

Polycystic Ovarian Syndrome

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Polycystic Ovarian Syndrome

- Definition & Diagnosis
- Clinical Significance: Link to Diabetes and Cardiovascular Risk
- Management
 - Lifestyle Strategies
 - Pharmacologic Therapies
 - Nutritional Supplements
- Practical Pearls

PCOS – Historical Perspective

- Originally described in 1935 as reproductive disorder characterized by
 - Enlarged sclerocystic ovaries
 - Menstrual disturbance
 - Obesity
 - Infertility
 - Hirsutism

Stein I and Leventhal M (1935) *Am J Obstet Gynecol* 29: 181-191

Goldzieher JW and Green JA (1962) *J Clin Endocrinol Metab* 22: 325-338

PCOS Diagnostic Criteria

NIH 1990 (“classic”)

- Chronic anovulation (irregular menses)
- Biochemical or clinical hyperandrogenism
 - Hirsutism
 - Acne
 - Androgen-dependent alopecia
- Finding of polycystic ovaries on ultrasound not necessary for diagnosis
- Exclusion of specific ovarian, adrenal or pituitary diseases

AES 2006

- Allows ultrasound findings of polycystic ovaries as substitute for irregular menses

Rotterdam 2003

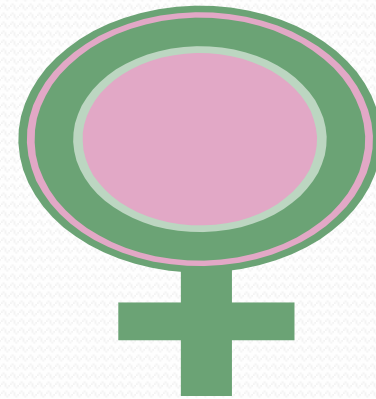
- Any 2 of the 3 criteria (chronic anovulation, clinical or biochemical hyperandrogenism, ultrasound finding of polycystic ovaries)

Differential Diagnosis of PCOS

- To make the diagnosis of PCOS, it is important to rule out other causes of the symptom complex:
 - Hypothalamic amenorrhoea (weight loss, exercise, anxiety, chronic illness) - **low FSH**
 - Pituitary adenoma - **high prolactin**
 - Hyperthyroidism - **low TSH**
 - Hypothyroidism - **high TSH**
 - Late-onset congenital adrenal hyperplasia - **high 17-OH-progesterone**
 - Premature ovarian failure - **high FSH**
 - Cushing's syndrome - **high cortisol**
 - Adrenal tumor - **very high Testosterone**

PCOS: Prevalence

5-15%



The most common cause of oligo/amenorrhea
and anovulatory infertility
The most common endocrinopathy in
reproductive age women, regardless of ethnicity

