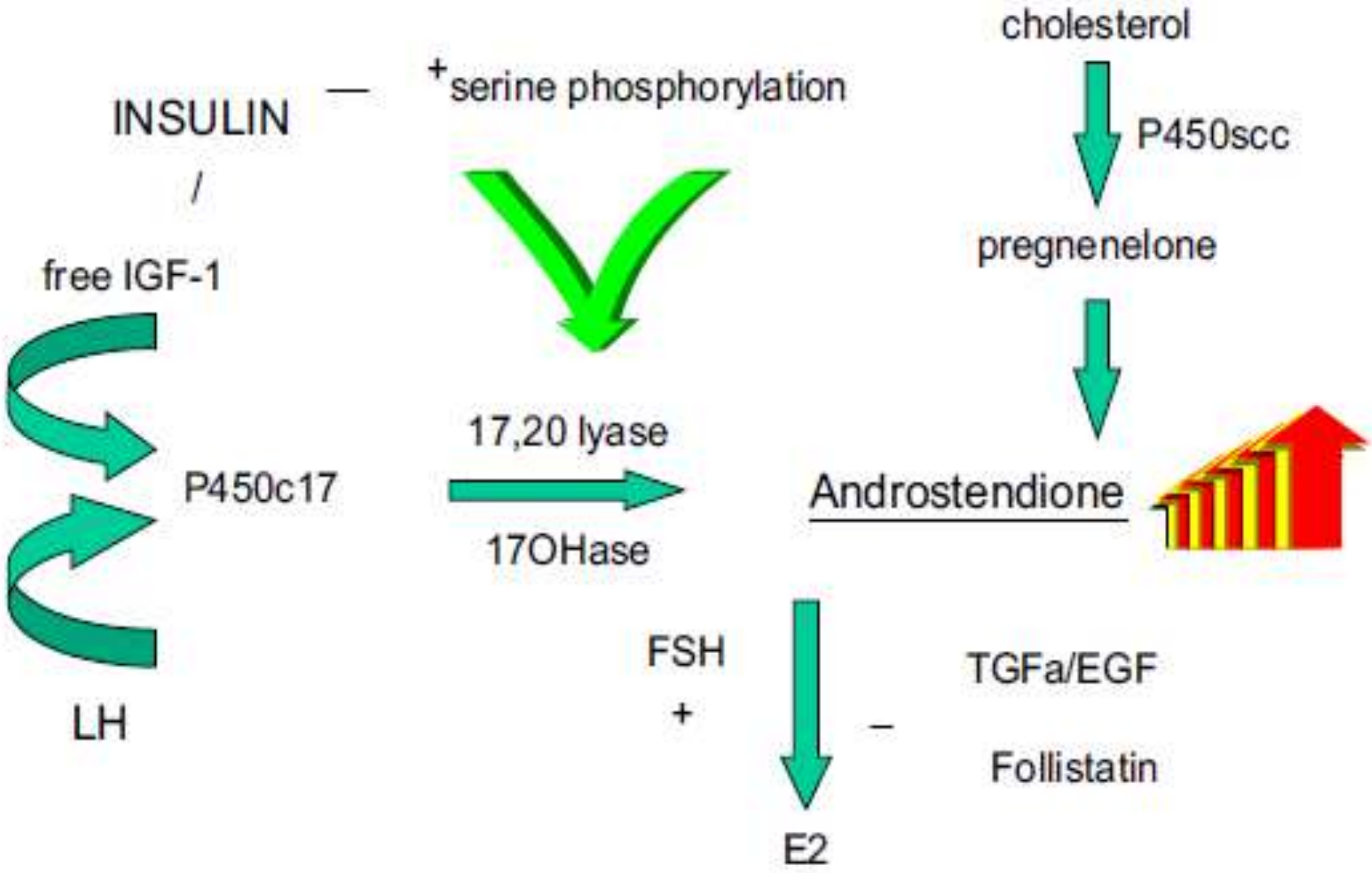


Insulin resistance

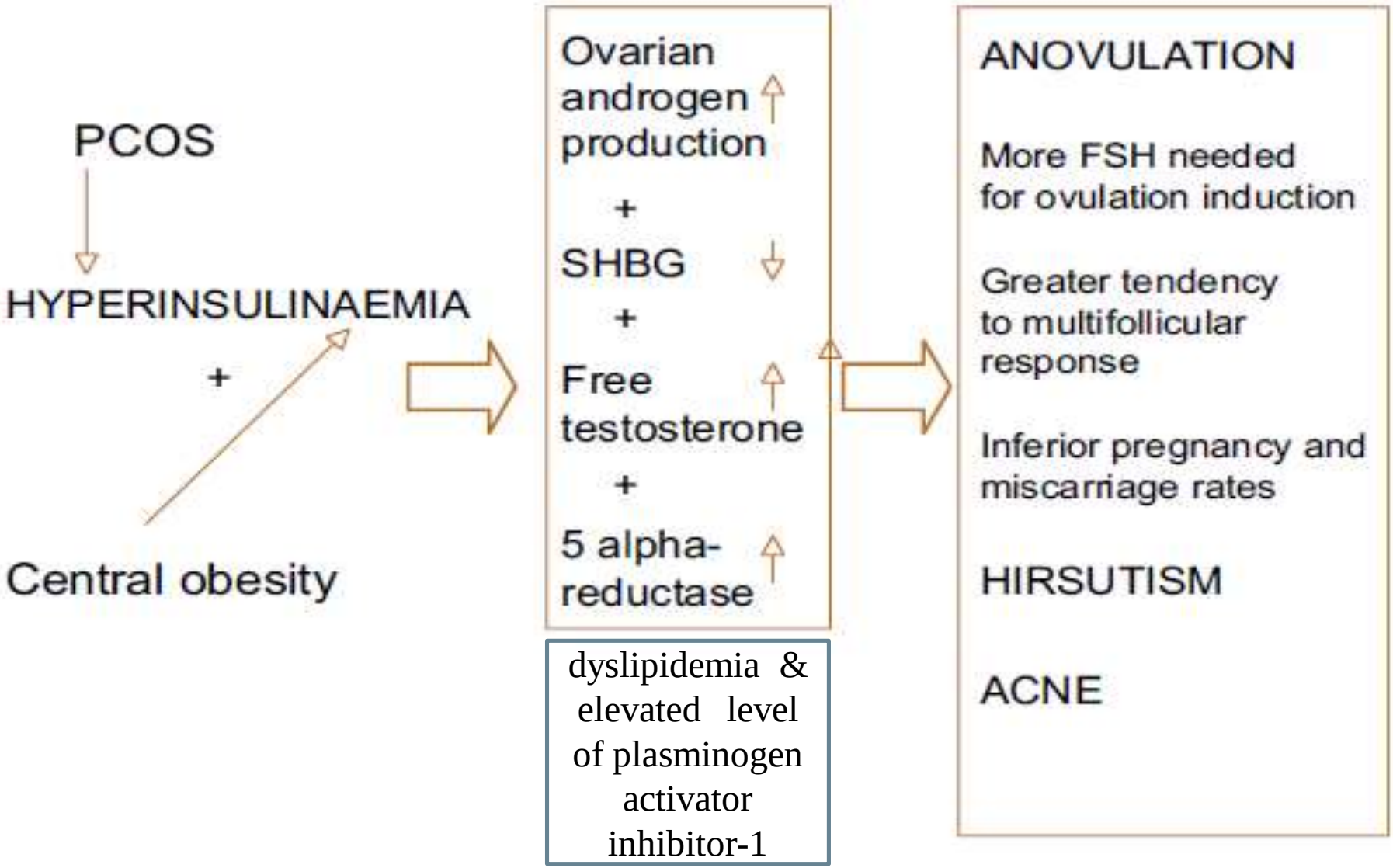
- Insulin resistance is defined as a reduced glucose response to a given amount of insulin and usually results from faults within the insulin receptor and post-receptor signalling.
- In the ovary, high levels of circulating insulin are thought to contribute both to excess androgen production and to anovulation.


Adrenal gland
IGFs
FSH
Insulin
Altered sex steroid levels
Hypothalamus
Abnormal GnRH secretion
Insulin resistance
Insulin ↑
Bioavailable E_2 ↑
Bioavailable T ↑
Bioavailable IGFI ↑
Ovary
LH
Pituitary
DHEAS ↑
T
A ↑
SHBG ↓
IGFBP1 ↓
LH ↑
FSH ↓
Skin
A
A
Aromatase
17βHSD
E_1
T
Adipose tissue
17βHSD
5α-red
E_2
DHT
Liver
Peripheral and target tissues

Insulin resistance (post receptoral defect)



Insulin resistance:



- **PCOS is just another form of diabetes (type III diabetes)??????**

What comes first, the hyperinsulinemia or the hyperandrogenism ?

- Insulin increases circulating androgen levels
- Glucose increases the circulating levels of both insulin and androgen
- Weight loss decreases the levels of both insulin and andrgens
- In vitro, insulin stimulates thecal cell androgren productions
- The experimental reduction of insulin levels in PCOS women reduces androgen levels
- After normalisation of androgen with GnRH-a, the hyperinsulin response to GTT remains abnormal in obese women with PCOS.

Sex hormone-binding globulin (SHBG) in PCOS

- A reduction in plasma sex hormone-binding globulin (SHBG), a transport carrier that binds estrogen and androgens and regulates their biological activities, is often used as an indicator of hyperandrogenism in women with PCOS.
- Low serum SHBG levels are considered a biomarker of abnormal metabolism and are related to insulin resistance (IR), compensatory hyperinsulinemia and abnormalities in glucose and lipid metabolism in PCOS patients.
- **SHBG is also associated with the long-term prognosis of PCOS.**
- SHBG gene polymorphism is correlated with the risk of PCOS.

The endometrium in women with PCOS

- The endometrium in women with PCOS is affected by hormonal and metabolic abnormalities:[1] .
  - has high levels of insulin-like growth factor-1 (IGF-1) activity [2] ,
  - decreased concentrations of sex hormone- binding globulin (SHBG) [3] ,
  - up-regulation of endometrial aromatase, hyperandrogenemia and hyperinsulinemia.
- Consequently, those molecular changes increase the potential for neoplastic changes within the endometrium [4]

1- Giudice, L.C. (2006) 2- Wu, M.-H., et al. (2004), 3- Jayagopal, V., et al. (2003) 4- Chittenden, B., et al. (2009)

Unopposed E2

- Anovulation⇨the progesterone levels are within suboptimal or absent effects over the endometrium⟹over-response to the proliferative effects of estrogen (E2) [1] .
- Insulin resistance and hyperinsulinemia especially in obese patients may trigger the development of PCOS in genetically predisposed individuals [2] .
- Therefore, in PCOS, the prolonged unopposed oestrogen, hyperinsulinemia, elevated free IGF-1 and androgens may further augment mitogenic activity within endometrial cells by activating mitogen-activated protein kinase (MAPK), leading to high prevalence of hyperplasia and possible transformation to endometrial cancer [3] [4] .

1- Chittenden, B., et al. (2009) 2- Al-Jefout et al (2017) 3- Venturoli, S., et al. (1988) 4-Park, J.C., et al. (2011)

Endometrial hyperplasia

- Up to one-third of endometrial carcinomas are assumed to be preceded by hyperplasia [1] .
- The prevalence of endometrial hyperplasia in women with PCOS varies from 1% to 48.8% [2]
- Anovulation - risk factor for EH, with or without atypia [3, 4].
- The prevalence of endometrial cancer among PCOS cases is not higher than those of the general population [5,6] .
- In women with PCOS is estimated to be around 20% - 37% [7] , which increases even more in obese women with PCOS [8]
- Conversely, a recent review stated that this risk is overestimated [9] .

1- Kurman, R.J., (1985) 2- Holm, N.S.L., et al. (2012) 3- Chamlian, D.L. and Taylor, H.B. (1970) 4- Ho, S.P., et al. (1997).5-Cheung, A.P. (2001) 6- Hardiman, P., Pillay, O.S. and Atiomo, W. (2003) 7-Lin, S.L., et al. (2013) 8- Fanta, M. (2013) 9-Eryilmaz, O.G., et al. (2012)

Endometrial thickness & EH in PCOS (Al-Jefout et al, 2018)

- There is some evidence showing that there is an increase in endometrial thickness throughout the menstrual cycle in infertile patients with PCOS, when compared to infertile patients without PCOS [1] .
- Several studies have attempted to find a predictive cut-off value to measure endometrial thickness in cases of patients with EH [2,3] .
- Though, it is still unclear at this stage to determine which PCOS patients need endometrial biopsy for the purpose of intervention to avoid any long term complications.

