PCOS and Metabolic Syndrome

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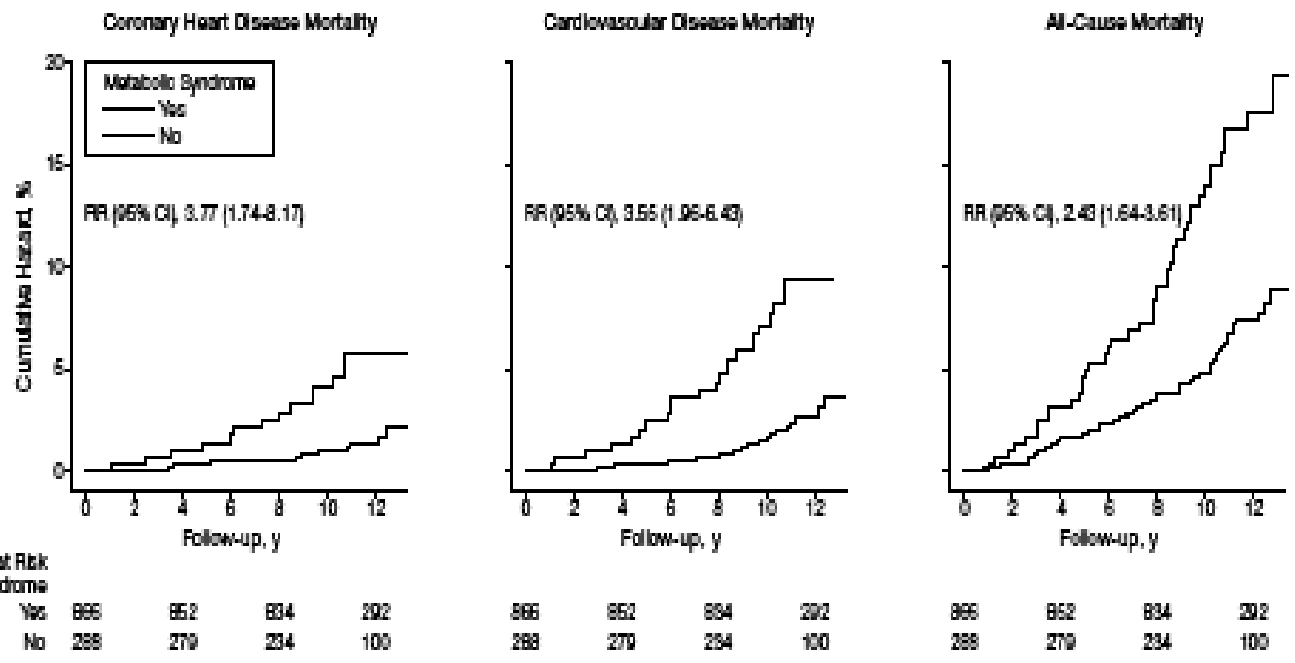
Metabolic syndrome

- The clustering of cardiovascular risk factor

- Proposed criteria
  - The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria, 2001
  - International Diabetes Foundation (IDF), 2005
  - American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI), 2005
  - IDF and AHA/NHLBI consensus criteria, 2010

Major health hazard

Figure. Unadjusted Kaplan-Meier Hazard Curves



RR indicates relative risk; CI, confidence interval. Curves for men with vs without the metabolic syndrome based on factor analysis (men in the highest quarter of the distribution of the metabolic syndrome factor were considered to have the metabolic syndrome). Median follow-up (range) for survivors was 11.6 (9.1-13.7) years. Relative risks were determined by age-adjusted Cox proportional hazards regression analysis.

Lakka et al., JAMA 2002

Definition

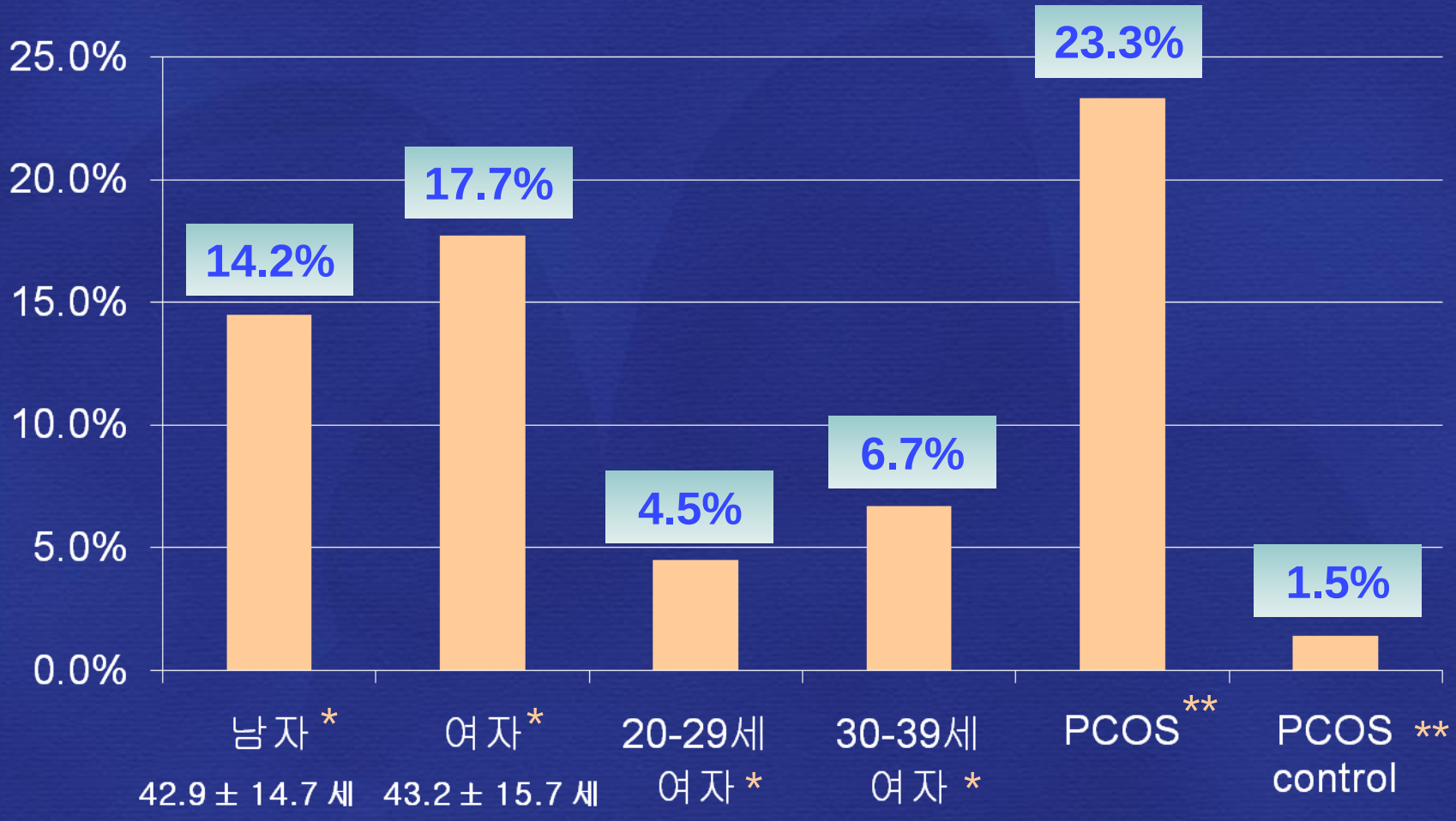
IDF and AHA/NHLBI consensus criteria, 2010

Three or more of the following:

- **Central obesity : population and country specific (80cm in Asian women)**
- **Elevated *triglycerides* ≥150 mg/dL (1.7 mmol/L)**
  or on drug treatment for this lipid abnormality
- **Reduced HDL-C : <50 mg/dL (1.3 mmol/L)**
  or on drug treatment for lipid abnormality
- **Hypertension : SBP ≥130 mm Hg or DBP ≥ 85 mm Hg**
  or on drug treatment for Hypertension
- **Elevated fasting plasma glucose : >100 mg/dL (5.6 mmol/L)**

Eckel et al., Lancet 2010

Prevalence



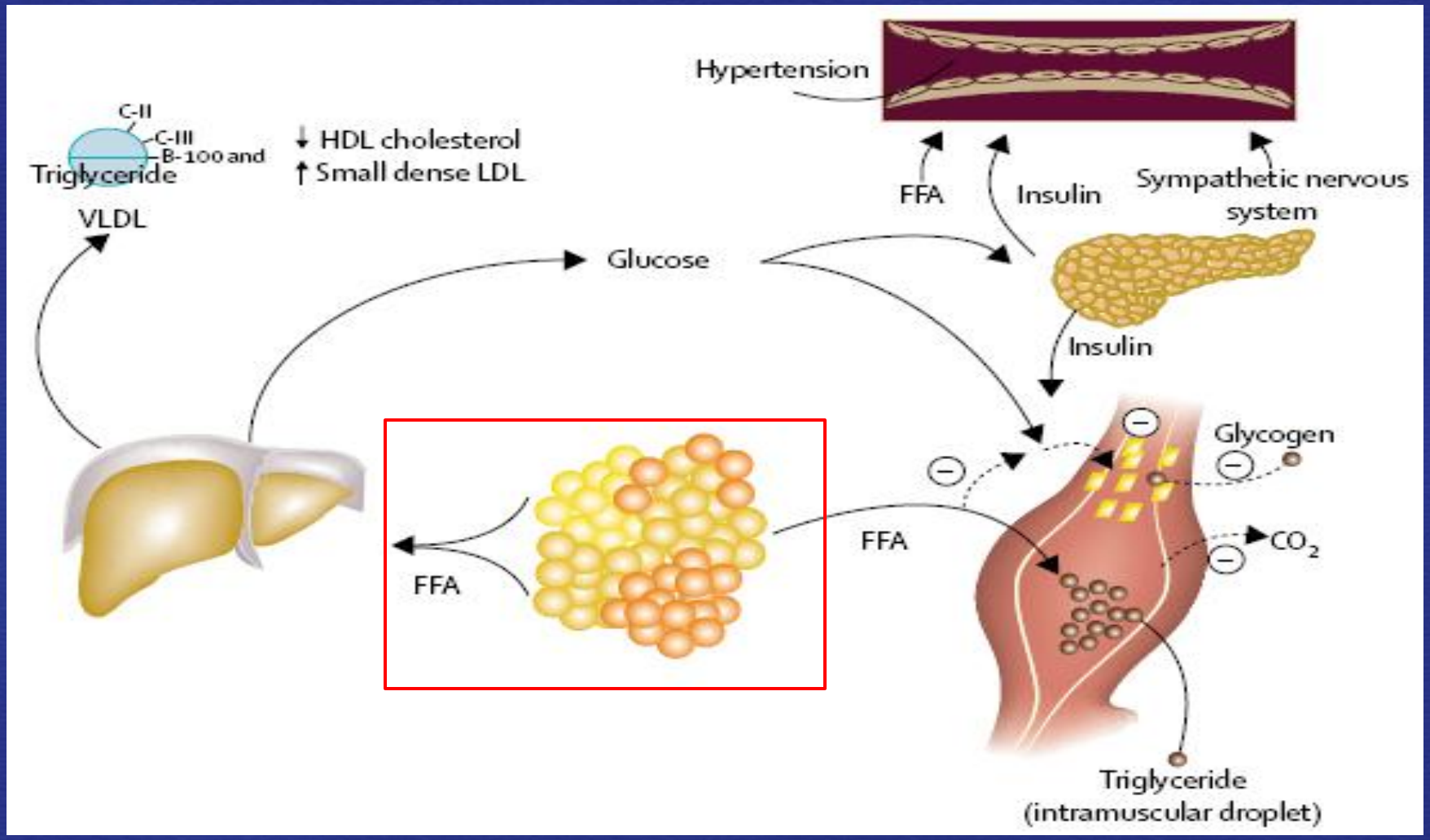
Park et al., Int J Epidemiol 2004; Chae et al., Hum Reprod 2008***