PCOS Clinical Features



Hirsutism



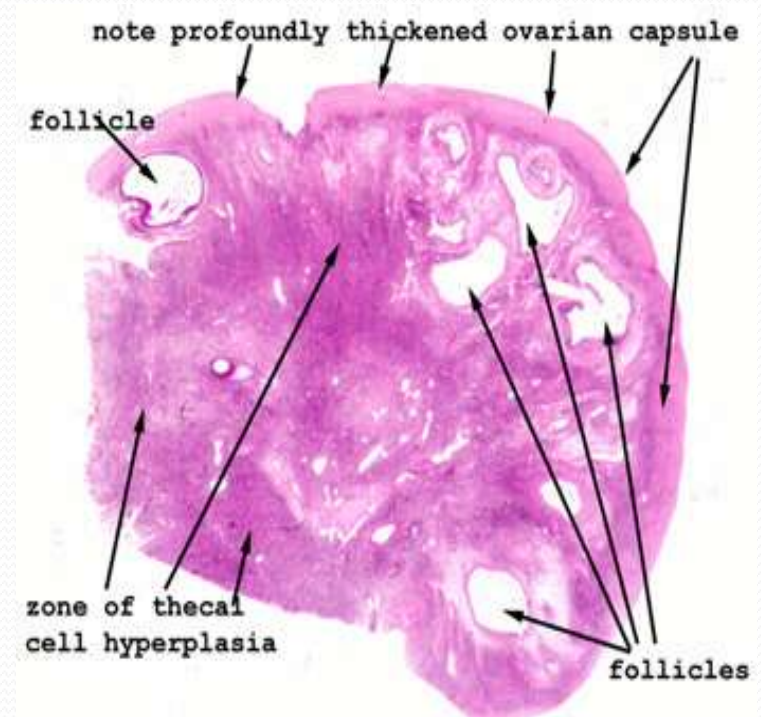
Acne

Measure height,
weight, BP, BMI,
Waist-Hip Ratio

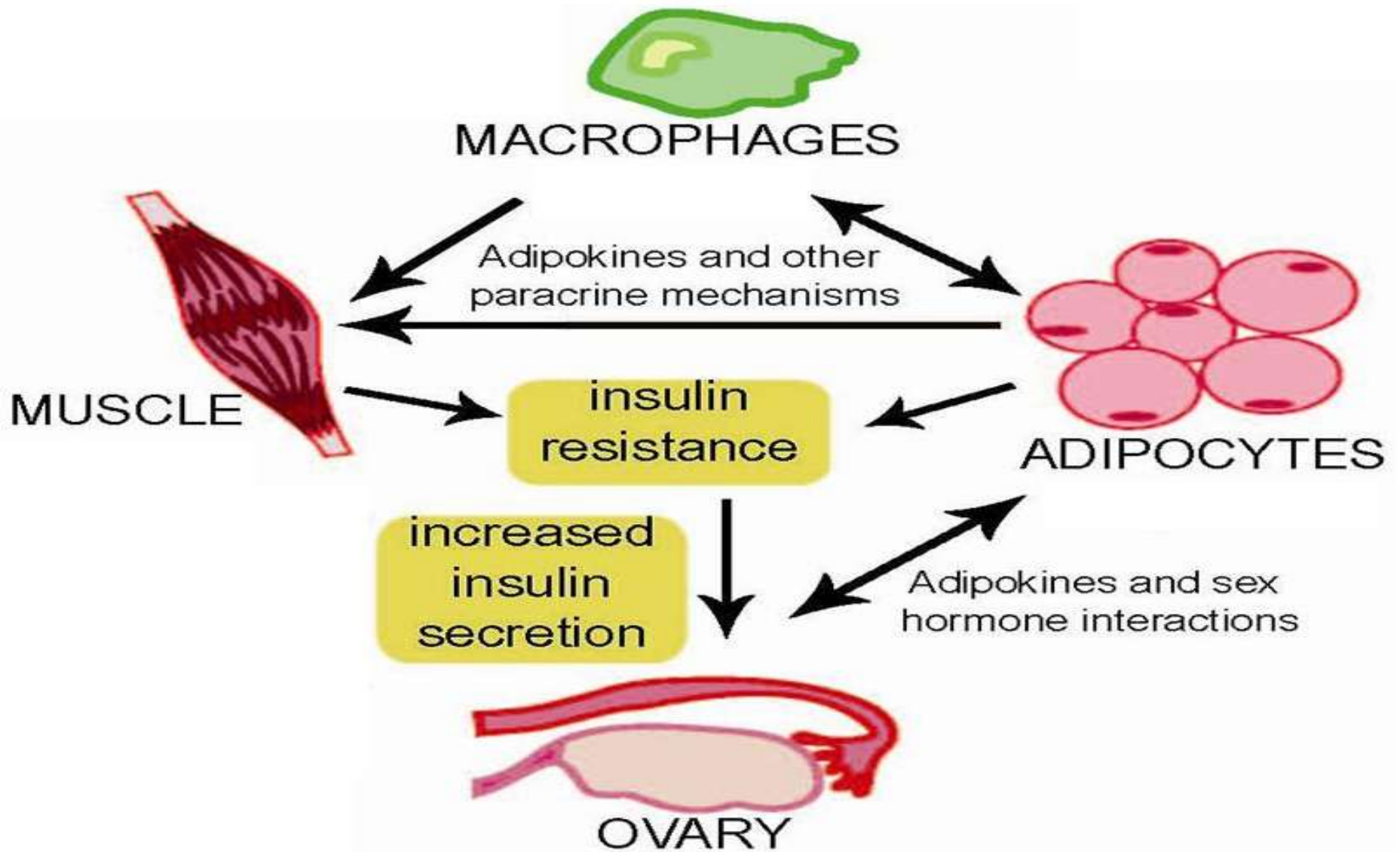


Acanthosis Nigricans

PCOS: Sonographic & Histological Features



Key Players in PCOS Pathogenesis



PCOS: Biochemical Profile

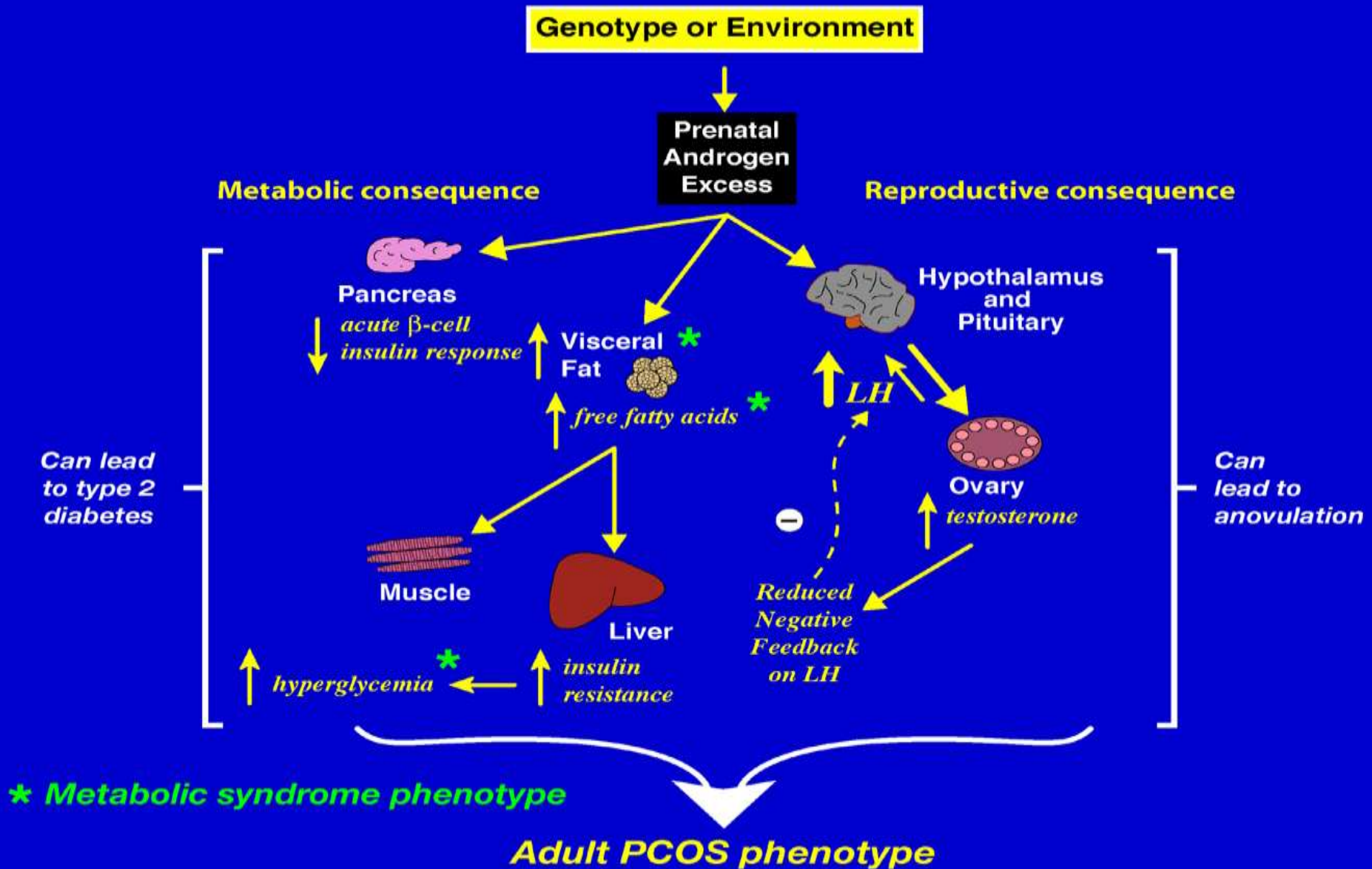
Hormonal Parameters

- Functional Ovarian Hyperandrogenism
 - ↑ Testosterone
 - ↑ Androstenedione
- Functional Adrenal Hyperandrogenism
 - ↑ DHEA-S
- ↓ SHBG (Sex Hormone Binding Globulin)
- ↑ LH / FSH Ratio
- ↑ Prolactin

Metabolic Parameters

- ↑ Triglycerides
- ↓ HDL
- ↑ Uric acid
- Abnormal oral glucose tolerance test
- ↑ Fasting insulin and C-peptide
- ↓ adiponectin
- ↑ PAI-1 and Endothelin-1 (marker of abnormal vascular reactivity)
- ↑ hs-CRP

Hypothesis for Prenatal Androgen Programming of Females for PCOS



PCOS: Health Consequences

Reproductive

- Infertility
- Increased risk of miscarriage
- Increased risk of gestational diabetes / preeclampsia
- Increased risk of endometrial cancer (RR 3.1)

