



PCOS

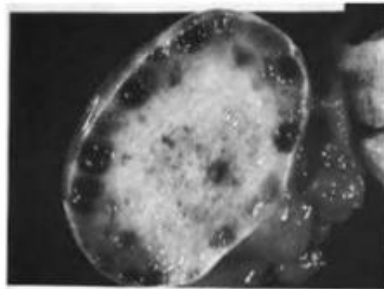
Polycystic Ovary Syndrome

Ferrara – 2016

Stein–Leventhal syndrome



Polycystic ovary syndrome (PCOS) was first reported in modern medical literature by Stein and Leventhal who, in **1935**, described seven women suffering from **amenorrhea**, **hirsutism**, **obesity** and **enlarged ovaries with multiple cysts**.



Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. *Am J Obstet Gynecol* 1935; 29:181-191.



SINDROME DELL'OVAIO POLICISTICO: CHE COSA E'?

✓ **DISENDOCRINOPATIA DELL'ETA' RIPRODUTTIVA**
(prevalenza 5-6%)

✓ **SI MANIFESTA A PARTIRE DALL'ADOLESCENZA**

✓ **SINDROME ETEROGENEA ENDOCRINO-METABOLICA:**

- ✓ Irregolarità mestruali, sterilità
- ✓ irsutismo, acne \longrightarrow **IPERANDROGENISMO**
- ✓ Ovaie policistiche
- ✓ Disturbi metabolici

IPERANDROGENISMO

CLINICO:

- IRSUTISMO
- ACNE
- ALOPECIA

BIOCHIMICO:

- \uparrow TESTOSTERONE TOTALE
- \uparrow TESTOSTERONE LIBERO
- \uparrow DHEAS
- \uparrow ANDROSTENEDIONE

Diagnostic criteria for the diagnosis of PCOS

NIH/NICHD 1992 ¹⁸	ESHRE/ASRM (Rotterdam criteria) 2004 ¹⁹	Androgen Excess Society 2006 ²⁰
Exclusion of other androgen excess or related disorders	Exclusion of other androgen excess or related disorders	Exclusion of other androgen excess or related disorders
Includes all of the following:	Includes <u>two</u> of the following:	Includes all of the following:
<ul style="list-style-type: none"> • Clinical and/or biochemical hyperandrogenism 	<ul style="list-style-type: none"> • Clinical and/or biochemical hyperandrogenism 	<ul style="list-style-type: none"> • Clinical and/or biochemical hyperandrogenism
<ul style="list-style-type: none"> • Menstrual dysfunction 	<ul style="list-style-type: none"> • Oligo-ovulation or anovulation • Polycystic ovaries 	<ul style="list-style-type: none"> • Ovarian dysfunction and/or polycystic ovaries



Abbreviations: ESHRE/ASRM, European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine; NIH/NICH, National Institutes of Health/National Institute of Child Health and Human Disease.

* such as congenital adrenal hyperplasia, Cushing syndrome, androgen-secreting tumor, hyperprolactinemia, and thyroid disorders

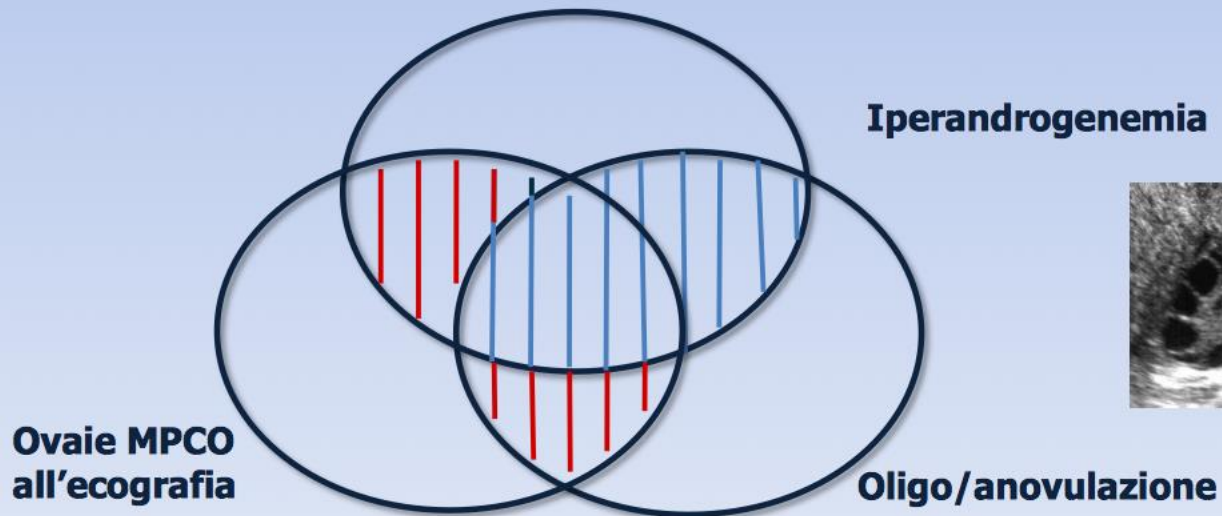
DIAGNOSI CRITERI DI ROTTERDAM (almeno 2 dei seguenti criteri)

