



EUROPEAN SCHOOL OF INTERNAL MEDICINE



Polycystic Ovary Syndrome and Cardiometabolic Risk



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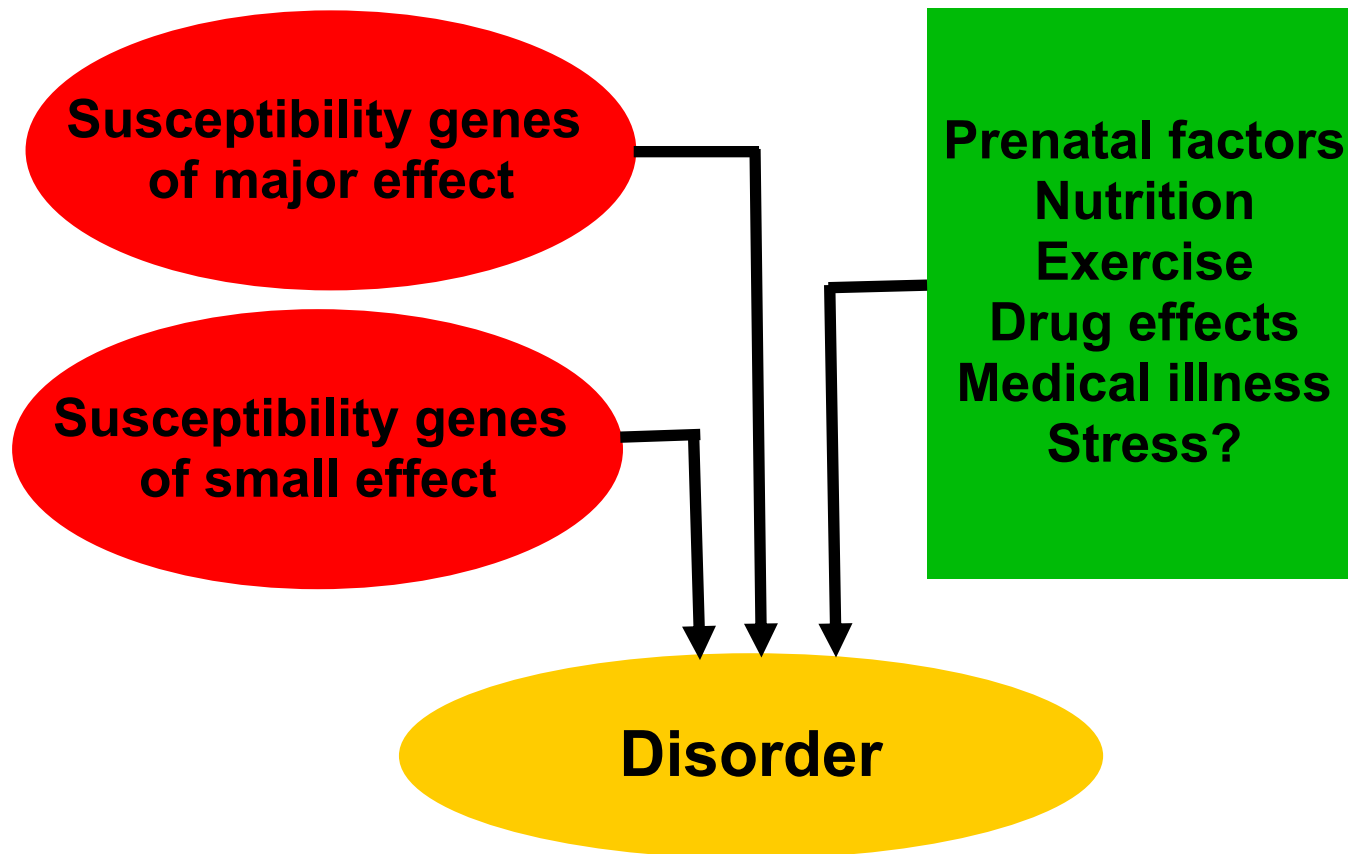
PCOS and Cardiometabolic Risk

Outline

- **PCOS: Definition(s) and significance**
- **PCOS and type 2 diabetes**
- **PCOS and risk of cardiovascular disease (CVD)**
- **PCOS as a chronic disorder**

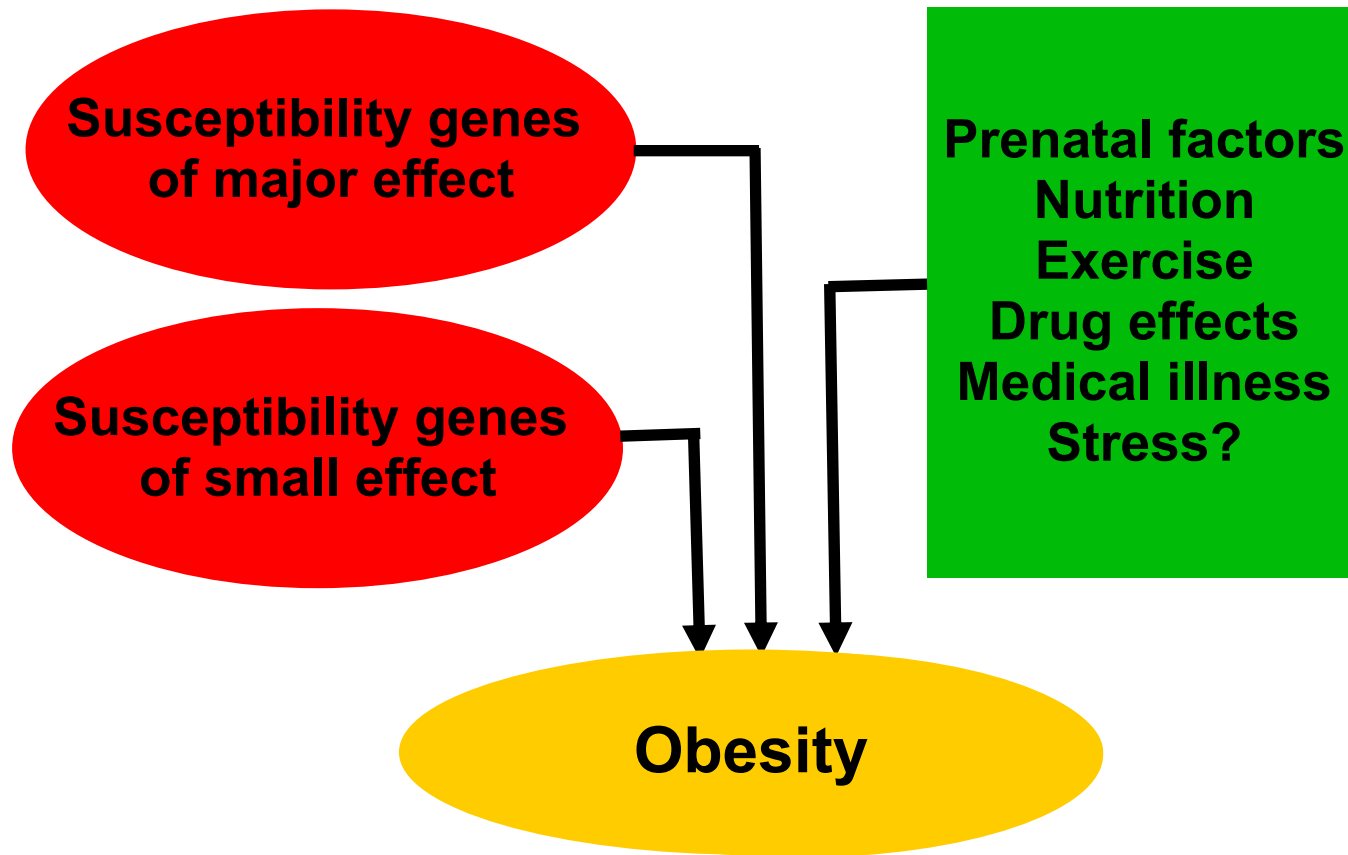
PCOS: definitions and significance

Conceptualizing a common and complex disorder



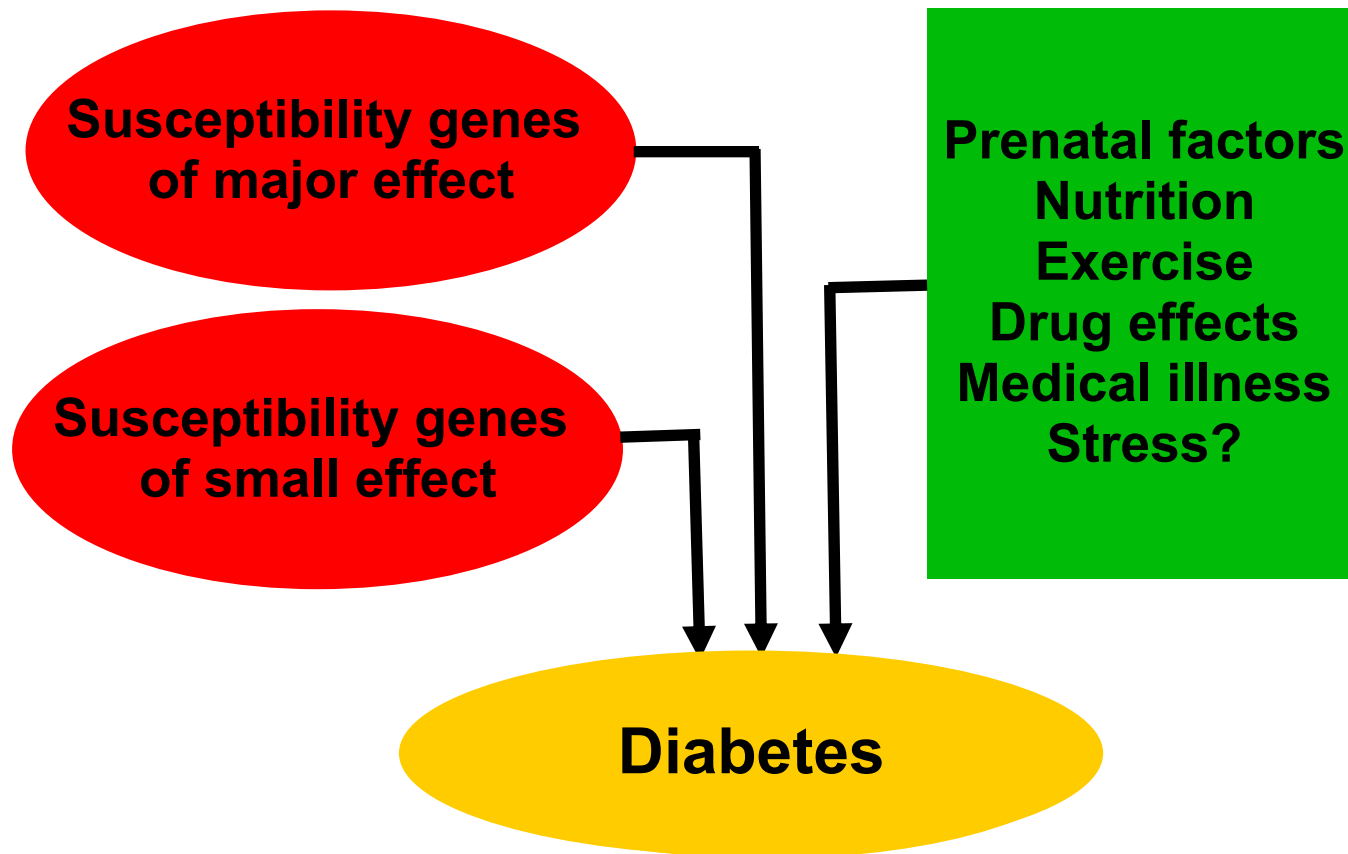
Definition of the phenotype

Conceptualizing a common and complex disorder



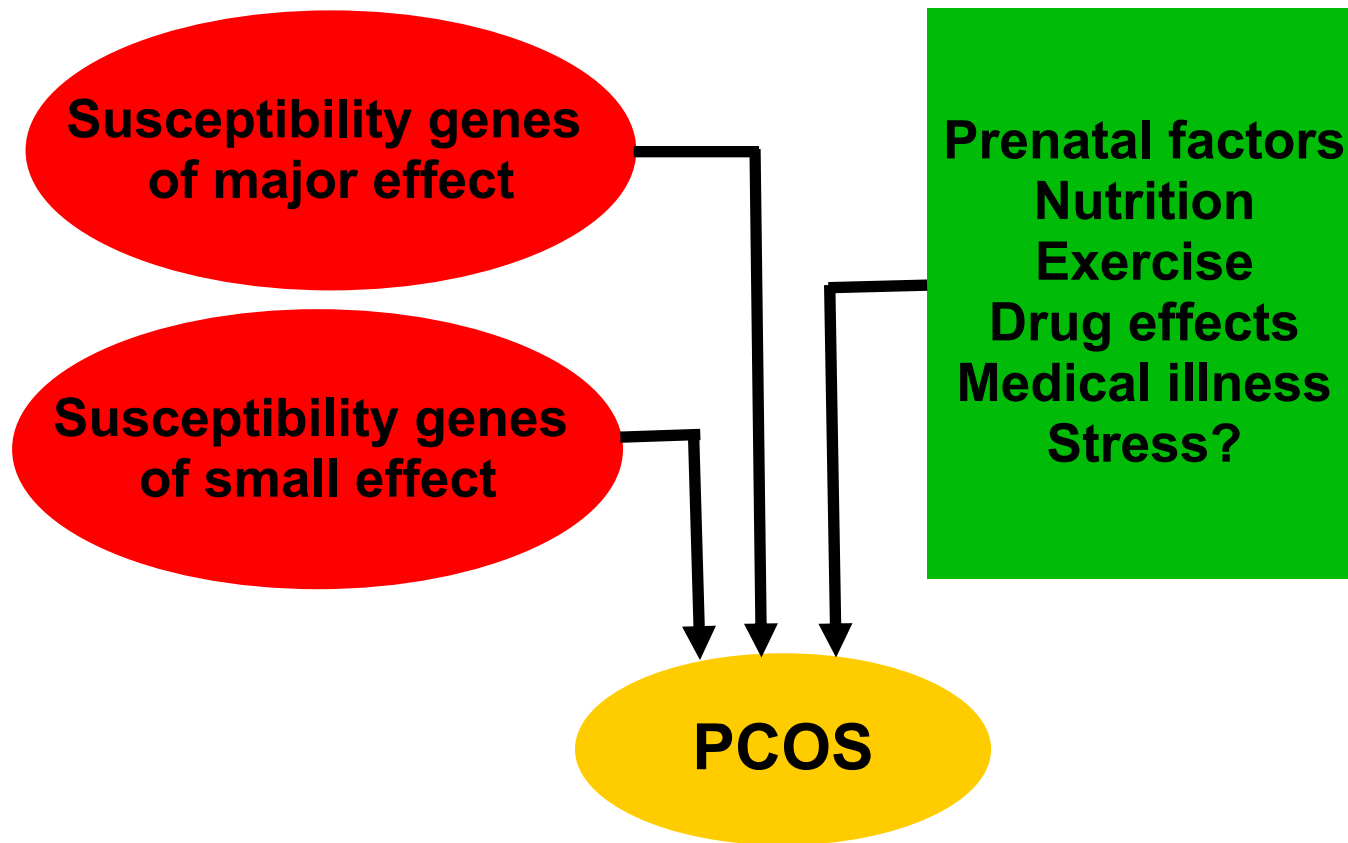
Phenotype: fat mass (BMI, waist..)

