Unità didattica: patologie gonadiche e l'iperandrogenismo femminile

- L'ovaio come organo endocrino nelle varie fasi della vita
- Gli iperandrogenismi: meccanismi fisiopatologici e quadri clinici
- La sindrome dell'ovaio policistico (PCOS)
- Diagnosi dell'iperandrogenismo
- Principi di terapia

www.fisiokinesiterapia.biz

Definizione iperandrogenismo

Condizione clinica/subclinica caratterizzata da eccessiva produzione o azione degli androgeni di origine surrenalica/ovarica nella persona adulta

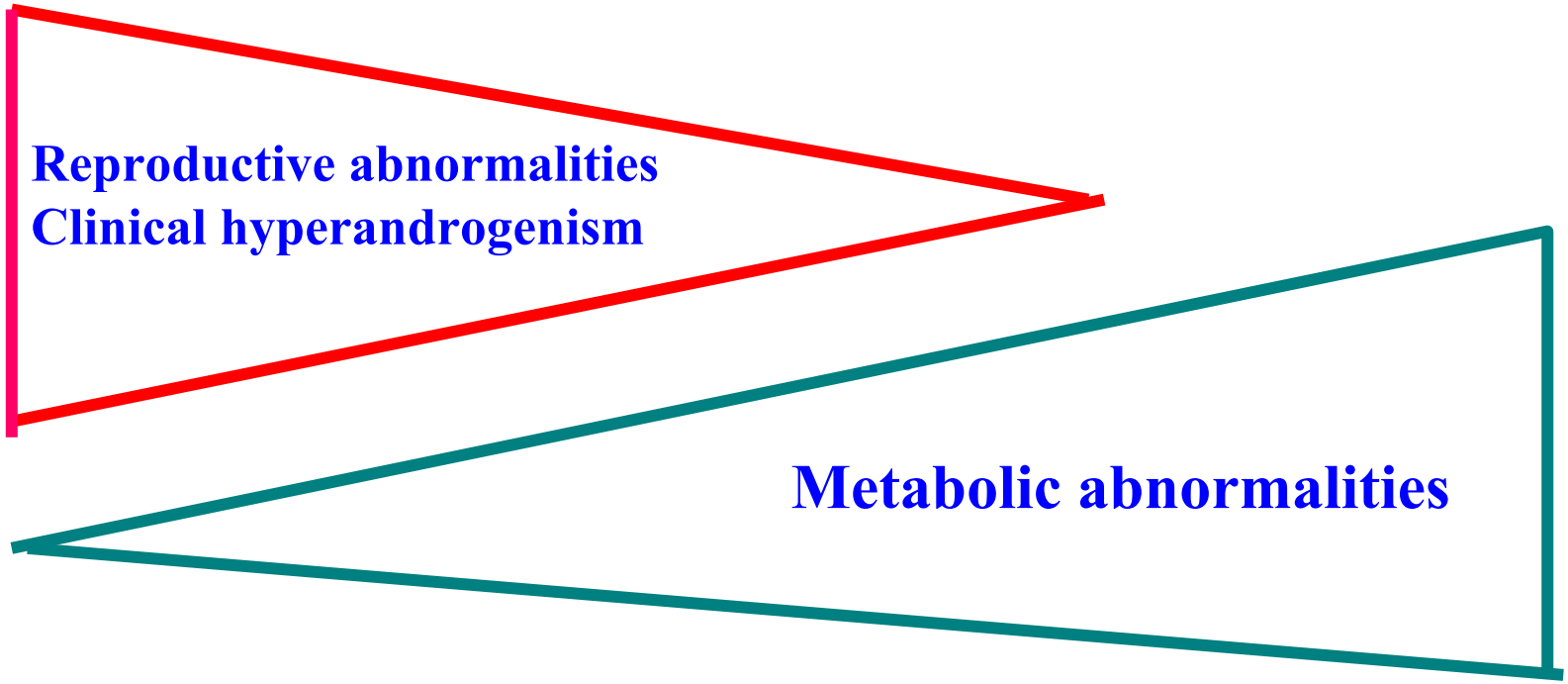
Definizione virilizzazione

Condizione clinica caratterizzata da eccessiva produzione /azione degli androgeni di origine surrenalica/ovarica con modificazioni dei caratteri sessuali primari nel feto, nel neonato, nel bambino e negli adolescenti

Cause dell'irsutismo

Surrenaliche	**– Iperplasia surrenalica congenita (deficit 21-idrossilasi, deficit 11β idrossilasi, deficit 3β idrossisteroidodeidrogenasi)** **– Cushing** **– Neoplasie**
Ovariche	**- PCOS** **- Neoplasie** **- Ipertecosi**
Idiopatico	**Irsutismo idiopatico (??)**
Genetico	**Disgenesie gonadiche**
Varie	**- Acromegalia, Ipotiroidismo, Obesità, IperPRL, Menopausa, Sindromi psichiatriche, ecc** **- Farmaci**