- Cicli Anovulatori
- Iperandrogenismo: Segni clinici (acne, alopecia, irsutismo) o biochimici
- All'Ecografia Transvaginale: numero di follicoli > di 12 in un singolo ovaio o ovaio aumentato di volume (> 10ml)



Definizione di Sindrome dell'ovaio micropolicistico Rotterdam 2004

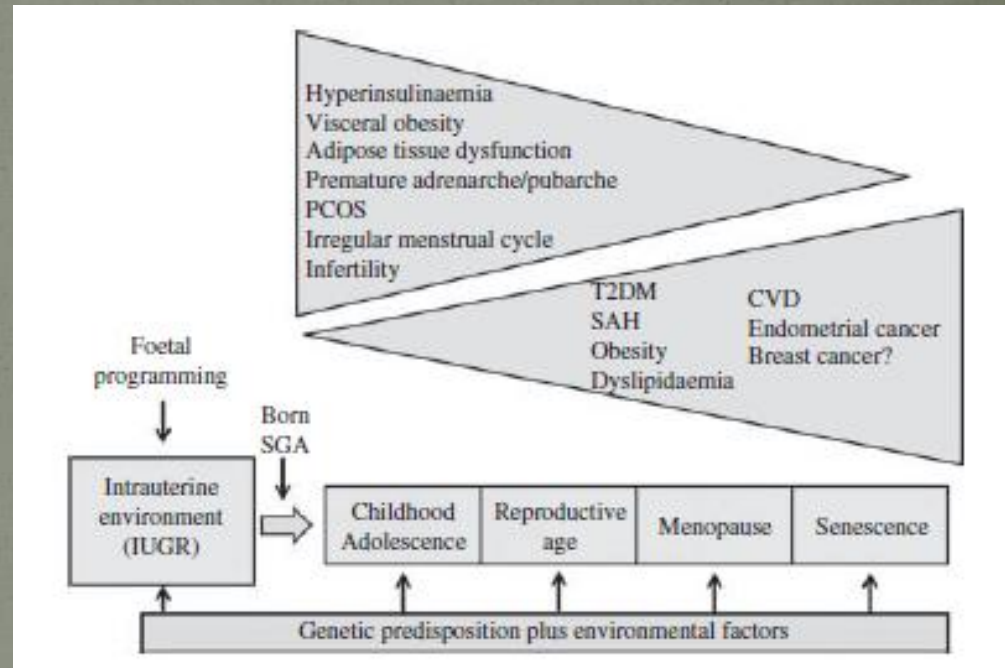
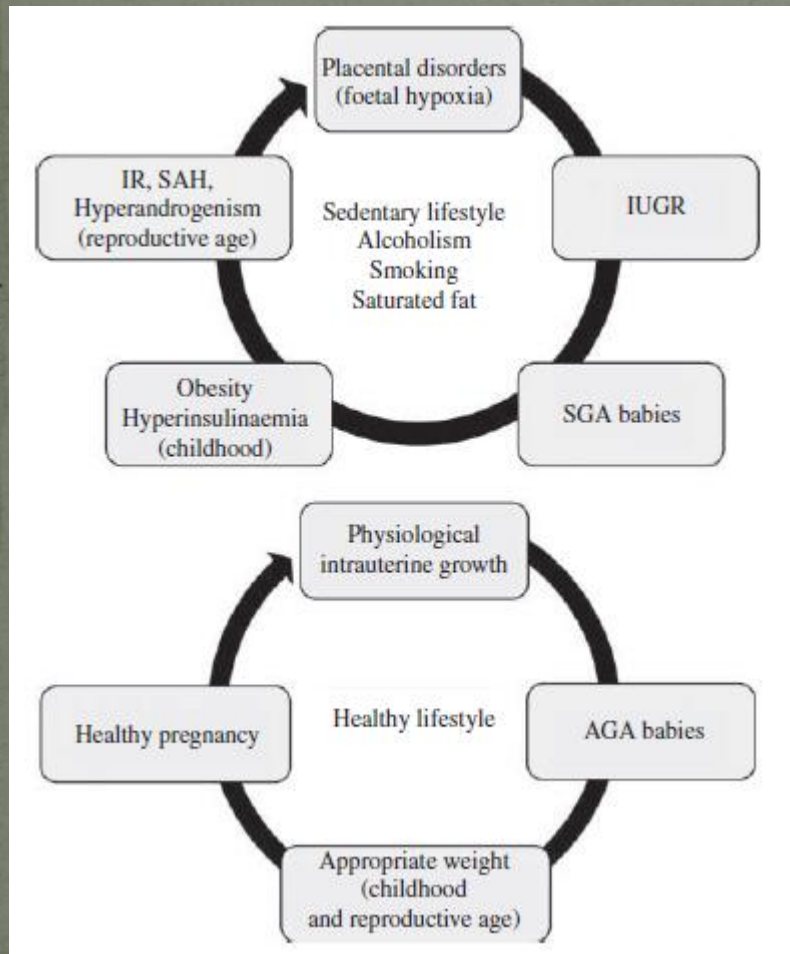
Diagnosi: 2 criteri su 3