Conceptualizing a common and complex disorder



Phenotype: hyperglycemia (glucose)

Conceptualizing a common and complex disorder

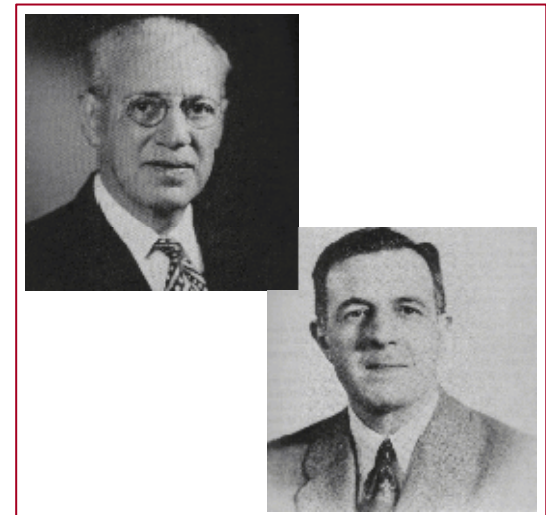


Syndrome phenotype???

PCOS – Original description*

- **Menstrual dysfunction/infertility**
- **Clinical hyperandrogenism**
- **Polycystic ovary morphology**
- **No hormonal / biochemical test**

*Stein&Leventhal, Am J Obstet Gynecol 1935



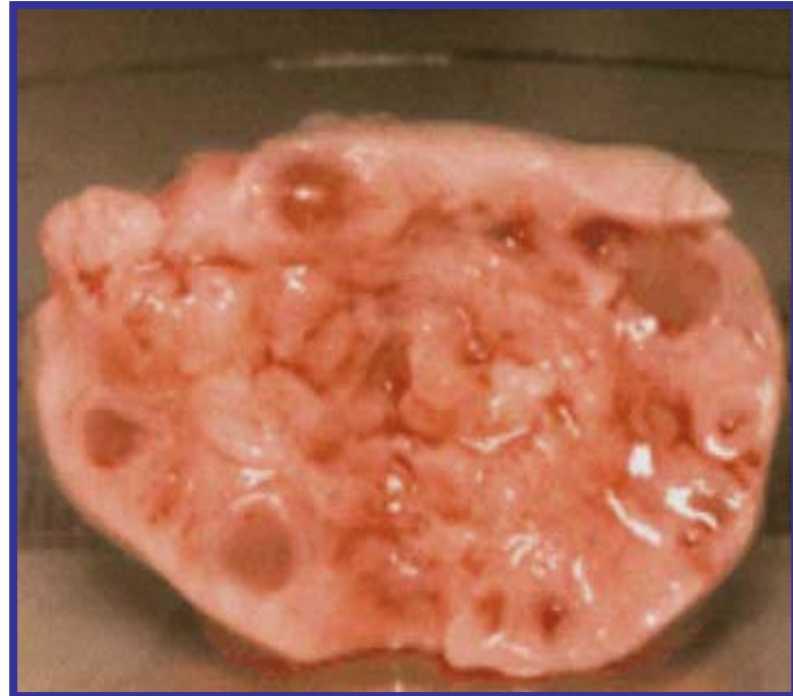
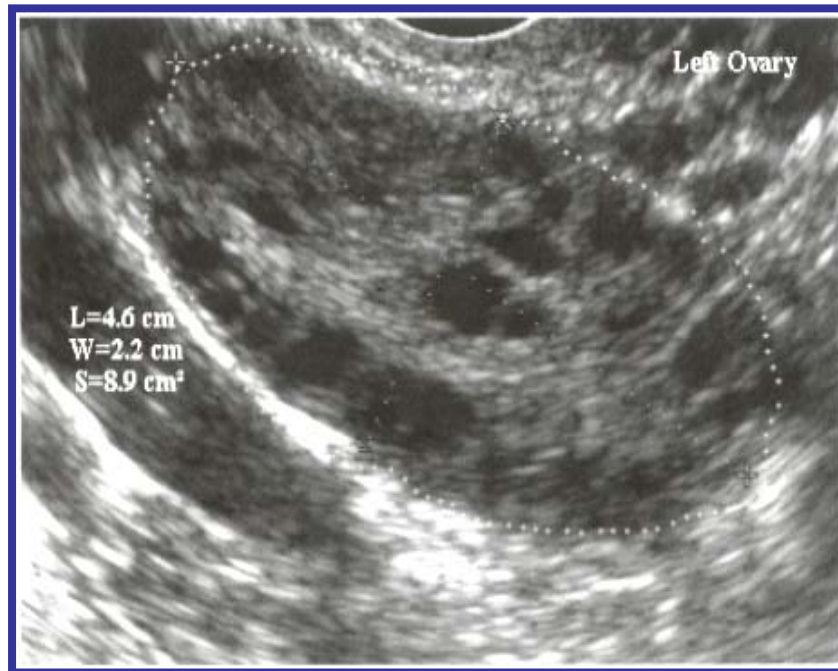
Menstrual dysfunction

Oligo-anovulation

- **Oligomenorrhea (Menses < 9/yr)**
- **Amenorrhea (no menses for 3 mos)**
- **Dysfunctional uterine bleeding**



Polycystic Ovary (PCO)



Kovacs, G. Polycystic Ovary Syndrome, Cambridge University Press, 2000

Hyperandrogenism

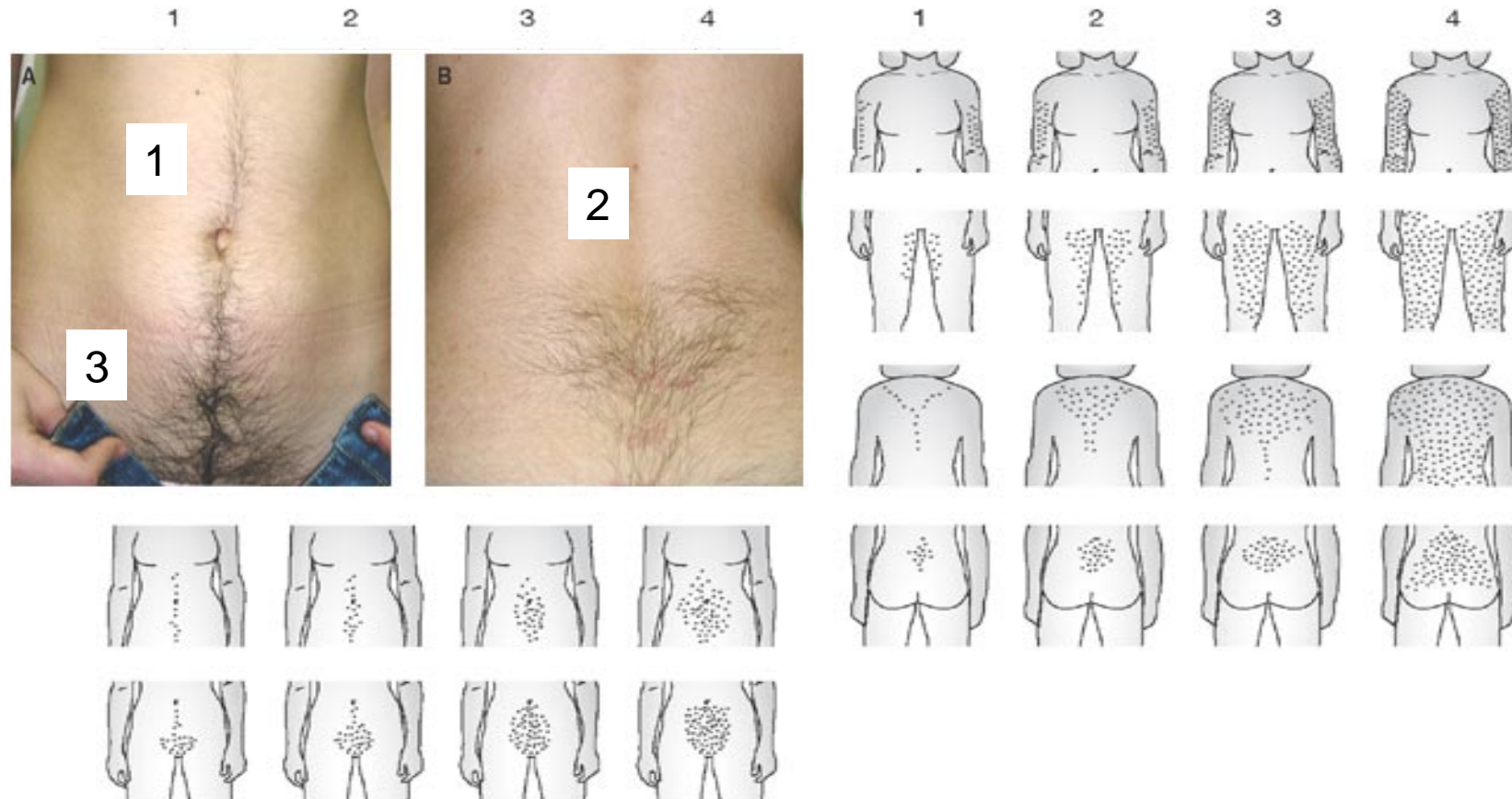
- **Hirsutism**
- **Acne**
- **Androgenic alopecia**
- **↑serum androgens**



Figure 1 Dr David Ferriman (1907–1990, photograph c. 1967) was a practicing endocrinologist with an interest in the disorders of the thyroid, adrenals and ovaries.

In 1961 he, along with Dr John Michael David Gallwey, a house officer at the time, published a study of 430 women attending a general medical outpatient clinic at the North Middlesex Hospital, North London, which became the basis for our current method for visually assessing the degree of facial and body terminal hair growth, and the presence of hirsutism in women (4) (photograph courtesy of Annabel Ferriman).

Ferriman-Gallwey Score



Hatch et al., 1981

Visually scoring hirsutism



Figure 3 Photographs depicting facial and body terminal hair growth scored according to the modified FG method.

All were taken on women who had not used laser or electrolysis for at least 3 months, not depilated or waxed for at least 4 weeks, not shaved or plucked for at least 5 days before the photograph. The photographs depict scores of 1 through 4 for the upper lip (A), chin (B), chest (C), arm (D), upper abdomen (E), lower abdomen (F), upper back (G), lower back (H) and thighs (I). The areas were photographed with a standard single-lens reflex camera (Nikon N50, Nikon Corp., Melville, NY, USA) equipped with a macro lens (Vivitar 50 or 100 mm Auto Focus Macro, Vivitar Corp., Newbury Park, Calif) and ring flash (Vivitar Macroflash 5000, Vivitar Corp.). For film, Kodacolor VR 200 ISO film (Eastman Kodak Co., Rochester, NY, USA) was used. Representative areas were selected. All photographs of hair were anonymized and all identifying information removed, meeting current Institutional Review Board for Human Use and Health Insurance Portability and Accountability Act of 1996 standards. Higher resolution versions of these images are available as Supplementary data.