Psychosocial

- Depression & anxiety
- Cosmetic concerns (hyperandrogenic symptoms)

Cardiometabolic

- Increased risk of type 2 Diabetes
- Hypertension
- Dyslipidemia
- Increased inflammation
- Increased cardiovascular disease risk
- Non-alcoholic steatohepatitis (NASH)
- Sleep apnea

PCOS and Cardiovascular disease

- In women under the age of 60 with CAD, 42% have PCOS (angiographic study of 143 women)
- Increased carotid intimal-medial thickness in women with PCOS aged >45
- Increased likelihood of multi-vessel coronary artery disease (OR 1.7)
- Increased risk of myocardial infarction by 4-7 fold
- Women with PCOS 30x more likely to have obstructive sleep apnea
- Severity of sleep apnea correlated with likelihood of impaired glucose tolerance

Birdsall et al. *Ann Int Med* 1997; 126: 32-5

J Clin Endocrinol Metab 2001;86:517-20

J Clin Endocrinol Metab 2006;91:36-42

AACE PCOS position statement. *Endocrine Practice* 2005; 11(2): 126-134

PCOS and Type 2 Diabetes

- 30-50% of obese women with PCOS develop IGT or Type 2 diabetes by the age of 30
- In two studies, 25-28% of premenopausal women with Type 2 diabetes have PCOS, frequently undiagnosed. (*Clin Endocrinol* 2000;52:81 & *Diabetes Care* 2001;24:1050)
- Prospective trials in U.S. of women with PCOS (*Diabetes Care* 1999;22:141 & *JCEM* 1999; 84:165):
 - 31-35% prevalence of impaired glucose tolerance
 - 7.5-10.0% prevalence of type 2 diabetes mellitus
- Women with PCOS in the U.S. or Australia:
 - Conversion rate from IGT to DM2 increased 2- to 5-fold (*Diabetes Care* 1999;22:141 & *Hum Reprod* 2001;16:1995)

Insulin Resistance and PCOS

- Insulin resistance
 - Universal feature of PCOS
 - intrinsic to PCOS, independent of obesity
 - seen in both obese and non-obese women with PCOS

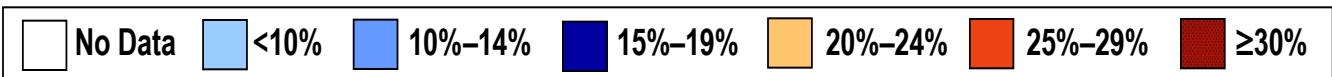
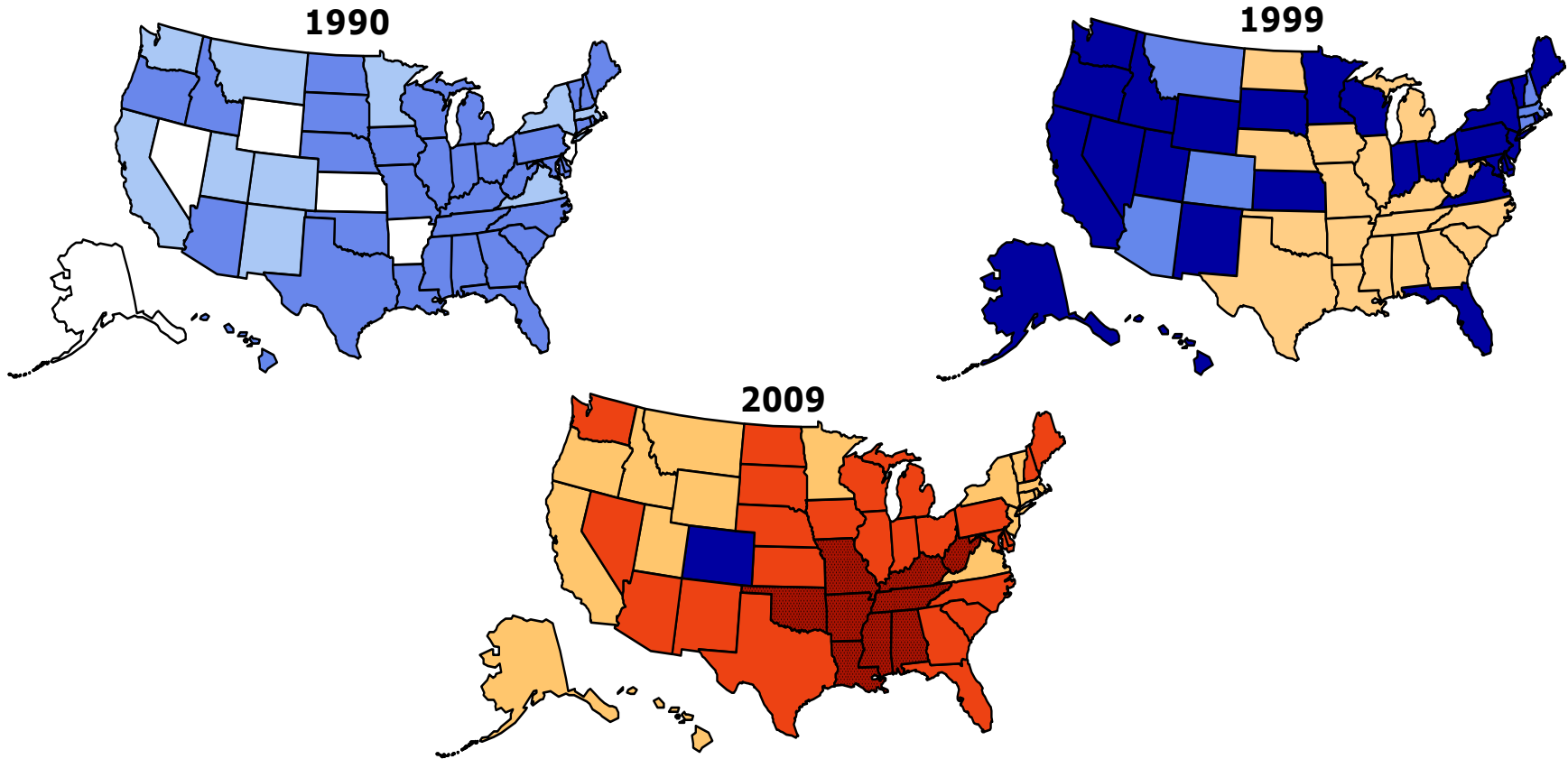
Lifestyle Factors in PCOS & Insulin Resistance