Epidemiology

- Affects women of reproductive age
- **Prevalence** in pre-menopausal women: **6-10%**
- Association with:
 1. **Overweight or obesity** [the body fat is usually deposited centrally (android obesity)]: **38-88%**
 2. **Dysglycaemia**: among women with PCOS, **10%** have T2-DM and **30-40%** develop early-onset IGT
 3. **Metabolic syndrome**: **34-46%**
 4. **Insulin resistance**: **50-90%**
 5. **Obstructive sleep apnoea (OSA)**: **5-10-fold higher** in PCOS than in BMI-matched control women. OSA is a condition which itself also independently associates with insulin resistance that, in turn, further worsens metabolic dysfunction in PCOS.

Risk factors



LA SINDROME DELL'OVAIO POLICISTICO

Changing Women's Health Paradigm



(GIOVANE)
AVANZATA)

(ETA' FERTILE)

(ETA' PIÙ

- **Disordini mestruali**
- **Irsutismo**
- **Contracezione**
- **Salute sessuale**
- **Infertilità**



- **Complicanze gravidiche**
- **Qualità della vita**
- **Diabete di Tipo 2**
- **Malattie Cardiovascolari**
- **Rischio Cancro (?)**

Human Reproduction 2012, 27(1): 14-24

La PCOS è caratterizzata da disordini della funzionalità riproduttiva nella giovane donna, mentre prevalgono i disordini metabolici nella donna in età fertile e in epoca più avanzata.