Mechanism – insulin resistance

- Most accepted and unifying hypothesis
- Defect in insulin action results in fasting hyperinsulinemia to maintain euglycemia
- Major contributor in insulin resistance
  - overabundance of circulating fatty acids
  - paracrine and endocrine effect of proinflammatory state

Eckel et al., Lancet 2005

Mechanism – obesity and insulin resistance



adopted from Harrison's Internal Medicine17th eds. (Eckel et al., Lancet 2005)

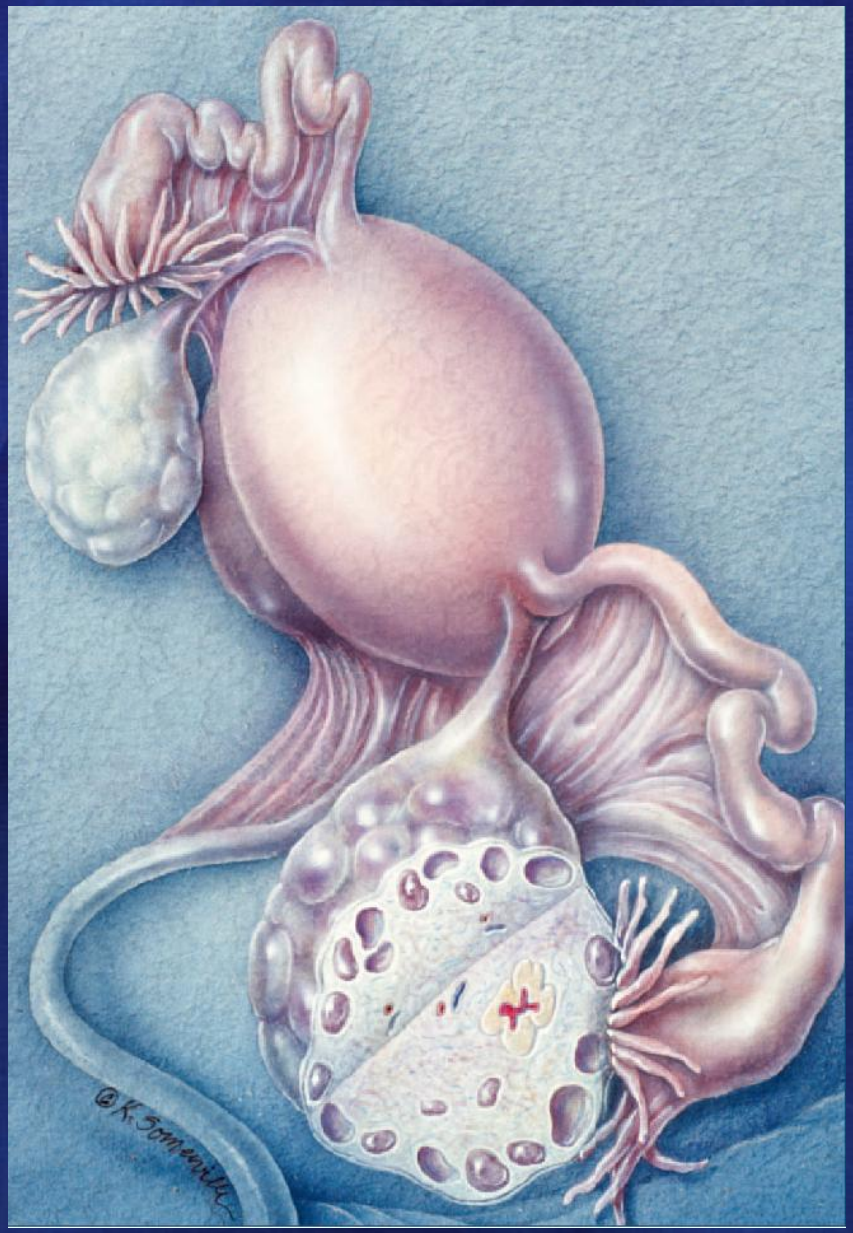
Clinical spectrum - core cluster

- Obesity (Central)
- Dyslipidemia
  - Hypertriglyceridemia
  - Low HDL cholesterol
  - Small, dense LDL particles
- Glucose intolerance
  - Impaired fasting glucose
  - Type 2 DM
- Insulin resistance
- Raised blood pressure/Hypertension

Clinical spectrum- other

- Microalbuminuria
- Hyperuricemia and gout
- Impaired fibrinolysis and increased coagulability
  - Elevated PAI-1, fibrinogen
- Markers of chronic inflammation
  - Elevated CRP
  - Pro-inflammatory cytokines (IL-1, IL-6, TNFα)
- Presence of fatty liver disease
- **Polycystic ovary syndrome**

PCOS

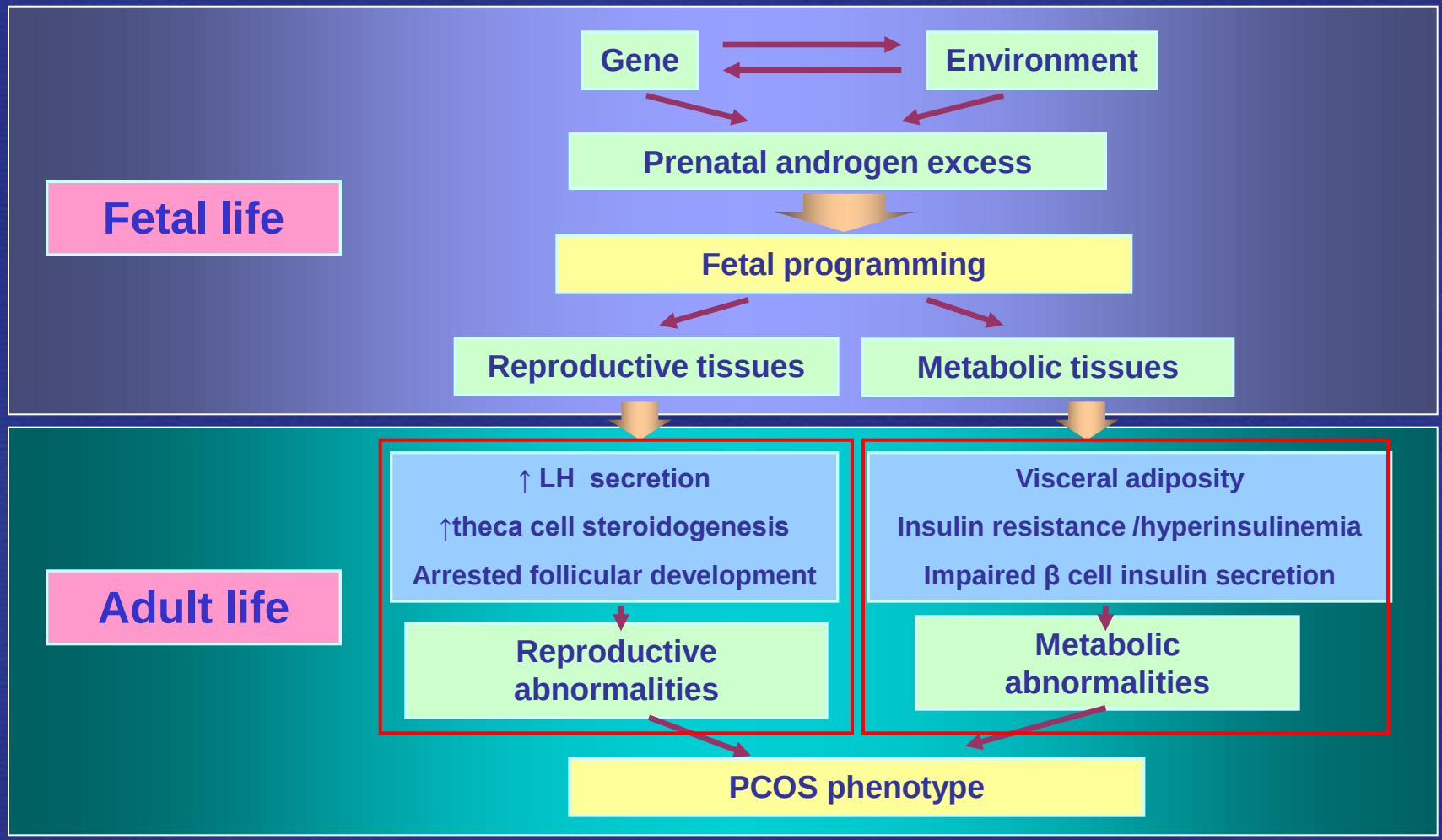


Baldwin CY and Witchel SF. Pediatr Ann 2006

다낭성 난소증후군

- 만성무배란과 남성호르몬 과다증세
  - 가임기 여성의 가장 흔한 (4%-8%) 내분비 질환
  - 여성불임의 흔한 원인: 무배란
  - 무월경, 희발월경, 부정출혈
  - 자궁내막암
- 인슐린 저항성과 연관된 남성호르몬 과다가 핵심기전임