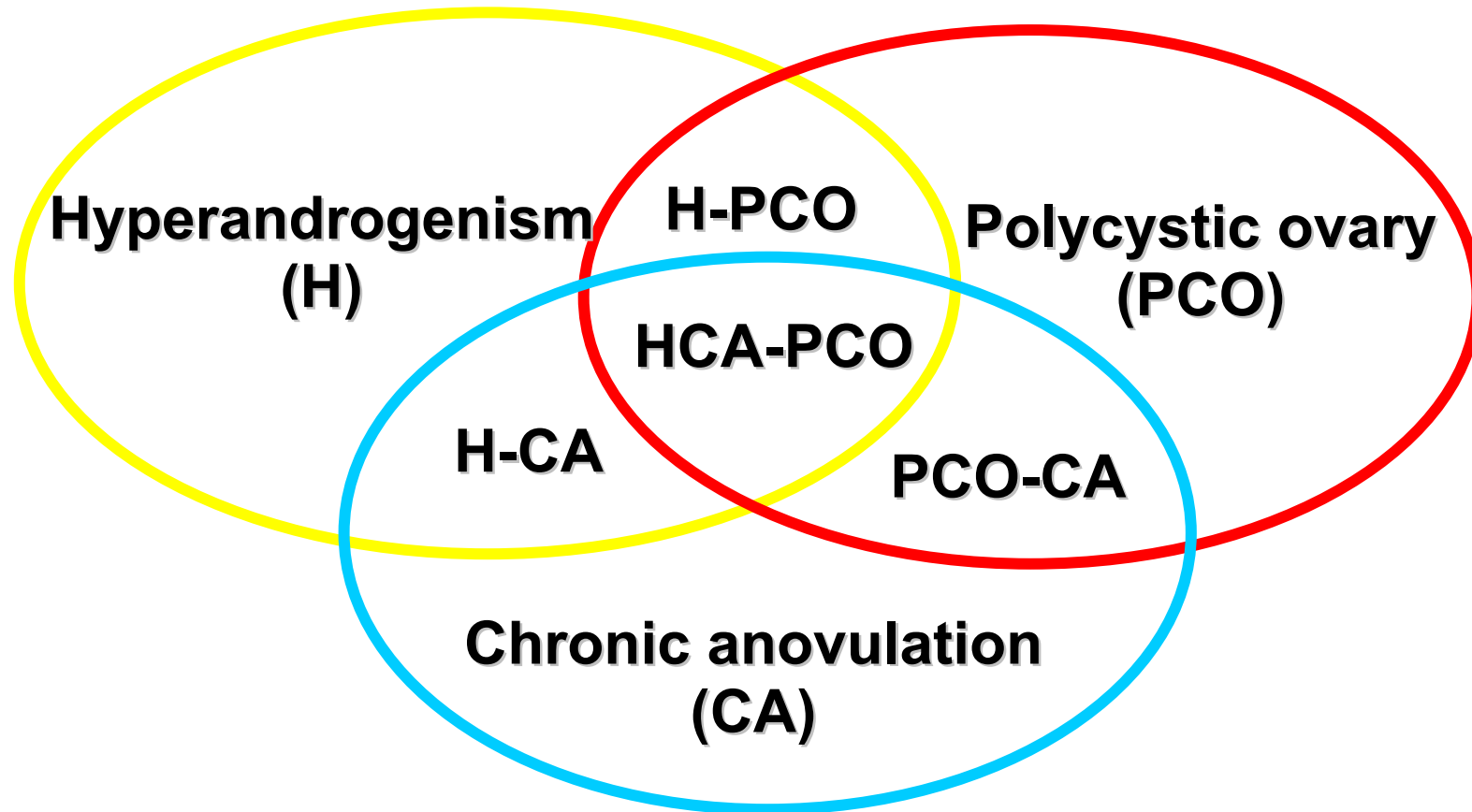
Figure 3 Continued

Revised PCOS Diagnostic Criteria (2003 Rotterdam)

1. **Oligo-anovulation**
 2. **Clinical hyperandrogenism and/or hyperandrogenemia**
 3. **Polycystic ovary (PCO)**
- (2 out of 3 necessary for the diagnosis)**
- **Exclusion of other associated disorders**

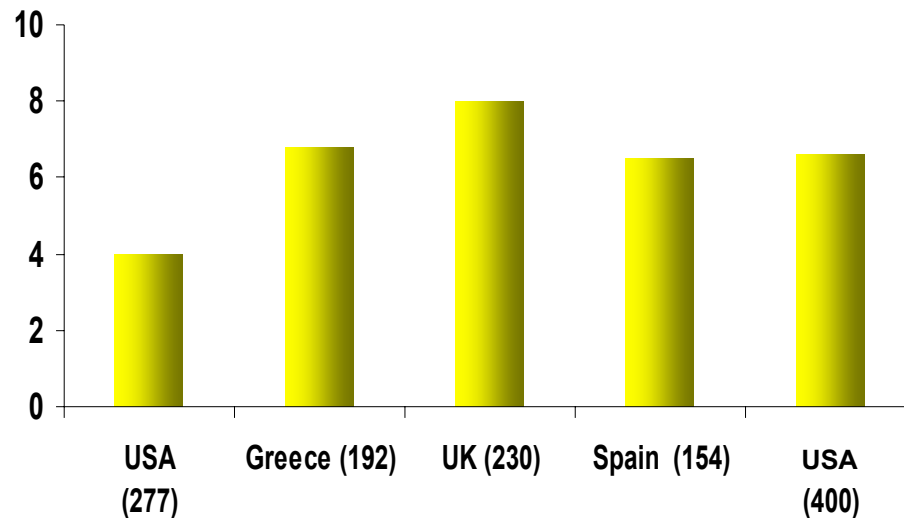
*Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group,
Hum Reprod & Fertil Steril 2004

PCOS - Phenotype



Changing phenotype through lifetime!

PCOS - prevalence



Azziz et al., J Clin Endocrinol Metab 1998

Diamanti-Kandarakis et al., J Clin Endocrinol Metab 1999

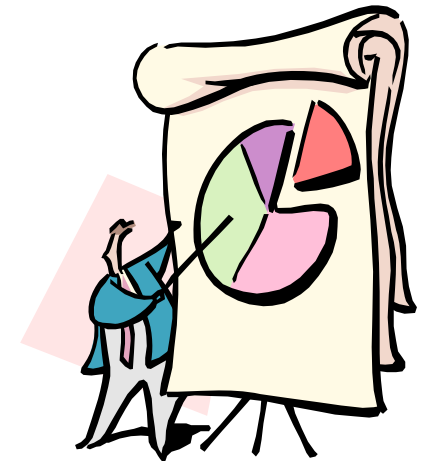
Michelmores et al., Clin Endocrinol 1999

Asuncion et al., J Clin Endocrinol Metab 2000

Azziz et al., J Clin Endocrinol Metab 2004

PCOS- Signs and symptoms

• Hirsutism	60-90%
• Oligomenorrhea	50-90%
• Infertility	55-75%
• PCO	50-75%
• Obesity	40-60%
• Amenorrhea	25-50%
• Acne	25%
• Dysfunctional uterus bleeding	30%
• Normal menstrual pattern	22%



PCOS – Why is it important?

- **Most common endocrine disorder of reproductive-aged women**
- **Most common cause of anovulatory infertility**
- **Public health impact**
 - **risk of diabetes**
 - **risk of cardiovascular disease**

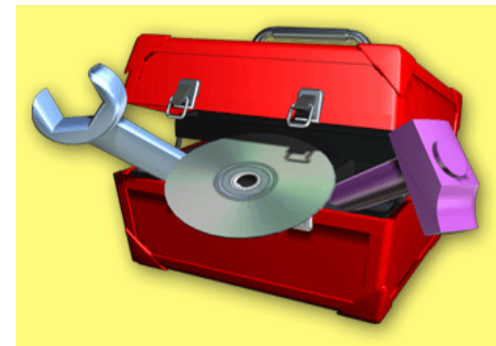
PCOS and type 2 diabetes

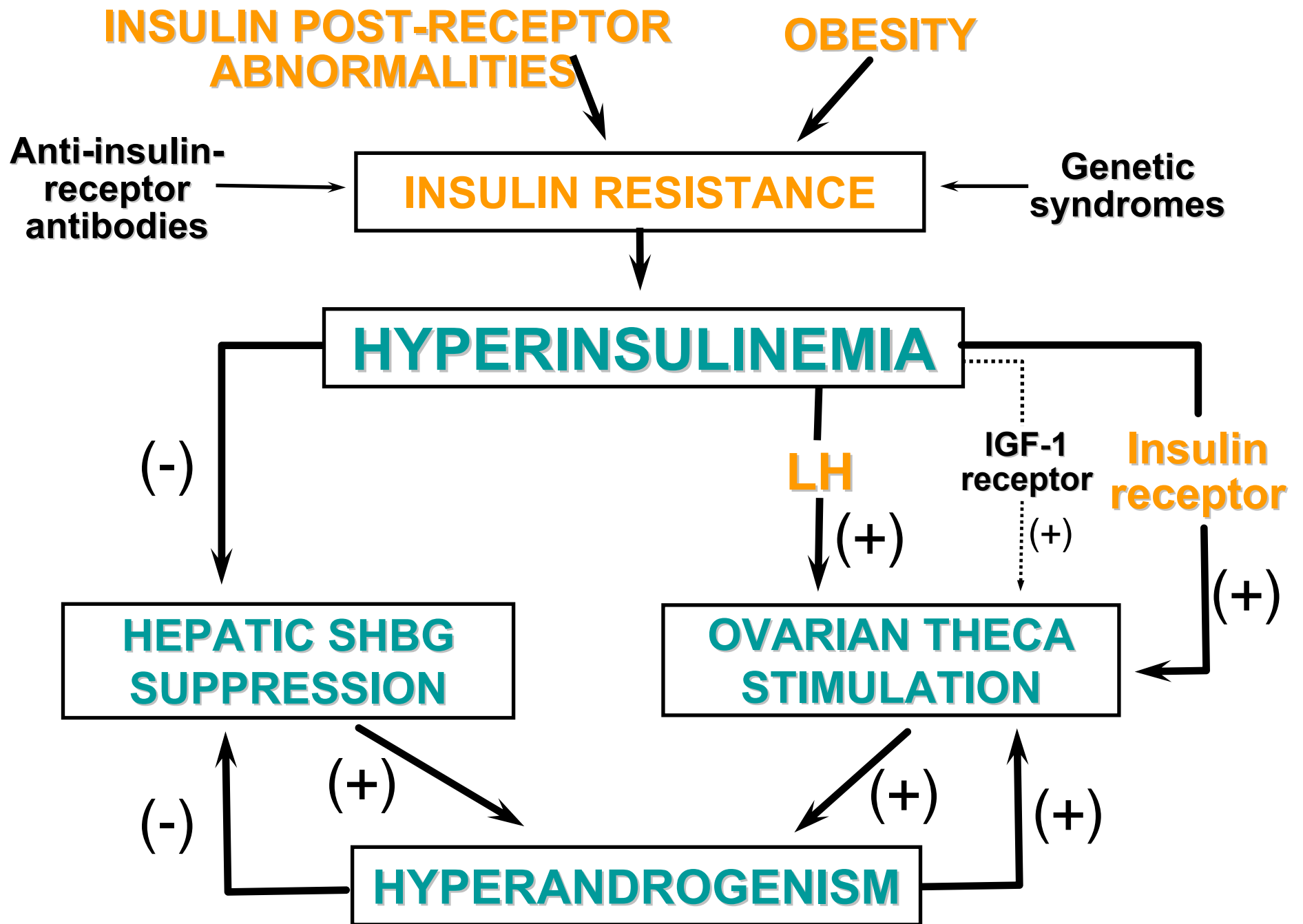
Insulin resistance and PCOS

- **Prevalence of insulin resistance**
 - **definition**
 - **assessment method**
 - **population characteristics**
- **Insulin resistance in up to 65% of PCOS women compared to age- and BMI-matched healthy controls***