Image 6 it 44

CLOSE X

Pathophysiology

Puberty

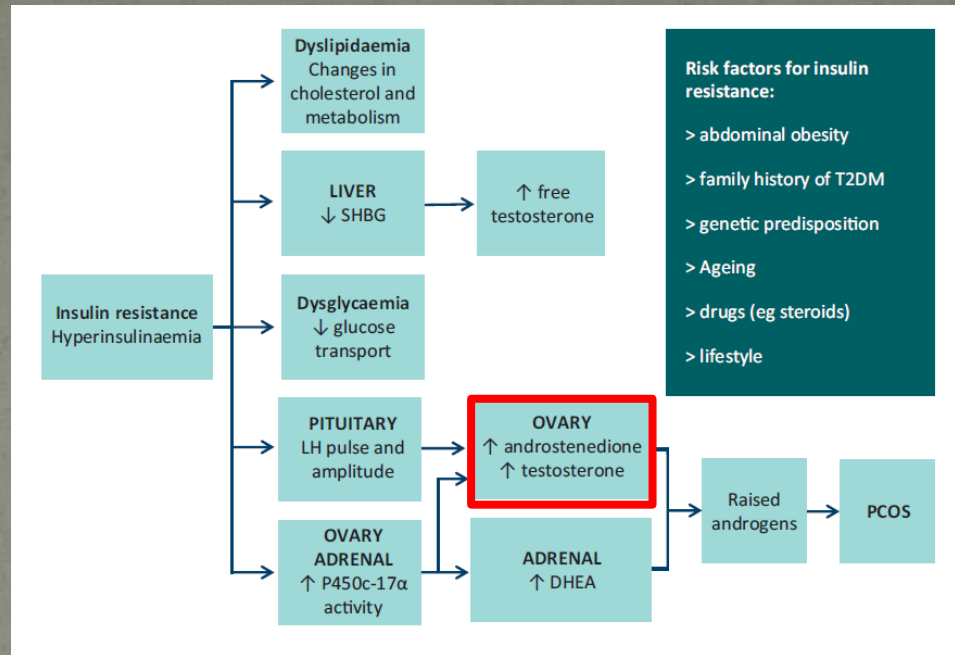
- Starts with the **maturation of the hypothalamic-pituitary-ovarian axis** and secretion of GnRH (whose activity is suppressed during childhood).
- **Varying GnRH pulse frequencies** trigger the pituitary to release luteinizing hormone (**LH**) and follicle-stimulating hormone (**FSH**), which stimulate ovarian theca and granulosa cells, respectively.

Theca cells produce androstenedione, which nearby granulosa cells aromatize into estradiol.

- The resulting estrogenic changes during puberty include **breast development, bone growth, and fat deposition.**
- During this period the **adrenal gland** also releases increasing amounts of androgens, such as dehydroepiandrosterone (**DHEA**) and DHEA-sulfate (**DHEAS**), which are **responsible for the development of pubic and axillary hair**, as well as acne.

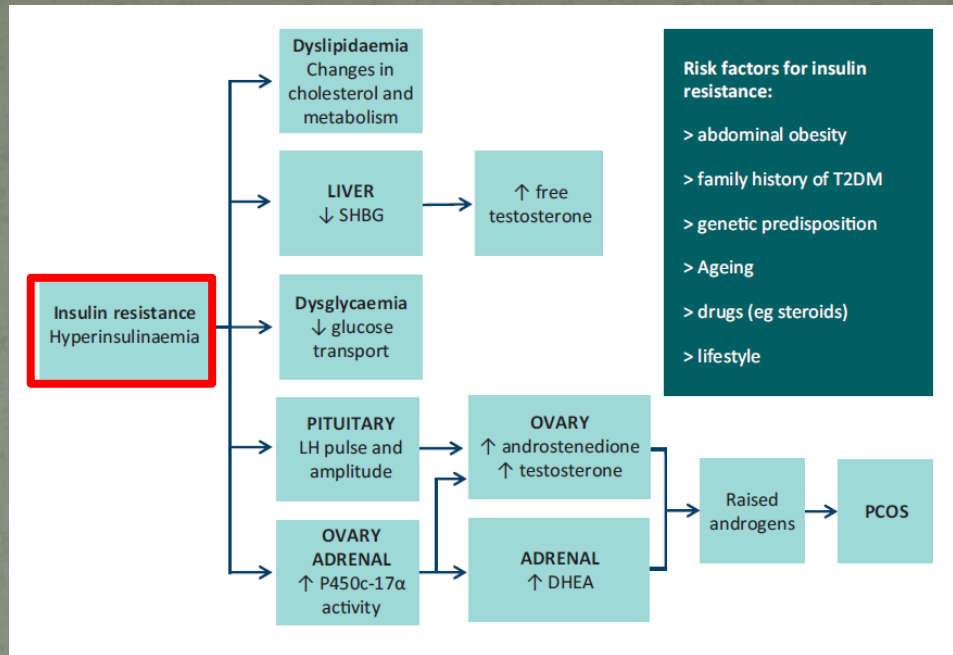
The subsequent increase in ovarian androgens also facilitates the development of sexual hair growth.