Obesity Trends* Among U.S. Adults

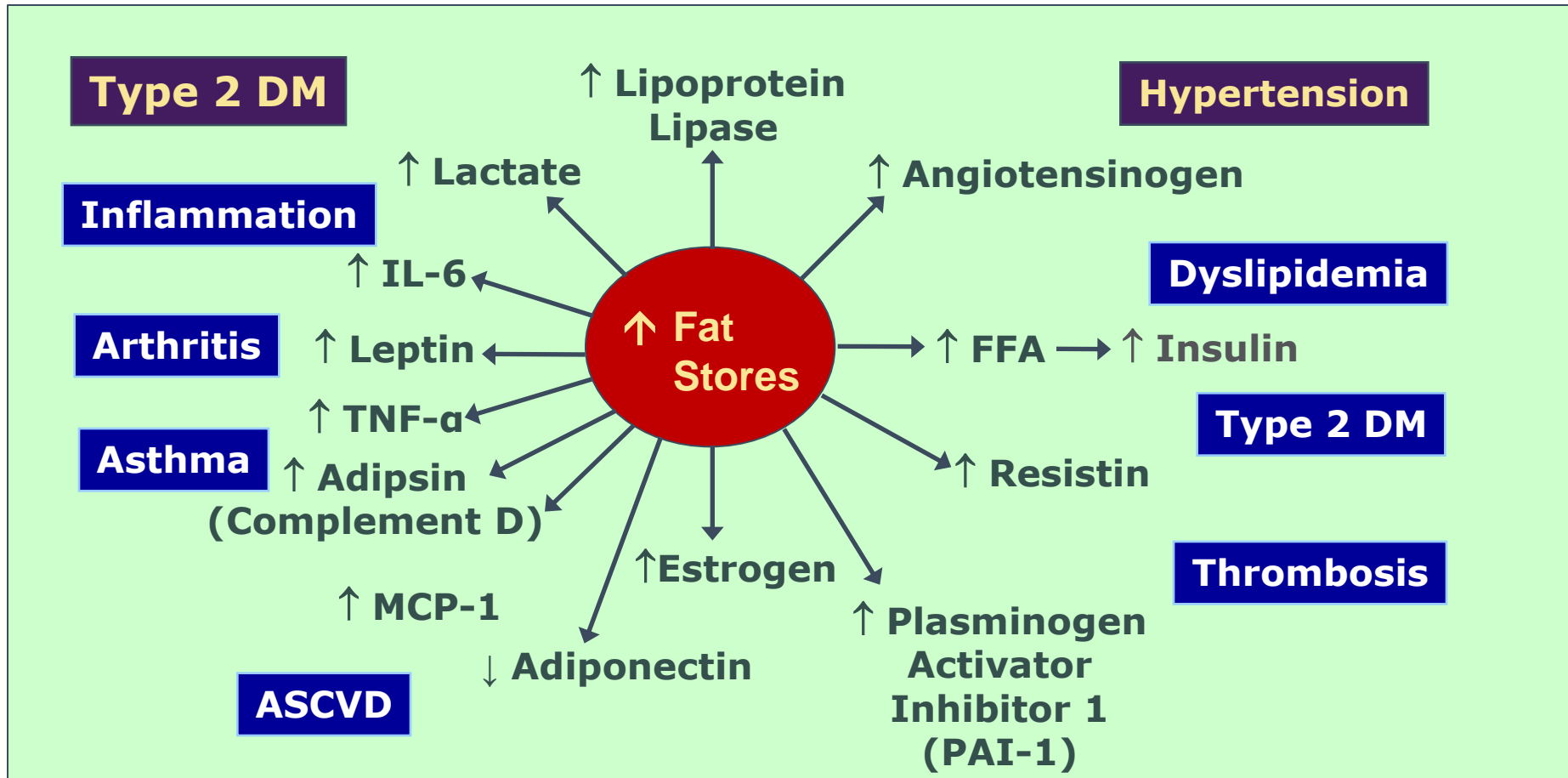
BRFSS, 1990, 1999, 2009

(*BMI ≥ 30 , or about 30 lbs. overweight for 5'4" person)



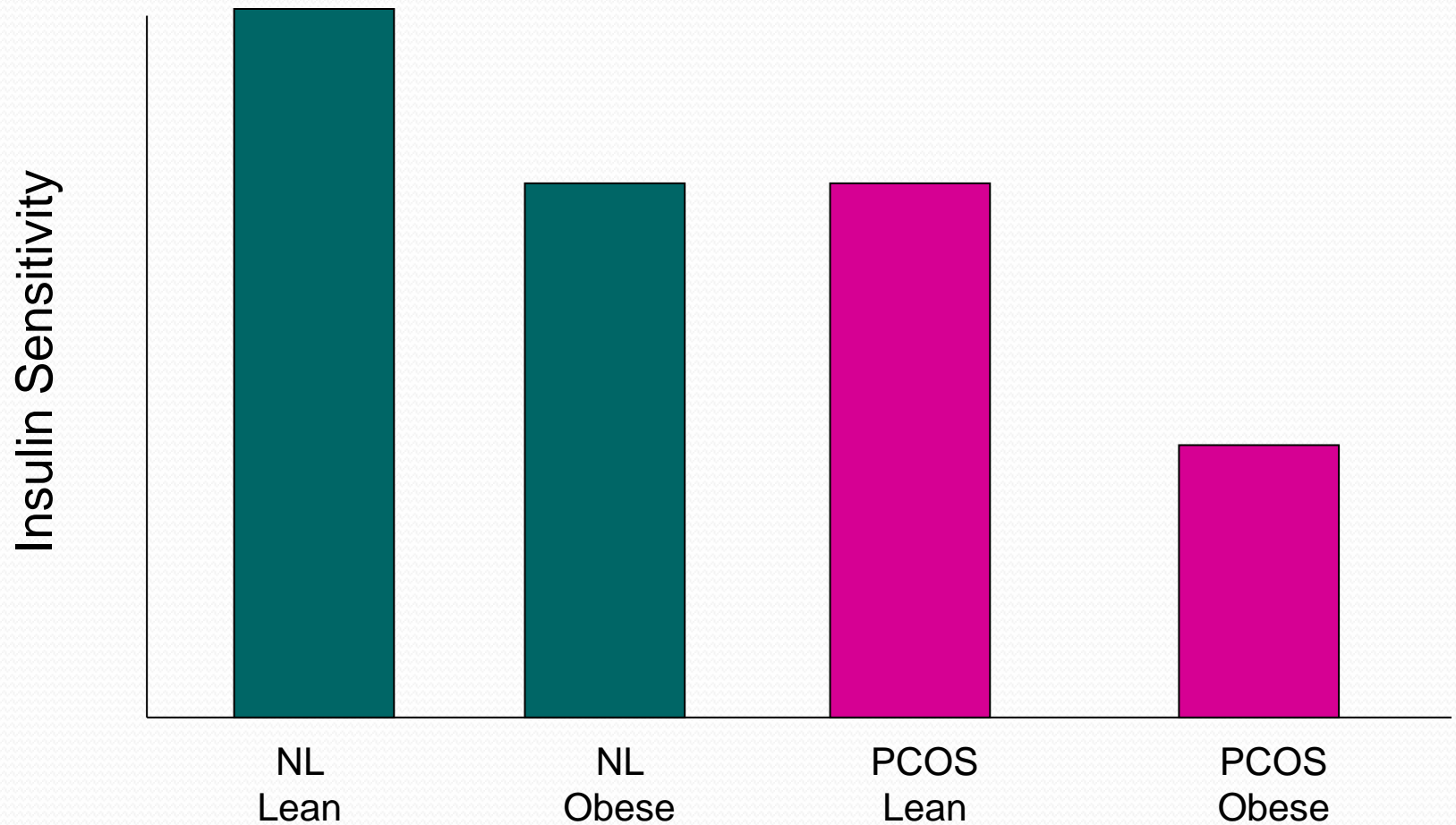
Source: Behavioral Risk Factor Surveillance System, CDC.