Development of PCOS Phenotype



Xita and Tsatsoulis. JCEM, 2006

다낭성 난소증후군의 진단 기준

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CONSENSUS STATEMENT

Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome

The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group

Rotterdam, The Netherlands

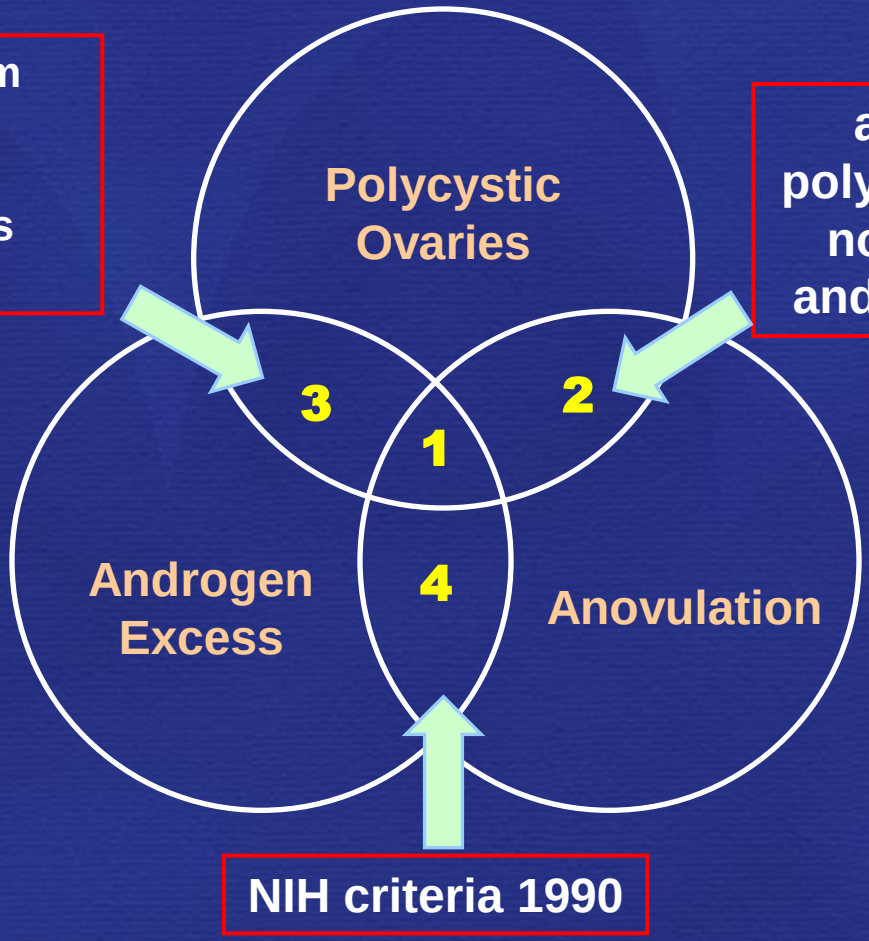
Received October 22, 2003; revised and

↑

1990, NIH Criteria

Subgroups of PCOS

hyperandrogenism (clinical and/or biochemical) polycystic ovaries regular cycles



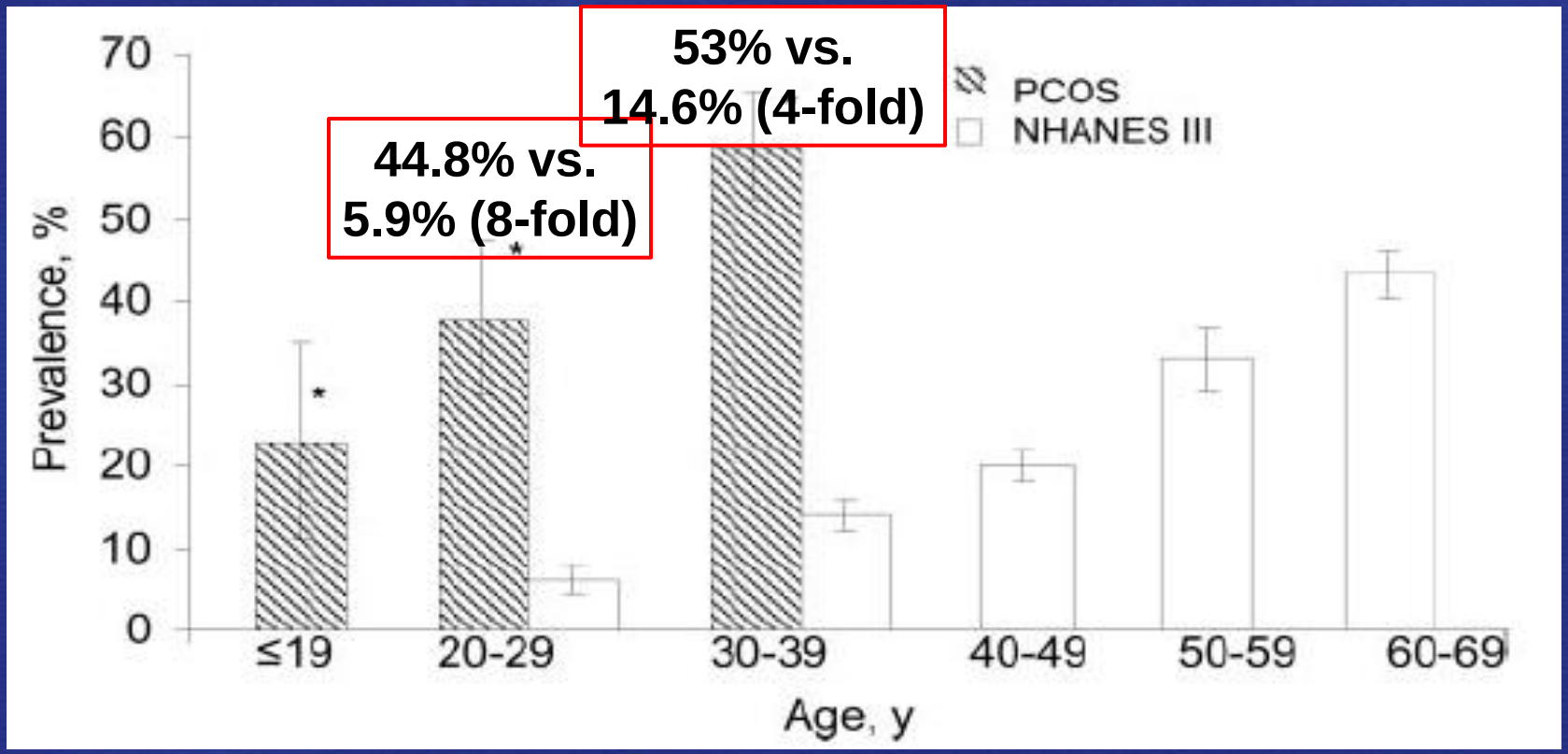
anovulation polycystic ovaries no evidence of androgen excess

1 IM+HA+PCO
2 IM+PCO
3 HA+PCO
4 IM+HA

Frank S. J Clin Endocrinol Metab 2006;91:786-9.

Metabolic syndrome : Prevalence in PCOS

- Apridonidze et al., 2005: 43% (46/106), USA



Apridonidze et al., 2005 JCEM

Prevalence in Korea

Human Reproduction Vol.23, No.8 pp. 1924–1931, 2008
doi:10.1093/humrep/den239
Advance Access publication on June 24, 2008

Clinical and biochemical characteristics of polycystic ovary syndrome in Korean women

Soo Jin Chae[1], Jin Ju Kim[1], Young Min Choi[1,2,3], Kyu Ri Hwang[1], Byung Chul Jee[1,2], Seung Yup Ku[1,2], Chang Suk Suh[1,2], Seok Hyun Kim[1,2], Jung Gu Kim[1] and Shin Yong Moon[1,2]

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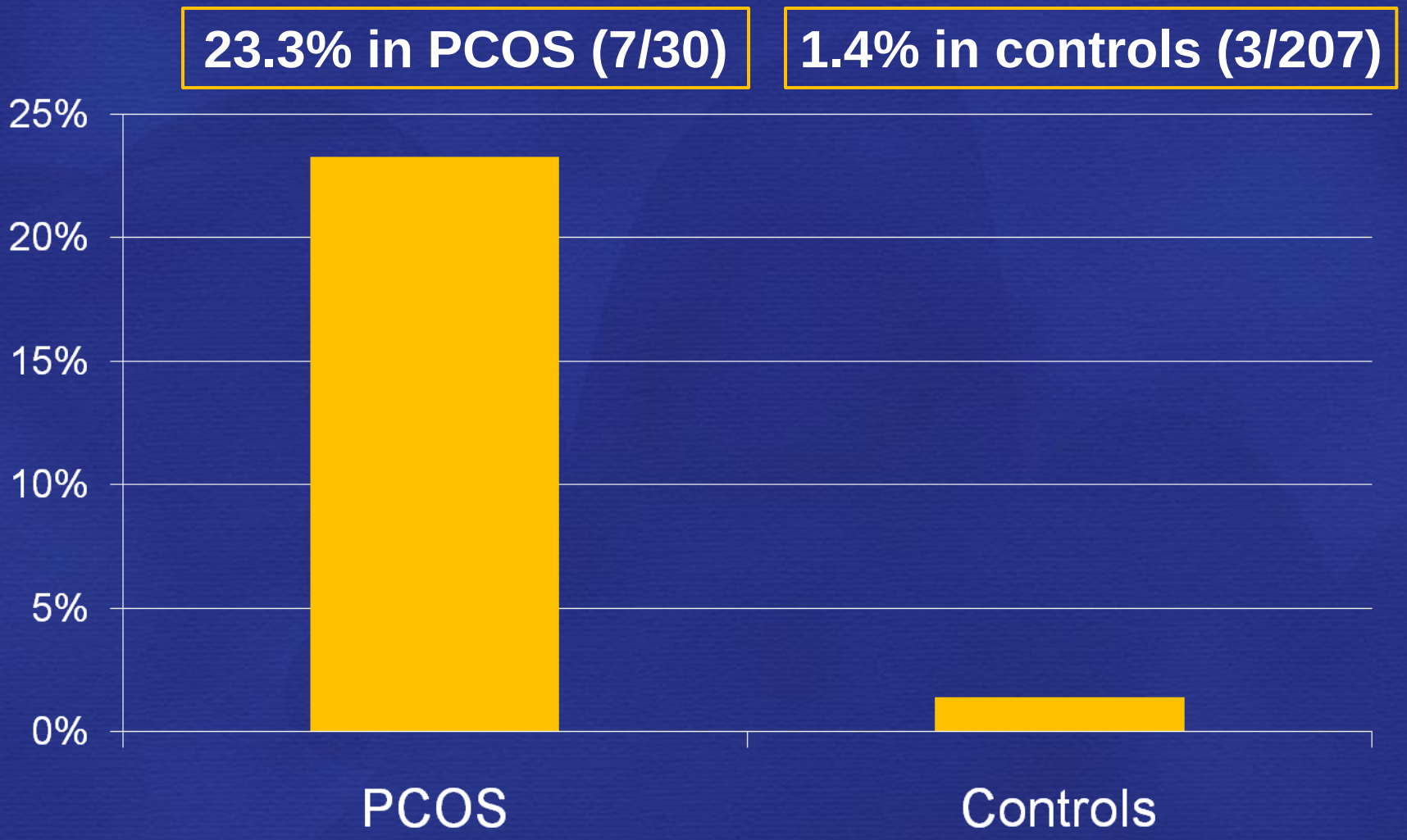
[3]Correspondence address. Fax: +82-2-762-3599; E-mail: ymchoi@snu.ac.kr