1- Eryilmaz, O.G., et al. (2012) 2- McCormick, B.A., et al. (2011) 3-Tingthanatikul, Y., et al. (2006)

Endometrial thickness & EH in PCOS (Al-Jefout et al, 2018)

- Our results showed that the prevalence of endometrial hyperplasia among infertile patients with PCOS is **18.3%.**
- This prevalence of EH is in concordance with the figures worldwide; 1% to 48.8%
- The high prevalence of EH in our population may be explained that these are infertility cases with long standing PCOS.
- Recently, McCormick et al. suggested an ET of 9.35 mm as the threshold to detect endometrial hyperplasia only **in obese patients with PCOS**, with100% sensitivity, 56% specificity, 100% negative predictive value, and 50% positive predictive value.
- Cheung, A.P. (2001) suggested 7 mm as a threshold with 100% sensitivity but with low specificity (27.8%) for endometrial hyperplasia POCS patients.

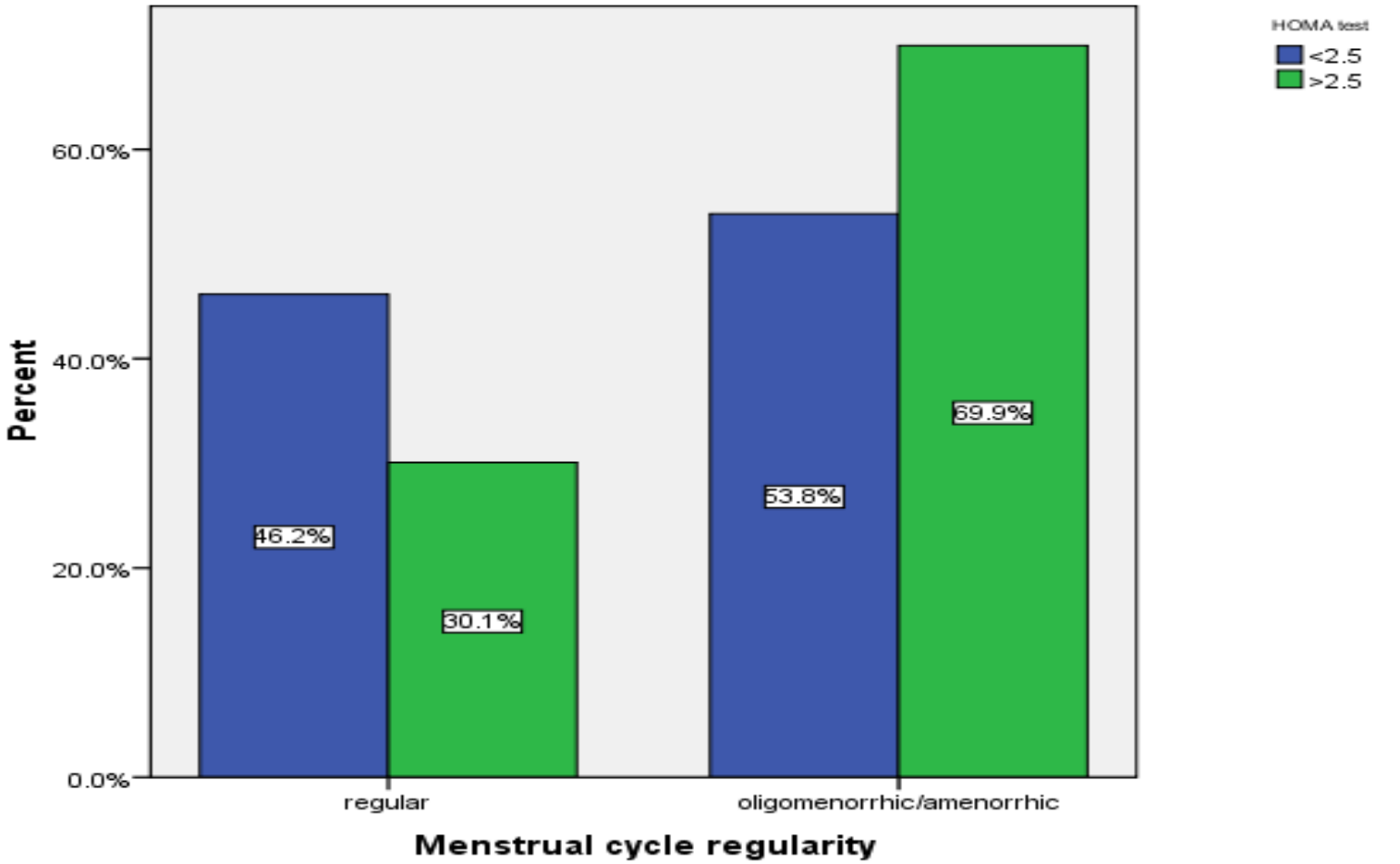
Endometrial thickness & EH in PCOS (Al-Jefout et al, 2018)

- We propose a new threshold value of **9.5 mm** of endometrial thickness measured in the follicular phase by vaginal U/S, which had a high sensitivity of **92.9%**, and moderate specificity of **51.85%** with positive predictive value of 47.8%, and negative predictive value of 100%.
- The cutoff value of 9.5 mm is more practical and it achieves a good predictive value in **obese and none-obese** women with PCOS.

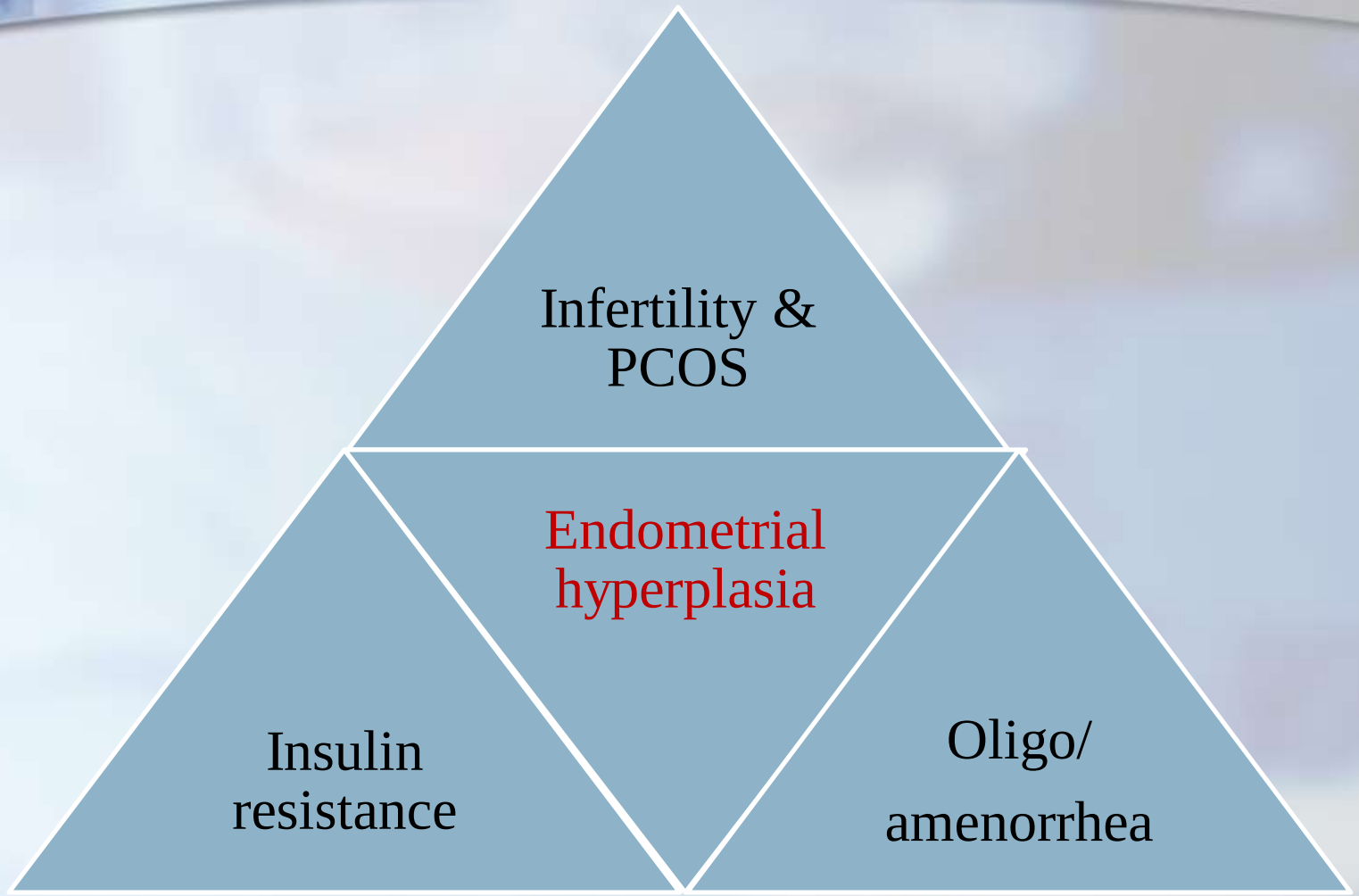
IR & oligo/amenorrhea in PCOS patients (Al-Jefout et al, 2018)

- IR values in PCOS patients correlate with high BMI and WC values
- There was a significant difference among four phenotype groups in terms of prevalence of IR ($X = 39$; $P < 0.01$). (Al-Jefout et al, 2017)
- In our study, partial correlation analysis; ET was positively correlated with insulin resistance ($r = 0.439$, $P = 0.007$), which points to the importance of insulin resistance in the pathophysiology of PCOS and associated long term possible risk for developing EH.
- In women with normal periods the HOMA-IR values were 2.96 (2.47-3.37) and were less than in women with **oligo/amenorrhea** 3.18 (2.77-3.79) with P value - 0.041. (Al-Jefout et al, 2017)
- In our study, women with oligo/amenorrhea or irregular cycles were 5.5 and 13.7 times more at risk of developing EH than women with regular cycles respectively.
- Cheung, A.P. (2001) has shown that the risk of endometrial hyperplasia raises by 43.2% (OR 1.4) in PCOS patients with amenorrhea for more than 3 - 6 months.

IR & Menstrual irregularities
(Al-Jefout et al 2017)



Triangle of EVEL in PCOS (Al-Jefout, 2020)



PCOS phenotypes

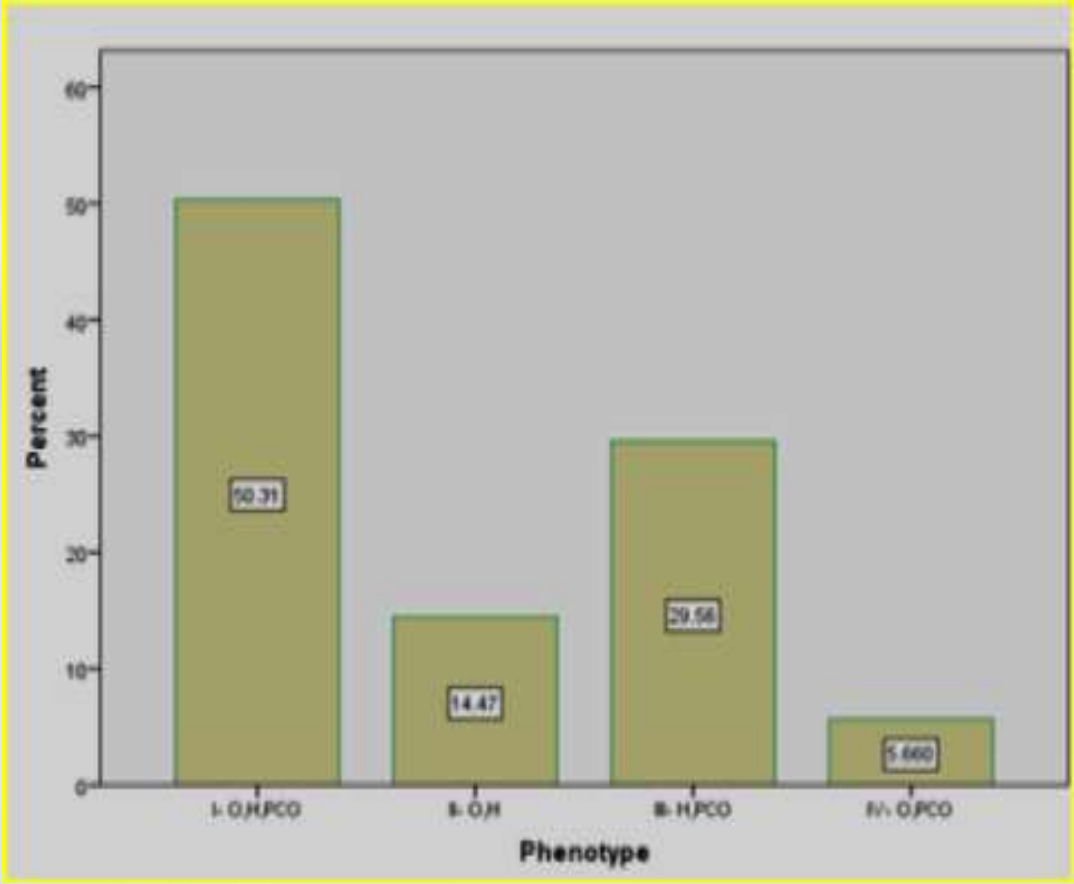
- (Phenotype A)
  - Androgen excess + ovulatory dysfunction + polycystic ovarian morphology
- (Phenotype B)
  - Androgen excess + ovulatory dysfunction
- (Phenotype C)
  - Androgen excess + polycystic ovarian morphology
- (Phenotype D)
  - Ovulatory dysfunction + polycystic ovarian morphology
    - (Al-Jefout et al 2017, Livadas and Diamanti-Kandarakis, 2012, National Institutes of Health (NIH),2012)

