DEFINITION

- Syndrome consisting of amenorrhea, hirsutism, and obesity in association with enlarged polycystic ovaries

- "Classic" features: signs of elevated androgens, such as hirsutism, and oligom-enorrhea or amenorrhea

- 3-7%

Rotterdam criteria - two of these three criteria are required

- Menstrual irregularity

- Symptoms or findings of hyperandr-ogenism

- Polycystic ovaries on US

Phenotype C - hyperandrogenism and polycystic ovaries in ovulatory women

Phenotype D - irregular cycles and polycystic ovaries in the absence of documented hyperandrogenism

Phenotype A - includes all three criteria with US findings of polycystic ovaries

Phenotype B - women with the NIH definition when there are no US findings

AEPCOS - hyperandrogenism, polycystic ovaries on us or menstrual irregularity (anovulation)

CRITERIA FOR DIAGNOSIS OF PCOS

TABLE 39.1 Criteria for Diagnosis of Polycystic Ovary Syndrome

Study*	Criteria
National Institute of Child Health and Human Development 1990	Menstrual irregularity Hyperandrogenism (clinical or biochemical)
ESHRE-ASRM 2003 Rotterdam criteria	Menstrual irregularity Hyperandrogenism (clinical or biochemical) Polycystic ovaries on ultrasound (two of three required)
AEPCOS Society 2006	Hyperandrogenism (clinical or biochemical) and menstrual irregularity Polycystic ovaries on ultrasound (either or both of the latter two)
NIH Workshop 2012	Endorsement of Rotterdam criteria, acknowledging its limitations, and suggesting the name PCOS should be changed

OVARIAN MORPHOLOGY

- 12 or more peripherally oriented cystic structures (2-9 mm)

- Total follicle count in each ovary - most diagnostic

- Ovarian volume of 10 ml or more

- Polycystic-appearing ovaries (PAO), polycystic ovarian morphology (PCOM), or simply PCO

THE DIAGNOSIS IN ADOLESCENCE

- Rotterdam criteria should not be used.

- All three criteria are firmly in place and at a minimum of 3 years postmenarche

MENSTRUAL IRREGULARITY

- Oligomenorrhea (cycles longer than 35 days)

- Menstrual frequency of every few months

- Frank amenorrhea (longer than 6 months missed)

- Best correlate of insulin resistance in women with PCOS.

- Subfertility of women with PCOS

ANDROGEN EXCESS OR HYPERANDR-OGENISM

- Ovary

- Adrenal gland

- Adrenal gland

- Adipose tissues

11-oxygenated androgens - most abundant androgens in women with PCOS

CHARACTERISTIC ENDOCRINE FINDINGS

- Abnormal gonadotropin secretion

- Increased gonadotropin-releasing hormone (GnRH) pulse amplitude

- Increased pituitary sensitivity to GnRH

- Elevated LH level or elevated LH/FSH ratio- not be used as diagnostic tools

- Increased levels of biologically active (non-sex hormone-binding globulin [shbg]-bound) estradiol

- Increase estrone → increased peripheral (adipose) conversion of androgen

- Increased levels of biologically active estradiol → elevated LH levels and anovul-ation

- Elevated androgens

- Serum testosterone levels - 0.55 to 1.2 ng/ml

- Androstenedione levels are usually from 3to5 ng/ml

INSULIN RERSISTANCE

- Insulin and insulin-like growth factor 1 (IGF-1) enhance ovarian androgen production

- High levels of insulin bind to the receptor for IGF-1

- The granulosa cells also produce IGF-1 receptor and IGF-binding proteins (IGFBPs).

- Paracrine control

-Enhancement of LH stimulation

-Production of androgens by the theca cells

- Elevated insulin levels stimulate adipocyte production of adipokines interfere → with the metabolism and breakdown of adipose tissue and further enhance IR

- Insulin resistance in peripheral tissues

INSULIN RERSISTANCE (cont)

- *Muscle*
- *Adipose*
- *Ovary or adrenal*
- Signaling abnormalities
- Euglycemia with peripheral IR
- Severe cases - beta cell (secretory) dysfunction
- Testing should be directed at ruling out diabetes and glucose intolerance
- Measurement of the level of hemoglobin A1C
- *Prediabetes greater than 5.8%*
- *Frank diabetes greater than 6%*
- Clamp test
- Intravenous frequent sampling glucose tolerance test, or insulin tolerance

ACANTHOSIS NIGRICANS (AN)