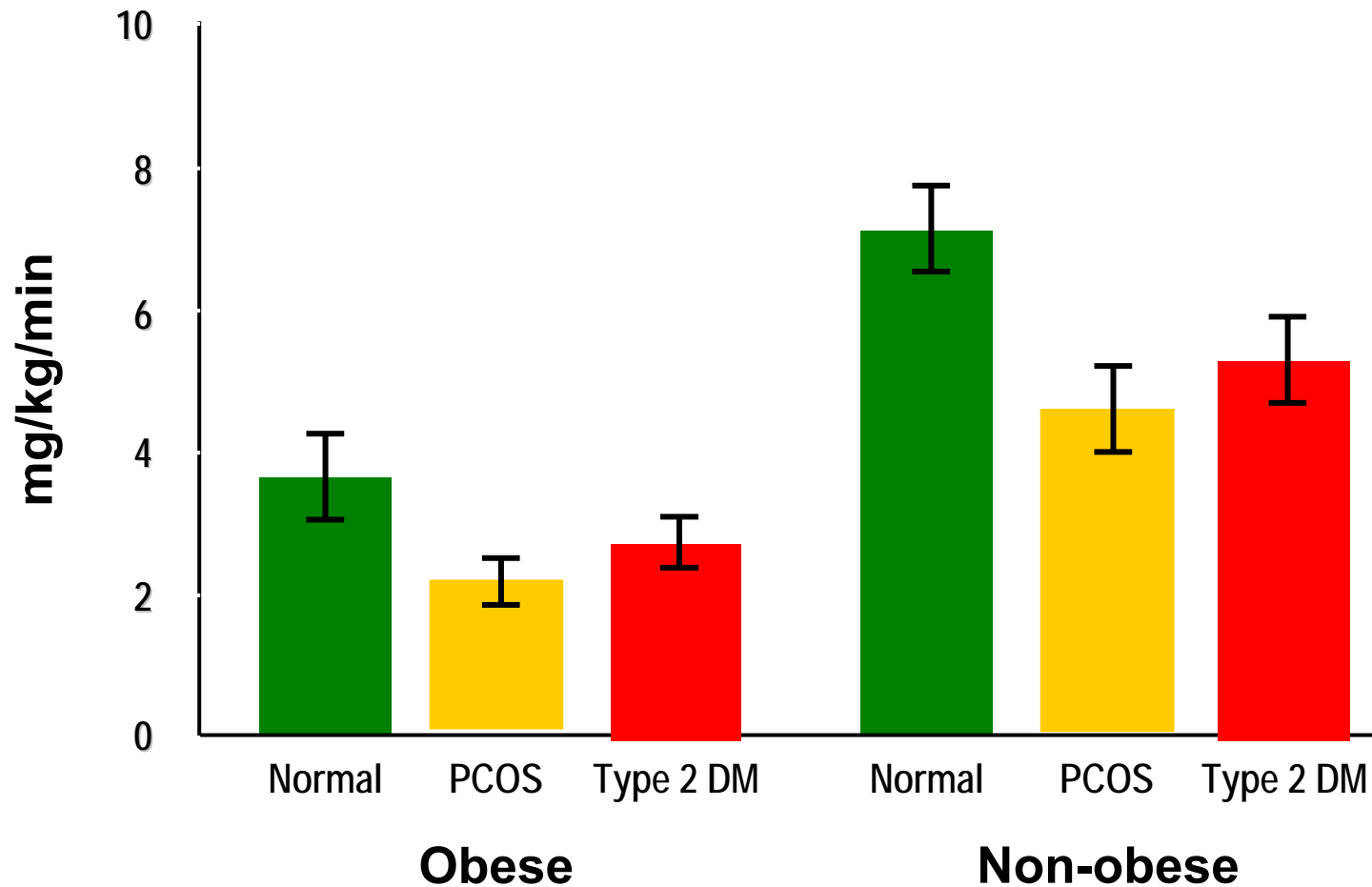
*Dunaif et al., Diabetes 1989

Legro et al., J Clin Endocrinol Metab 1998

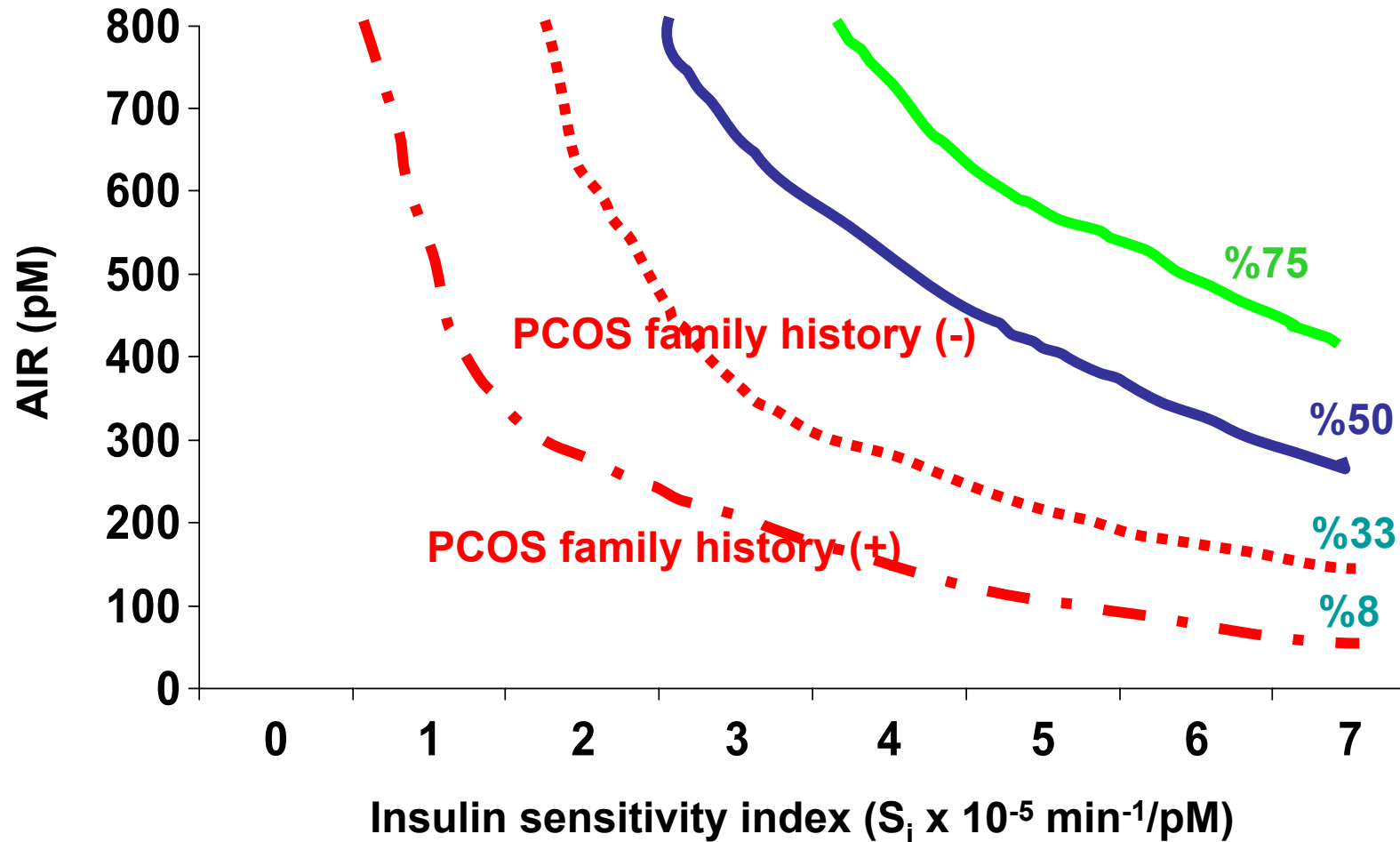




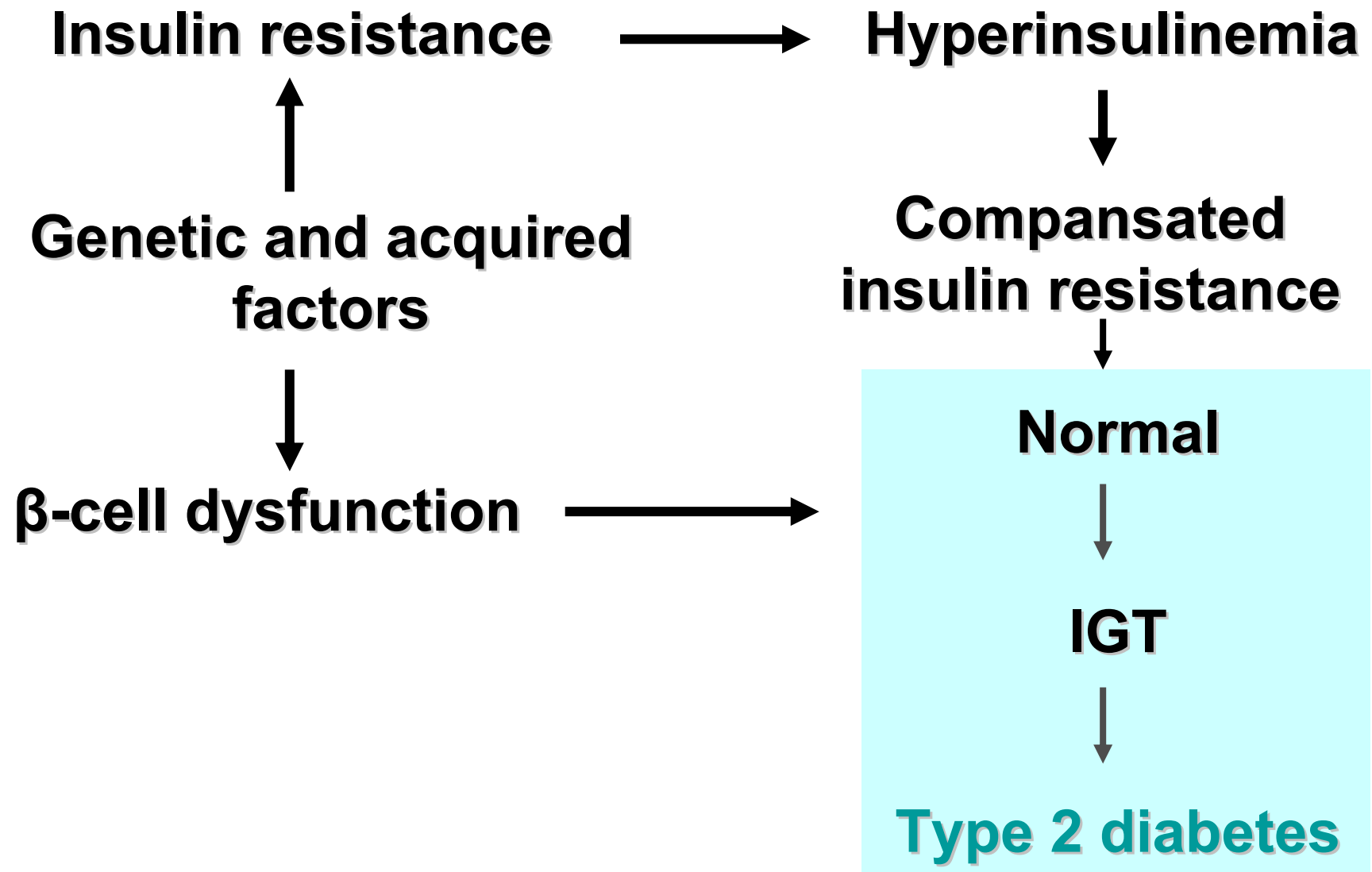
Insulin-mediated glucose disposal in PCOS



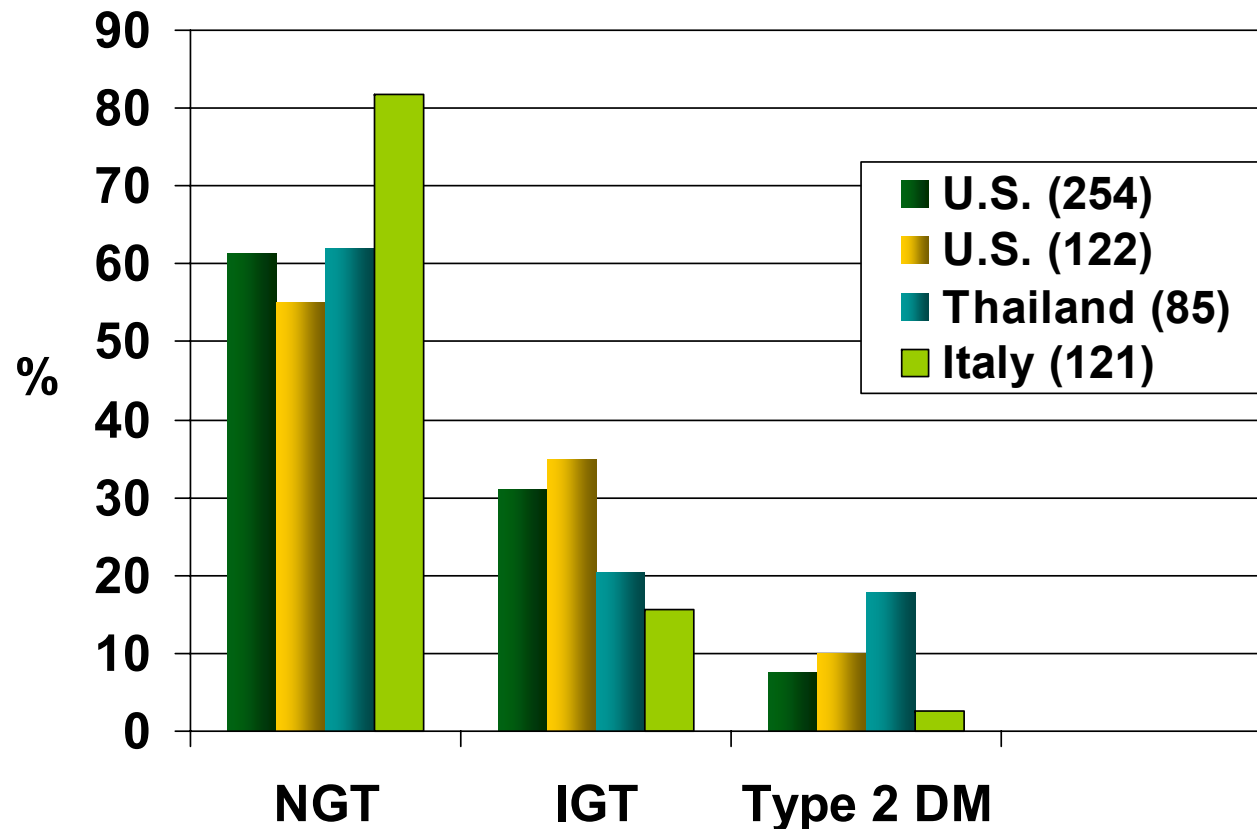
β -cell dysfunction in PCOS



PCOS – Type 2 Diabetes



Prevalence of glucose intolerance in PCOS



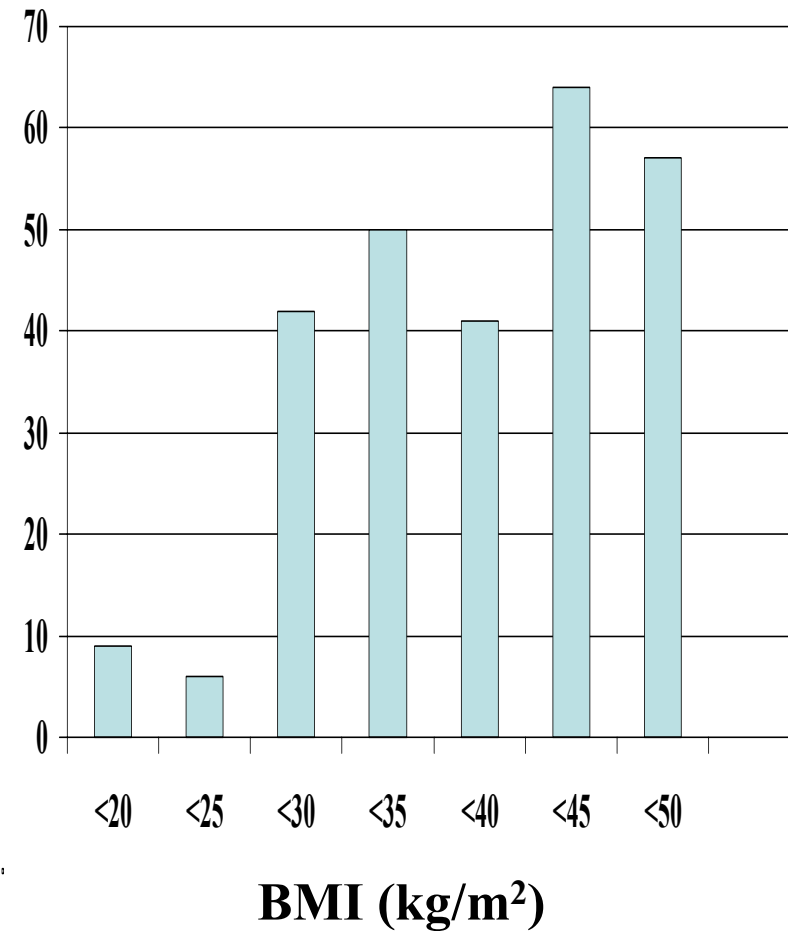
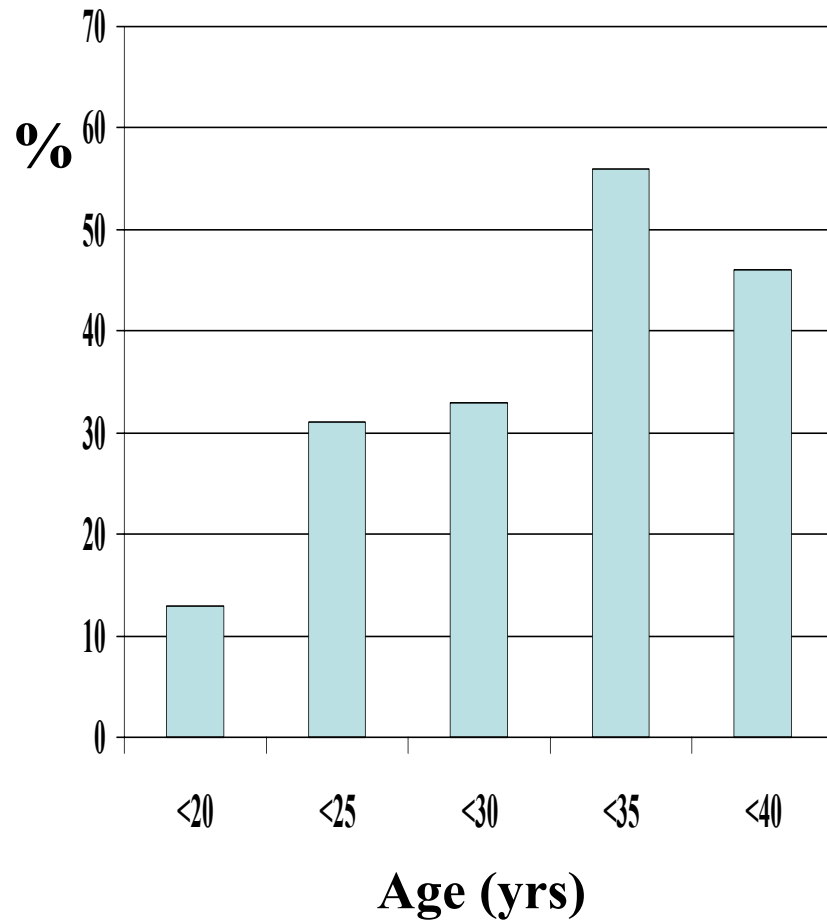
Legro et al., J Clin Endocrinol Metab 1999

Ehrmann et al., Diabetes Care 1999

Weerakiet et al., Int J Gynecol Obstet 2001

Gambineri et al., Diabetes 2004

Prevalence of glucose intolerance by age and BMI in PCOS



PCOS and glucose intolerance

Risk factors for diabetes in PCOS

- Age
- BMI
- Waist circumference / WHR
- History of diabetes in first-degree relatives
- PCOS diagnosis!