Lean PCOS

- Very challenging
- 20-30 % of PCOS
- Diabetes mellitus, IR, and metabolic abnormalities are all significantly lower in lean women with PCOS
- Normal Insulin levels, however, they may have insulin hypersensitivity
- Reactive hypoglycemia (50%)- early marker for PCOS or IR
- Higher LH levels due high β-endorphin
- High pressure pain threshold
- Low vitamin D levels
- Resistance exercise alone can improve hyperandrogenism, reproductive function, and body composition by decreasing visceral fat and increasing lean muscle mass
- Recommended to use L-carnitine

Prevalence of different PCOS phenotypes
(Al-Jefout et al, 2017)

- The most common phenotype in our study was
  - type I - 50.3% (n = 80/159),
  - Type III (women with hyperandrogenism, polycystic ovaries and normal ovulatory cycles; H/PCO-ovulatory PCOS) 29.6% (n = 47/159).
  - Type II women had chronic anovulation and hyperandrogenism but normal ovarian morphology, (H/O), 14.5% (n = 23/159)
  - Type IV - 5.7% (n = 9/159) (O/PCO, no hyperandrogenism but chronic anovulation and polycystic ovaries).



SCIENTIFIC REPORTS

Article | Open Access | Published: 13 July 2017

Insulin resistance and obesity among infertile women with different polycystic ovary syndrome phenotypes

Moamar Al-Jefout, Nedal Alnawaiseh & Aiman Al-Qtaitat

- This study investigates insulin resistance (IR) and obesity in different PCOS phenotypes among infertile women (n = 213), of whom 159 had PCOS and 54 women without PCOS, recruited as a control group.
- IR was observed in 133 (83.6%) women with PCOS and in 25 (46.3%) women without PCOS ($p < 0.001$). IR was significantly associated with PCOS only among women with central obesity ($\chi 2 = 35.0$, $p < 0.001$) and not for the normal category ($\chi 2 = 4.04$, $p < 0.058$). The LH/FSH ratio was not significantly different among the PCOS group (n = 37, 23.3%) compared to the control group (n = 9, 16.7%) ($p = 0.308$).
- Among women with PCOS, the most common phenotype was type I (50.3%), with type III (29.6%), type II (14.5%) and type IV (5.7%). Type I had the highest values of fasting insulin (median = 12.98 mU/mL) and HOMA IR values (significant difference among the four phenotypes, $p = 0.009$ and 0.006, respectively) and is associated with severity of the disease. There was no difference in glucose levels.

Comparison of PCOS phenotypes in different ethnic groups.

	Type I H + O + PCO	Type II H + O	Type III H + PCOS	Type IV O + PCO
In our study (%)	50%	14.6%	28.9%	5.7%
Chinese study (%)[23]	26.8%	7.6%	13.4%	52.2%
Italian study (%)[21]	53.9%	8.9%	28.8%	8.4%
Iranian study (%)[22]	32.1%	14.8%	4.3%	46.8%

Clinical Presentation History

- Reproductive history
  - Menstrual dysfunction occurs in 75% to 85% of patients 9
  - Oligomenorrhea or amenorrhea (infrequent or absent menstrual bleeding) is the most common pattern, with most intervals greater than 35 days 3
  - Polymenorrhea (less than 21-day intervals) is relatively rare 3
  - Onset usually develops in adolescence; may start at menarche, or shortly thereafter 9
  - In some adolescents, condition is noted by absence of established regular menses 3
  - Note that ovulatory dysfunction can be present subclinically, with no obvious disruption in regularity of vaginal bleeding 9

History of clinical hyperandrogenism

- Hair and skin concerns
- Excessive terminal body hair growth is a common concern
- Hirsutism develops gradually and worsens with weight gain
- Acne can occur with hirsutism; overall, acne is less common as a presenting complaint (15%-30% of patients)
- During adolescence, acne is not considered a firm sign of hyperandrogenism; however, if it persists into the mid-20s or 30s, it is often a sign of hyperandrogenism
- Hair loss, when it occurs, is most pronounced over vertex or crown and spares frontal hairline

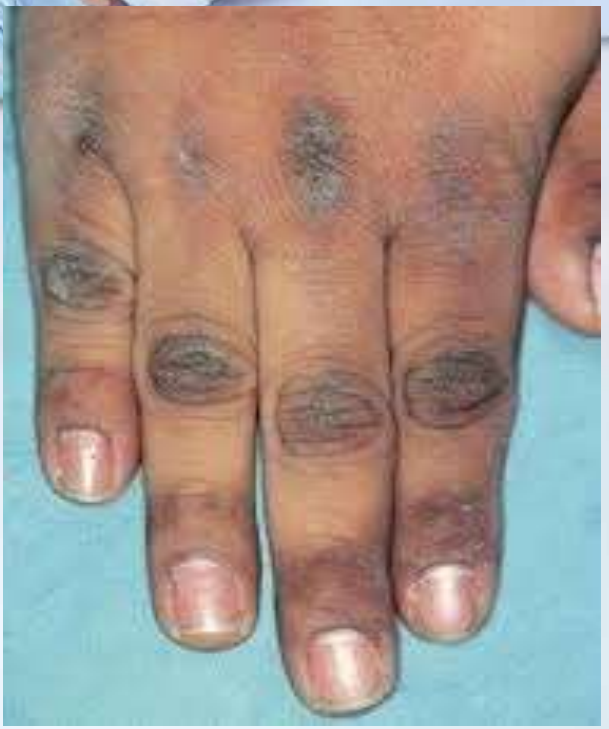
Physical examination

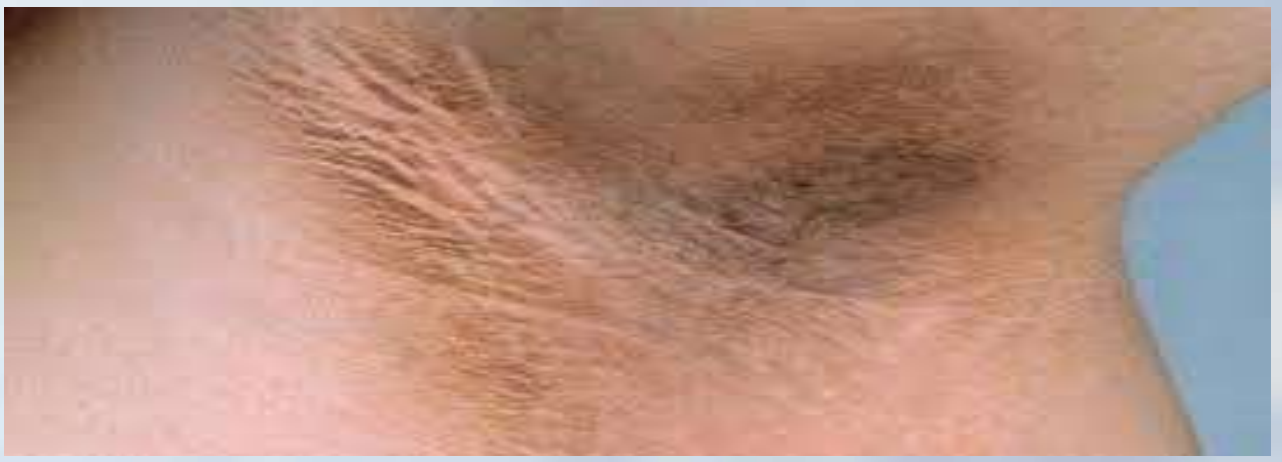
- Signs of hyperandrogenism
  - Hirsutism (about 75% of patients; more severe in abdominally obese patients)
  - Excessive terminal hair that appears in a male pattern (eg, chest, midline lower abdomen, above lip)
  - Terminal hairs grow more than 5 mm in length, are pigmented, and have a central core of compacted cells, which gives a denser color and coarser feel and shape
  - Substantial numbers of terminal hairs over chin, neck, lower face, and sideburns indicate androgen excess
  - Ferriman-Gallwey score of 8 or higher is generally considered to represent hirsutism
  - Acne (60% of patients, at some point)
  - Acanthosis nigricans (37% of patients)
  - Androgenic alopecia (about 5% of patients)
  - Typically affects vertex or crown in diffuse pattern
  - Acrochordons: (fibroepithelial polyps, skin tags, papillomas) are common benign neoplasms of the skin, often associated with obesity.

Physical examination

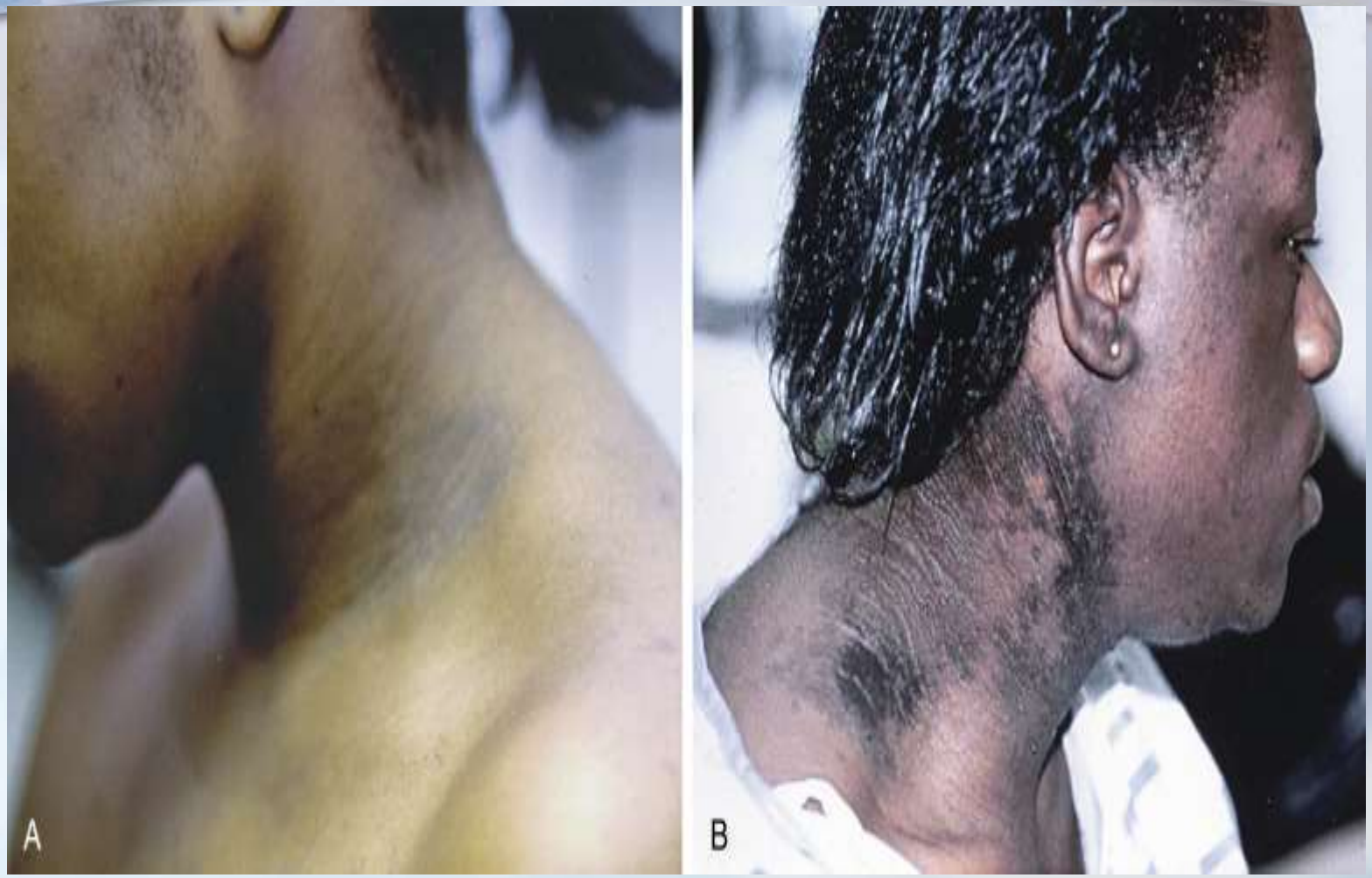
- Overweight or obesity (about 75% of patients)
- Central distribution of adiposity can also be present in those with BMI in reference range
- Overweight: BMI of 25 kg/m^2 or higher
- Obese: BMI of 28 kg/m^2 or higher
- Waist circumference greater than 88 cm is considered abdominal obesity in women
- Waist to hip ratio greater than 0.8 is considered unhealthy