Age-related changes in the PCOS phenotype



PCOS: Diagnostic criteria revised (1999 ➡ 2003)

- **1999 criteria (both 1 and 2)**
  1. **Chronic anovulation**
  2. **Clinical and/or biochemical hyperandrogenism, and**
  3. **Exclusion of other aethiologies**

- **Revised 2003 criteria (2 out of 3)**
  1. **Oligo- and/or anovulation**
  2. **Clinical and/or biochemical signs of hyperandrogenism**
  3. **Polycystic ovaries (PCO) (US)**
  4. **Exclusion of other aethiologies (CAH, androgen-secreting tumors, Cushing's syndrome, etc.)**

Hyperandrogenemia and PCOS

- Factors determining increased androgen levels and action:
  - increased ovarian synthesis (P450c17)
  - decreased SHBG synthesis
  - adrenal source
  - increased ARs (< CAG repeats) function
  - altered aromatase activity ?

Main pathogenetic factors of the PCOS phenotype

Hyperandrogenism

Responsible for:

- signs/symptoms of androgen excess, including anovulation
- reduced SHBG
- abdominal fatness,
- insulin insensitivity (?)
- lipid anbormalities

Hyperinsulinemia and insulin resistance

Responsible for:

- the metabolic syndrome
- abdominal fatness

Co-factor favouring:

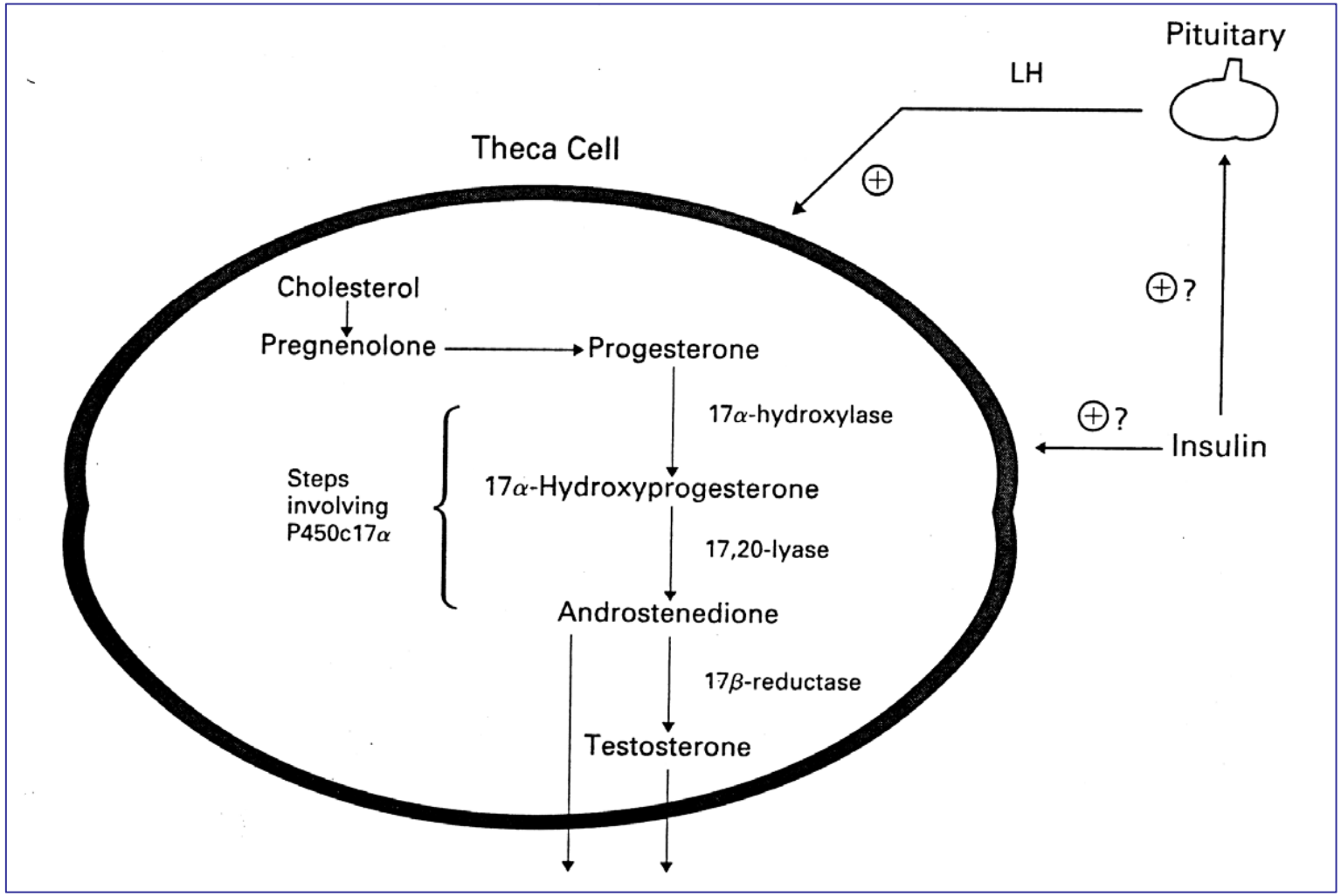
- andogen excess
- reduced SHBG
- anovulation