Risk factors for diabetes*

- Age \geq 45y
- BMI \geq 25 kg/m²
- Family history of diabetes
- Physical inactivity
- Race / ethnicity
- IFG/IGT
- History of GDM
- Hypertension
- HDL-C \leq 35 mg/dl and/or TG \geq 250 mg/dl
- **Polycystic ovary syndrome**
- History of vascular disease

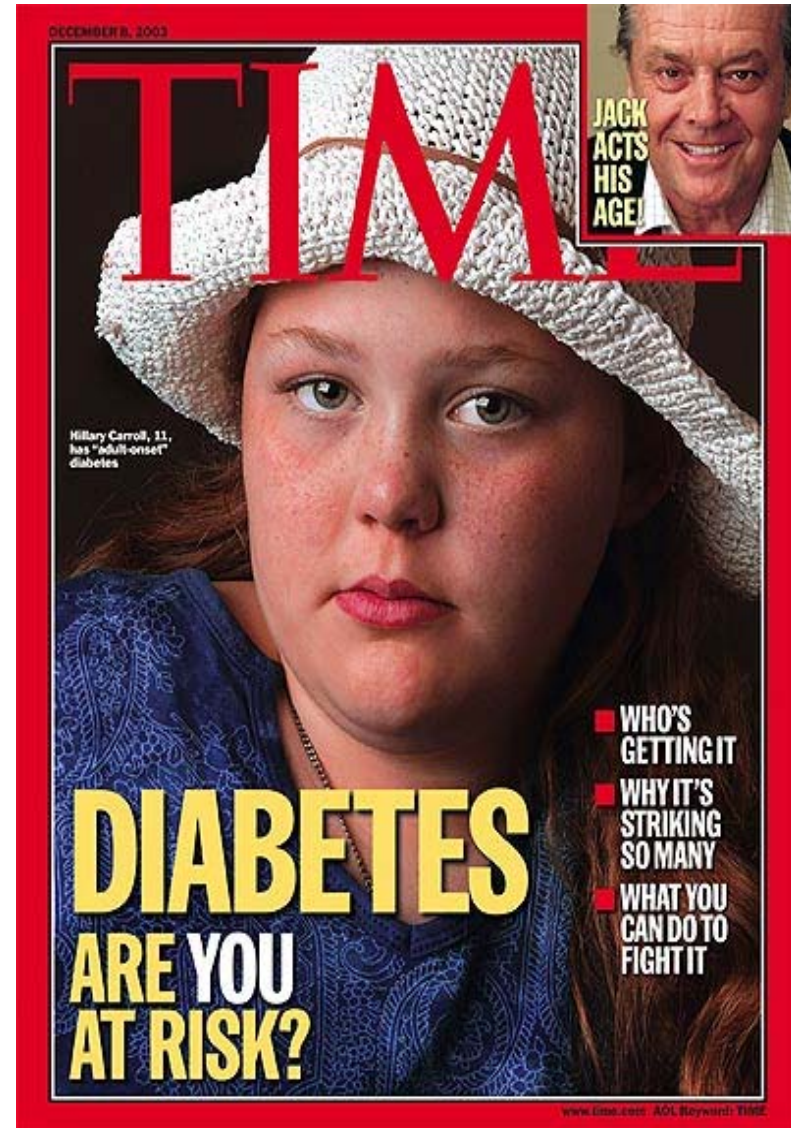
*ADA, 2010



PCOS and diabetes risk*

- Screening for glucose intolerance at diagnosis
- 2h OGTT
- 2h OGTT annually in NGT PCOS
- No test of insulin resistance are necessary to make the diagnosis of PCOS nor are they needed to select tx

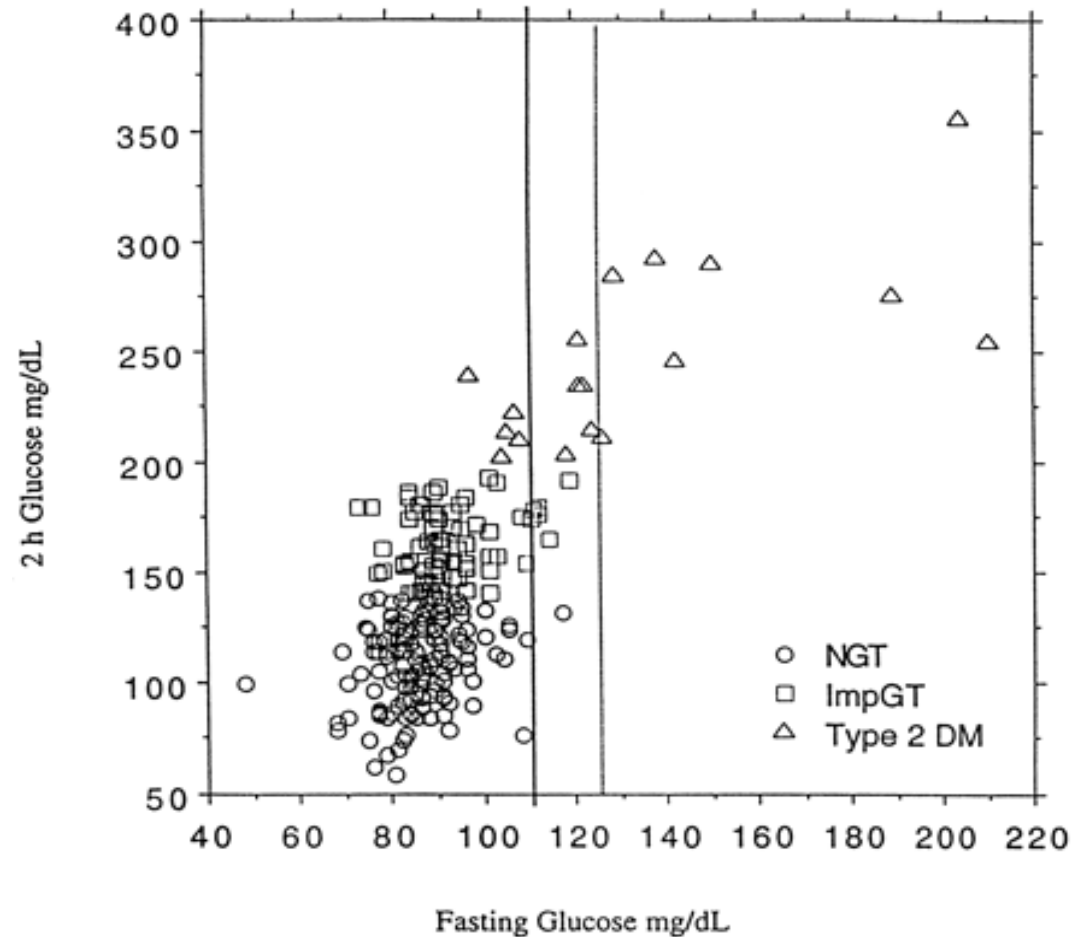
*Yildiz BO. Nature Rev Endocrinol 2008



FPG vs. 2h PG in PCOS*

Diagnosis of
glucose intolerance

OGTT – FPG alone
(OR, 8.28; 95% CI
4.66-15.34)



*Legro RS et al., J Clin Endocrinol Metab 1999
Legro RS, Obstet Gynecol Clin North Am. 2001

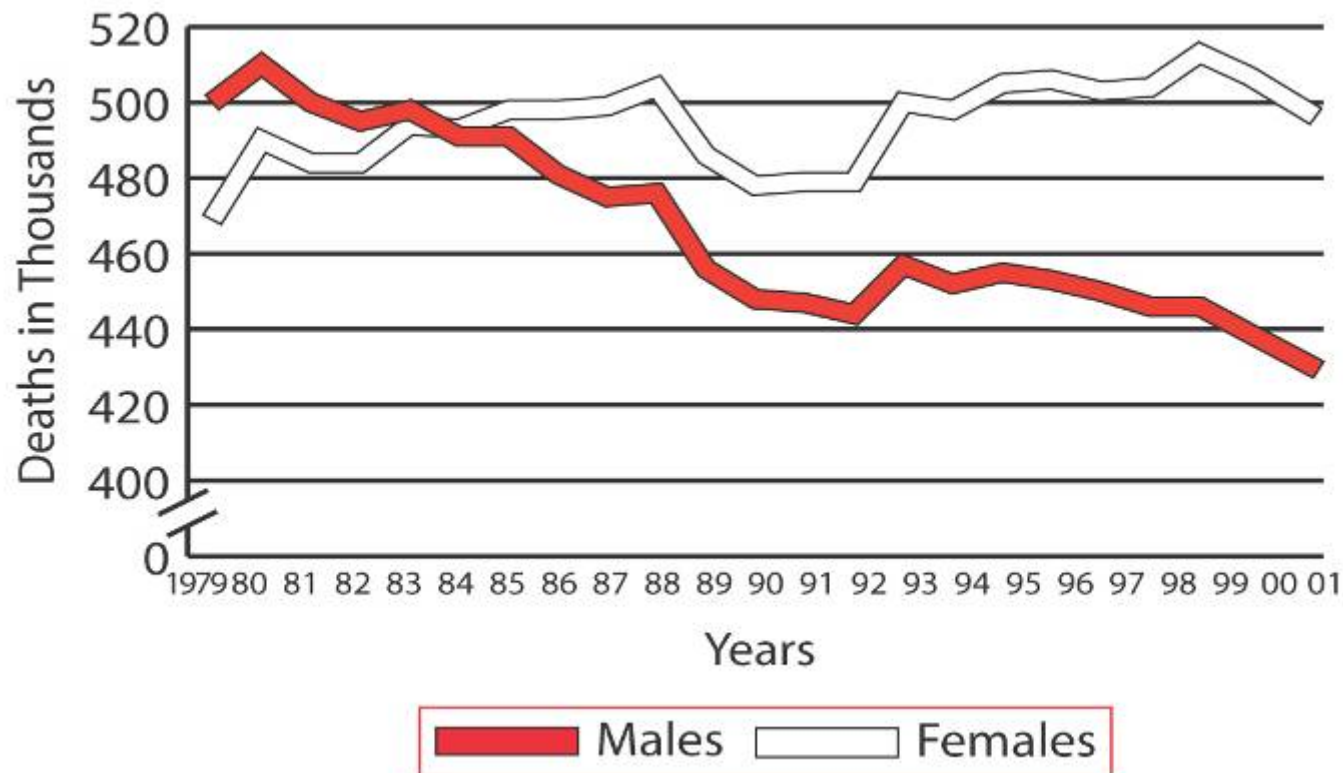
PCOS – A high risk condition for cardiovascular disease?



Remember to ski and snowboard responsibly. www.boerisasa.com

boeri
it's your head

Cardiovascular disease – A significant health problem in women too!