Acanthosis Negricans

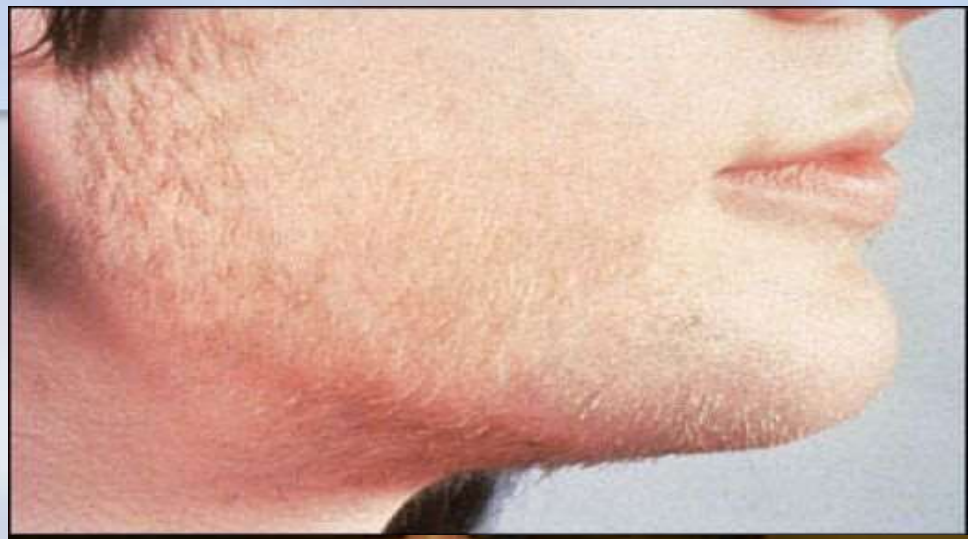


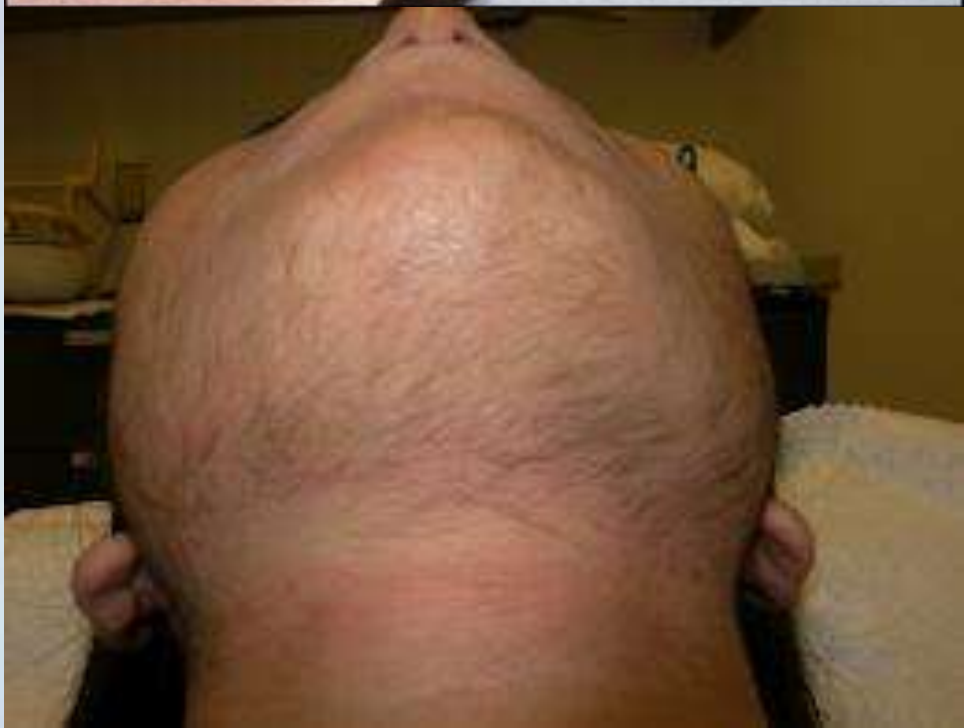


Acanthosis Negricans

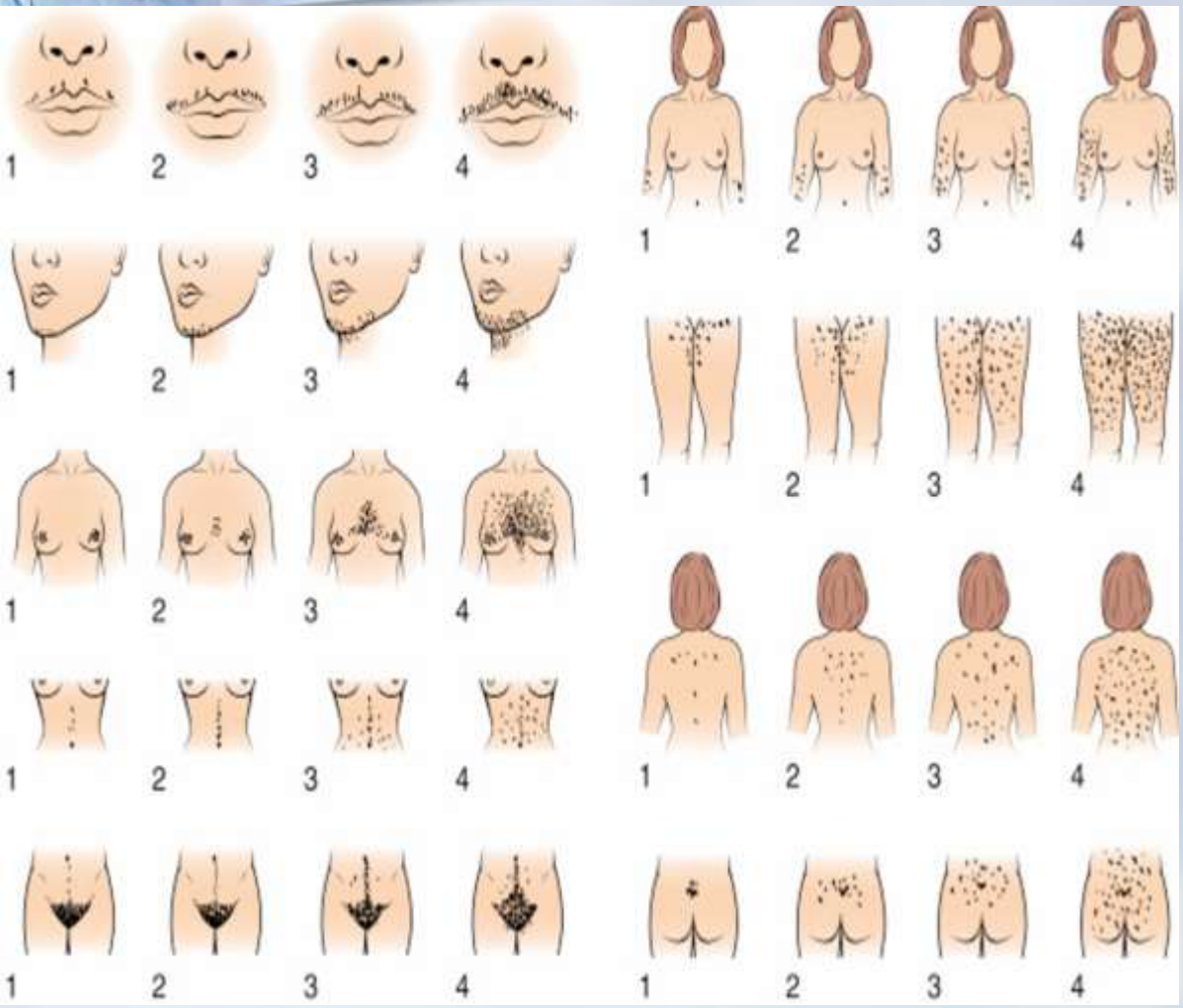


Hirsutism



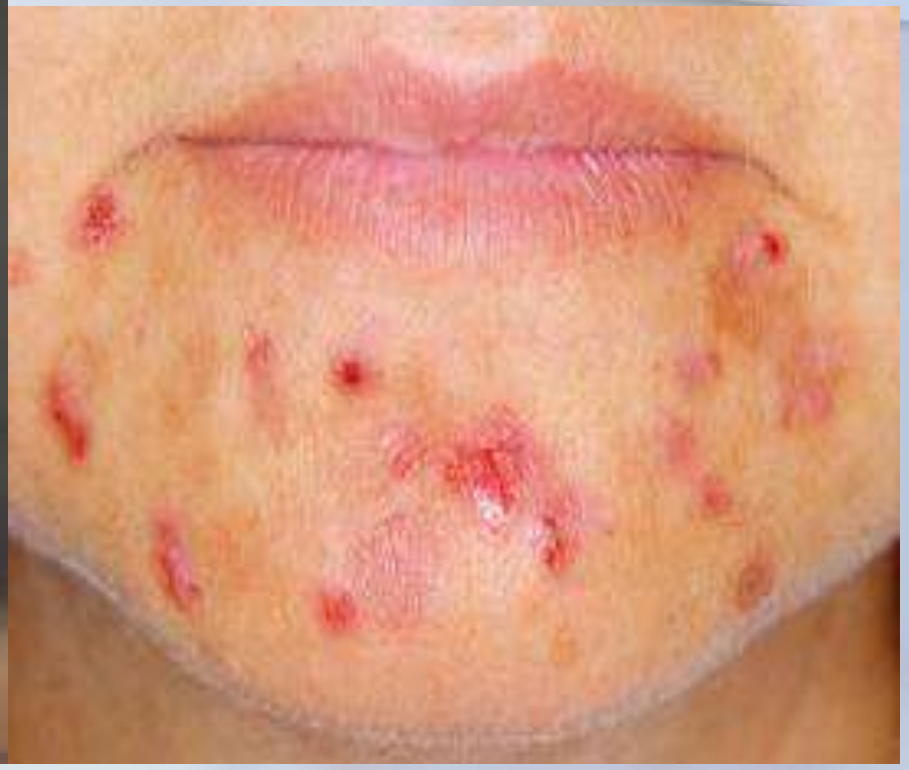


Ferriman–Gallwey scoring system

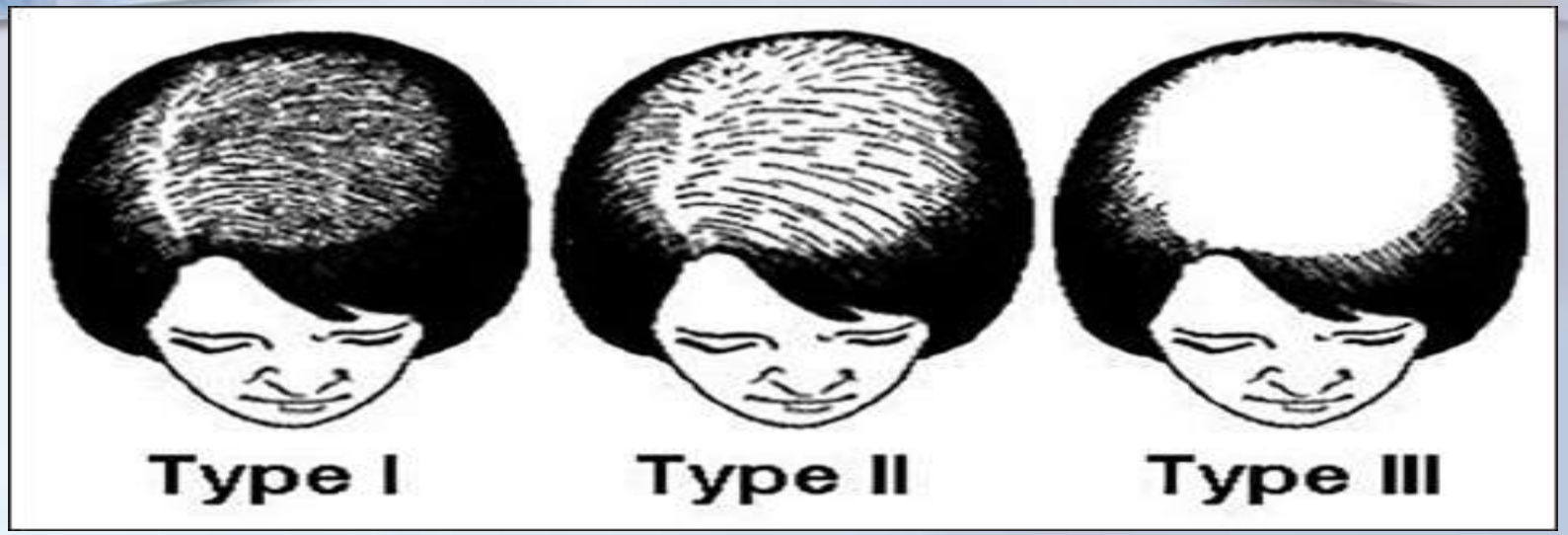


- The Ferriman-Gallwey scoring system is used to quantify the amount of hair growth.
- Each area of the body is scored for the amount of hair.
- A score 6–8 corresponds to mild hirsutism,
- A score 8–15 corresponds to serious and more than 15 corresponds to overt hirsutism.