Chae et al., 2008 Hum Reprod

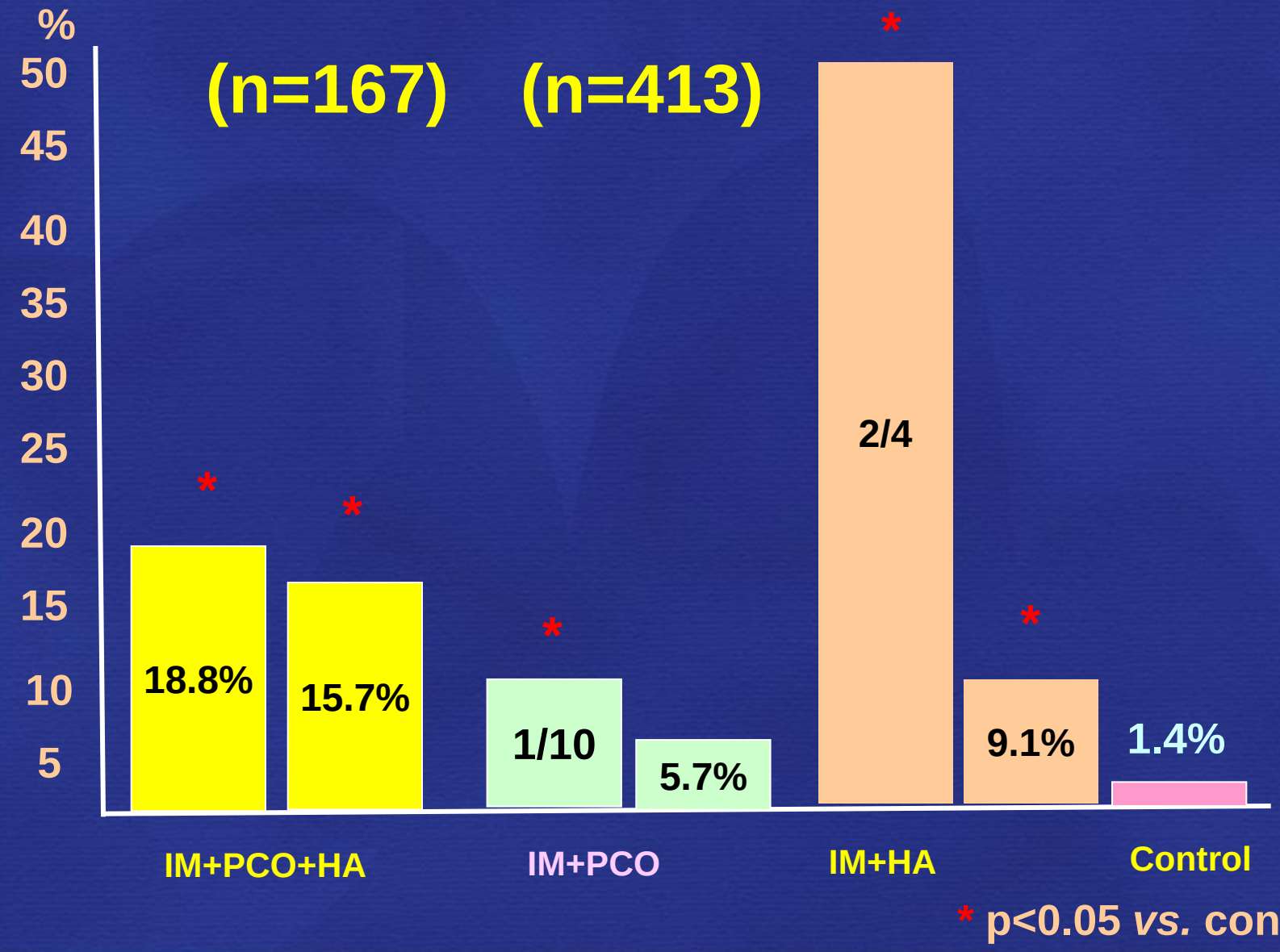
Prevalence in Korea



NCEPIII

Chae et al., 2008 Hum Reprod

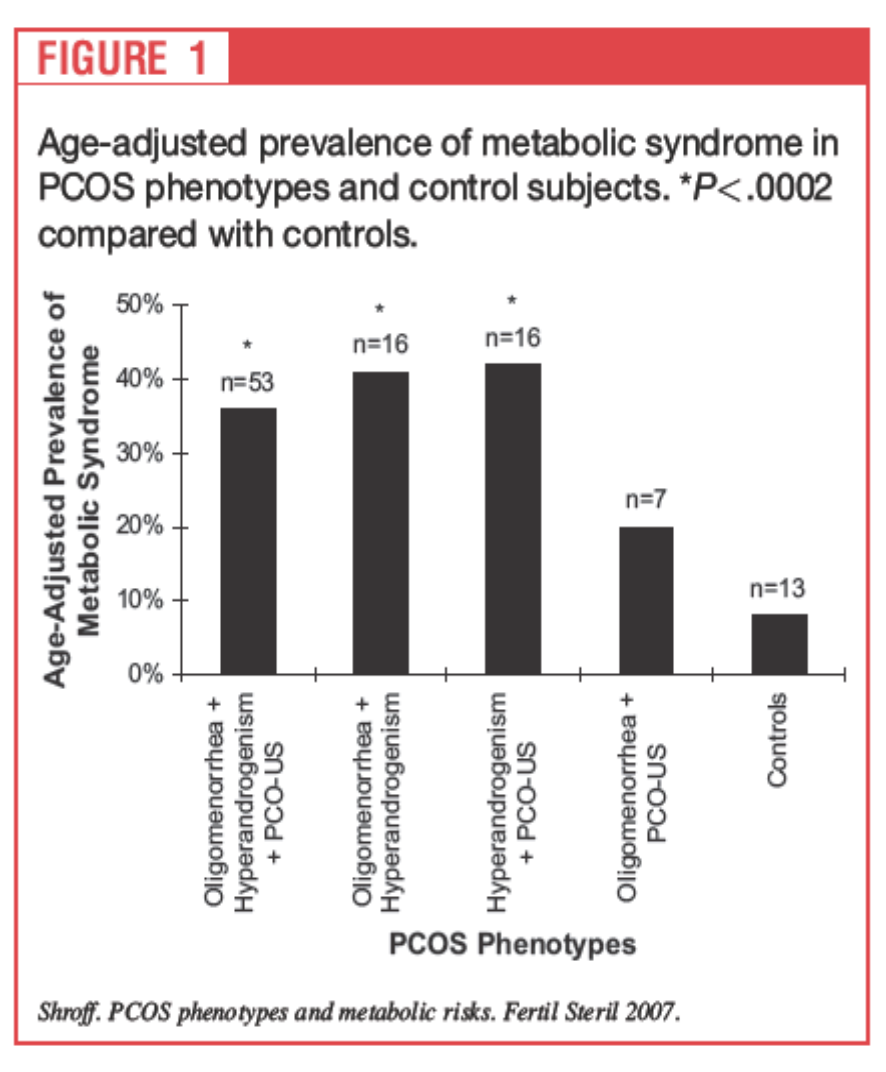
아형에 따른 대사증후군 빈도 차이가 보고됨



* p<0.05 *vs.* control

Chae et al., 2008 Hum Reprod; Data on 2010-01

아형에 따른 대사증후군 빈도 차이가 보고됨



No significant difference in the prevalence of metabolic syndrome between women with O+P (20.3%) and control subjects (8.3%), even in obese women.

(PCOS, n=258, USA)

Shroff et al., 2007 Fertil Steril

Individual components of metabolic syndrome

- Central obesity in PCOS
- Type 2 DM in PCOS
- Dyslipidemia in PCOS
- Cardiovascular events

Obesity in PCOS

- The prevalence of obesity in women with PCOS is 60.0% in Causasians. (Azziz et al., 2004)

- In SNUH, the prevalence of obesity in women with PCOS
  - **25.2%** (39/155) (Chae et al., 2008)
  - **18.3%** (103/564) (updated data on 2010-03)

Azziz et al., 2004 JCEM; Chae et al., 2008 Hum Reprod

Central obesity

- Increased abdominal fat has been linked to insulin resistance and increased cardiovascular risk.
- Evaluation of central obesity
  - Measurement of waist circumference
  - CT or MRI scan
  - Abdominal ultrasound
  - DXA

Wajchenberg 2000 Endocr Rev

Central obesity in PCOS

Central obesity is the most common component of the metabolic syndrome in women with PCOS.

TABLE 2. Prevalence (%) of individual components of the metabolic syndrome in PCOS women

Components of the metabolic syndrome	Caucasian	African-American	Other[a]	Overall
Waist circumference > 88 cm	79	94[b]	65	80
HDL cholesterol < 50 mg/dl	67	58	70	66
Triglycerides ≥ 150 mg/dl	32	22	52	32
Hypertension ≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic	22	20	15	21
Fasting glucose ≥ 110 mg/dl	4	12	3	5