Excess Adipose Tissue Can Cause Increased Expression of Some Hormones, Suppression of Others, and Can Lead to Inflammation and Disease



DM = diabetes mellitus; FFA = free fatty acid; PAI-1 = Plasminogen Activator Inhibitor-1; MCP-1 = Monocyte Chemoattractant protein-1; TNF- α = Tumor Necrosis Factor-alpha; IL-6 = Interleukin-6.

Insulin Sensitivity in Normal Women And Women with PCOS



Nonobese PCOS Patients Need OGTT

- Impaired glucose tolerance (IGT) was found in 16% of both obese and nonobese adolescents with PCOS
- Data source: study of 70 adolescent girls referred to a specialty clinic for menstrual irregularity (Yale PCOS Clinic)
- Mean age 15.6yrs, BMI mean 31.4 (range 19-46)
- 64 (91%) met AES criteria for PCOS diagnosis (40 were obese. Mean BMI 36 for obese group and 24 for nonobese group)
- Androgen Excess Society guidelines recommend OGTT in all girls and women with PCOS, regardless of age or BMI

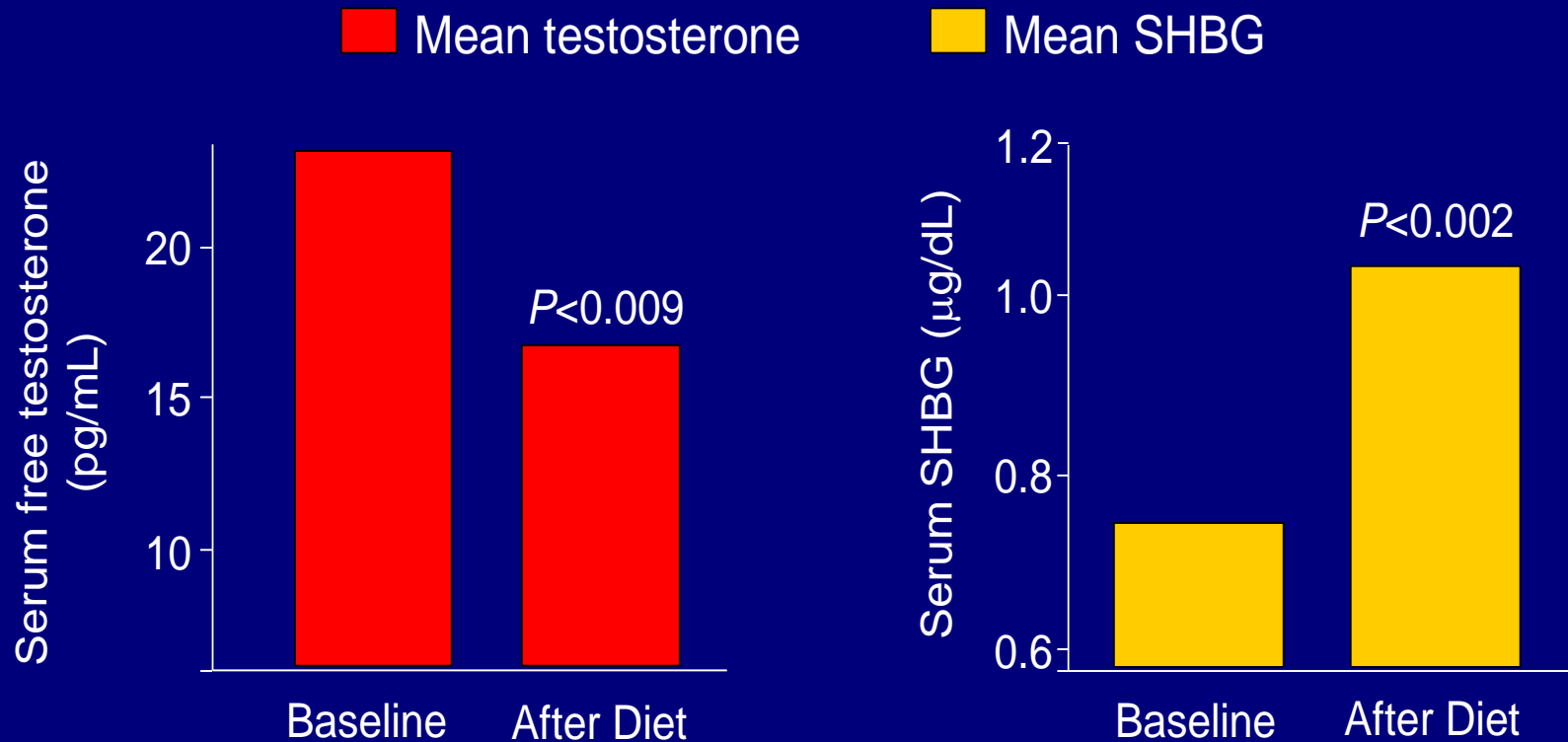
Management of PCOS

- The overall aims of treatment are to:
 - Correct the high androgen levels and adverse metabolic effects
 - Restore menstrual cyclicality
 - Manage the cosmetic symptoms and signs
 - Restore fertility if desired
 - Long-term health - Chronic disease prevention
 - Diabetes prevention
 - Cardiovascular disease risk reduction
 - Cancer prevention

PCOS – Metabolic Management

- Lifestyle management is the foundation of treatment
- Weight Reduction
 - Up to half of women with PCOS are overweight or obese
 - Abdominal obesity is typical
 - Even lean women with PCOS tend to have increased omental and visceral fat
 - Modest weight loss of 5 – 10% can restore menstrual cyclicity
 - Healthy eating and exercise essential for management of both hormonal and metabolic aspects of PCOS
 - Multidisciplinary approach to weight management

Effect of 1000-kcal Diet for 7 Months in 13 Women With PCOS (>5% Weight Loss: 12% ± 5%)



- Improved menstrual pattern in 11/13 women (5 conceived)

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WEAPONS
OF MASS
EXPANSION.