Alopecia and acne

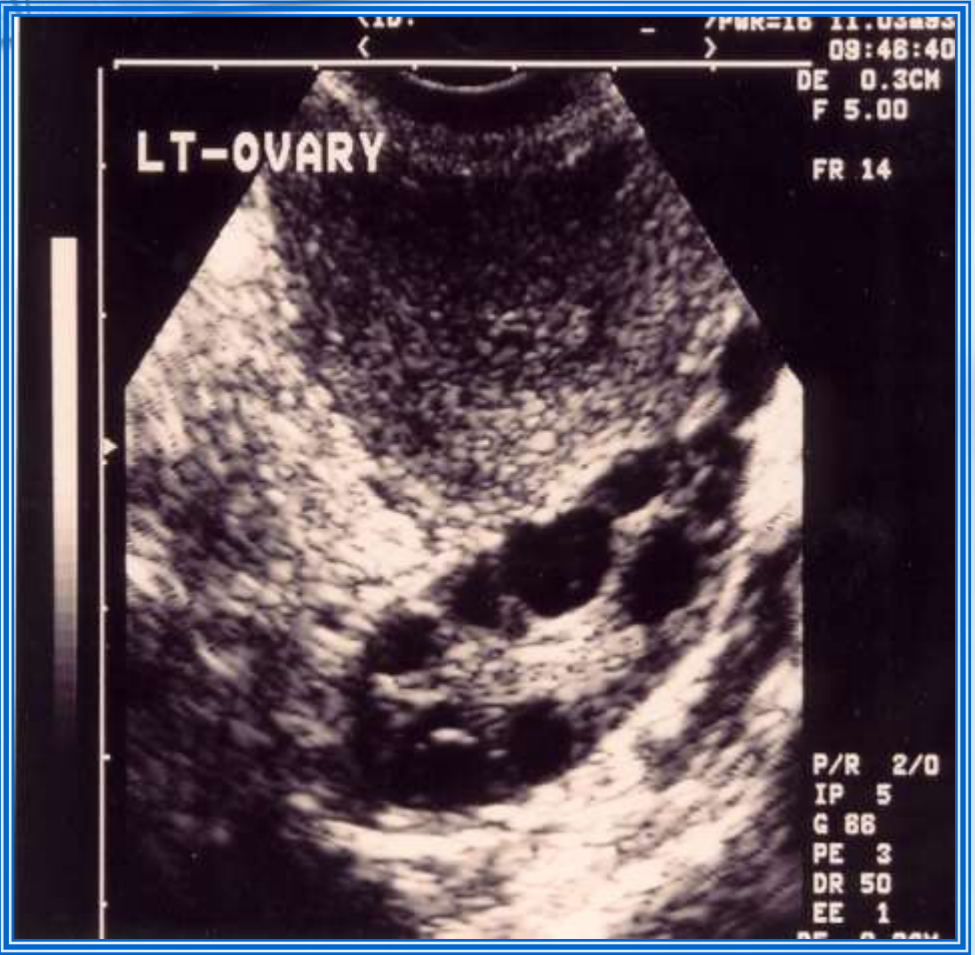


Ludwig's classification of hair loss among females



- Grade I: Perceptible thinning of the hair on the crown, limited in the front by a line situated 1-3 cm behind the frontal hairline
- Grade II: Pronounced rarefaction of the hair on the crown within the area seen in Grade I.
- Grade III: Full baldness (total denudation) within the area seen in Grades I and II.

PCOM



Ultrasonic Criteria of PCOM At least one of the following:

- 25 or more follicles measuring 2–9 mm in diameter,
- increased ovarian volume (>10 cm3).

- **The absence of PCO on U/S does not exclude PCOS**
- **Necklace appearance**

PCOM Vs PCOS

- Polycystic ovaries are detected in 19-33%of the “normal population”, of whom approximately 80% have symptoms of PCOS, albeit usually mild.
- ∴ 20%of women with polycystic ovaries are symptom free.
- The presence of polycystic ovaries may be a marker for increased reproductive and metabolic risk.
- Polycystic ovaries are associated with increased ovarian reserve and a reduced rate of ovarian aging

Differential Diagnosis for Polycystic Ovary Syndrome

- Androgen secreting tumor
- Exogenous androgens
- Cushing syndrome
- Nonclassical congenital adrenal hyperplasia
- Acromegaly
- Genetic defects in insulin action (Leprechaunism, Rabson Mendenhall syndrome, Lipodystrophy)
- HAIR-AN syndrome
- Primary hypothalamic amenorrhea
- Primary ovarian failure
- Thyroid disease

Work up

- History & PE
- WC & BMI
- TSH and prolactin.
- FBS, Fasting Insulin (> ≤12 milliunits/L (≤30 mIU/mL)) and calculating HOMA test (>1.3%)- the best for Insulin resistance (Al-Jefout et al 2017)- not in the common practice!
- An oral glucose tolerance test (OGTT), fasting plasma glucose or HbA1c
- Lipid profile.
- DHAES
- SHBG
- AMH
- 17 alpha- Hydroxyprogesterone
- FAI (free androgen index)- SHBG and Free/Total Testosterone
- FSH, LH, P4 & oestradiol
- Ultrasound Examination: Determination of polycystic ovaries, identify endometrial abnormalities

waist circumference measurement

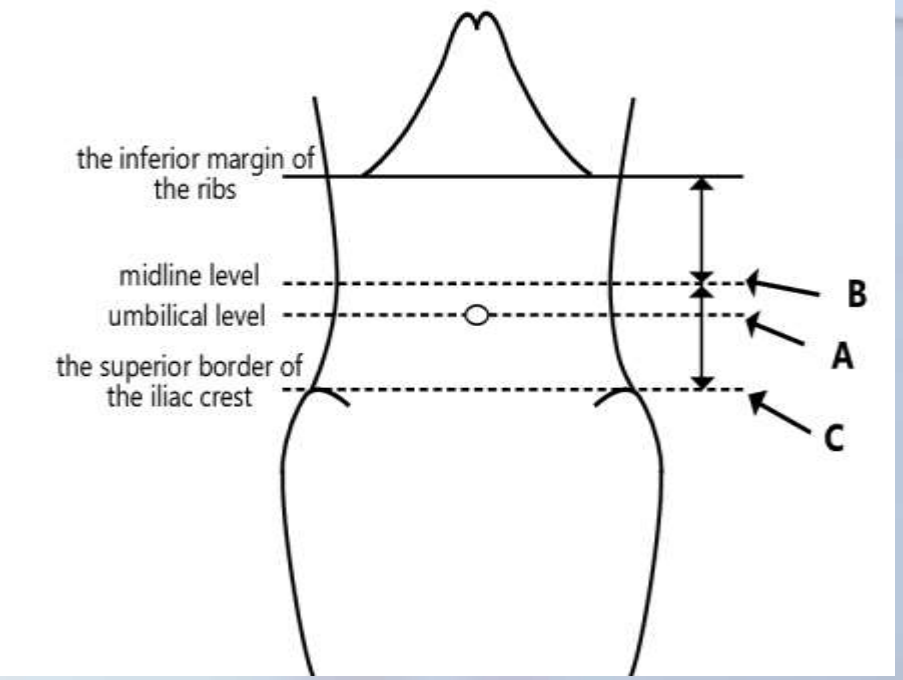
Range:

<79 cm normal

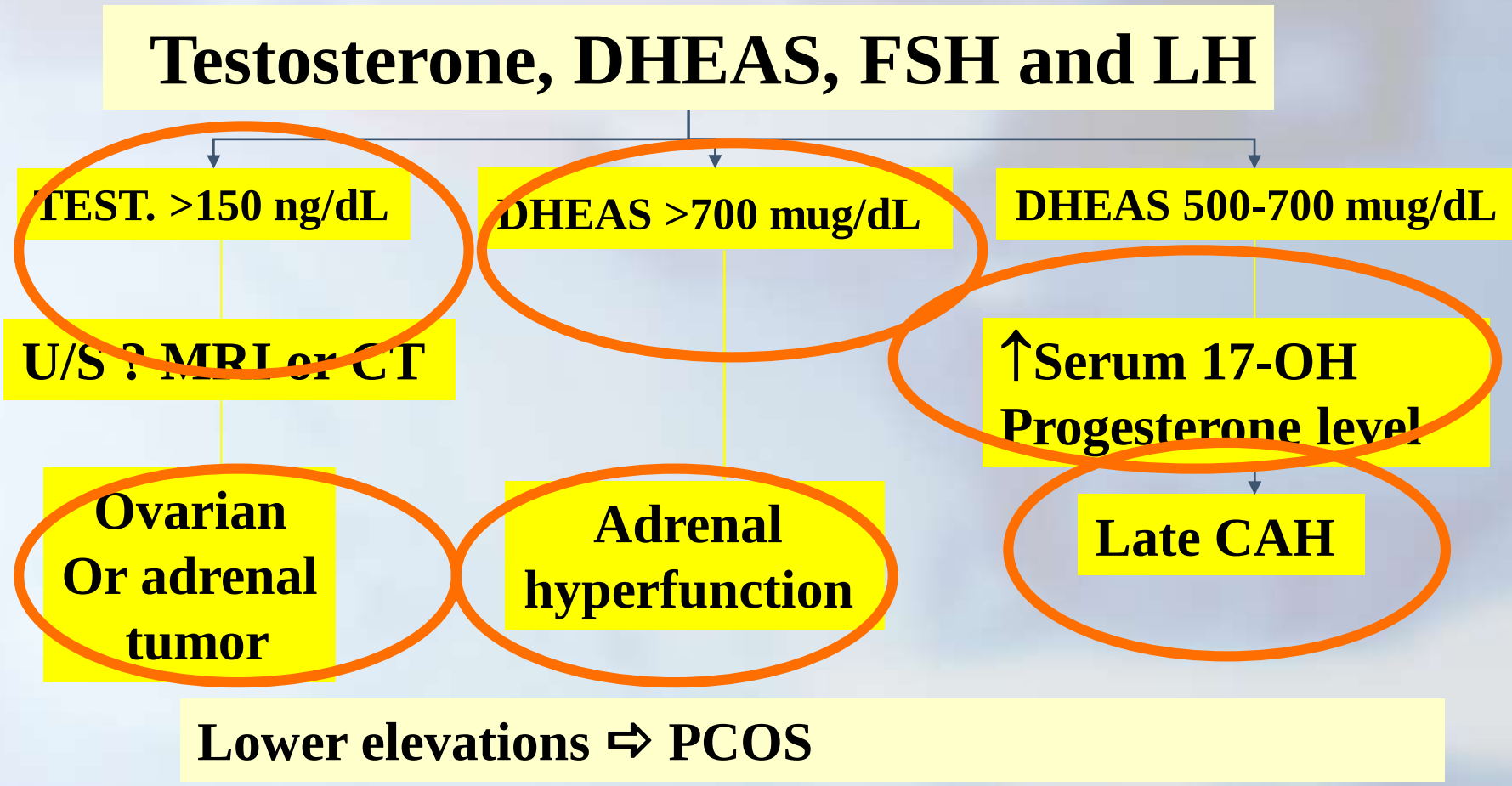
80-84 cm- overweight

84-88 cm- obese

>89 cm morbidly obese



Signs of androgen excess



Assessment of biochemical hyperandrogenism

- About 70% of patients with PCOS diagnosed by NIH criteria will have elevated serum *free testosterone levels*
- Free androgen index (Testosterone/SHBG x 100).
- Exclusion of NCAH:

morning serum 17-hydroxyprogesterone concentration greater than 150 ng/dL in the early follicular phase strongly suggests the diagnosis

LH/FSH Ratio

- The ratio of greater than 2 is only present in approximately 40% of PCOS (Al-Jefout et al 2017).
- The cutoff value for the LH/FSH ratio is quite dependent on the assay used to measure these gonadotropins, making difficult its broad application in clinical practice.
- In addition, the high proportion of obesity in PCOS may confound the measurement, explaining the normal LH/FSH ratio found in many patients, particularly if the assessment is based on a single LH and FSH determination.