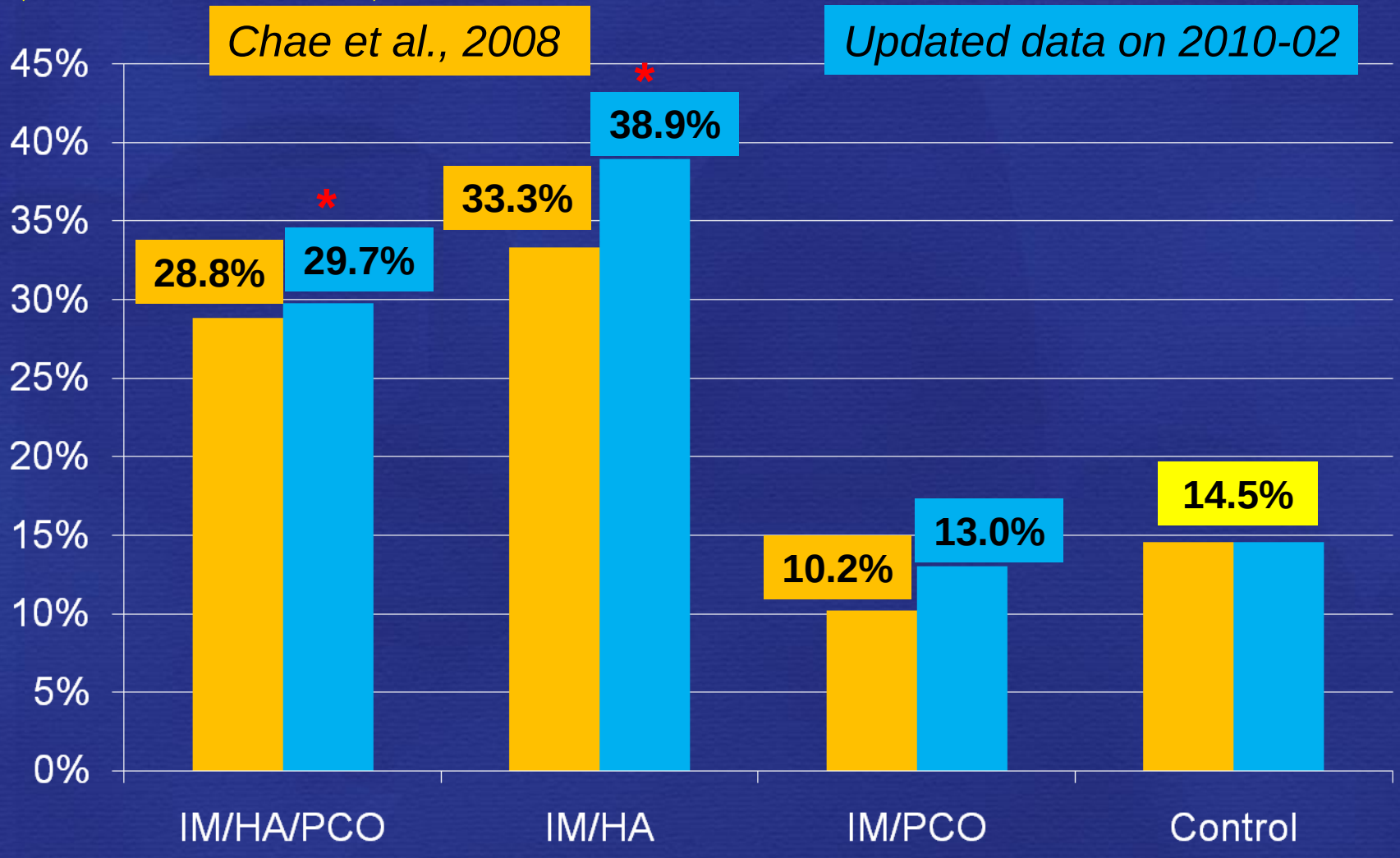
Ehrmann et al., 2006 JCEM

Prevalence of individual components of metabolic syndrome – SNUH data

Components	Korea (2008, n=162)	Korea (2010, n=386)	Caucasian (2006)
Waist circumference	23.1%	26.5%	79%
HDL cholesterol	30.0%	22.5%	67%
Triglyceride	26.7%	10.0%	32%
BP ≥ 130/85 mmHg	20.8%	13.7%	22%
Fasting glucose ≥ 100mg/dl	10.7%	8.4%	4% (≥ 110mg/dl)

Ehrmann et al., 2006 JCEM; Chae et al., 2008 Hum Reprod; Data on 2010-02

Prevalence of abdominal obesity in PCOS (WC> 80cm)



Chae et al., 2008 Hum Reprod; Data on 2010-02

Central obesity and insulin resistance in PCOS

- Carmina et al., 2007
  - Objective
    - Determine whether abdominal fat quantity is larger in PCOS than weight-matched controls
    - Assess whether PCOS patients and controls with similar abdominal fat quantity present similar insulin sensitivity
  - 110 PCOS patients and 112 weight matched controls
  - Dual X-ray absorptiometry (DXA)

Carmina et al., 2007 JCEM

Central obesity and insulin resistance in PCOS

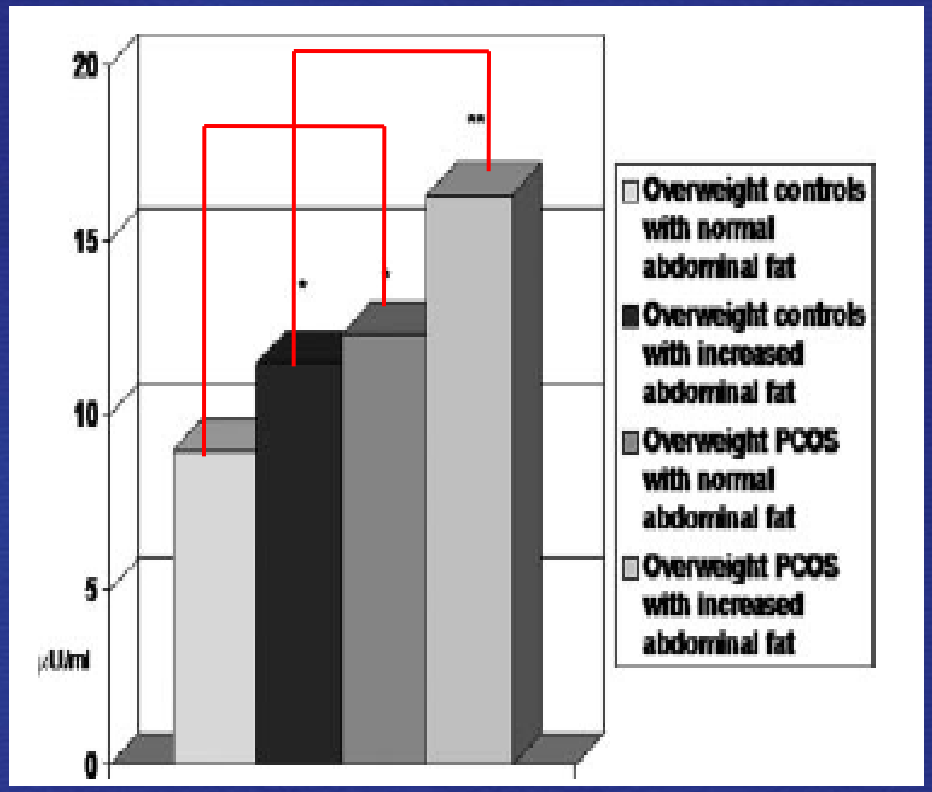
Fat parameter by total-body DXA in PCOS and weight matched controls

	PCOS (n = 110)	Controls (n = 112)
BMI	28.0 ± 5.5	28.0 ± 5.6
Waist circumference (cm)	92.4 ± 15.1[a]	88.2 ± 12.8
Total fat (g)	27,307 ± 10,182	27,020 ± 10,143
Trunk fat (g)	11,830 ± 5,772	10,981 ± 5,320
Trunk fat *vs.* total fat (%)	41.4 ± 6.1[a]	38.9 ± 6.3
R1 fat (g)	785 ± 387[a]	679 ± 363
R1 fat *vs.* total fat (%)	2.78 ± 0.50[a]	2.46 ± 0.49

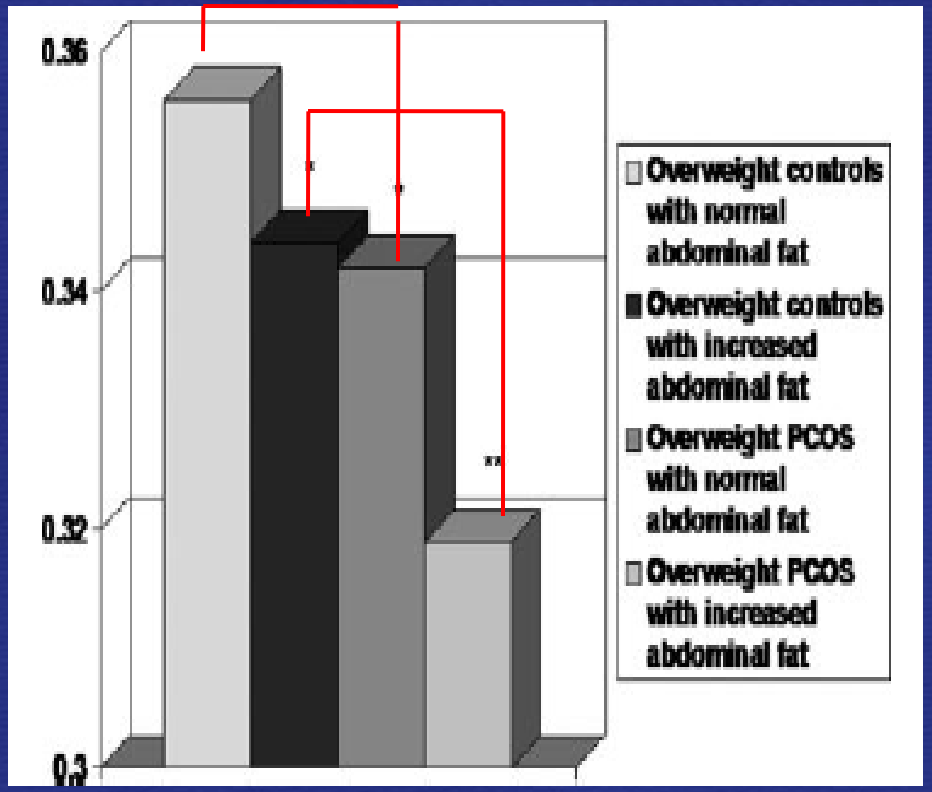
Compared with weight-matched controls, PCOS patients had similar quantity of total and truncal fat, but higher quantity of central abdominal fat.

Carmina et al., 2007 JCEM

Central obesity and insulin resistance in PCOS



Fasting insulin



QUICKI

Carmina et al., 2007 JCEM

Central obesity and insulin resistance in PCOS

- Carmina et al., 2007
  - PCOS patients with increased central abdominal fat had significantly higher insulin and reduced QUICKI than controls with similar quantities of central abdominal fat.
  - Overweight PCOS patients with normal central abdominal fat had significantly higher insulin and reduced QUICKI than overweight controls with normal central abdominal fat.
  - Abdominal fat may not be the only determinant of insulin resistance in PCOS.

Carmina et al., 2007 JCEM

PCOS에서 체중감량의 역할

- 비만한 가임기 여성
  - 기저 체중의 약 5-10%만으로도 유의한 배란률 증가 (Kiddy et al., 1992)
  - Clark 등 (1998)
    - 67명의 비만한 불임 여성 (평균 체질량 지수 37.4 ± 6.9)
    - 6개월간 약 10.2kg 정도의 체중감량
    - 전체 67명중 60명에서 자발적인 배란, 52명에서 (18명은 자연임신) 임신에 성공함

체중감량은 대사증후군의 다양한 구성 요소 및 임신과 관련한 문제까지도 한꺼번에 해결할 수 있는 유력한 치료법임 .

Individual components of metabolic syndrome

- Central obesity in PCOS
- Type 2 DM in PCOS
- Dyslipidemia in PCOS
- Cardiovascular events
- Non alcoholic fatty liver disease and PCOS

Type2 DM and PCOS

- Hyperinsulinemic insulin resistance is an universal feature of PCOS: 50-70% PCOS women have insulin resistance and hyperinsulinemia

  Azziz et al., Fertil Steril 2009

- Cohort studies of women with PCOS in the U.S.
  - Prevalence of impaired glucose tolerance (31-35%) and T2DM (7.5-10.0%) is higher in women with PCOS compared to the general population (1.6% and 2.2% in NHANES III study)

    Ehrmann et al., Diabetes Care 1999
  - Prevalence of impaired glucose tolerance (30%) was also high in adolescents with PCOS.