PCOS: Symptomatic Management

- Oral Contraceptives
 - Choose progestin with low androgenic potential (Norgestimate / Desogestrel / Drospirenone)
 - Increases SHBG levels
 - Suppresses androgen production
 - Effective in reducing acne & hirsutism
 - Cycle regulation and thus reducing risk of endometrial hyperplasia/cancer
- Antiandrogens
 - Spironolactone
 - Cypoterone acetate (not available in US)
 - Flutamide
 - Finasteride (Propecia)
 - Eflornithine cream (Vaniqa)

OCPs vs Insulin Sensitizing Drugs in PCOS

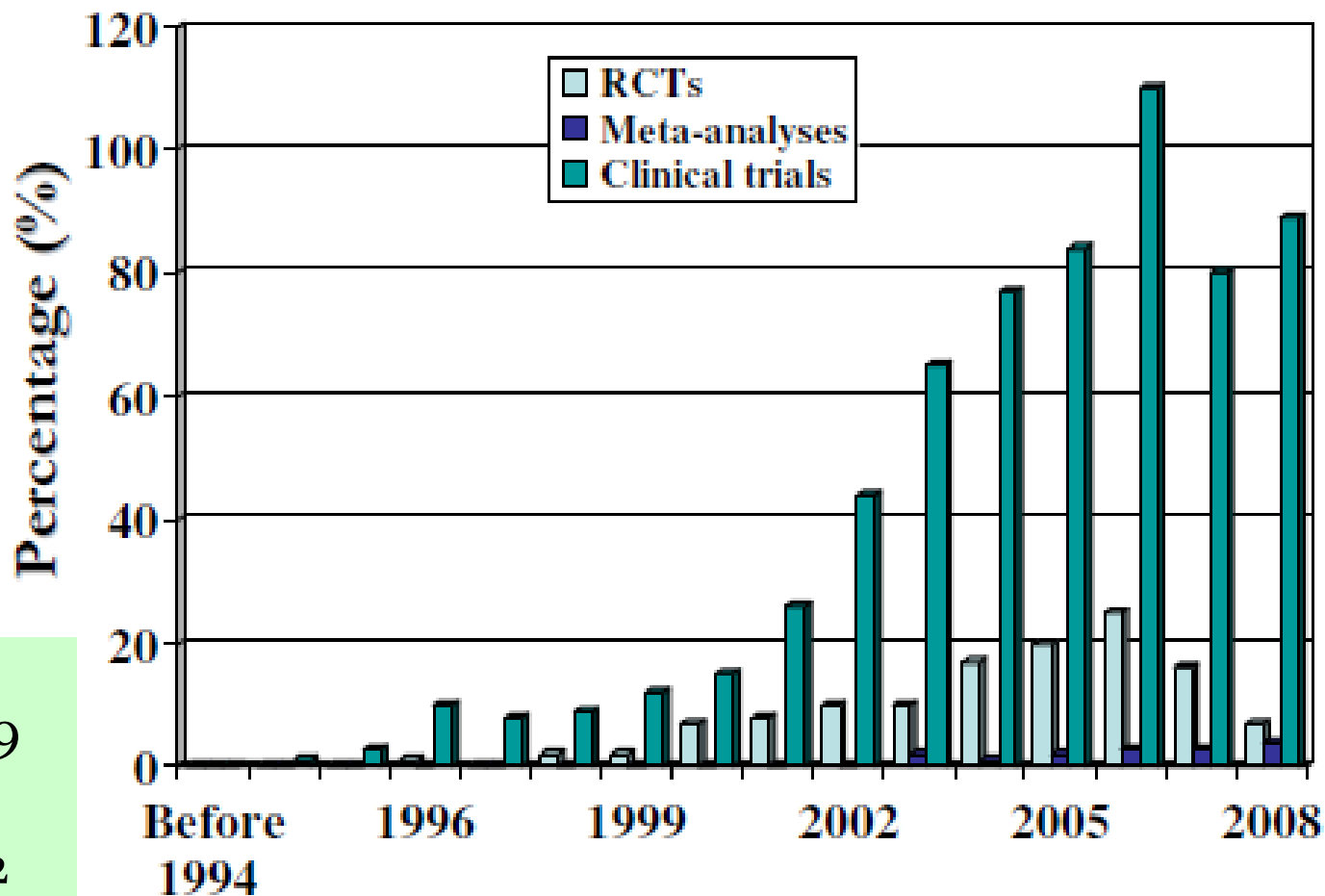
Oral Contraceptives

- May worsen insulin resistance
- May induce glucose intolerance
- May increase serum triglycerides
- May increase risk for DM2
- May increase risk for cardiovascular disease

Insulin Sensitizing Drugs

- Improves insulin sensitivity
- Improves glucose tolerance
- May reduce serum triglycerides
- Reduces plasma PAI-1
- Reduces Endothelin-1
- Reduced CRP

Studies on Insulin-Sensitizing Drugs in PCOS



- Clinical trials: 819
- RCTs: 113
- Meta-analyses: 12

Studies of Insulin-Sensitizing Agents in PCOS

Citation	Metformin	Serum Androgens	Ovulation
De Leo et al (<i>Fertil Steril.</i> 1999;72:282-285)		–	Improved
Glueck et al. (<i>Metabolism.</i> 1999;49:511)		Decreased	–
Nestler et al. (<i>N Engl J Med.</i> 1998;338:1876)		Decreased	Improved
Diamanti-Kandarakis et al. (<i>Eur J Endocrinol.</i> 1998;138:269)		Decreased	–
Morin-Papunen et al. (<i>Fertil Steril.</i> 1998;69:691)		–	Improved
Nestler et al. (<i>J Clin Endocrinol Metab.</i> 1997;82:4075)		Decreased	–
Velazquez et al. (<i>Obstet Gynecol.</i> 1997;90:392)		–	Improved
Ehrmann et al. (<i>J Clin Endocrinol Metab.</i> 1997;82:524)		No change*	–
Nestler & Jakubowicz. (<i>N Engl J Med.</i> 1996;335:617)		Decreased	–
Crave et al. (<i>J Clin Endocrinol Metab.</i> 1995;80:2057)		No difference from diet alone	–
Velazquez et al. (<i>Metabolism.</i> 1994;43:647)		Decreased	–

*Mean BMI = 39 kg/m²

Studies of Insulin-Sensitizing Agents in PCOS (cont'd)

Troglitazone

Citation	Serum Androgens	Ovulation
Ehrmann et al. (<i>J Clin Endocrinol Metab.</i> 1997;82:2108)	Decreased	—
Dunaif et al. (<i>J Clin Endocrinol Metab.</i> 1996;81:3299)	Decreased	—
Hasegawa et al. (<i>Fertil Steril.</i> 1999;71:323)	Decreased	Improved