Adolescents at risk of PCOS

- For adolescents who have features of PCOS but do not meet diagnostic criteria, an “increased risk” could be considered and reassessment advised at or before full reproductive maturity, 8 years post menarche. This includes those with PCOS features before combined oral contraceptive pill (COCP) commencement, those with persisting features and those with significant weight gain in adolescence. CPP
- It is important to screen and diagnose adolescent PCOS in order to prevent the development of future infertility, type II DM, cardiovascular disease, and even endometrial cancer.
- **Lifestyle modification is of the greatest benefit for adolescents in terms of management.**

  (Yii MF. Gynecological Endocr. 25(10):634-9, 2009).
- Treatment with OCP, progestins, antiandrogens, or insulin-lowering drugs is critical in reducing the development of adulthood infertility, diabetes, metabolic syndrome, and endometrial carcinoma in patients with PCOS.

PCOS Rx

- **Treatment depends on the needs of the patient and preventing long term health problems**
- **Weight reduction results in improvement in all symptoms of PCOS.**
- **Lifestyle changes in women with PCOS improves** hyperandrogenism and insulin resistance

  (Cochrane review, Moran LJ, 2011)
- A loss of only 7% to 10% of body weight can result in improved insulin resistance, a significant reduction in testosterone, decreased abdominal fat, and resumption of menses.
- **lifestyle (diet and exercise) intervention improves FSH, SHBG, total testosterone, androstenedione, FAI and FG score in women with PCOS. (Liza Haqq, 2014) Metanalysis**

Metformin

Metformin

- biguanide class
- Metformin is the only antidiabetic drug that has been conclusively shown to prevent the cardiovascular complications of diabetes.
- It helps reduce LDL lesterol and triglyceride levels, and is not associated with weight gain
- The most serious potential adverse effect of biguanide use is lactic acidosis, the incidence for which is 9 per 100,000 person-years

Metformin

- In combination with the COCP, metformin could be considered in adolescents with PCOS and BMI ≥25 kg/m2 where COCP and lifestyle changes do not achieve desired goals
- In combination with the COCP, metformin may be most beneficial in high metabolic risk groups including those with diabetes risk factors, impaired glucose tolerance, or high-risk ethnic groups
- In combination with the COCP, antiandrogens should only be considered in PCOS to treat hirsutism, after six months or more of COCP and cosmetic therapy have failed to adequately improve symptoms

Metformin

- Adverse effects, including gastrointestinal side-effects that are generally dose dependent and self-limiting, need to be the subject of individualized discussion.
- Starting at a low dose, with 500 mg increments 1-2 weekly and extended release preparations may minimize side effects.
- Metformin use appears safe long-term, based on use in other populations, however ongoing requirement needs to be considered and use may be associated with low vitamin B12 levels

Metformin

- The use of metformin as first line solo infertility therapy has not been supported by randomized trials.
- Clomiphene is roughly three times more effective at achieving live birth compared to metformin

  (Legro RS, N Engl J Med 356:551-566, 2007).
- Meta-analysis has suggested there may be some benefit to pregnancy by adding clomiphene to metformin, particularly in obese women with PCOS compared to clomiphene alone (OR 2.67)

  (Creanga AA, Obstet Gynecol 111:959-968, 2008).
- **Currently the use of metformin alone as a first line therapy for infertility in PCOS does not appear supported by the literature. RCOG**

Metformin

- Metformin seems to be safe when continued into pregnancy as no increase in congenital abnormalities, teratogenicity or adverse effects on infant development have been recorded.
- One RCT showed reduction in:
  - GDM – 9 fold reduction

    (Begum, M. R., 2009)
  - PL, MC and IUGR.
- Whether metformin should be continued into the pregnancy is still disputed.

Other benefits of metformin

- Short-term metformin therapy improves arterial stiffness and endothelial function in young women with PCOS. (Cantrell, L, 2009).
- The combination of metformin and simvastatin could lead to a better reduction of T and LH levels and thus reversing the LH:FSH ratio, lipid profile, and insulin resistance. (Kazerooni, T, 2009).
- Metformin may also prevent Endometrial cancer in PCOS. (Mohammad Shafiee, 2014)

Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome

- No evidence that metformin treatment before or during ART cycles improves live birth or pregnancy rates.
- The risk of OHSS in women with PCOS and undergoing IVF or ICSI cycles was reduced with metformin.

Cochrane review (L O Tso et al, 2009)

Cochrane review
(Thomas Tang et al, 2010)

- Thirty one trials (2537 women) were included for analysis, 27 of them using metformin and involving 2150 women.

Authors' conclusions

- In agreement with the previous review, metformin is still of benefit in improving clinical pregnancy and ovulation rates.
- However, there is no evidence that metformin improves live birth rates whether it is used alone or in combination with clomiphene, or when compared with clomiphene.
- Therefore, the use of metformin in improving reproductive outcomes in women with PCOS appears to be limited

Breaking NEWS

- The U.S. Food and Drug Administration is announcing today that agency laboratory testing has revealed levels of the nitrosamine impurity N-Nitrosodimethylamine (NDMA) above the agency's acceptable intake limit in several lots of the extended-release (ER) formulation of metformin.
- Patients should continue taking metformin tablets even after recalls occur, until they consult with their health care professional who can prescribe a replacement.

Letrozole

- Off-label letrozole is a first line therapy used to achieve pregnancy with live birth for subfertile women with polycystic ovary syndrome
- Letrozole Oral tablet; Adult premenopausal females: Limited studies indicate 2.5 mg, 5 mg, or 7.5 mg PO once daily on days 3 through 7 of the menstrual cycle may be effective; alternatively, a 20-mg single dose on day 3 of the menstrual cycle has also been studied.
- Ovulation and pregnancy rates are similar to those achieved with clomiphene.
- Ensure patient is NOT pregnant prior to starting letrozole, as letrozole may cause birth defects.
- Note: Anastrozole, which is a potent and highly selective aromatase inhibitor, is ineffective for ovulation induction

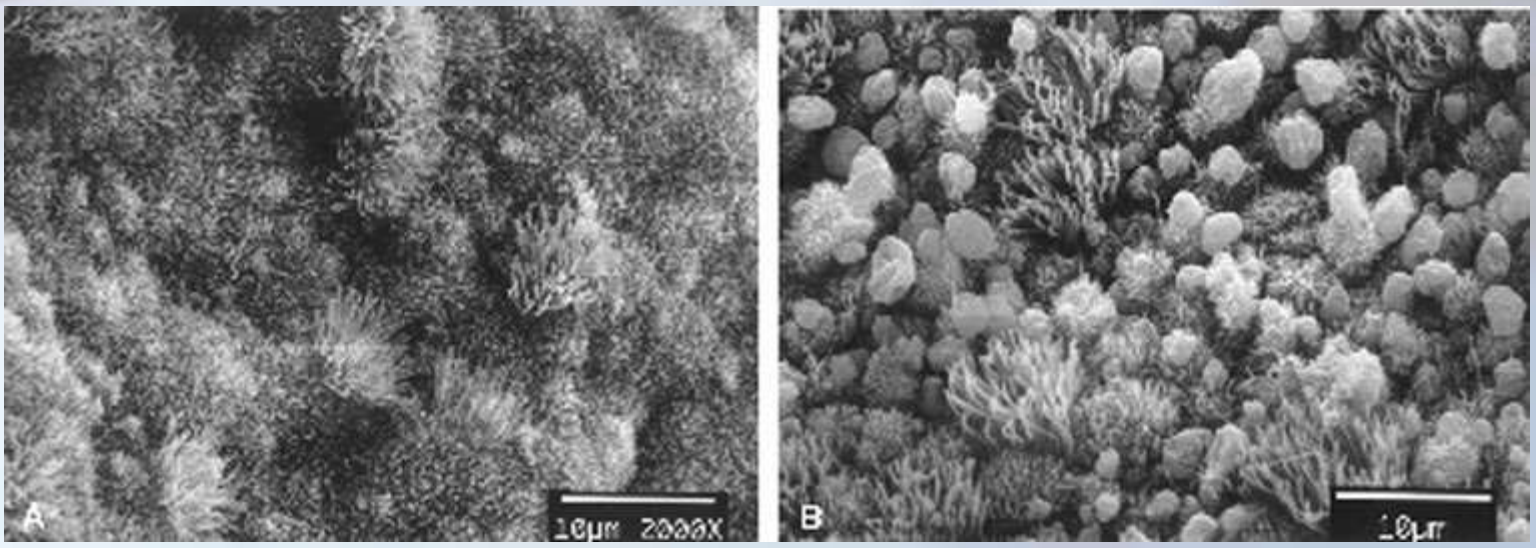
Clomiphene citrate (CC)

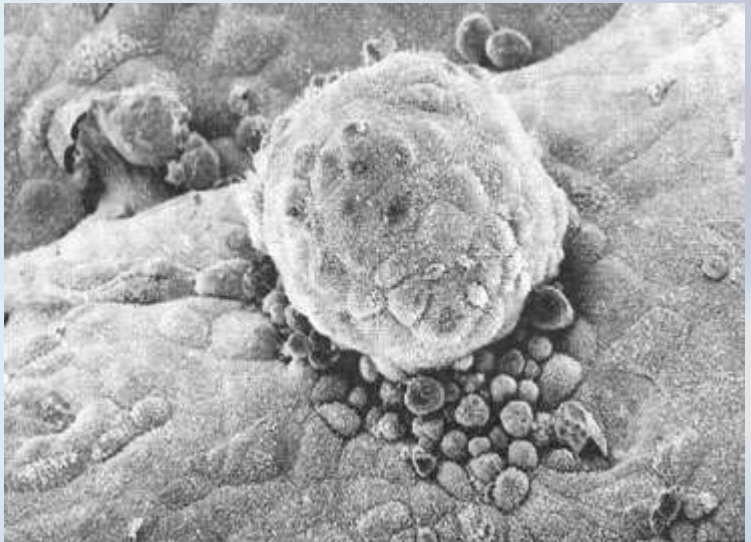
- CC acts by blocking oestrogen receptors.
- This induces release of FSH.
- CC will restore ovulation in approximately 75% and induce pregnancy in 35–40% of anovulatory women with PCOS.
- The reasons for the differential in ovulation and pregnancy rates are thought to be mainly due to the anti-oestrogen effects of CC on endometrial development and cervical mucus.

CC

- In some women, CC blocks the endometrial oestrogen receptors and suppresses pinopode formation, both essential for implantation, to such an extent that implantation may be impeded.
- This adverse response to CC cannot be overcome by adding oestrogen preparations, but substitution of CC with tamoxifen (20 mg for every 50 mg of clomiphene) can avoid the problem.