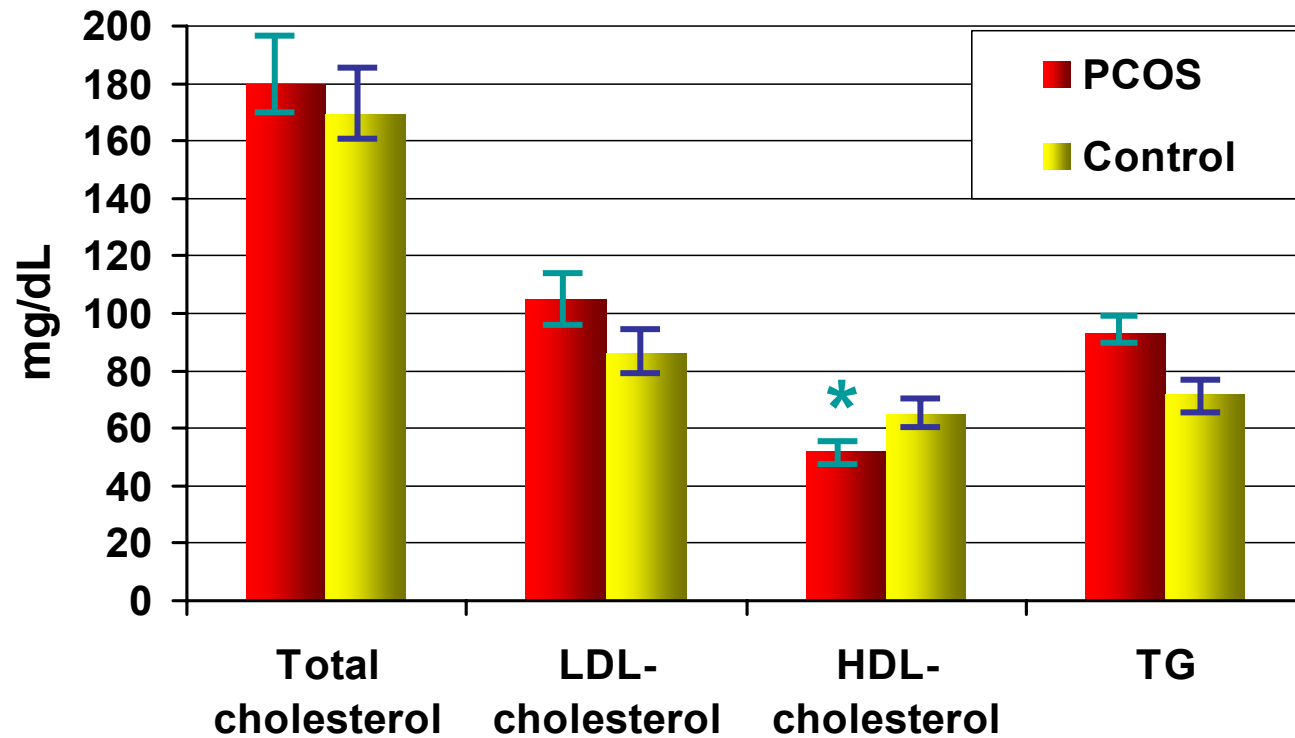


Source: CDC/NCHS

PCOS and CVD risk

- **CVD risk factors in PCOS**
 - oligomenorrhea
 - insulin resistance / glucose intolerance
 - hyperandrogenism
 - dyslipidemia
 - obesity
 - dysfibrinolysis
- **Increased prevalence of CVD?**

Lipid and Lipoprotein Alterations in PCOS



*p<0.001

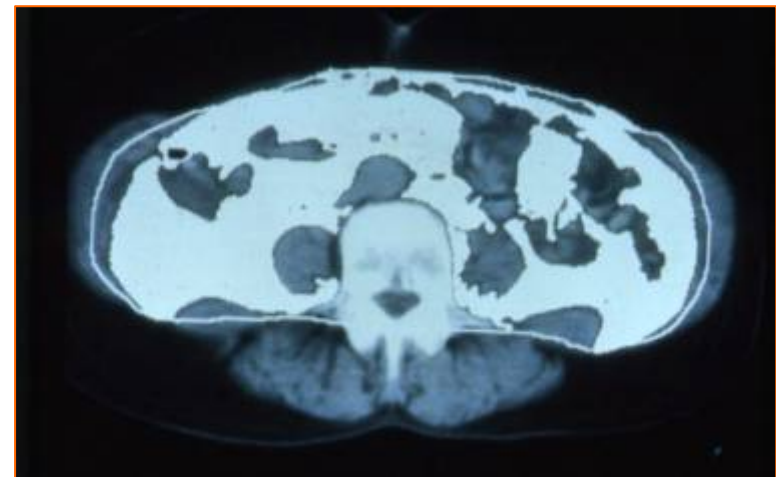
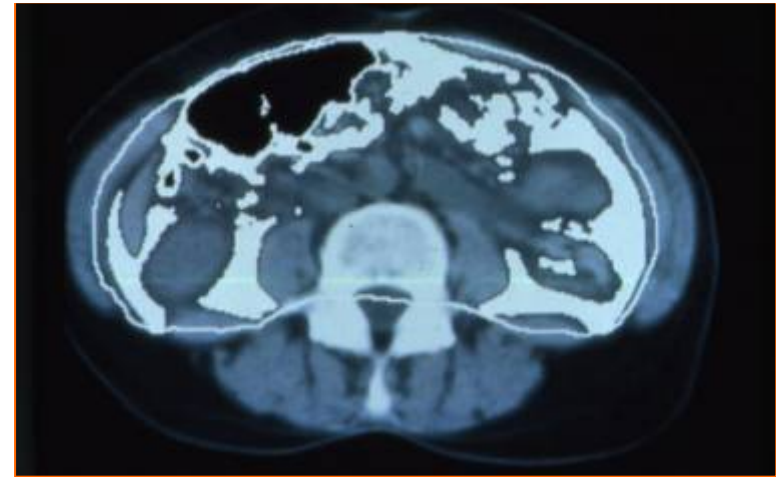
Yildiz et al., J Clin Endocrinol Metab. 2002

Prevalence of lipid abnormalities according to NCEP criteria

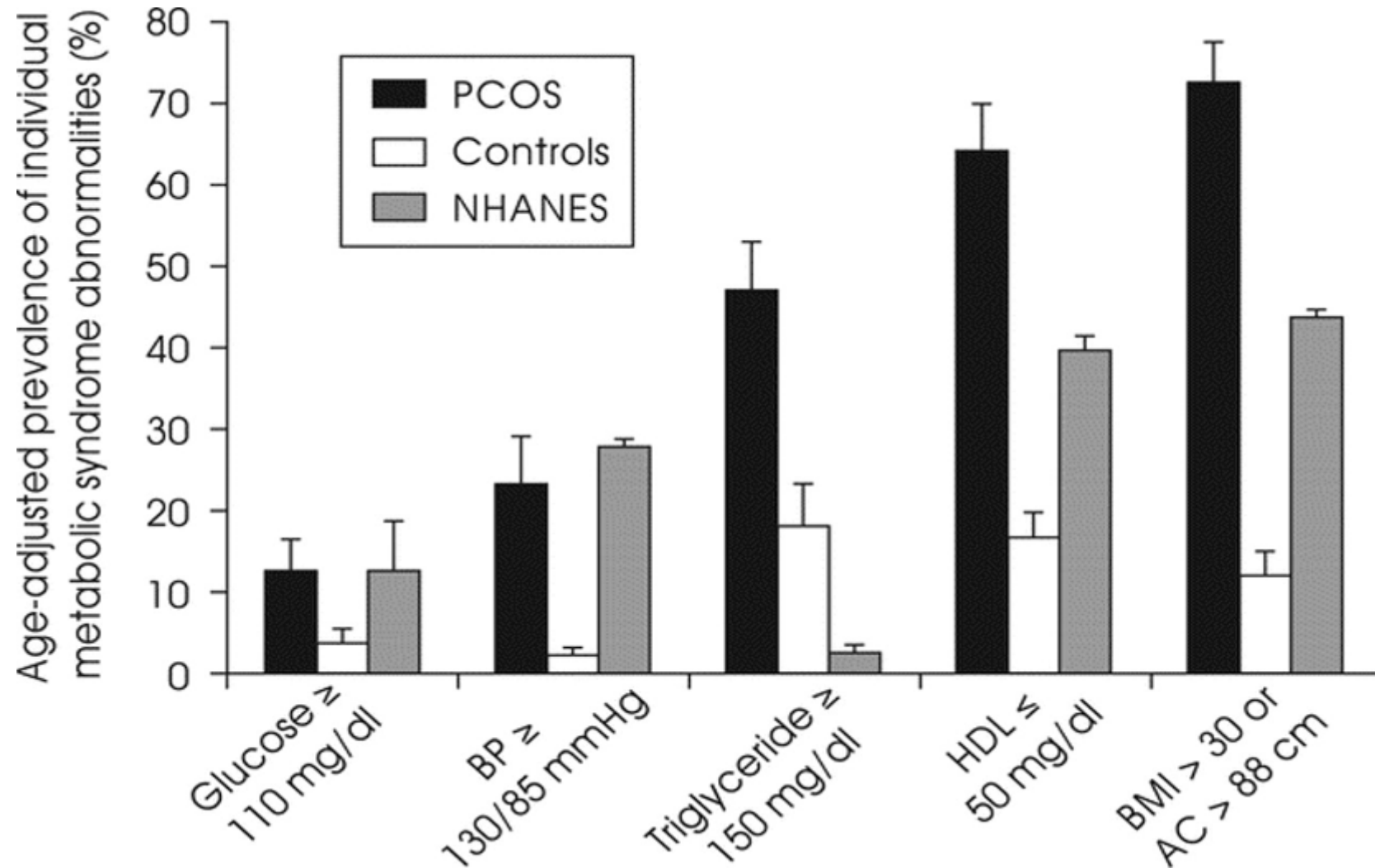
	All subjects (n=398)
% High Total cholesterol (mg/dl)	8.8%
% Low HDL-C (mg/dl)	14.6%
% High LDL-C (mg/dl)	8.5%
% High TG (mg/dl)	2.5%

Obesity in PCOS

- **About 50% of PCOS**
- **Android distribution**
- **Insulin resistance**
- **Sex hormone binding globulin**
- **Adverse lipid profile**
- **Risk of type 2 diabetes**