Summary of insulin effects related to ovarian function

Effect	*Organ*
Directly stimulates steroidogenesis	Ovary
(P450 c17)	Ovary
Sinergizes with LH/ FSH	Ovary
Stimulates 17 α-hydroxylase	Ovary, adipose tissue
Stimulates or inhibits aromatase	Ovary
Up-regulates LH receptors	Ovary
Promotes ovarian growth/cyst formation synergistically with LH/hCG	Ovary
Down-regulates insulin receptors	Ovary
Up-regulates type I IGF or hybrid rec.	Ovary, liver
Inhibits IGFBP-1 production	
Potentiates the effects of GnRH on LH FSH	Hypothalamus/pituitary
Inhibits SHBG production	Liver

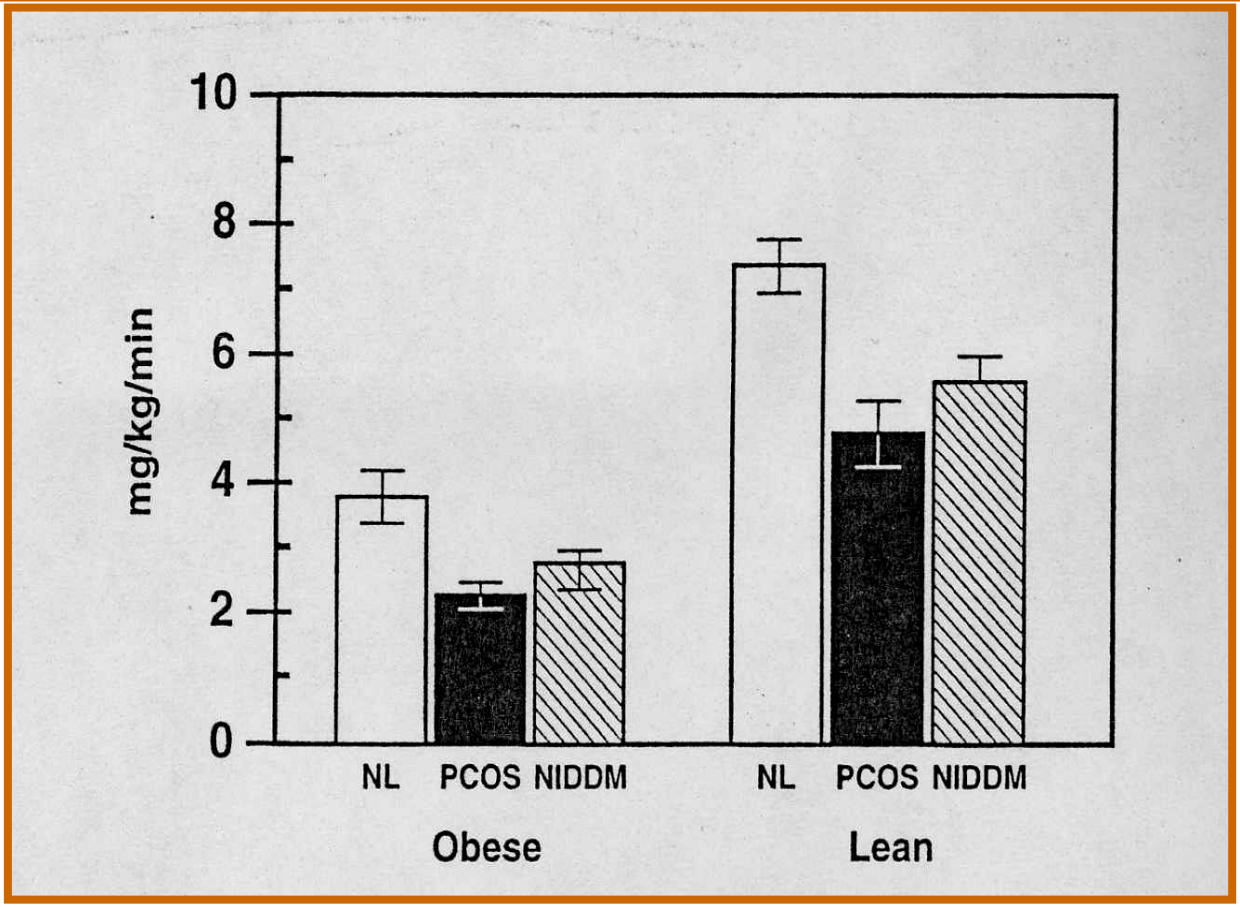
Poretsky L, *Endo Rev 1999*

The thecal P450c17 as a target for LH and insulin



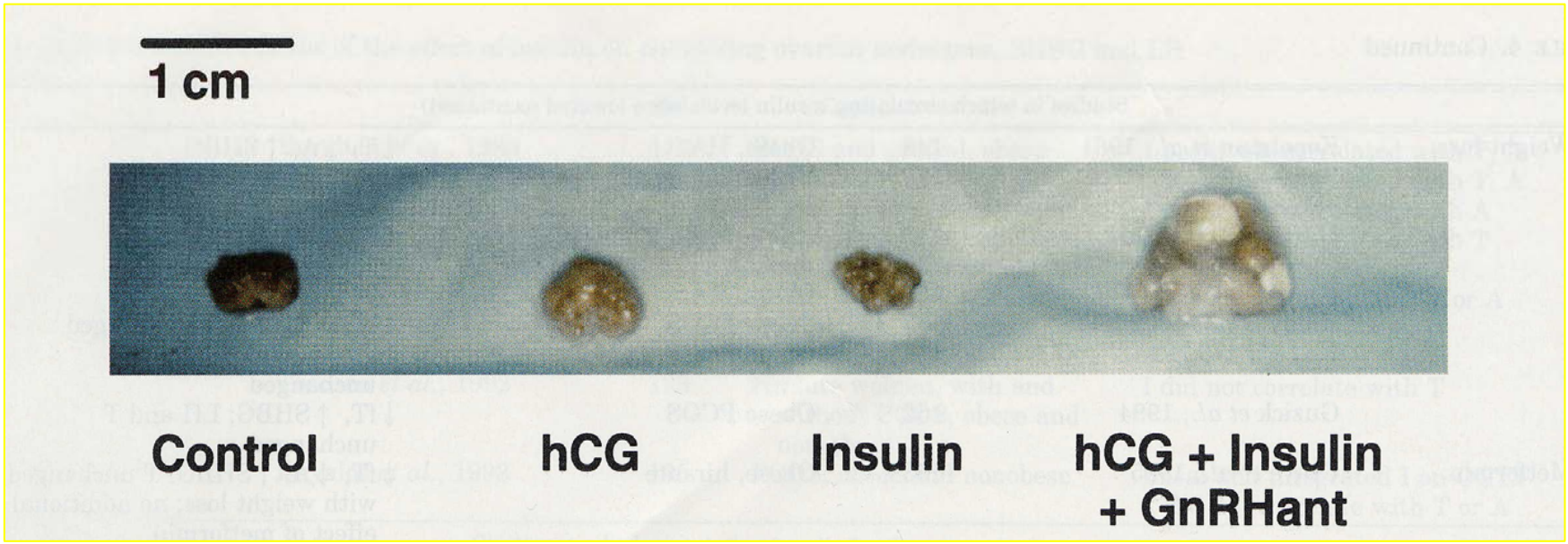
Insulin Resistance Syndrome or Metabolic Syndrome is an integral part of the PCOS (affects 2/3 of the PCOS women)

Insulin-mediated glucose disposal at steady-state insulin levels of ~ 100 µU/mL is decreased by 35-40% in PCOS compared with age- and weight-matched control women