Pinopodes

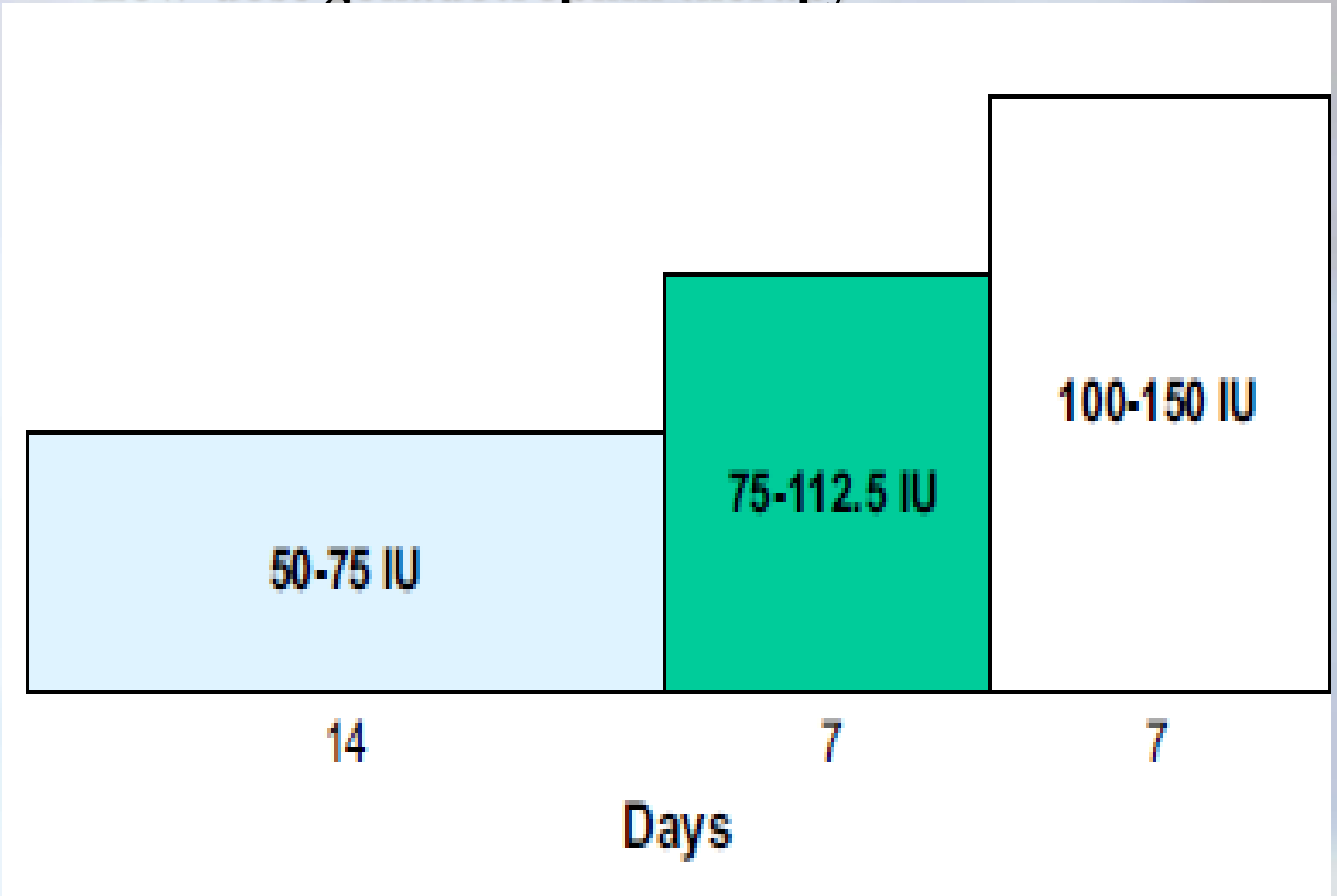




CC-resistant

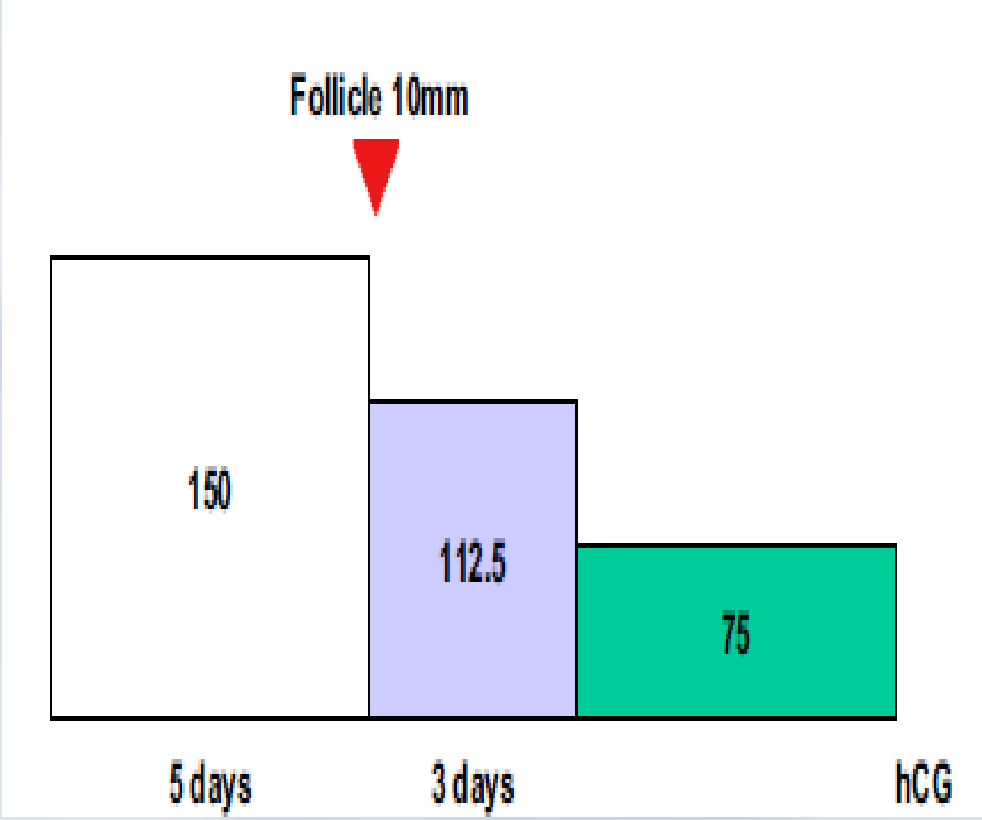
- CC resistance is more common in very obese women and those with very high serum androgen, insulin or LH concentrations.
- In CC-resistant PCOS patients, CC and metformin combination and laparoscopic ovarian drilling, in selected cases, should be considered before gonadotropin administration.
- Strategies for clomiphene-resistant patients include the addition of a:
  - corticosteroid such as dexamethasone,
  - extended duration of clomiphene,
  - Other novel therapies.
  - IVF as last resort.

Low-dose gonadotrophin therapy



Step-down protocol

- Prevention of OHSS.
- Reduction in Multiple pregnancies.



Laparoscopic ovarian drilling

- Laparoscopic ovarian surgery could be second line therapy for women with PCOS, who are clomiphene citrate resistant, with anovulatory infertility and no other infertility factors
- Laparoscopic ovarian surgery could potentially be offered as first line treatment if laparoscopy is indicated for another reason in women with PCOS with anovulatory infertility and no other infertility factors
- Risks need to be explained to all women with PCOS considering laparoscopic ovarian surgery

Laparoscopic ovarian drilling

- An ovulation rate of 60-84% and a pregnancy rate of 50% were experienced within 1 year of LOD in many reports.

(Gjonnaess, 1984; Abdel Gadir *et al.*, 1990; Kovacs *et al.*, 1991; Armar and Lachelin, 1993; Naether *et al.*, 1994; Li *et al.*, 1998; Felemban *et al.*, 2000; Amer *et al.*, 2002a)

- LOD is more successful in lean women (BMI< 25) with PCOS

(Duleba *et al.* 2003)

- If no ovulation results within 2–3 months of LOD, administration of CC will induce ovulation in some women who were previously resistant to CC.
- If this is not successful, a low-dose FSH protocol can be applied.

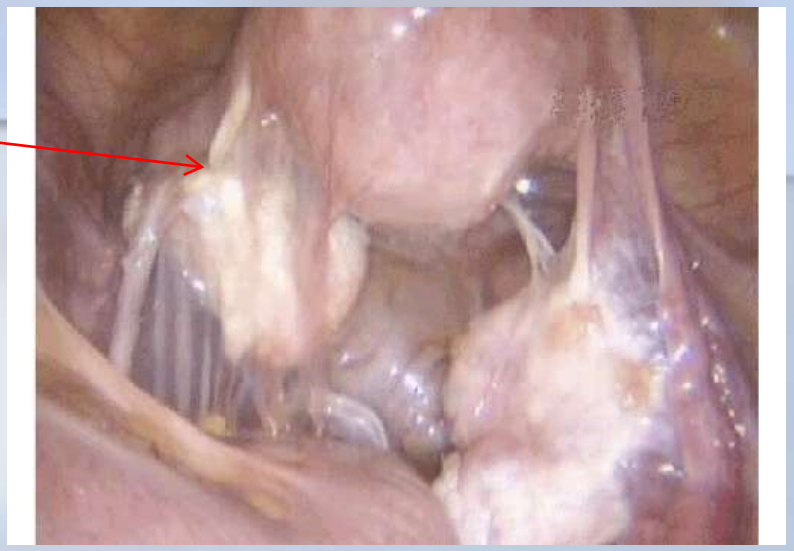
LOD Vs Metformin

- Although metformin results in a better attenuation of insulin resistance and hormonal profile. However, laparoscopic ovarian drilling is associated with higher rates of ovulation and pregnancy.

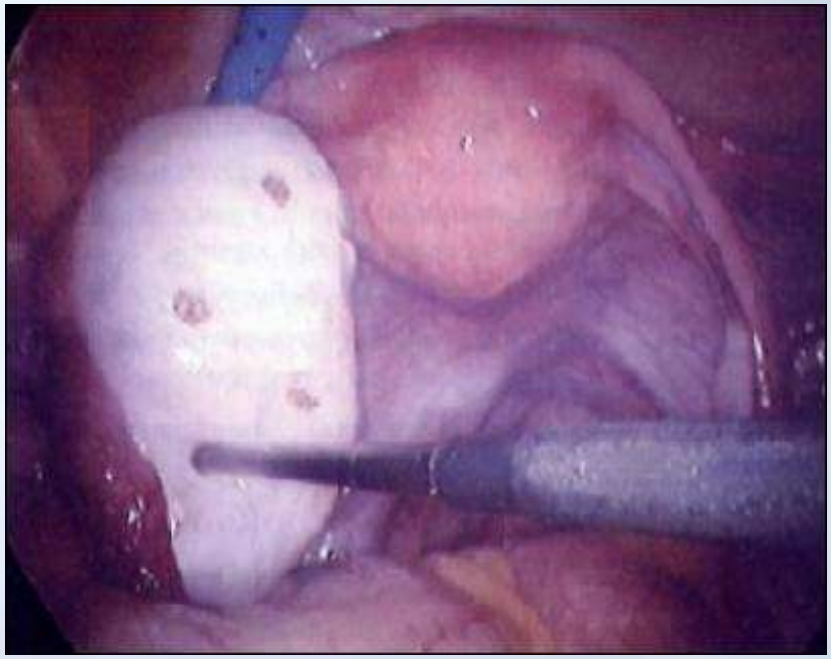
(Hamed HO. International Journal of Gynaecology & Obstetrics. 108(2):143-7, 2010 Feb)

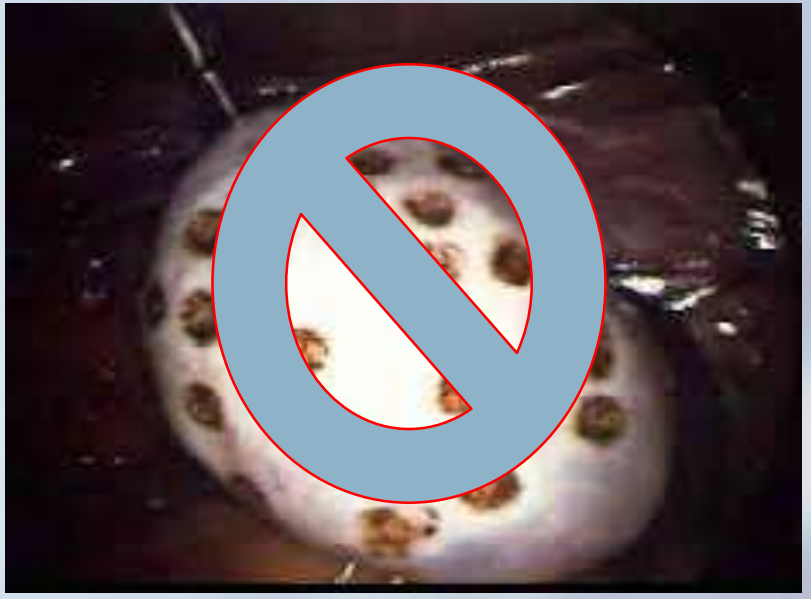
LOD complications

- Pereovarian adhesions.
- Premature ovarian failure- very rare.
- Hartman's Solution for prevention!



(Rajashekar L, 2008)





Unilateral Vs Bilateral LOD

- Unilateral drilling cauterization of ovary is equally efficacious as bilateral drilling in inducing ovulation and achieving pregnancy.
- Unilateral ovarian drilling may be a suitable option in clomiphene citrate resistant infertility patient of PCOS which can replace bilateral ovarian drilling with the potential advantage of decreasing the chances of adhesion formation.

(K. K. Roy, 2009)

In vitro fertilization (IVF)

- In the absence of an absolute indication for IVF ± intracytoplasmic sperm injection (ICSI), women with PCOS and anovulatory infertility could be offered IVF as third line therapy where first or second line ovulation induction therapies have failed
- In women with anovulatory PCOS, the use of IVF is effective and when elective single embryo transfer is used, multiple pregnancies can be minimized
- Women with PCOS undergoing IVF ± ICSI therapy need to be counselled prior to starting treatment including on:
  - Availability, cost and convenience.
  - Increased risk of ovarian hyperstimulation syndrome.
  - Options to reduce the risk of ovarian hyperstimulation.

PCOS and pregnancy

(CM.Boomsma, Human Reproduction Update, 2006), Meta-analysis

- **Fifteen of 525 identified studies were included, involving 720 women presenting with PCOS and 4505 controls.**
- A significantly higher risk of gestational diabetes
- PIH
- PET
- preterm birth.
- Their babies had a significantly higher risk of admission to a NICU.