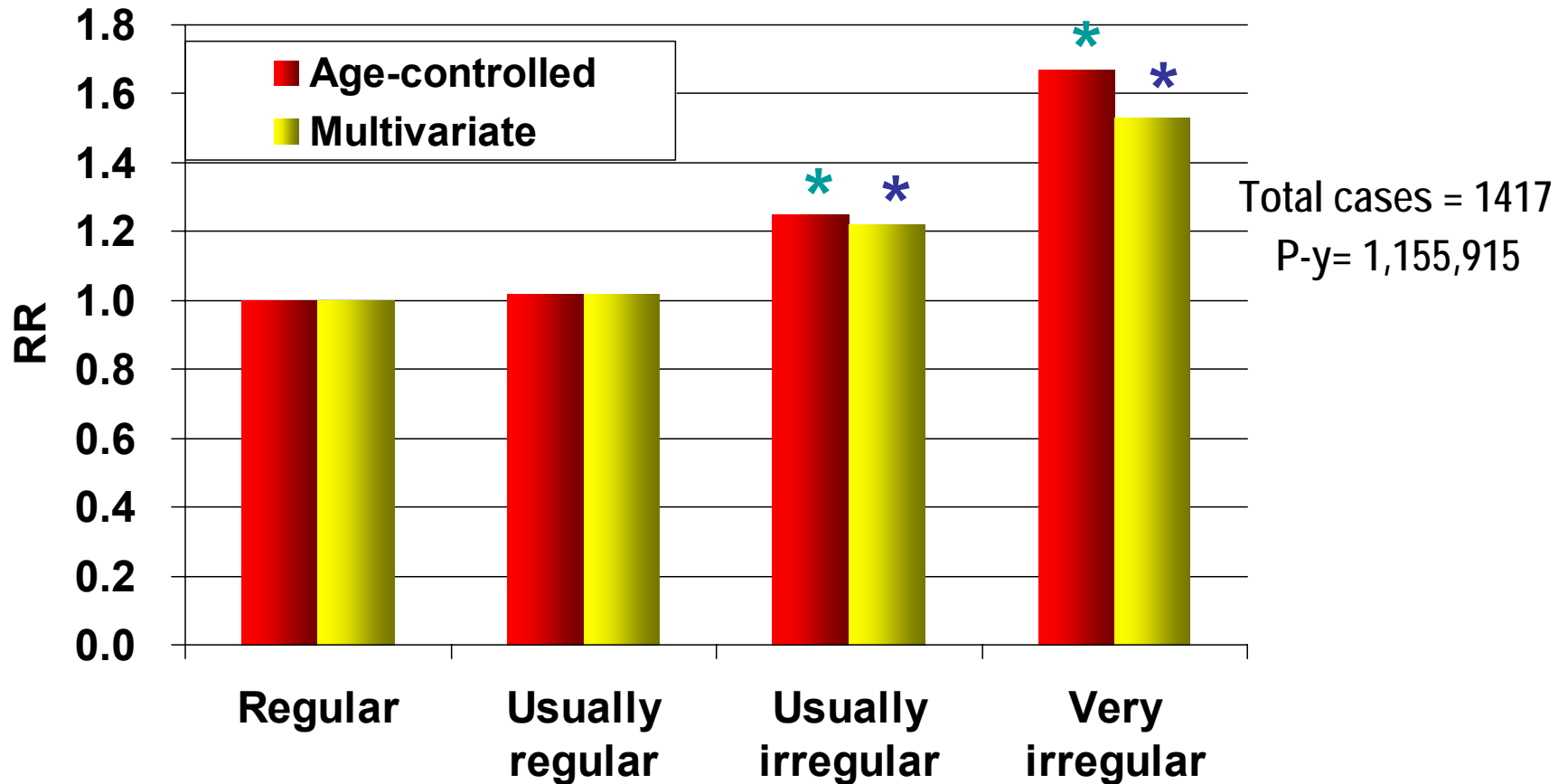


PCOS and metabolic syndrome*

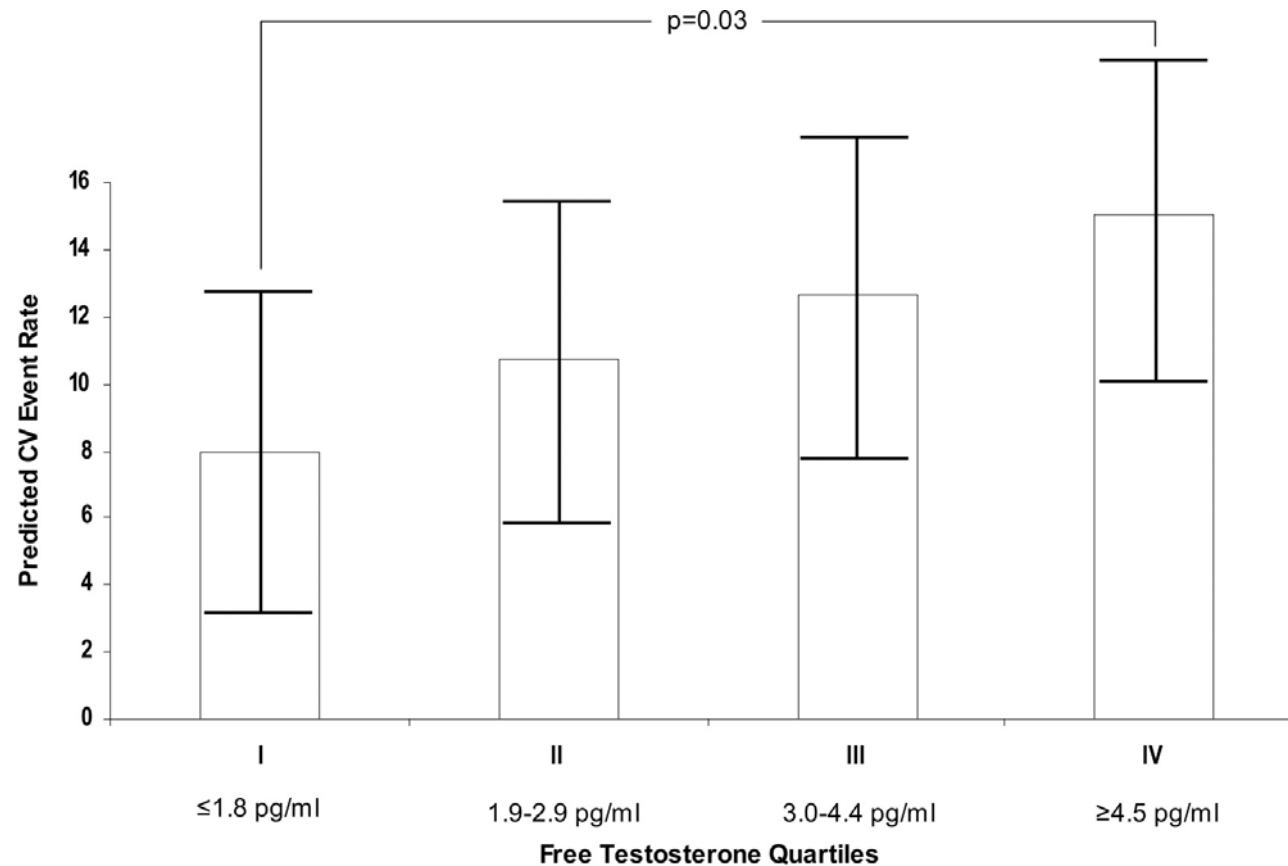


*Dokras et al., Obstet & Gynecol 2005

Menstrual irregularity and CVD risk (NHS)*



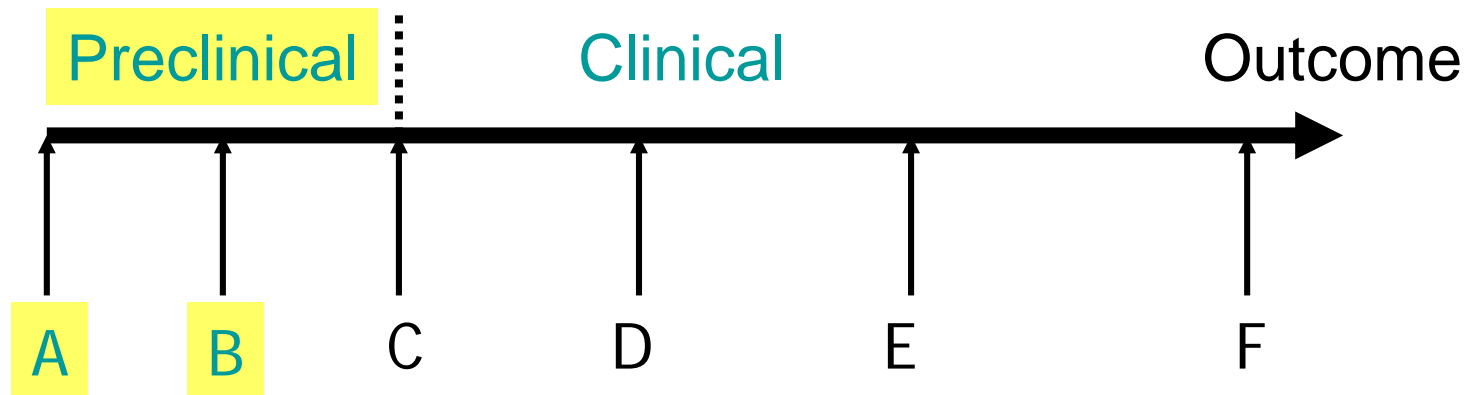
CV event rate and androgen excess in postmenopausal women (WISE study)



*Predicted CV Event Rate is based on a multivariable Cox model including HOMA, waist circumference, and a history of diabetes.

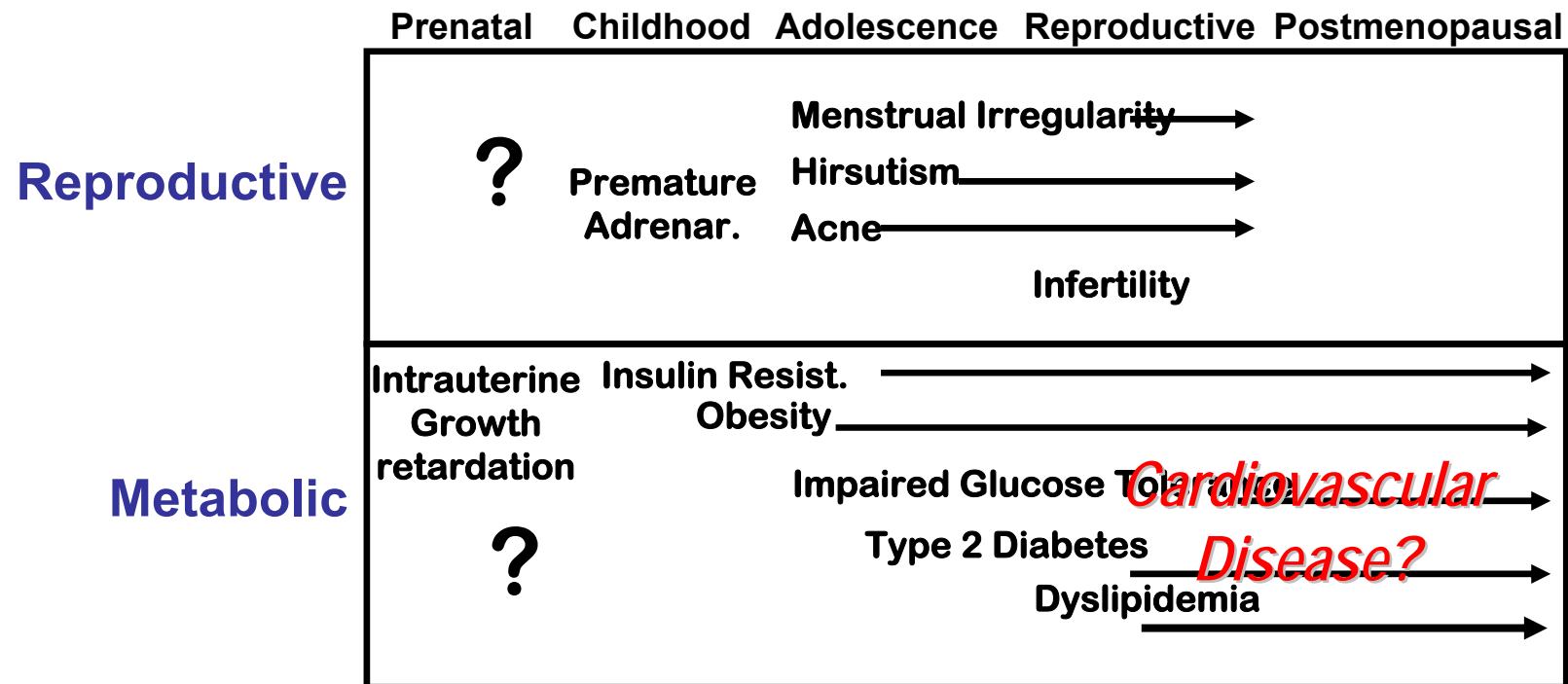
PCOS as a chronic disorder

Natural history of a disorder

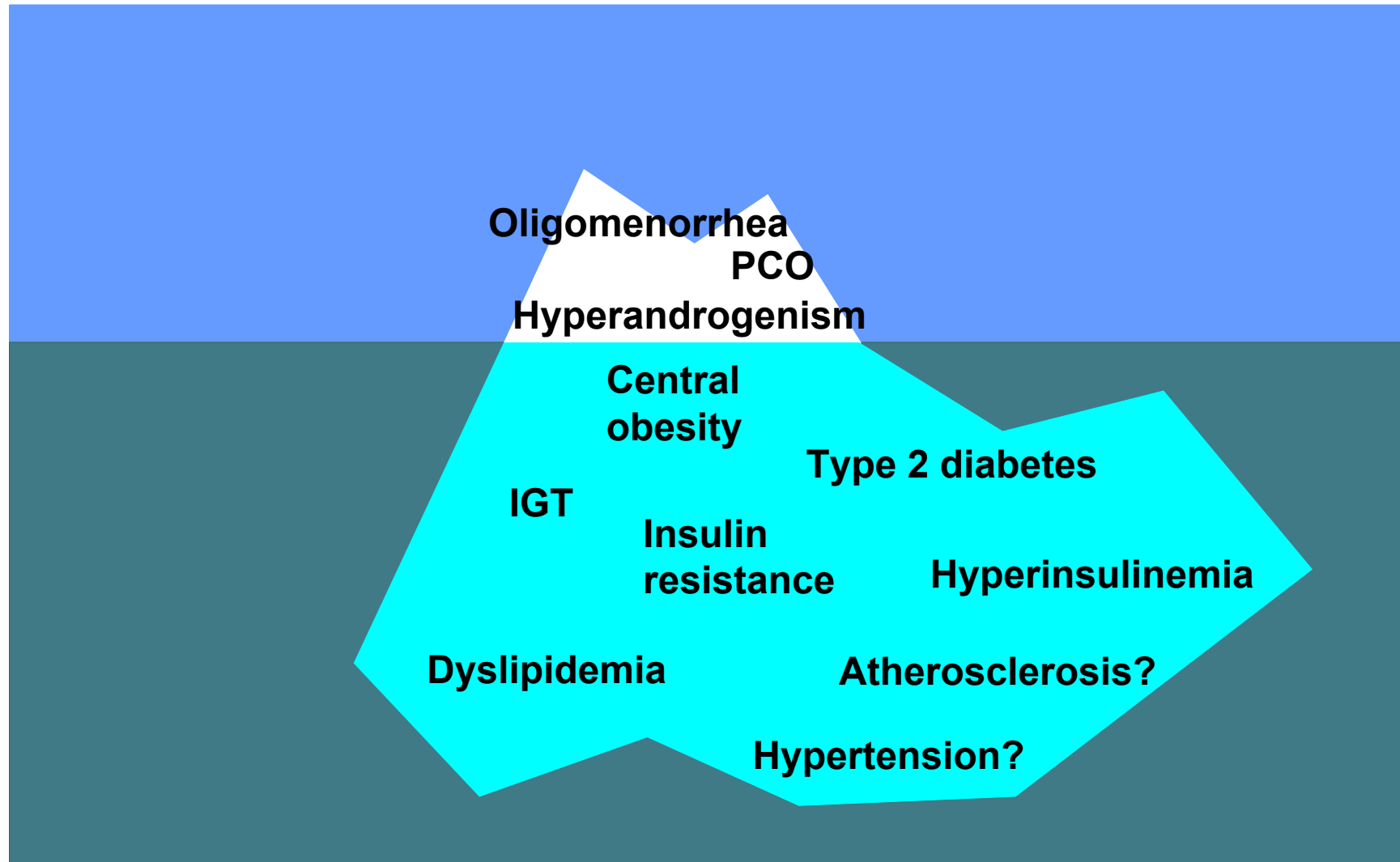


- A. Biologic onset of the condition
- B. Pathologic evidence detectable by screening
- C. Signs and symptoms
- D. Health care sought
- E. Diagnosis
- F. Treatment

PCOS across the lifespan



PCOS and cardiometabolic risk



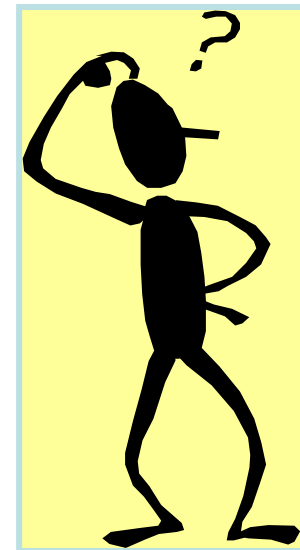
Metabolic syndrome diagnostic criteria in PCOS*

Risk factor	Cut-off
Abdominal obesity (waist circumference)	> 88 cm
TG	≥ 150 mg/dl
HDL-C	≤ 50 mg/dl
Blood pressure	≥ 130 / ≥ 85 mmHg
Fasting and 2h OGTT glucose	≥ 110 mg/dl and/or 2h glucose ≥ 140 mg/dl