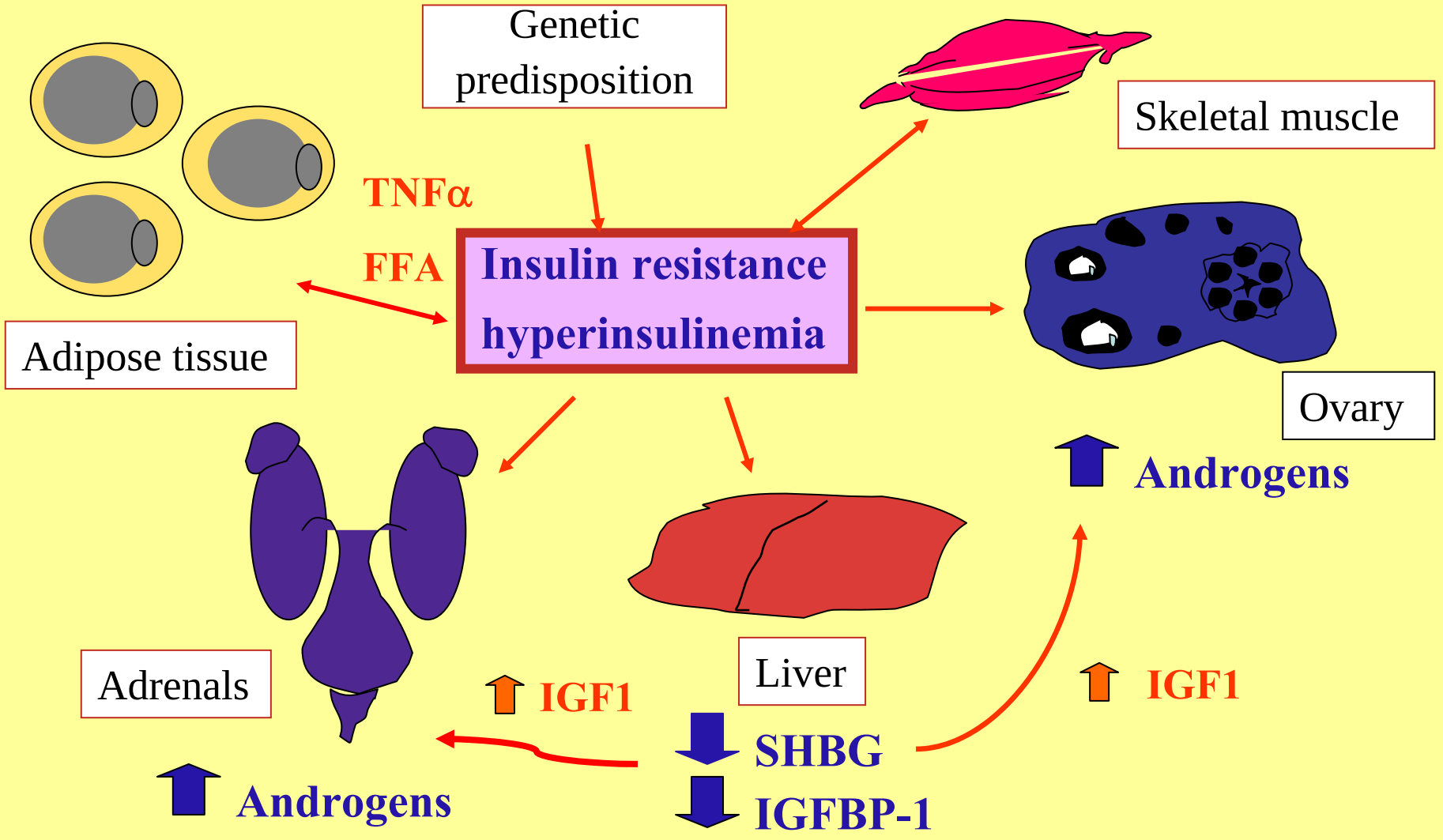
Dunaif A, *Diabetes 1992*

The effects of 23 days injections of normal saline (control), hCG, insulin, or insulin plus hCG and GnRHant on gross ovarian morphology in rats (female Sprague-Dawley rats)