D-Chiro-inositol

Citation	Serum Androgens	Ovulation
Nestler et al. (<i>N Engl J Med.</i> 1999;340:1314)	Decreased	Improved

Effects of Insulin Sensitizers on Overall Health of Women With PCOS

	Metformin	Troglitazone	DCI
Prevention of diabetes	yes (DPP)	yes (Tripod)	?
Triglycerides	↓	↓	↓
Hypertension	↓	↓	↓
PAI-1	↓	↓	
Weight	↓ ↔	↓ ↔ ↑	

PAI-1=plasminogen activator inhibitor

DPP=Diabetes Prevention Program

National Institute of Diabetes and Digestive and Kidney Diseases, 1998. Velázquez EM et al. *Metabolism*. 1994;43:647-654. Ehrmann DA et al. *J Endocrinol Metab*. 1997;82:2108-2116. Nestler JE, Jakubowicz DJ. *N Engl J Med*. 1996;335:617-623. Velázquez EM et al. *Metabolism*. 1997;46:454-457. Nestler JE et al. *N Engl J Med*. 1999;340:1314-1320. ADA. *Diabetes Care*. 1996;19(suppl 1):1-114. Iwamoto Y et al. *Diabetes Care*. 1996 Feb;19:151-156.

Insulin-Sensitizing Drugs: Metabolic Effects

Metformin

- Weight reduction
- ↓ BP
- ↓ Trig and LDL, ↑ HDL
- ↓ thrombotic tendency
- Reduces development of type 2 diabetes (DPP)
- ↓ arterial stiffness and improves endothelial function

Thiazolidinediones

- ↓ intra-abdominal fat
- May cause weight gain
- ↓ BP
- ↓ Trig, ↑ HDL
- ↓ thrombotic tendency
- Shown in one study to decrease diabetes in women with GDM history

Insulin Sensitizing Drugs: Reproductive Effects

Metformin

- >50% resumption of menstrual cyclicity
- Ovulation induction (alone or in conjunction with clomiphene citrate)
- Reduces risk of ovarian hyperstimulation with gonadotrophins
- Increases pregnancy rates
- Reduces miscarriage risk
- Reduces gestational diabetes
- Pregnancy category B

Thiazolidinediones

- Increases SHBG
- Reduces testosterone levels
- Increases ovulation
- Pregnancy category C