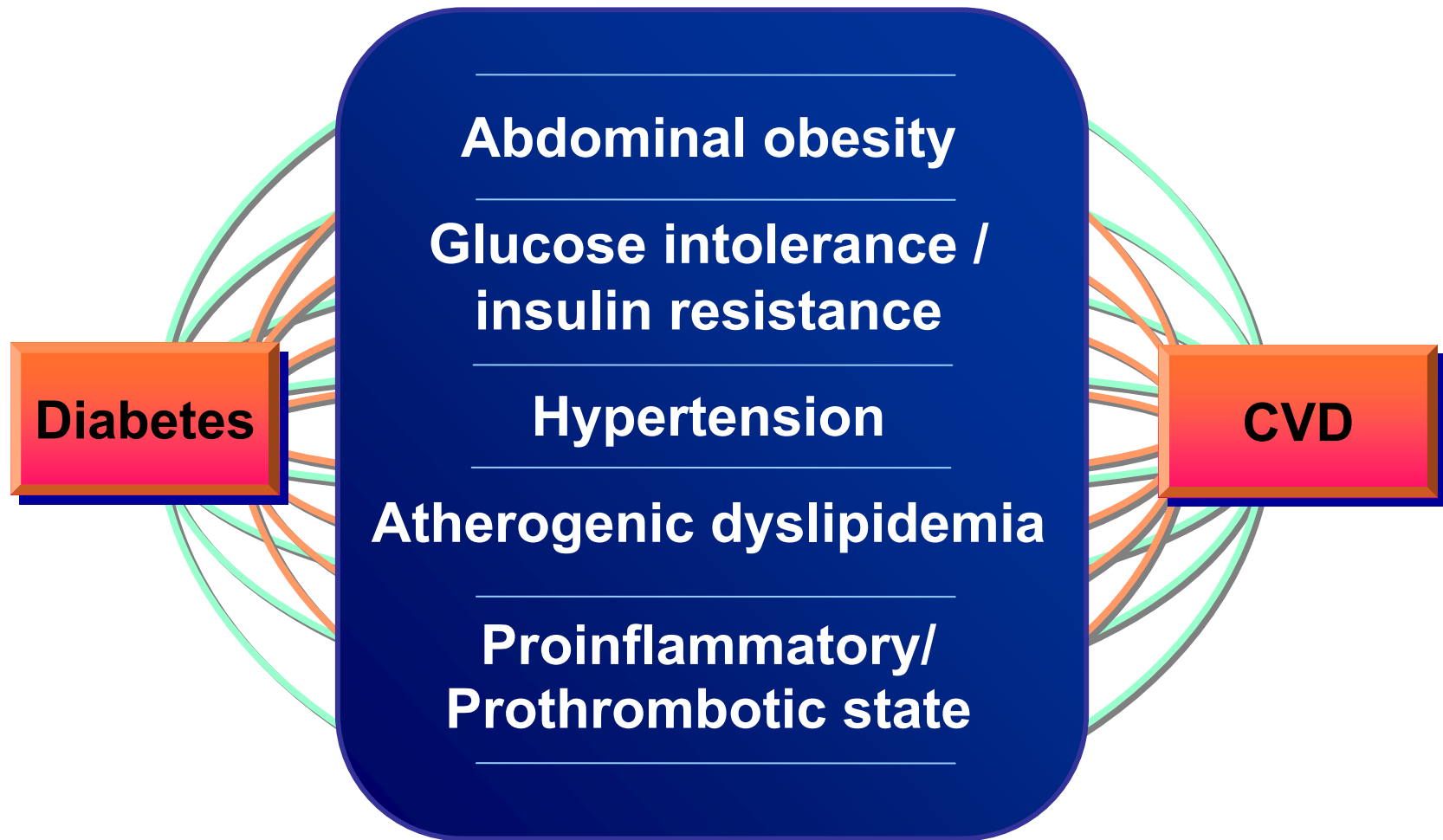
*3 out of 5 sufficient for the diagnosis

Metabolic syndrome - definitions

- **WHO**
- **EGIR**
- **NCEP-ATP III**
- **IDF**
- **Others**

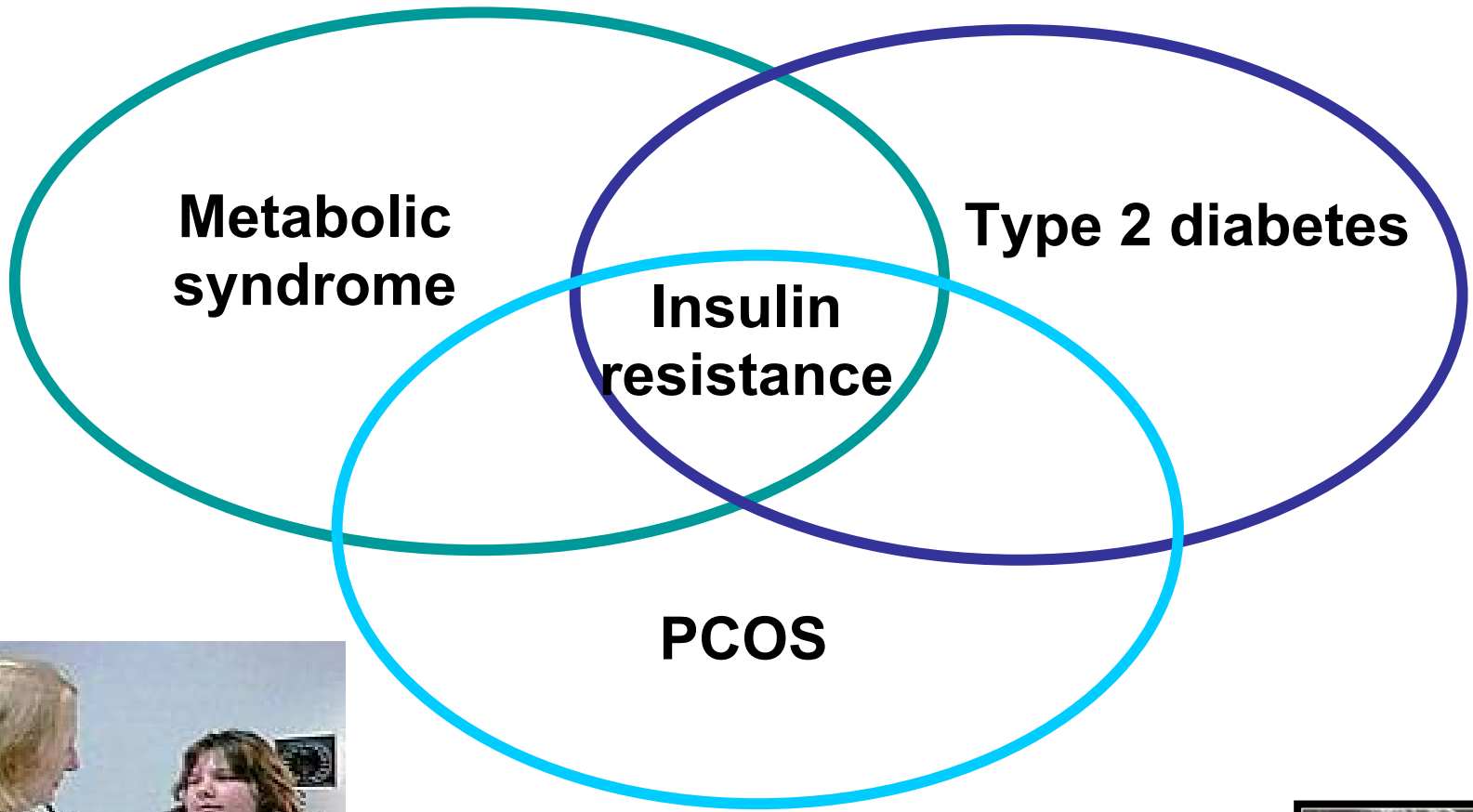


Metabolic syndrome

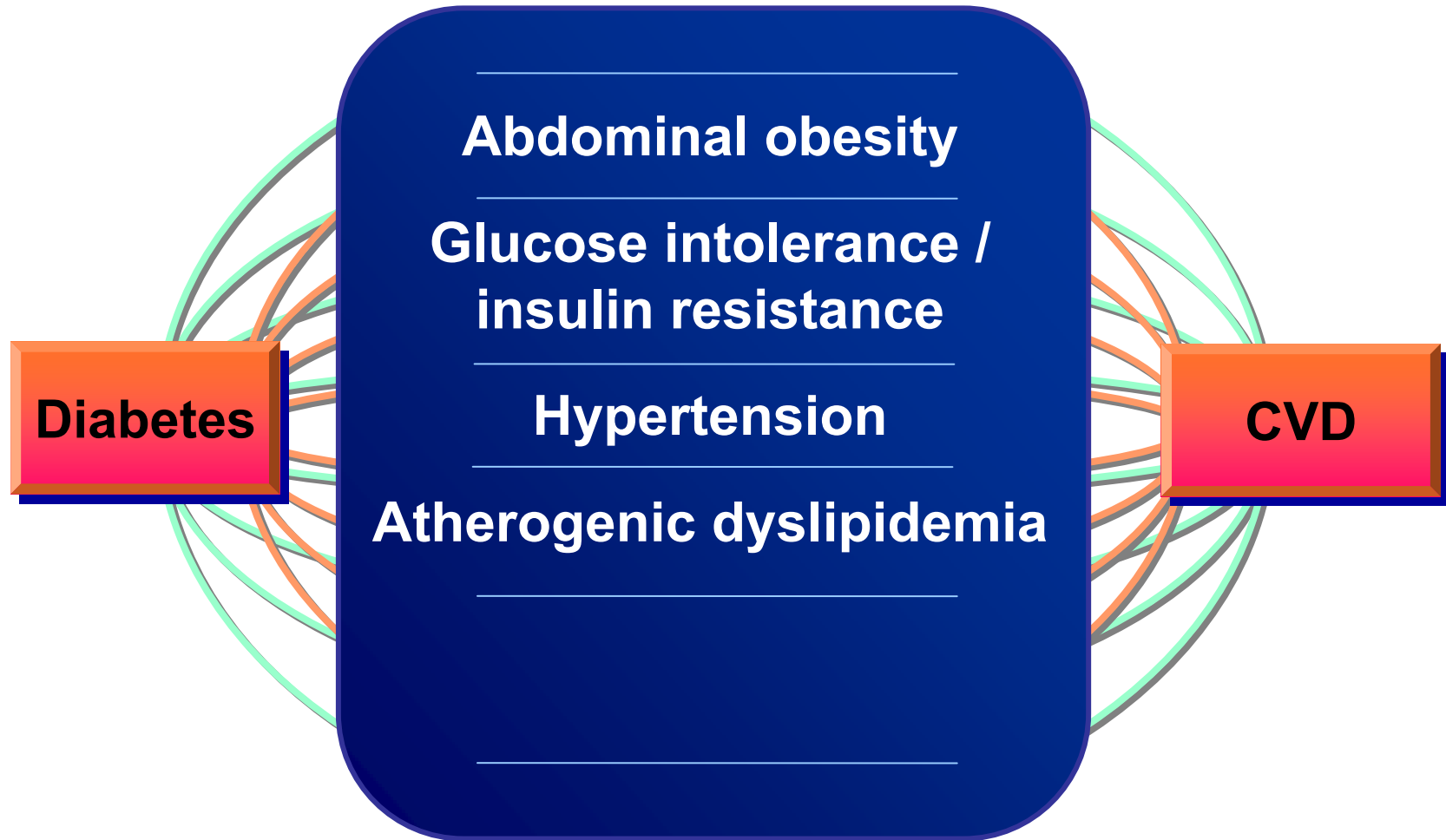


National Cholesterol Educational Program (NCEP), Adult Treatment Panel (ATP) III; 2004.

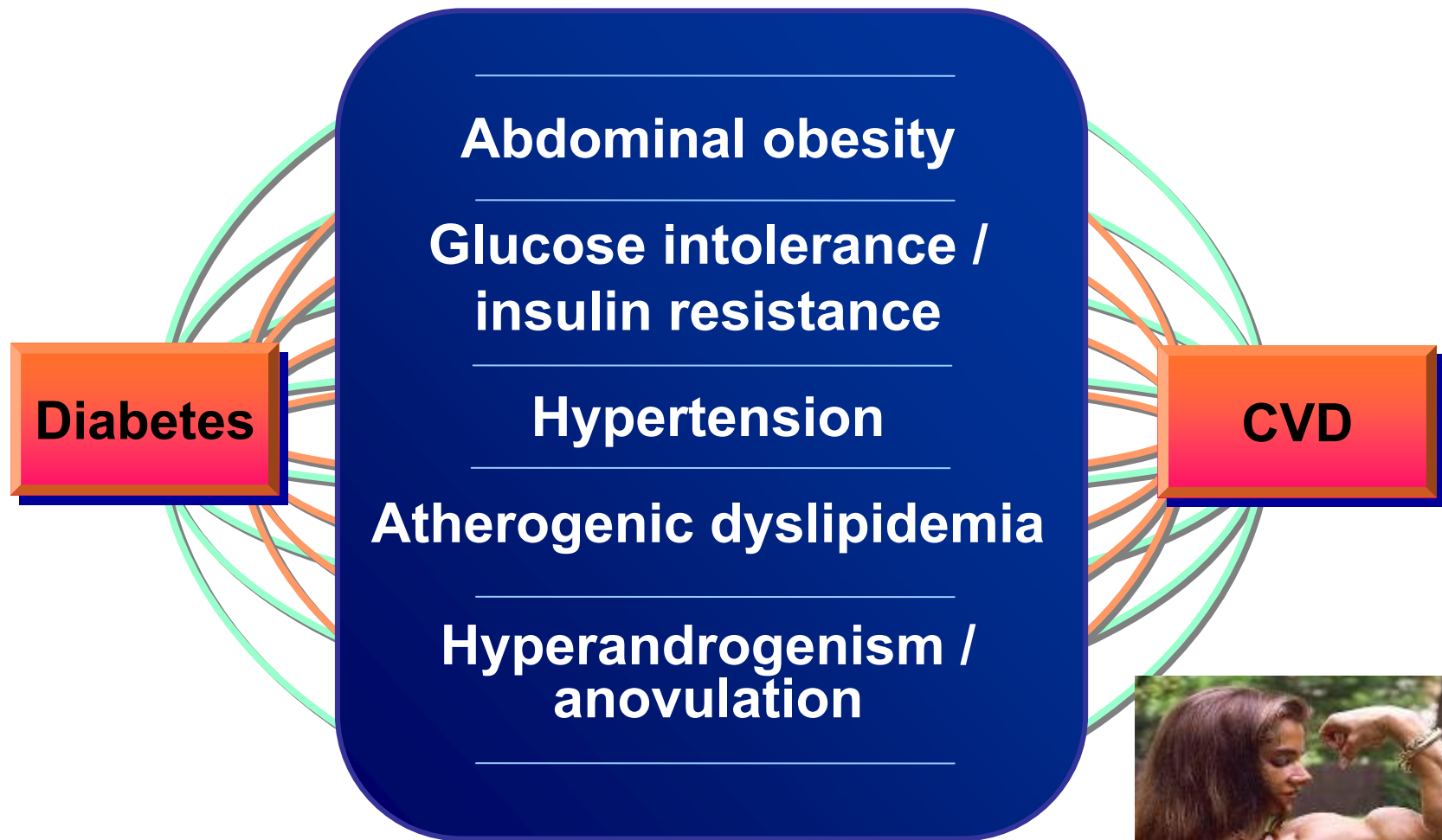
MS-T2DM-PKOS



Metabolic syndrome = Syndrome X



PCOS: Syndrome XX



Management of cardiometabolic risk in PCOS

- **Clinical evaluation**
 - Anthropometric measurements
 - OGTT, fasting lipids
- **Maintenance of ideal weight**
 - Caloric intake
 - Physical activity
- **Pharmacological therapy**
 - Metformin





Galega officinalis
French Lilac