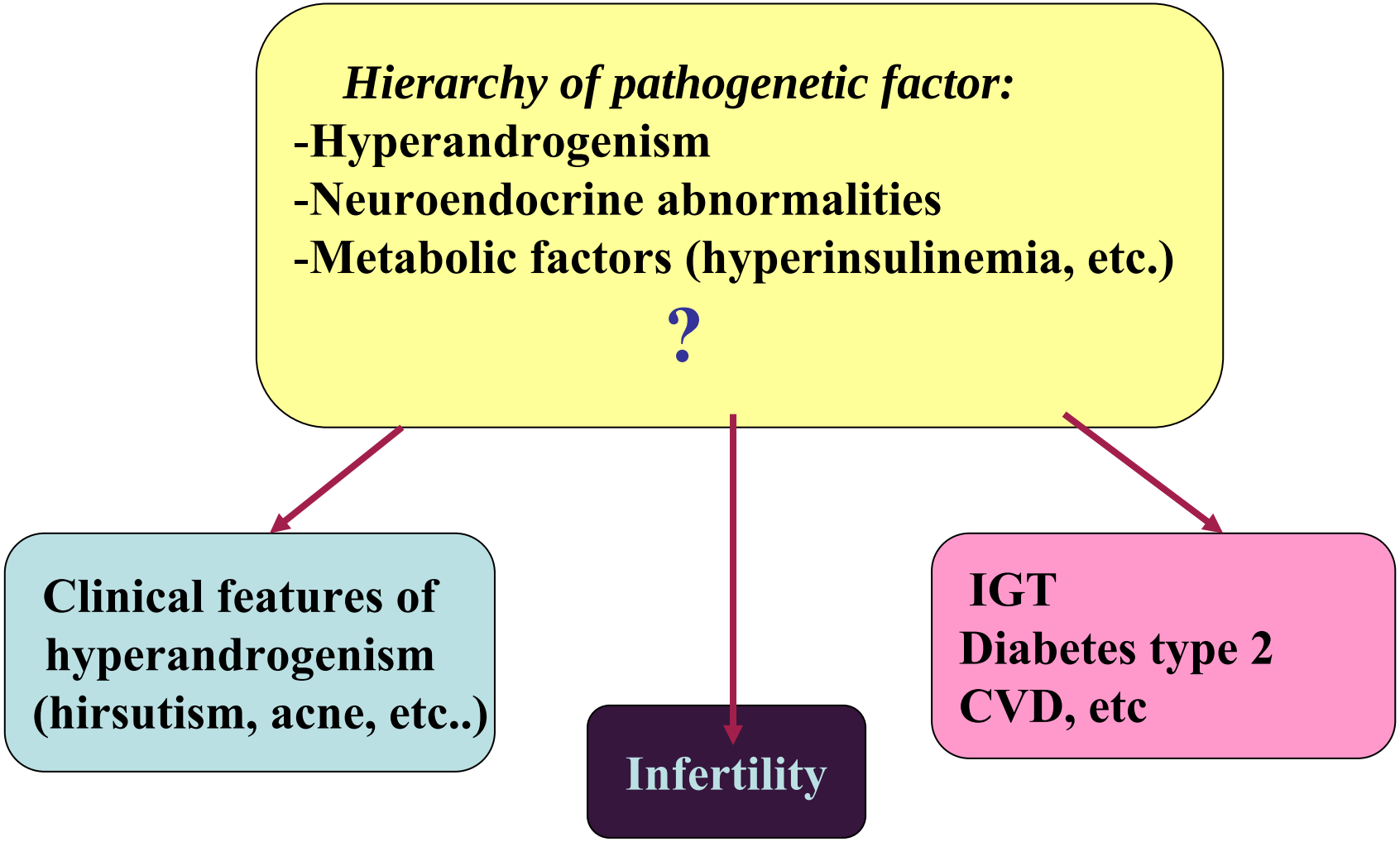


Poretsky L, *Metabolism 1992*

Pathogenesis of insulin resistance and role of hyperinsulinemia in the pathophysiology of PCOS