Although the exact etiology of PCOS is unclear, **androgen excess** is proposed to be a core defect.



Increased androgen levels, primarily produced by the ovaries (with a smaller contribution from the adrenals and peripheral adipose tissue) **interfere with hypothalamic sensitivity to negative feedback from the ovary**, thereby **increasing GnRH pulse frequency**.

- This persistently rapid pulse frequency favors **increased LH secretion**, which in turn **stimulates the ovarian theca cells to produce more androgens**.
- The relative **decrease in FSH secretion** leads to **less aromatization of androgens to estradiol and impaired follicular development**, resulting in the prolonged periods of oligomenorrhea.



Insulin stimulates ovarian theca cell synthesis of androgens and inhibits hepatic production of SHBG.

Together, these effects result in **increased circulating free androgen levels**, thus perpetuating the underlying pathophysiology of PCOS.

In addition, insulin resistance promotes release of non-esterified fatty acids from the liver and adipose tissue due to decreased lipoprotein lipase activity, which contributes to the dyslipidemia that is associated with PCOS

ESAME OBIETTIVO E SINTOMATOLOGIA

- **Manifestazioni da iperandrogenismo: alopecia, irsutismo (score di Ferriman-Gallway), acne**
- **BMI: >25 sovrappeso; >30 obesità;**
- **Alterazioni mestruali: oligomenorrea 60%; amenorrea 30%;**

Clinical signs

Menstrual disturbances commonly observed in PCOS include:

- **Oligomenorrhea*** (cycle length: >35 days and <3 month)
- **Amenorrhea****
- **Prolonged erratic menstrual bleeding or Abnormal Uterine Bleeding**