PCOS and pregnancy cont…

- A higher perinatal mortality (OR 3.07; 95% CI:1.03–9.21), unrelated to multiple births.
- **In conclusion, women with PCOS are at increased risk of pregnancy and neonatal complications.**
- Pre-pregnancy, antenatal and intra-partum care should be aimed at reducing these risks.

Oral contraceptive choices

- Inert Oral tablet, Norgestimate, Ethinyl Estradiol Oral tablet; Adult and Adolescent females: Follow dose as for routine contraception.
- Ethinyl Estradiol, Desogestrel Oral tablet, Inert Oral tablet; Adult and Adolescent females: Follow dose as for routine contraception.
- Drospirenone, Ethinyl Estradiol Oral tablet, Inert Oral tablet; Adult and Adolescent females: Follow dose as for routine contraception for specific product as specified in product label: 1 tablet PO daily of selected product. Treatment for 6 to 12 months may be required; OCs have limited utility when the underlying cause of the condition is not related to a hypoestrogenic or hyperandrogenic state.

PCOS treatment in women not seeking fertility

- Life style modification
- Anti-androgens- aldactone
- COCP containing drospirinon- YAZ
- Insulin sensitizing agents- metformin

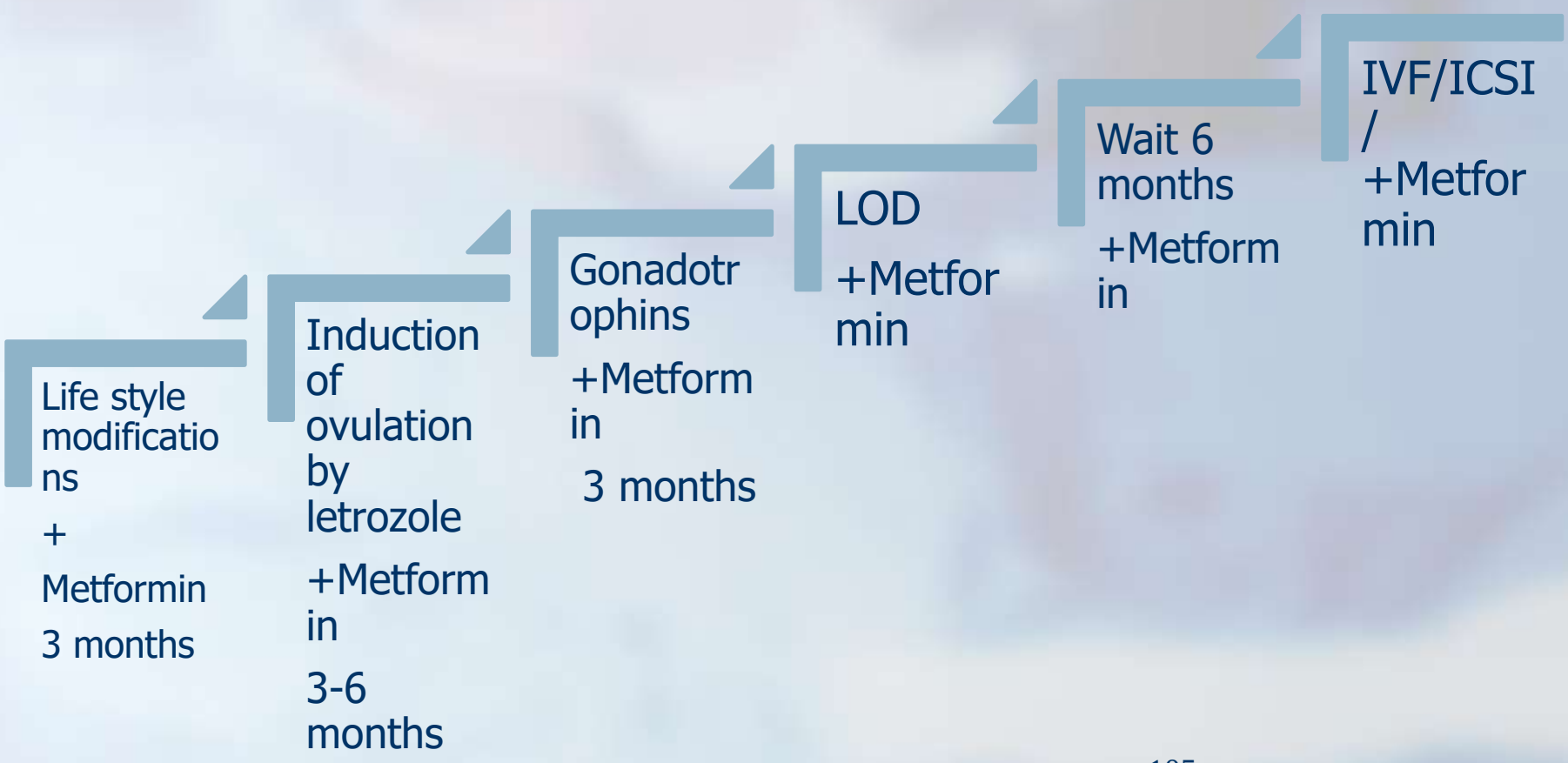
Antiandrogens

- In combination with the COCP, antiandrogens could be considered for the treatment of androgen-related alopecia in PCOS
- In PCOS, antiandrogens must be used with effective contraception, to avoid male foetal undervirilisation. Variable availability and regulatory status of these agents is notable and for some agents, potential liver toxicity requires cautionFinasteride (second line antiandrogen for hirsutism; 87 off-label use)
- Finasteride Oral tablet [Alopecia]; Adult, non-pregnant women: 5 mg PO once daily either alone or in combination with oral contraceptives shown to reduce hirsutism in women with mild hirsutism; minimal adverse reactions compared to other antiandrogens.

Antiandrogens

- Primarily used to treat hirsutism (clinical hyperandrogenism), often in combination with an oral contraceptive
- Spironolactone (first line antiandrogen for hirsutism and acne)
- Effective in decreasing degree of hirsutism and, to a lesser extent, acne Spironolactone Oral tablet; Adult females: 50 to 200 mg/day PO in 1 or 2 divided doses.
- Finasteride (second line antiandrogen for hirsutism; 87 off-label use)
- Finasteride Oral tablet [Alopecia]; Adult, non-pregnant women: 5 mg PO once daily either alone or in combination with oral contraceptives shown to reduce hirsutism in women with mild hirsutism; minimal adverse reactions compared to other antiandrogens.

Proposed protocol for PCOS and infertility (Al-Jefout)



Proposed protocol for PCOS and without infertility (Al-Jefout)

Life style modifications +

Metformin

6 months

(If IR)

COCP (drospirinone)

Aldactone

Life style modifications

6 months

(If no IR)

COCP (drospirinone)

Aldactone

Revaluation after 6 months

COCP +/- Metformin

Revaluation

Key Points

- Polycystic ovary syndrome is a heterogeneous endocrine disorder that occurs in about 5% to 10% 1 of reproductive-aged women
- Common clinical manifestations include oligomenorrhea, acne, and hirsutism
- Diagnosis is made when at least 2 of the following occur: hyperandrogenism (clinical and/or biochemical); ovulatory dysfunction; or polycystic ovarian morphologic features
- Important comorbidities include obesity, type 2 diabetes, obstructive sleep apnea, depression, and nonalcoholic fatty liver disease
- Treatment addresses several issues, including overweight/obesity, metabolic abnormalities, anovulation, acne, hirsutism, endometrial protection, infertility, and cardiovascular risk factors
- For most components of disease, primary treatment is weight loss

Key Points

- First line pharmacologic therapy is oral contraceptives, which are effective for reducing signs of hyperandrogenism and regulating menstrual cycle 3
- Additional pharmacologic options include metformin for metabolic dysfunction and clomiphene or letrozole for ovulation induction 4 5
- Complications include those related to pregnancy (eg, increased risk of adverse maternal, fetal, and neonatal outcomes) and increased risks of endometrial cancer, nonfatal stroke, and possibly cardiovascular events 6
- Polycystic ovary syndrome is a lifelong disorder, and institution of pharmacologic therapy and lifestyle measures to improve metabolic and endocrine status are intended to reduce future likelihood of cardiovascular disease

Case # I

- A 17-year-old nulliparous adolescent female, who may have only one kidney, presents with primary amenorrhea. She denies weight loss or excessive exercise. On examination, she is 165 cm in tall and weighs 55 kg. Her blood pressure is 140/88 mm Hg. mFG>12, Ludwig I, Acanthosis Nigricans +. Her thyroid gland is normal. She has appropriate Tanner stage IV breast development, axillary and pubic hair, and female external genitalia for the exception of mild enlargement of the clitoris.
- Most likely diagnosis and your DD?
- Next step in diagnosis:
- If your primary diagnosis is right what is your plan of management?

Case # I

- A 23-year-old G0P0 woman presents to the office with complaints of irregular cycles since menarche. Upon further questioning, she has also noticed an increase in facial hair and acne for many years. She denies any history of medical problems and has a strong family medical history of diabetes. On examination, she is noted to have a normal blood pressure (BP), pulse, respiratory rate, and temperature. She is obese with a body mass index (BMI) of 34 kg/m2, WC- 91 cm. She is noted to have mFG >12, Ludwig-II and acanthosis nigricans ++ (of neck and inner thighs). Her pelvic examination is limited by her obesity but normal. She does not desire pregnancy at this time. Her pregnancy test is negative.
- What is the most likely diagnosis?
- What complications is the patient at risk for?
- What is your next diagnostic step?
- What is your therapeutic plan for this patient?

Case # II

- A 42-year-old parous woman has noticed increasing hair growth on her face and abdomen over the past 6 months. She denies the use of steroid medications, weight changes, or a family history of hirsutism. Her menses previously had been monthly, and now occur every 35 to 70 days. Her past medical and surgical histories are unremarkable. On examination, her thyroid is normal to palpation. She has excess facial hair and male-pattern hair on her abdomen. Acne is also noted on the face. The cardiac and pulmonary examinations are normal. The abdominal examination reveals no masses or tenderness. Examination of the external genitalia reveals possible clitoromegaly. Pelvic examination shows a normal uterus and cervix and an 8-cm, right adnexal mass.
- What is the most likely diagnosis?
- What is the probable management?

- Please suggest a treatment plan for the following endometriosis cases

Case history #1

- A 20-year-old nulliparous married female presents with a history of progressively worsening menstrual pain and heavy prolonged periods that is now affecting her QoL.
- She misses 2 to 3 days of work each month. She finds no relief from ibuprofen. Her marriage is being affected by associated stress and pain during intercourse.
- On vaginal examination, her pelvic musculature is moderately tender. Her uterus is of normal size and minimally tender and not mobile. Rectovaginal examination reveals uterosacral nodularity and exquisite tenderness.
- She is also known case of VW disease.
- She is not planning for pregnancy for the coming 4 years.

Case history #2

- A 32-year-old P2 female presents with a history of progressively worsening menstrual pain that is now causing her distress for most of the month. She misses 2 to 3 days of work each month. She finds no relief from ibuprofen. Her marriage is being affected by associated stress and pain during intercourse. On vaginal examination, her pelvic musculature is moderately tender. Her uterus is of normal size and minimally tender and not mobile. Rectovaginal examination reveals uterosacral nodularity and exquisite tenderness.
- She is also know case of Sickle cell Anemia disease.
- She is not planning for pregnancy for the coming 2 years.

Case history #3

- A 39-year-old female presents to you as she and her husband have been trying to conceive for the past 2 years and have been unsuccessful.
- She has no complaints except for some mild lower abdominal bloating. Her past medical and surgical history is unremarkable. Her sister has recently been diagnosed with endometriosis.
- On examination, she is thin and in no distress.
- Pelvic examination reveals normal not tender mobile uterus and 6-8 cm bilateral adnexal mass.
- U/S scan reveals 8 cm bilateral adnexal masses resembling endometriomata

Case history #5

- A 39-year-old female presents to you as she and her husband have been trying to conceive for the past 2 years and have been unsuccessful.
- She has no complaints except for some mild lower abdominal bloating. Her past medical and surgical history is unremarkable. Her sister has recently been diagnosed with endometriosis.
- On examination, she is thin and in no distress.
- Pelvic examination reveals normal not tender mobile uterus
- U/S scan reveals 3 cm unilateral adnexal mass resembling endometrioma

Case history #6

- A 17 -year-old Virgo intacto female presents with a history of progressively worsening menstrual pain that is now causing her distress for most of the month. She misses 2 to 3 days of school each month. She finds no relief from ibuprofen.

Case history #7

- Grand multipara 39 year-old. C/O heavy prolonged periods with dysmenorrhea and deep dyspareunia (VAS 6-8/10) for the last 6 months.
- Her Hb-9.5 gm/L
- She is not pregnant. O/E- 14 weeks enlarged tender and mobile uterus with no adnexal masses


Thank You!