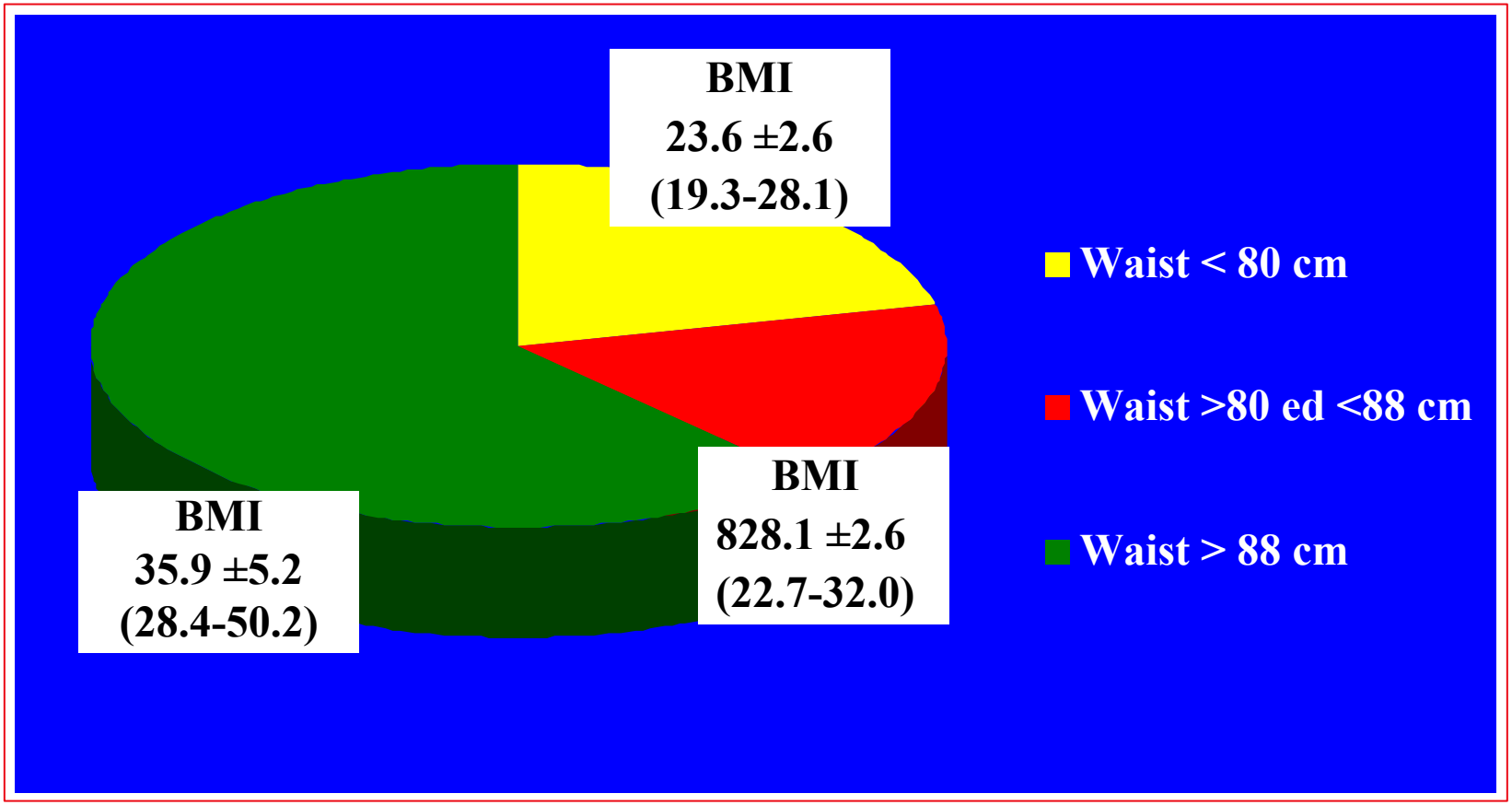
Pathophysiology of PCOS



Main features of most women with the PCOS

- Hyperandrogemia
- Oligo-amenorrehea
- Hirsutism
- Insulin resistance
- Hyperinsulinemia
- Obesity (>50%)
- Abdominal/visceral body fat distribution
- Features of the metabolic syndrome

Prevalence of the abdominal phenotype in obese women with the PCOS (cohort. n° = 126)



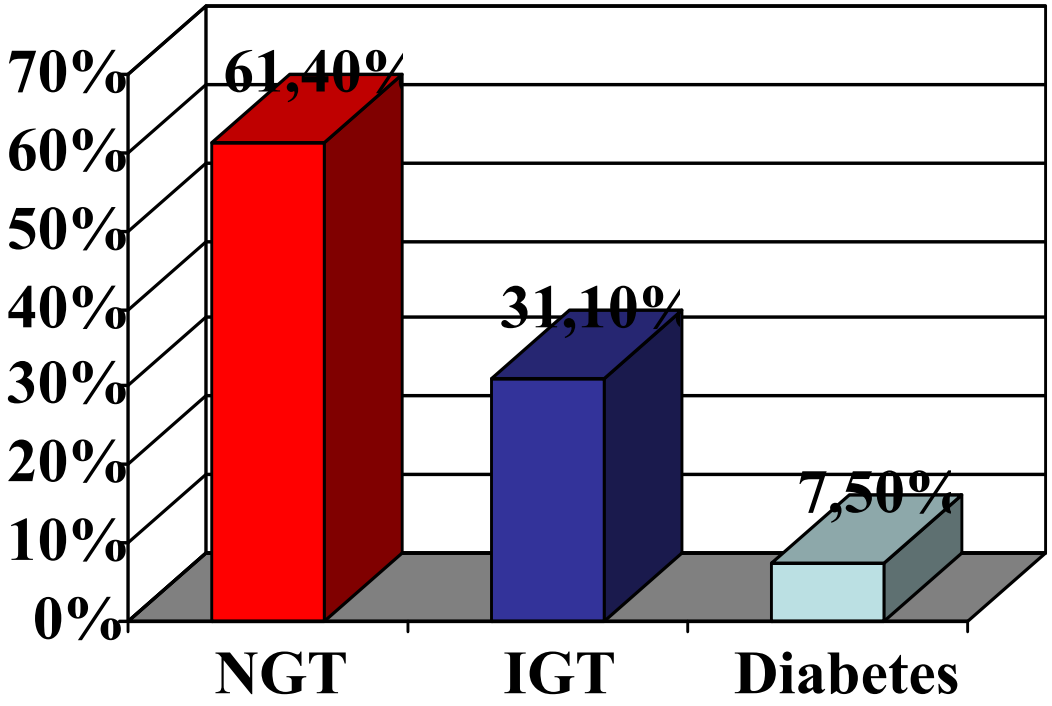
Clinical identification of the Metabolic Syndrome