However, **30%** of women with PCOS have **normal menses**

*Approximately 85%–90% of women with oligomenorrhea have PCOS

**Approximately 30%–40% of women with amenorrhea have PCOS

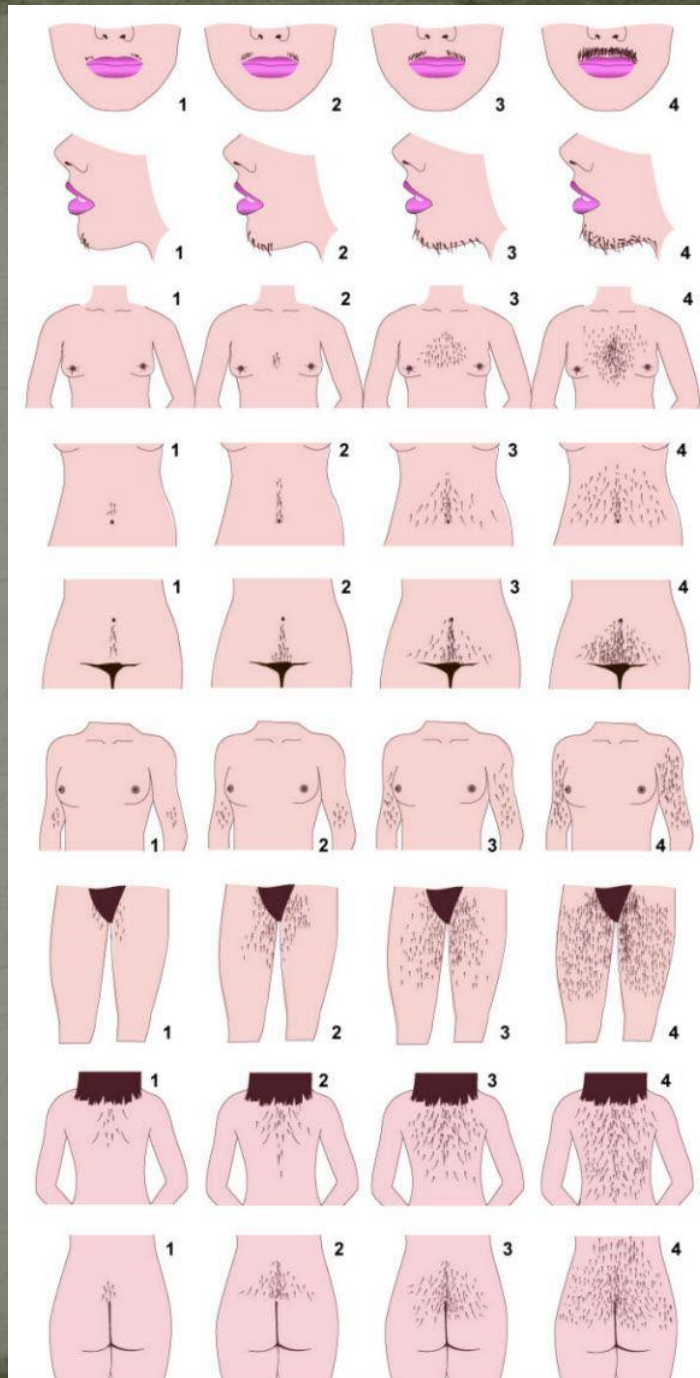
Androgen excess

Increases the activity of 5α -reductase in the hair follicles and the hair growth

Hirsutism:

- Up to 70% of women with PCOS*
- Ferriman-Gallwey scoring system for hirsutism, used to evaluate hair growth at 7 sites: upper lip, chin/face, chest, back, abdomen, arms, and thighs. A score of 0 is given in the absence of terminal hair growth and a score of 4 is given for extensive growth. A total score of 8 or more is indicative of hirsutism.

*Over 90% of normally menstruating women with hirsutism are identified through ultrasound to have polycystic ovaries



Androgen excess

Causes the activation of sebaceous glands



Seborrhea: increased production of sebum by sebaceous follicles

Acne: a skin disorder that occurs when the pores of the skin become clogged with oil, dead skin cells, and bacteria.

- Less prevalent in PCOS and less specific
- Approximately 25-30% of adult women with PCOS present with acne

Obesity and Insuline-resistance

Obesity

- BMI >30
- *The* body fat is usually deposited centrally (**android obesity**)
- Fat is an extraglandular source of androgens
- Worsens lipidic profile

Insuline-resistance

- Acanthosis nigricans (typical of diabetic patients): increased thickness of skin in neck and groin folds, that appears hyperpigmented, due to the deposition of insuline in derma.



Metabolic disorders

Increased risk of developing **Metabolic Syndrome:**

- Abdominal circumference > 88 cm
- At least 2 of the following disorders:
 - Triglycerids >150 mg/dl
 - HDL chol < 45 mg/dl
 - SBP \geq 130 mmHg or
DBP \geq 85 mmHg
 - Fasting glucose \geq 100 mg/dl

Infertility

- **40% of women with PCOS**
- PCOS is the most common cause of **anovulatory infertility**
- Approximately 90%–95% of anovulatory women presenting to infertility clinics have PCOS

- Women with PCOS have a **normal number of primordial follicles** and **primary and secondary follicles are significantly increased.**

However, due to derangements in factors involved in normal follicular development, **follicular growth stops** as follicles reach a diameter of 4–8 mm. Because a **dominant follicle does not develop**, ovulation does not ensue.

- In addition, **spontaneous abortion** occurs more frequently in PCOS with incidences ranging **42%–73%**

LA SINDROME DELL'OVAIO POLICISTICO

Complicazioni del Concepimento e della Gravidanza nella Pcos

- Prematura luteinizzazione delle cellule della granulosa
- Disfunzione paracrina del fattore di crescita
- Alterazione dello spazio intrafollicolare e deficit della maturazione degli ovociti
- **L'embrione di sesso femminile può essere esposto a un eccesso di androgeni**
- La percentuale di aborti è simile a quella della popolazione sub-fertile
- **Aumenta la % di diabete gestazionale (40–50%) e di macrosomia fetale**
- **Aumenta la % di complicanze correlate all'ipertensione indotta dalla gravidanza (5%)**
- Aumenta il rischio di TC e di parti pre-termine e post-termine
- **Aumenta la % di bambini piccoli per l'epoca gestazionale (10–15%)**

Diagnosis

Blood tests

ESHRE/ASRM (Rotterdam criteria) 2004¹⁹

Exclusion of other
androgen excess or
related disorders

Includes two of the
following:

- Clinical and/or biochemical hyperandrogenism
- Oligo-ovulation or anovulation
- Polycystic ovaries