- *30% of hyperandrogenic women*
- *50% of women with PCOS who are hyperandrogenic and obese*
- Velvety hyperpigmentation
- *Nape of the neck*
- *Axilla*
- *Vulva regions*

Hyperandrogenism, **IR**, and **AN** (HAIR-AN syndrome)

-Associated with insulin receptor antibodies

-Very high insulin levels

- *Severe IR*

ACANTHOSIS NIGRICANS

ANTIMÜLLERIAN HORMONE IN PCOS

Müllerian-inhibiting substance (MIS) or AMH

-Glycoprotein produced by the granulosa cells of preantral follicles

- *Elevated in women with PCOS*
- Pathophysiology of anovulation in PCOS
- Used as a blood test to substitute for US findings of a polycystic ovary

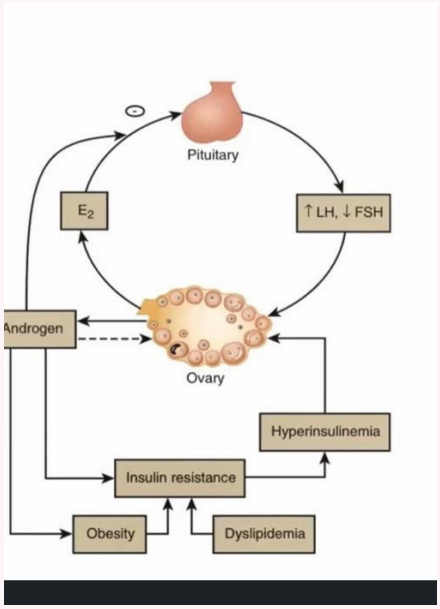
>4.7 ng/mL → PCOS

PATHOPHYSIOLOGIC CONSIDERATIONS

Genetic predisposition

- Susceptibility genes
- *2p16.3*
- *2p21*
- *9q33.3*
- *LH/human chorionic gonadotropic (HCG) receptor thyroid adenoma locus*
- *DENND1A*
- *Environmental factors*

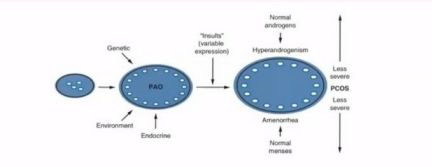
PATHOPHYSIOLOGIC CONSIDERATIONS



PATHOPHYSIOLOGIC CONSIDERATIONS

- *Genetic factors*
- *Environmental factors*
- *Endocrine disturbances*
- PAO: normal menses, normal androgen levels, and normal ovulatory function and parity may develop a full-blown syndrome (PCOS)
- Normal homeostatic factors → ward off stressors or insults
- Homeostatic mechanisms → symptoms of PCOS to emerge with varying degrees of severity
- 2 Major insults
- *Weight gain*
- *Psychological stress*

PATHOPHYSIOLOGIC CONSIDERATIONS



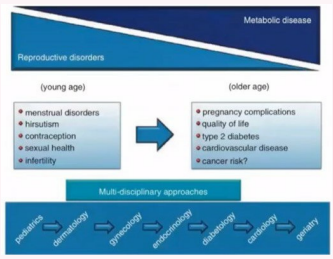
CONSEQUENCES OF POLYCYSTIC OVARY SYNDROME

- Metabolic risk
- Cardiovascular risks
- Cancers risk with aging

Multidisciplinary approach

- With aging
- *Cardiovascular disease*
- *Hypertension*
- *Metabolic syndrome*
- *Diabetes*
- *Cancer (endometrial and ovarian)*

CONSEQUENCES OF POLYCYSTIC OVARY SYNDROME



WEIGHT GAIN/OBESITY AND METABOLIC SYNDROME

- Weight → major predictor of abnormal metabolic findings → cardiovascular (CV) disease risks
- Increased abdominal and visceral fat in women with PCOS
- Treatment: lifestyle management
- Metabolic syndrome
- *Diabetes*
- *CV disease (CVD)*

WEIGHT GAIN/OBESITY AND METABOLIC SYNDROME

Adult Treatment Panel III criteria (3 of 5)

- Waist circumference >88cm
- High-density lipoprotein
- Triglycerides >150 mg/dl
- Blood pressure >130/85 mmhg
- Fasting blood sugar >110 mg/dl)

DIABETES

- Type 2 diabetes mellitus is more prevalent (2-3 times higher)
- Screen for diabetes in the overweight population with PCOS
- *Oral glucose tolerance test*
- Management
- *Diet and exercise*
- *Metformin - doses of 1500 mg/day*