    Palmert et al., JCEM 2002

Screening for glucose intolerance in PCOS

- All PCOS patients should be screened for IGT with a 2-h oral glucose tolerance test
  - IGT: 140-199 mg/dL
  - T2DM: ≥ 200 mg/dL

- Perform regardless of BMI
  - Only those who are obese or those who are lean with other risk factors (minority report)

- Fasting serum glucose, insulin, HbA1c are not helpful.

Salley et al. AE and PCOS society, JCEM, 2007

Screening for glucose intolerance in PCOS

- Follow-up of women with PCOS for detection of abnormal glucose tolerance based on expert opinions (not evidence based)
  - Rescreen patients with NGT at least every 2 years or earlier if additional risk factors exist.
  - Screen patients with IGT annually for the development of D2DM.

Salley et al. AE and PCOS society, JCEM, 2007

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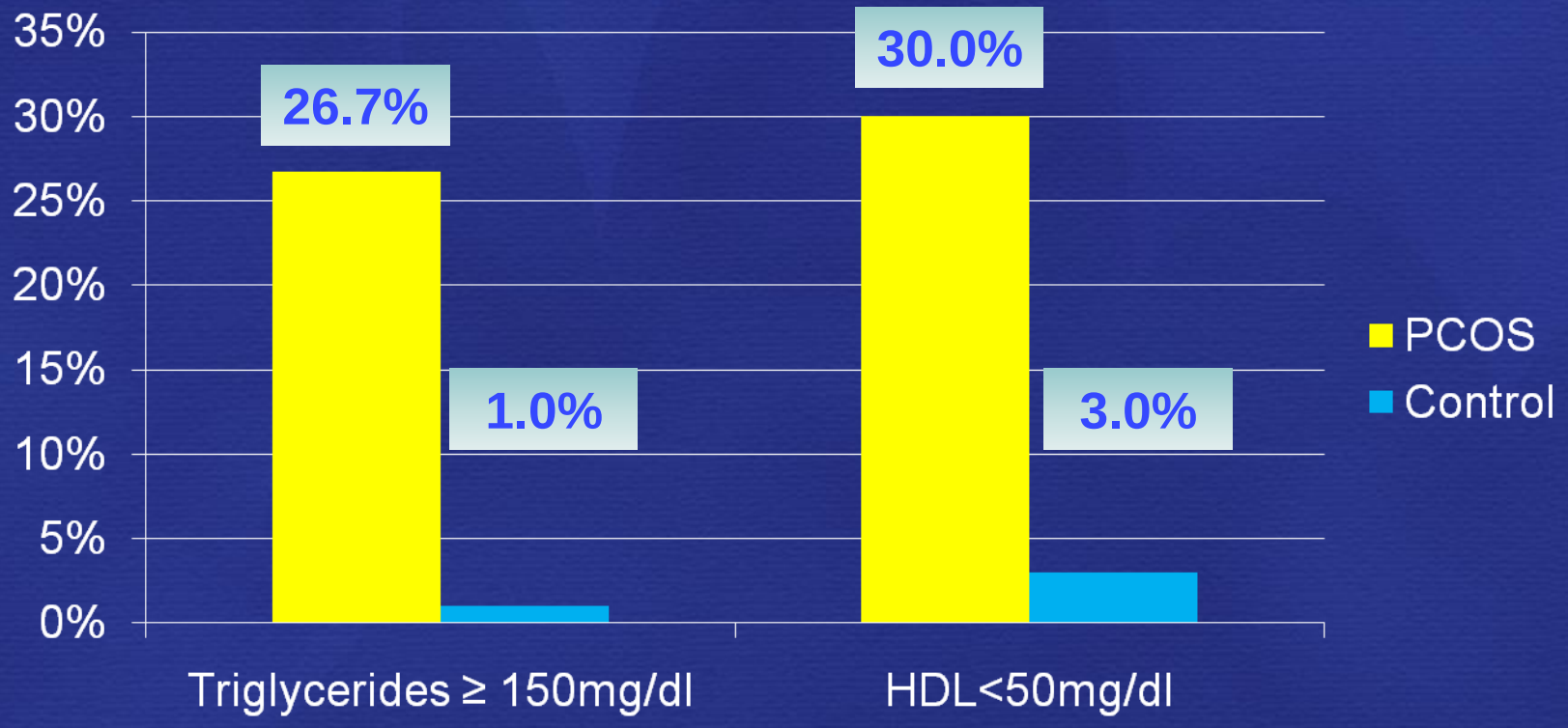
- Central obesity in PCOS
- Type 2 DM & PCOS
- Dyslipidemia in PCOS
- Other CVD risk factors in PCOS
- Non alcoholic fatty liver disease and PCOS

Dyslipidemia in PCOS

- Dyslipidemia of insulin resistance
  - Decreased HDL-C/Increased TG
  - Increased small, dense LDL-C



Chae et al., 2008 Hum Reprod; Azziz et al. AE and PCOS society, Fertil Steril, 2009

Dyslipidemia in PCOS

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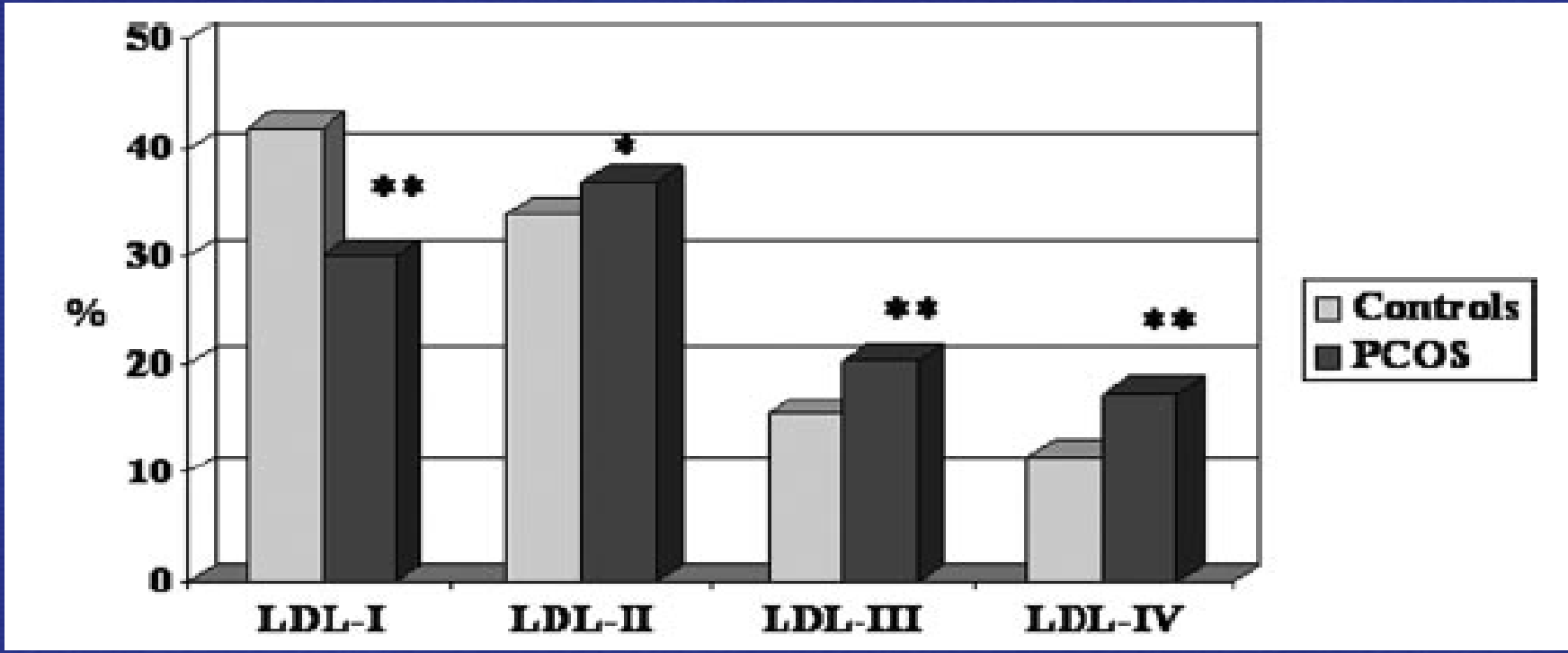

Bernis et al., 2007 J Clin Endocrinol Metab ; Azziz et al. AE and PCOS society, Fertil Steril, 2009

Elevated LDL-C levels in PCOS compared with weight matched controls

Non-obese patients and controls

	PCOS (n=42)	Control (n=27)	*P* value*
Fasting insulin (μU/mL)	12 ± 4	11 ± 6	.52
Fasting gucose (mg/dL)	83 ± 8	82 ± 5	.87
LDL-C (mg/dL)	181 ± 34	156 ± 39	<.001
HDL-C (mg/dL)	45 ± 11	43 ± 9	.99
TG (mg/dL)	103 ± 58	105 ± 74	.99

* Adjusted for age and include a Bonferroni correction
Obesity: BMI ≥ 27kg/m^2

Legro et al., Am J Med, 2001

Elevated LDL-C levels in PCOS compared with weight matched controls

Obese patients and controls

	PCOS (n=135)	Control (n=35)	*P* value*
Fasting insulin (μU/mL)	27 ± 16	17 ± 9	.001
Fasting gucose (mg/dL)	89 ± 11.3	87 ± 8	.44
LDL-C (mg/dL)	130 ± 32	117 ± 23	.006
HDL-C (mg/dL)	35 ± 10	31 ± 14	.002
TG (mg/dL)	194 ± 219	140 ± 88	.04

* Adjusted for age and include a Bonferroni correction
Obesity: BMI ≥ 27kg/m^2

Legro et al., Am J Med, 2001

Dyslipidemia in PCOS

- Elevated LDL-C levels in PCOS
  - A finding not usually noted in insulin resistance state
  - May be related to
    - Hyperandrogenemia (Wild et al., 1995; Graf et al., 1990) or
    - Genetic or environmental (Sam et al., 2005; Sam et al., 2006; Recabarren et al., 2008)
  - Remain elevated but stable over time into the menopause (Talbott et al., 1998).

Azziz et al. AE and PCOS society, Fertil Steril, 2009

Contents

- Central obesity in PCOS
- Type 2 DM & PCOS
- Dyslipidemia in PCOS
- Cardiovascular events
- Non alcoholic fatty liver disease and PCOS

Cardiovascular events in PCOS

- Evidence for increased CVD morbidity and mortality is inconclusive, yet suggestive.

- Initial studies did not find an increased prevalence of nonfatal/fatal CVD in women with PCOS (Pierpoint et al., 1998; Wild et al., 2000)

Wild et al., JCEM, 2010

Cardiovascular events in PCOS

- Recent study of the Women's Ischemia Evaluation Study (WISE) confirmed that women with PCOS have a larger number of cardiovascular events.
  - Multi-vessel CVD
    - 32% of PCOS women compared with 25% of non-PCOS women (odds ratio, 1.7)
    - Event free survival (including fatal and nonfatal events) was significantly lower in PCOS compared with non-PCOS women.