PCOS – Other Potential Drug Treatments

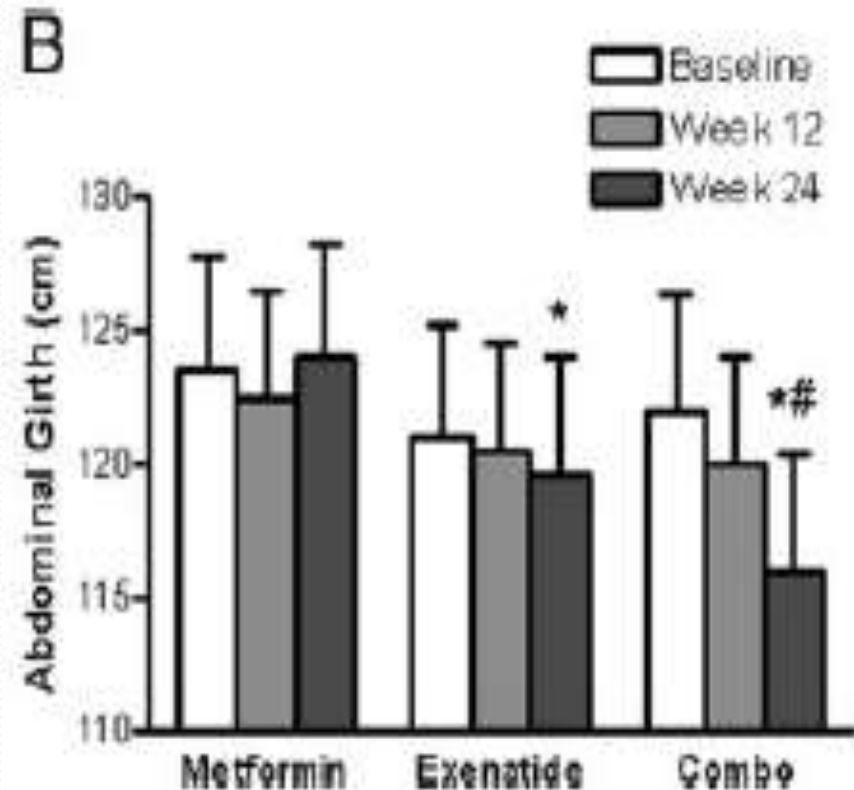
- **Simvastatin**

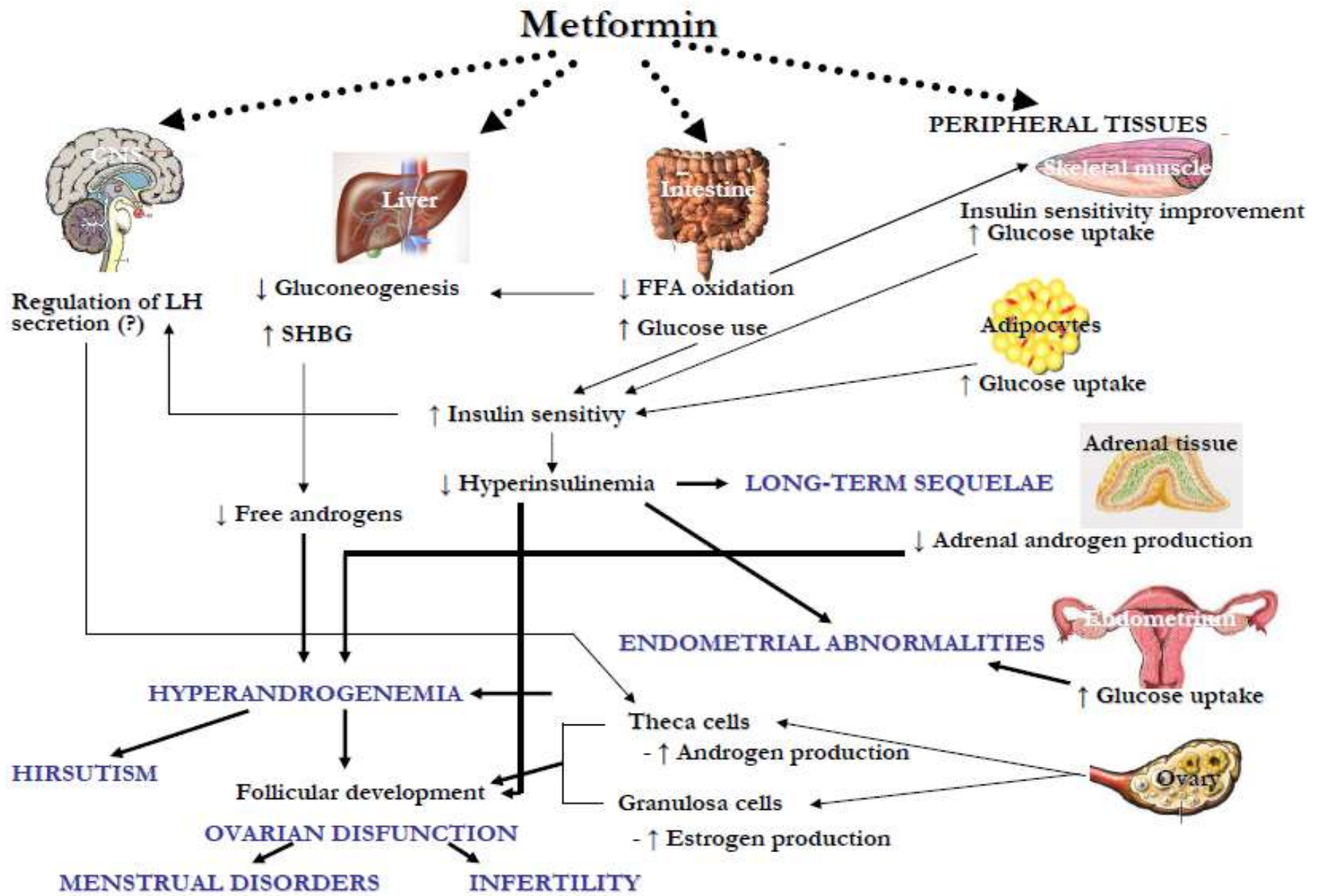
- 3month prospective randomized study of 136 women with PCOS (mean age ~ 25, BMI ~ 24)
- simvastatin 20mg/d reduce total testosterone by 17.1%
- hs-CRP, sVCAM-1, fasting insulin and insulin sensitivity also improved
- Potential mechanisms of action
 - ↓ availability of products in mevalonate pathway
 - ↓ MAPK-1 activity
 - ↓ cytoplasmic reactive oxygen species
 - ↓ proliferation and steroidogenesis of theca-interstitial cells

PCOS – Other Potential Drug Treatments

Exenatide (Byetta)

- 24 week study of 60 overweight women with PCOS (BMI > 27; age 18–40 yr)
- Randomized to metformin 1000mg bid, exenatide 10mcg sq bid, or combo
- Combo exenatide & metformin was superior in reducing weight, abdominal girth and markers of insulin resistance
- All treatments reduced testosterone levels and improved menstrual frequency
- Exenatide restores first- and second-phase insulin secretion, which is attenuated in women with PCOS, as well as promote weight loss, thereby potentially further improving insulin sensitivity





Palomba S, Falbo A, Zullo F & Orio F Jr. Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: a comprehensive review. *Endocrine Reviews* 2009 30 1–50.

PCOS – Environmental Exposures

- PCOS has been linked to excessive androgen exposure in the womb
- Women with PCOS found to have higher levels of BPA
- BPA can cross the placenta and lead to epigenetic changes

Woodruff *et al.* Fert Steril 2008;89:e1-20

Ikezuki *et al.* Hum Reprod 2002;17:2839-41

Takeuchi *et al.* Endocr J 2004;51:165-9

Crain *et al.* Fert Steril 2008;90:911-40

Nutritional Supplements Potentially useful in PCOS

- D-chiro-inositol
 - the inositol isomer D-chiro-inositol administered orally decreases serum triglyceride and testosterone levels, modestly decreases blood pressure, and induces ovulation in obese women with PCOS
- Myoinositol (precursor to d-chiro-inositol)
- Pinitol (precursor to d-chiro-inositol)
- EPA-DHA (fish oil omega 3 fatty acids)
- Vitamin D₃
- N-Acetylcysteine

How Myo-Inositol Works

1. Myo-inositol (MI) improves the way the ovarian follicles use insulin and glucose
2. Supplementing with MI, a precursor to D-*chiro*-inositol (DCI) , may offset a defect in ovarian tissue availability or altered metabolism of DCI, permitting the activation of enzymes that control glucose metabolism and energy production in the ovaries
3. Providing MI at 4 grams per day increases MI in human follicular fluid influencing follicular maturity - a marker of good quality oocytes and increased fertility.

NOTE:

- DCI and MI - two of the nine naturally occurring isomers of inositol.
- Both MI and DCI isomers improve ovarian insulin sensitivity.
- MI is widely distributed in nature where DCI is rare.

Gerli S et al. Randomized double-blind placebo-controlled trial: effects of myo-inositol on ovarian function and metabolic factors in women with PCOS *Eur Rev Med Pharmacol Sci* 2007;11:347-54

Diagnostic Algorithm for PCOS

Any 2 of the following 3 criteria:

- Oligomenorrhea or amenorrhea
- Hyperandrogenism (hirsutism, acne, alopecia) or hyperandrogenemia (eg. elevated total or free testosterone)
- Polycystic ovaries on ultrasonography

All of the following disorders ruled out:

- Hyperprolactinemia
- Nonclassical congenital adrenal hyperplasia
- Cushing's syndrome
- Androgen-secreting neoplasm
- Acromegaly
- Thyroid dysfunction

Polycystic ovary syndrome

Ancillary studies

Risk assessment for
Endometrial carcinoma

Risk assessment for
Glucose intolerance

Risk assessment for
Cardiovascular disease

Risk assessment for
obstructive sleep apnea

Endometrial biopsy
if indicated

Oral glucose-tolerance test

Lipids, hsCRP, etc.

Polysomnography
if indicated

PCOS: Clinical Pearls

- Most common endocrinopathy in reproductive age women (* need early recognition of syndrome*)
- Clinical diagnosis (irregular menses and hyperandrogenism)
- Shift of paradigm: Not only reproductive disorder! Need to address metabolic defect and cardiometabolic risks
- Evaluation – hormonal parameters, fasting glucose & OGTT (with insulin levels), lipids with other atherogenic markers; appropriate eval for sleep apnea and cardiovascular disease
- Management approach - *aggressive reduction of CV risk factors*
 - Multidisciplinary team approach with support / resources for patients
 - Lifestyle management
 - Diet, exercise, sleep, minimize exposure to environmental toxins
 - Pharmacologic treatment
 - First line medication - Metformin
 - Second line medications – statins, thiazolidinediones, GLP-1 agonists
 - Use of OCPs with low androgenic progestin for cycle regulation and symptomatic treatment of skin manifestations (acne, hirsutism, alopecia)
 - BP lowering agents as indicated