QUALITY-OF-LIFE ISSUES

Poor quality of life

- Burden of being overweight
- Having irregular cycles
- Decreased fertility
- Skin concerns such as acne and hirsutism
- Depression
- Anxiety disorder

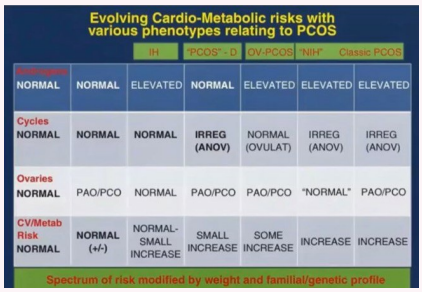
CARDIOVASCULAR CONCERNS

- Lipid and lipoprotein abnormalities
- Hypothetical scheme for increasing CV risk in women with PCOS with various phenotypes.

CARDIOVASCULAR CONCERNS (cont)

- "Unless a woman with PCOS has "classic" features of PCOS and has diabetes and obesity, there is no evidence for increased CV morbidity and mortality in women with PCOS."

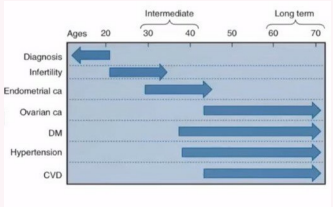
CARDIOVASCULAR CONCERNS



CANCERS IN POLYCYSTIC OVARY SYNDROME

- Endometrial cancer can begin at a younger age
- *Long-term anovulation*
- *Unopposed estrogen stimulation of the endometrium*
- Increased risk for endometrial and ovarian cancer
- Milder phenotypes - little or no increased risk
- Endometrial cancer - increased at least 2-3 fold
- Ovarian cancer - 2.5 time increased
- Use of oral contraceptives
- Metformin - inhibitory effects on various cancers

CANCERS IN POLYCYSTIC OVARY SYNDROME



OVARIAN AGING: PCOS AND MENOPAUSE

- Ovaries decrease in size and androgen levels decrease

- As women with PCOS age

- Become more regular and ovulatory

- Decrease in the total follicular cohort

- Lower levels of AMH

-Preserved fertility in women with PCOS as they age

Menopause

- Hirsutism may still be prevalent T

- Persistence of the metabolic issues

- Continued vigilance in managing and following

TREATMENT OF POLYCYSTIC OVARY SYNDROME

➢ Androgen excess and symptoms of hyperandrogenism

➢Irregular bleeding and risks of endometrial disease as a result of unopposed estrogen stimulation from anovulation

➢Fertility concerns and subfertility, mostly because of anovulation

Lifestyle management

- Use of an OC, with or without an antiandrogen - Androgen excess

- OCS -> Reduce the risk of endometrial cancer

- Supplying the missing progesterone in anovulatory - Irregular bleeding

- Progestogen therapy

- 2 to 3-month intervals

- Medroxyprogesterone acetate (5-10mg)

- Norethindrone acetate (2.5 to 10 mg)

- Ovulation induction - subfertility

TREATMENT OF SUBFERTILITY IN PCOS

Ovulation induction

- Metformin

- Clomiphene - after obtaining a semen analysis

-Letrozole - 2.5 to 5 mg/day, 5 days; first-line treatment

- Gonadotropins - Low-dose is highly effective as a second-line treatment

- pulsatile GnRH - less effective

- ovarian diathermy or drilling - second-line therapy, particularly in clomiphene failures

Adjunctive measures

-Dexamethasone

- Dopamine agonists

- Thiazolidinediones

IVF - fail to conceive with ovulation induction over 6 cycles and with other infertility factors

METABOLIC AND WEIGHT CONCERNS

Exercise regimens

Metabolic syndrome (MBS)

- Combination of diet and metformin

- • Reduce weight by 5-7%

- Reduce insulin resistance Improve metabolic parameters

Bariatric surgery

Antiandrogens (flutamide)

Drospirenone and 17alpha- ethinylestradiol (EE2) with flutamine and metformin - adolescents

METABOLIC AND WEIGHT CONCERNS

TABLE 39.4 Treatment for Women with Polycystic Ovary Syndrome

Complaint	Treatment Options
Infertility	Letrozole, clomiphene, with or without metformin, gonadotropins, ovarian cautery ("drilling")
Skin manifestations	Oral contraceptive + antiandrogen (spironolactone, finasteride), GnRH agonists
Abnormal bleeding	Cyclic progestogen, oral contraceptives
Weight, metabolic concerns	Diet/lifestyle management, metformin

GnRH, Gonadotropin-releasing hormone.