Hormones:

- ↑ LH
- FSH ↓
- ↑ LH/FSH
- ↑ Testosterone
- ↑ DHEA-S
- SHBG ↓
- Estradiol ↓
- ↑ Estrone

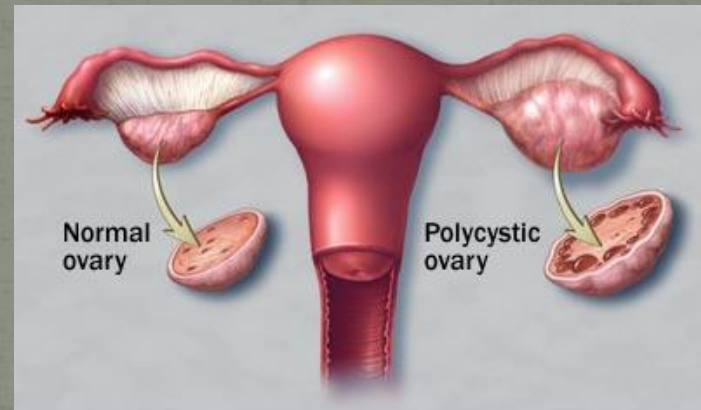
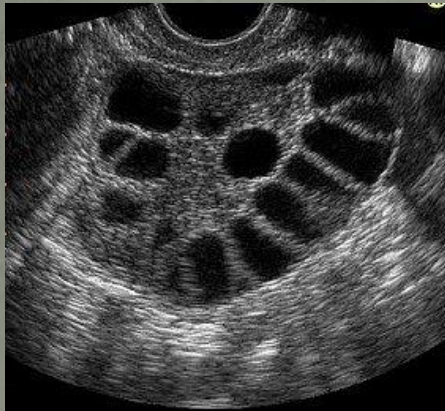
Metabolic test:

- ↑ Glycemia
- ↑ Insuline
- ↑ LDL
- HDL ↓
- ↑ Triglycerids

Diagnosis

US pattern

The criteria for polycystic ovarian morphology proposed by the Rotterdam consensus group includes the presence of 12 or more follicles measuring between 2 and 9 mm in diameter and/or an increased ovarian volume of greater than 10 cm³.



This presentation in one ovary sufficiently defines the polycystic ovary, but a US pattern suggestive for the presence of multiple cysts is not exclusive of PCO syndrome.

CRITERI ECOGRAFICI PER LA DIAGNOSI DI PCOS

Adams et al, 1985

- Almeno 10 follicoli (diametro 2-8 mm) in sede sottocorticale
- Stroma ovarico più denso nella porzione centrale
- Volume aumentato



Attualmente si considera policistico:

- 6 o più follicoli
- Stroma iperecogeno
- Distribuzione dei follicoli intraparenchimale (fase 1) e sottocorticale (fase 2)

Treatment

Androgen excess

1. Control menstrual cycle ciclicity
2. Correct infertility
3. Reduce acne, hyrsutism and seborrhea

Androgen excess

- **E/P oral contraceptive:**
 - Inhibits LH production
 - Promotes liver production of SHBG
 - Reduce 5α -reductase activity
- **Finasteride, flutamide (antiandrogens)**
 - Skin problems
 - Competes with androgen receptors or reduce 5α -reductase activity
 - Teratogenic effects (combine with a contraceptive!)

Infertility

Citrate clomiphene

- Binds to hypothalamic estrogen receptors causing their depletion and determining insensibility to estrogens by target cells
- In this way, hypofysis increases the production of FSH and LH
- Regularization of ovulatory cycles in 75% of women
- Pregnancy obtained in 18-20% of cases

Ovary drilling

Laparoscopic Multiple electrocautery of the ovary

Assisted reproductive techniques

Metabolic disorders

1. Control glycemia and insuline
2. **Reduce weight**

Metabolic disorders

- Anti-insulinemic drugs (metformin):
 - Reduces liver production of glucose
 - Improves peripheral glucose absorption by peripheral tissues
- Healthy lifestyle
- Healthy diet (hypocaloric diet regimen)
- Physical exercise

Loss of weight ameliorates Insuline-resistance in order to let a regular ovulatory cycle restart in 90% of women!!