Shaw et al., JCEM, 2008

Cardiovascular events in PCOS

- Additional studies give further support to the association between PCOS and CVD.

- Krentz *et al. (2007)*
  - Cross-sectional study of 713 postmenopausal women (mean age, 73.8 yr)
  - Stepwise graded association between CVD and numbers of features of putative PCOS (premenopausal menstrual irregularity, hirsutism, or current biochemical hyperandrogenism)

Krenz et al., Menopause 2007

Cardiovascular events in PCOS

- Azevedo *et al (2006)*
  - Case-control study of 414 postmenopausal women (mean age, 60.4 yr)
  - Women with premenopausal menstrual irregularity (as a putative sign of PCOS) an increased odds ratio for coronary vascular disease.

- The recent epidemiological data suggest more frequent CVD in classic PCOS.

Azevedo et al., *Arq Bras Endocrinol Metabol 2006; Wild et al., JCEM 2010*

Assessment of Cardiovascular Risk - Consensus Statement by the AE-PCOS

- Measure waist circumference and BMI at every visit (Rosenzweig et al., 2008)
- BP be routinely checked at each visit
- A complete lipid profile (total cholesterol, LDL-C, non-HDL-C, HDL-C, and triglycerides)
  - If normal, reassessed every 2 yr or sooner if weight gain occurs.

Wild et al., JCEM 2010

Assessment of Cardiovascular Risk - Consensus Statement by the AE-PCOS

- A 2-h post 75-g oral glucose challenge
  - PCOS women with a BMI greater than 30 kg/m2,
  - Lean PCOS women with advanced age (40 yr), personal history of gestational diabetes, or family history of T2DM
- Normal glucose tolerance be rescreened every 2 yr or sooner if additional risk factors are identified
- Those with IGT should be screened annually for T2DM
- Endorse HemoglobinA1c for risk assessment, but further studies will be needed

Wild et al., JCEM 2010

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- Central obesity in PCOS
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- Dyslipidemia in PCOS
- Other CVD risk factors in PCOS
- Non alcoholic fatty liver disease and PCOS

Nonalcoholic fatty liver disease (NAFLD) and PCOS

- Nonalcoholic fatty liver disease
  - One of the most common causes of chronic liver disease
  - Hepatic manifestation of metabolic syndrome
  - Obesity and insulin resistance is core feature
  - Nonalcoholic steatohepatitis (NASH)
    - More aggressive form of NAFLD
    - Higher risk for advanced fibrosis, cirrhosis, HCC

Nonalcoholic fatty liver disease (NAFLD) and PCOS

- **Alanine aminotransferase (ALT) activity was abnormal in 30% of 70 female infertility patients with PCOS, which represents suspected NAFLD.**

  Schwimmer et al., FS 2005

- **41% of PCOS women present NAFLD.**

  Cerda et al., J Hepatol 2007

- **Fatty liver was identified in 55% of subjects with PCOS, nearly 40% of whom were lean women**

  Gambarin-Gelwan et al., Clin Gastroenterol Hepatol 2007

SNUH Data Nonalcoholic fatty liver disease

	PCOS (n=242)	Control (n=1,167)	*P* *	95% CI
Age	30.4 ± 4.9	30.8 ± 4.9	.237	
BMI	21.3 ± 3.2	20.3 ± 3.2	<.0001	
AST (IU/L)	18.0 (16.7,19.3)	17.3 (16.0, 18.6)	. 023	
ALT (IU/L)	14.2 (12.5,15.9)	12.8 (11.3, 14.3)	.001	
GGT (IU/L)	14.9 (13.3, 16.5)	13.8 (12.4, 15.2)	.014	
NAFLD on abdominal USG (%)	8.3% (20/242)	4.3% (50/1167)	.010	2.01 (1.18-3.45)

Assess ALT, GGT, alkaline phosphatase and abdominal USG, in all PCOS women having metabolic syndrome

Carmina. J Hepatology 2007

Unpublished, 2010

Conclusion

- PCOS is not just a reproductive disease, but a systemic condition as a component of metabolic syndrome.

Age-related changes in the PCOS phenotype throughout lifespan

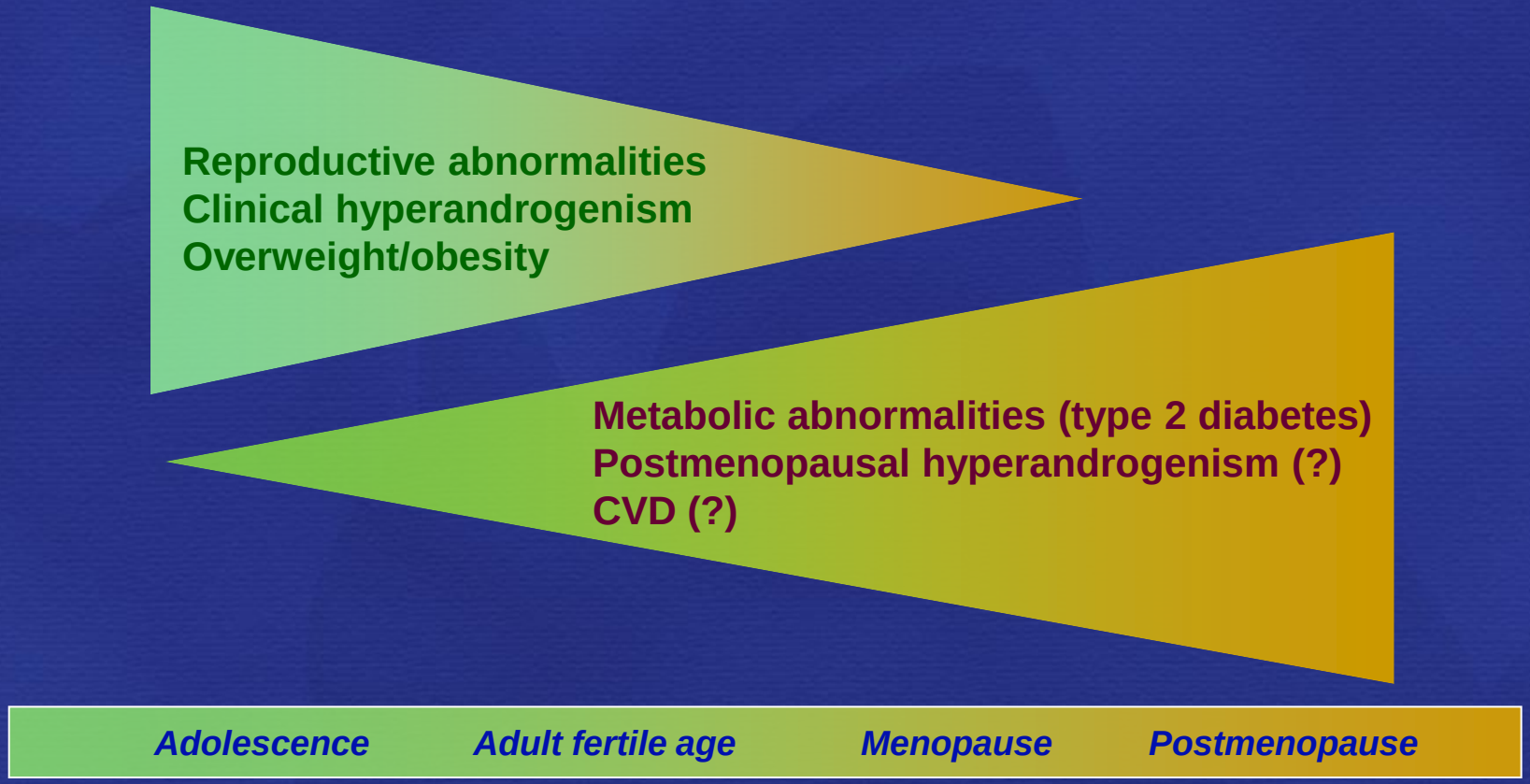


FIGURE 1. Age-related changes in the PCOS phenotype throughout a life span.
The question marks identify still debatable topics.

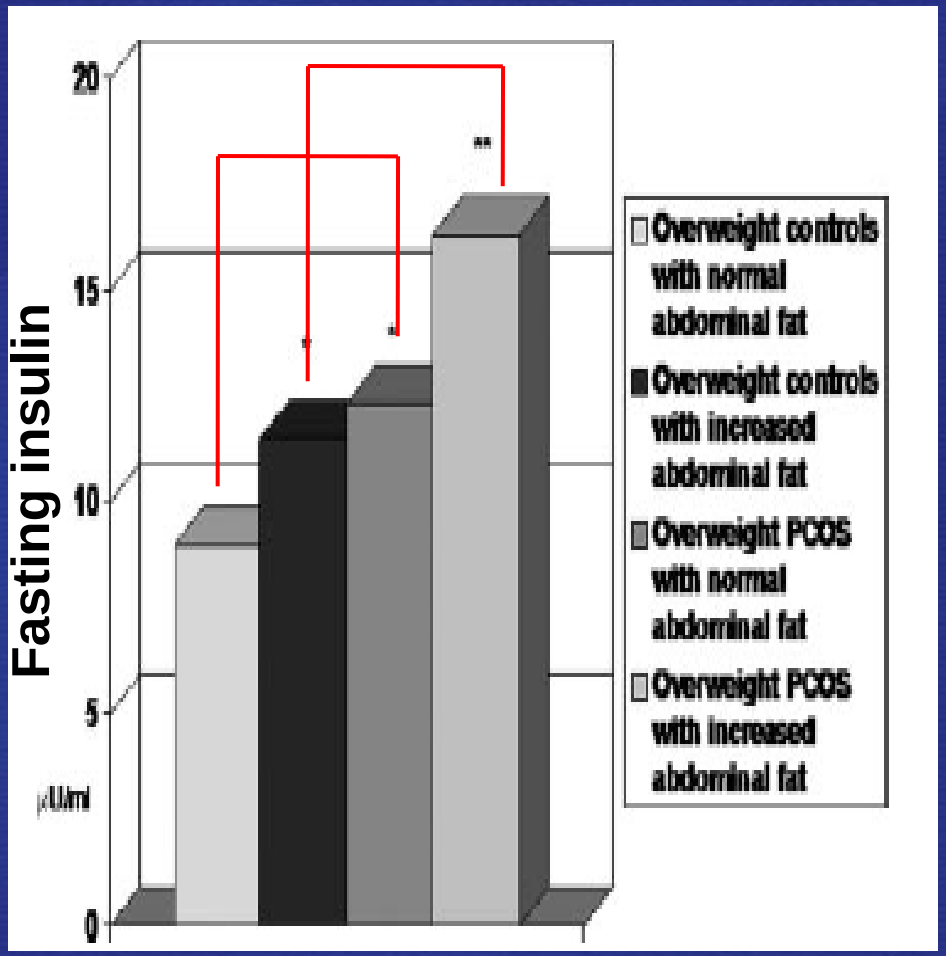
Pasquali R and Gambineri A. Ann N Y Acad Sci 2006;1092:158-74.