- **Abdominal obesity (waist circumference:**
  - » **men > 102 cm**
  - » **women > 88 cm)**
- **Triglycerides (≥ 150 mg/dL)**
- **HDL-cholesterol (men < 40 mg/dL**
  - » **(women < 50 mg/dL)**
- **Blood pressure (≥139/≥85 mm Hg)**
- **Fasting glucose (≥110 mg/dL)**

JAMA, 2001, Third Report of the National Cholesterol Education Program (NCEP) Expert Panel - ATPIII

Prevalence of type 2 diabetes and impaired glucose tolerance (IGT) in 245 PCOS

(Legro et al. J Clin Endocrinol Metab, 1999, 84: 165-169)



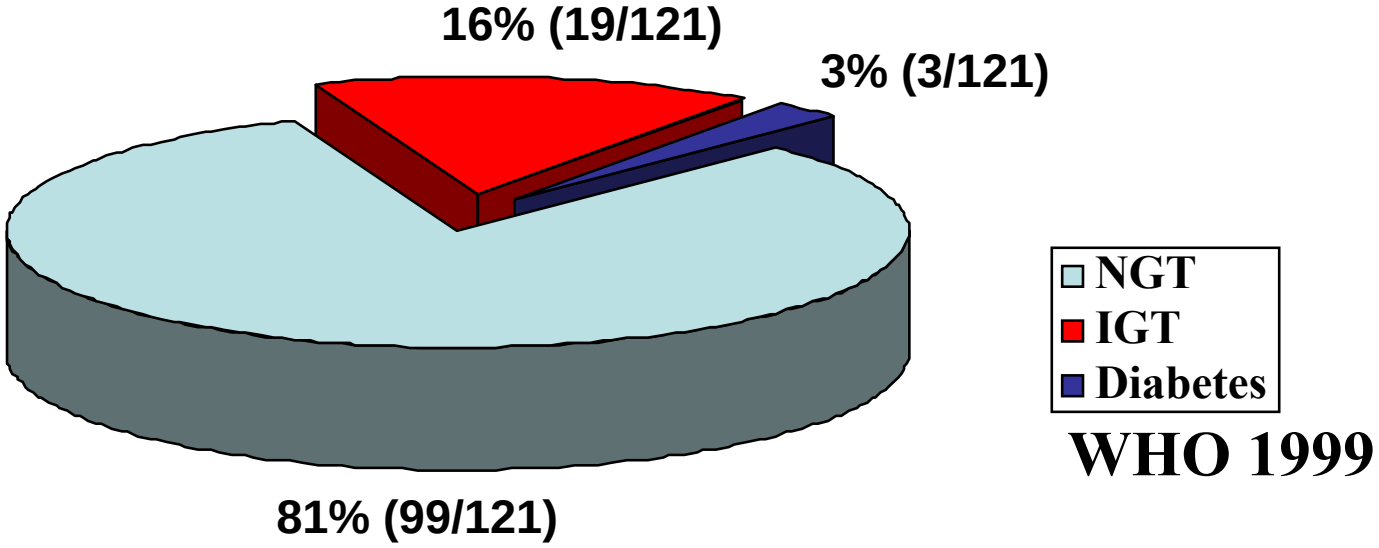
WHO 1985

(3.2% ADA 1997)

Impaired glucose tolerance and type 2 diabetes in women with the PCOS: predictive factors and hormonal, metabolic and clinical correlates

121 PCOS women

Age : 14-40 years



WHO 1999

PCOS and cardioscular risk factors and events

The existing data suggest that PCOS may adversely affect or accelerate the development of an adverse CR risk profile, and even of subclinical signs of atherosclerosis, but it does not appear to lower the age of clinical presentation to the premenopause.

Future studies to identify the risk of CV events in PCOS women will benefit from clear and extensive phenotyping of PCOS al baseline, from a prospective design, from larger sample sizes, and from longer follow-up.

Treatment of hyperandrogenism and related features in PCOS by antiandrogens

Antiandrogens:

- ciproterone acetate
- spironolactone
- flutamide
- finesteride
- GnRH analogues

Cosmetic dermatology

Treatment of hyperandrogenism and related features in PCOS by reducing hyperinsulinemia and improving insulin resistance

General: **Diet**

Exercise *(no studies)*

Drugs: ***- Favouring weight loss***

Sibutramine *(no studies)*

Orlistat *(no studies)*

- Inhibiting insulin secretion

Diazoxide

Somatostatin analogues

- Enhancing insulin sensitivity

Biguanides (metformin)

Thiazolidinediones

D-*chiro*-inositol

Antiandrogens *(controversial)*

A proposed "intregrated way" to treat PCOS women