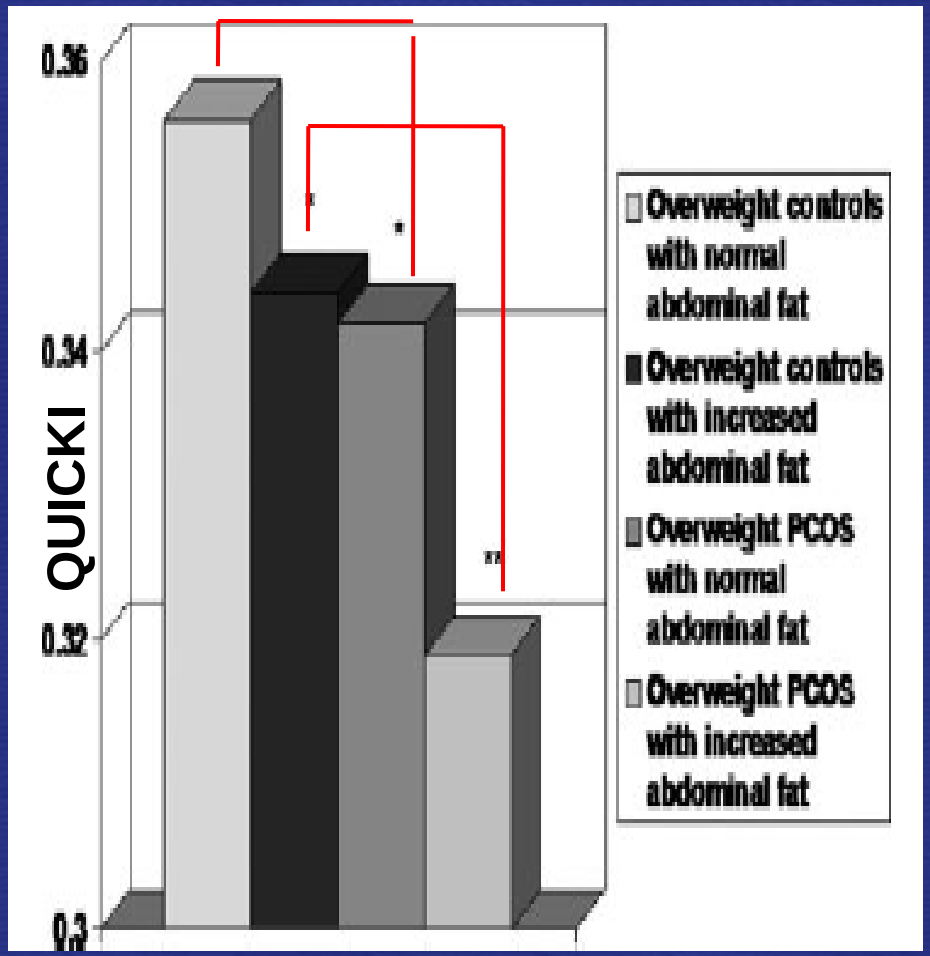
Thank you for attention !!

Conclusion

- Cardiovascular disease is a significant cause of morbidity and mortality.
- Metabolic risk factors, such as those clustered in the metabolic syndrome, have been identified and are targeted in efforts to reduced the risk of CVD
- Core pathophysiology: obesity and insulin resistance
- PCOS is not just a reproductive disease, but a systemic condition as a component of metabolic syndrome.

Central obesity and insulin resistance in PCOS





Carmina et al., 2007 JCEM

Cardiovascular events

- Evidence for increased CVD morbidity and mortality is inconclusive, yet suggestive
- The Women's Ischemia Evaluation Study (WISE)
  - Confirmed that women with PCOS have a larger number of cardiovascular events.
  - Multivessel CVD was observed in 32% of PCOS women compared with 25% of non-PCOS women (odds ratio, 1.7)

Wild et al. JCEM 2010

Cardiovascular events

- Cross-sectional study of 713 postmenopausal women (mean age, 73.8 yr) and found in nondiabetic women

  between CVD and numbers of features of putative PCOS, as defined by premenopausal menstrual irregularity, hirsutism, or current biochemical hyperandrogenism.

Krentz et al., Menopause 2007

Other CVD risk factors in PCOS

- Castella et al., 2008
  - Women with PCOS have been reported to have subclinical CVD and increased abdominal fat.
  - Evaluate the relationship between visceral fat (VF) and early markers of CVD in PCOS women

Castella et al., HR, 2008

Other CVD risk factors in PCOS

Cardiovascular profile in overweight PCOS women compared to age- and BMI-matched controls

	PCOS (n=200)	Control (n=100)	*P* value*
Age (years)	24.6 ± 3.2	24.0 ± 2.8	.11
BMI (kg/m^2)	28.5 ± 2.8	28.8 ± 2.7	.37
SBP (mmHg)	118 ± 9	117 ± 8	.35
DBP (mmHg)	80 ± 4.8	79 ± 4.6	.08
Carotid intima media thickness (mm)	0.46 ± 0.16	0.38 ± 0.09	<.001
Flow-medicated dilation (%)	13.7 ± 2.3	17.8 ± 2.2	<.001
CRP (mg/L)	1.9 ± 0.8	0.8 ± 0.4	<.001
WBC (cell/mm^3)	7350 ± 380	5260 ± 230	<.001
PAI-1 (IU/mL)	2.6 ± 0.7	1.7 ± 0.6	<.001
Visceral fat (mm)	31.4 ± 7.3	28.0 ± 6.1	<.001

Cascella et al., HR, 2008

Other CVD risk factors in PCOS

Final model of multiple linear regression analysis of carotid intima media thickness as dependent variable in PCOS

	Unstandardized coefficient	standardized coefficient	*P* value
Visceral fat	0.003	0.424	<.001
FMD	0.009	0.238	.002
CRP	0.062	0.663	<.001
Constant	0.167		

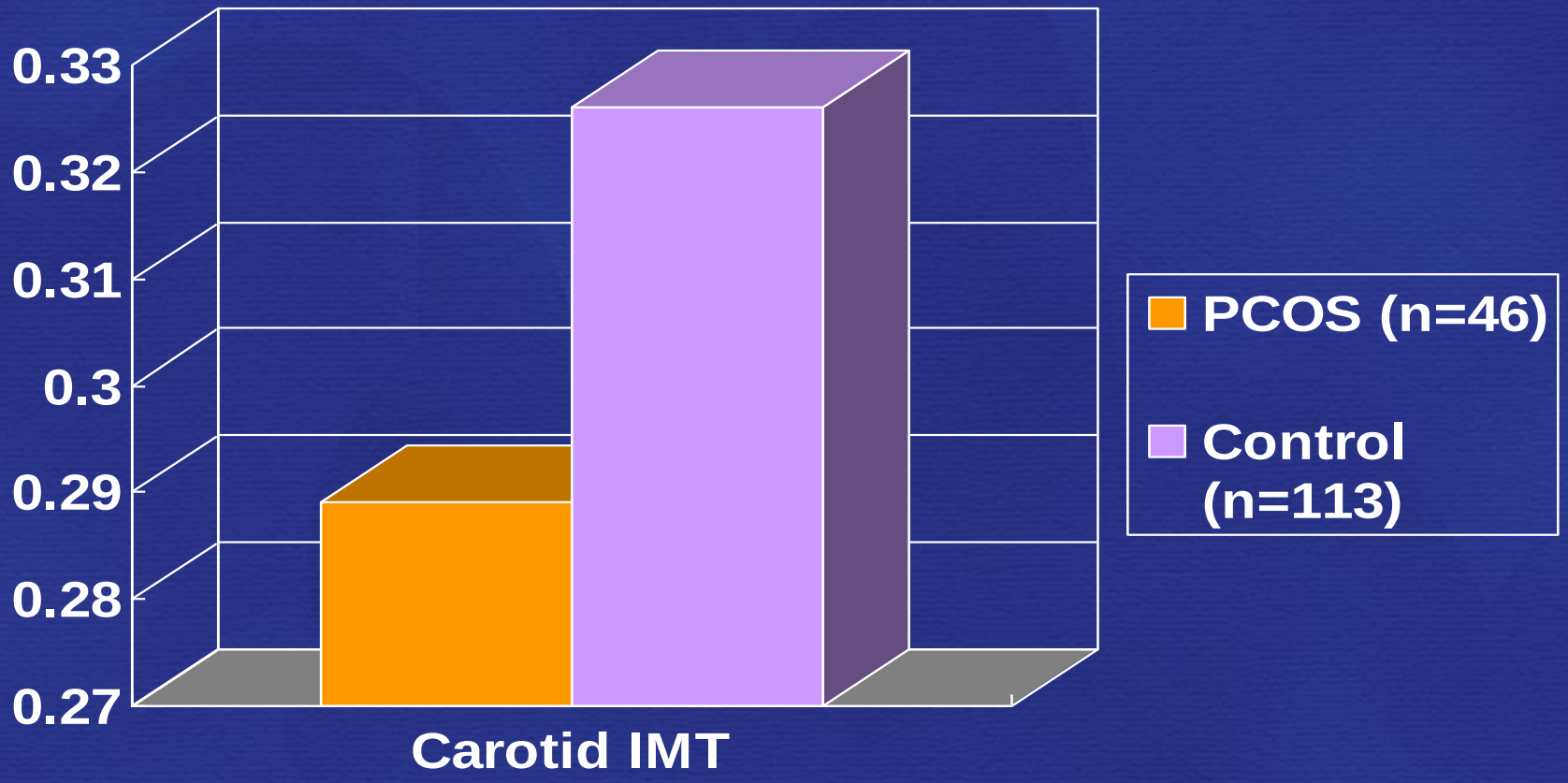
Carotid intima media thickness was positively affected by visceral fat and CRP

Visceral fat is associated with subclinical CVD in PCOS

Cascella et al., HR, 2008

SNUH Data Carotid intima media thickness

P value =.233 after controlling for age & BMI



Mean age was 30.5±4.7 for PCOS and 32.7±3.9 for controls (*P*=.002)

Unpublished

Screening for cardiovascular risk factors in PCOS

- Standard recommendation for routine assessment of cardiovascular disease are lacking
- In all women with PCOS
  - Measure waist circumference (reflection of visceral adiposity)
  - Measure BP
  - Fasting lipid profile
  - Glucose 2 hours after oral ingestion of a 75g glucose
  - Determine if the presence of metabolic syndrome
  - Repeat BP and fasting lipid profile annually

Baillargeon. ASRM, 2008