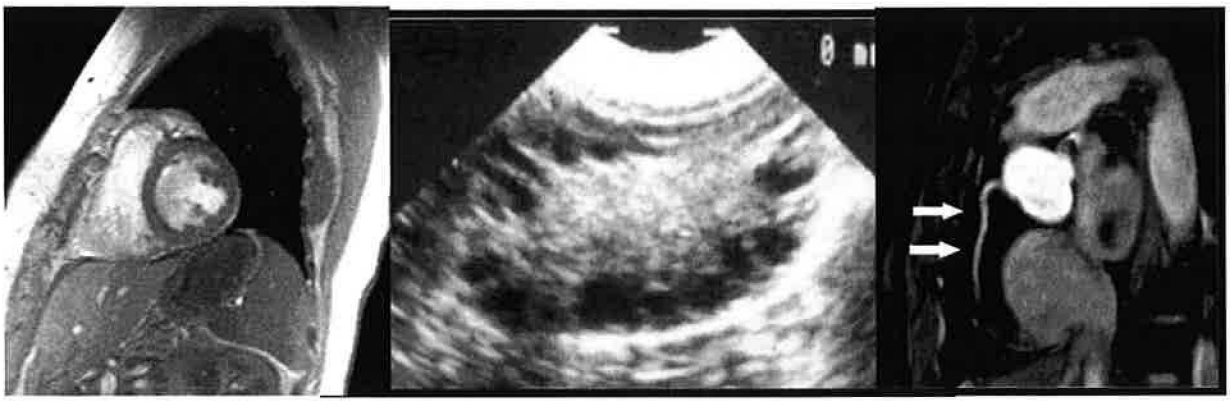

The Cardiovascular Risk Paradox in Polycystic Ovarian Syndrome

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This is to acknowledge that Alice Y. Chang, MD, MSCS has not disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Chang will be discussing off-label uses in his/her presentation.

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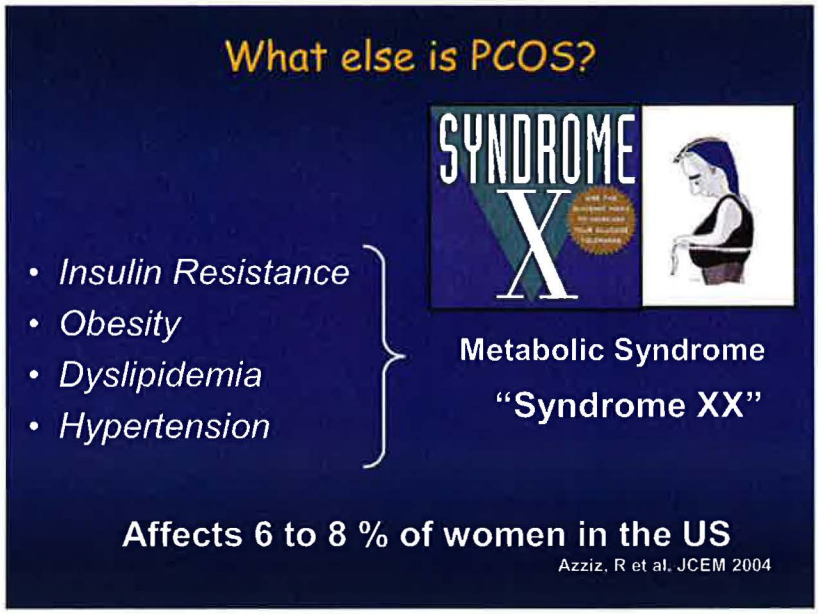
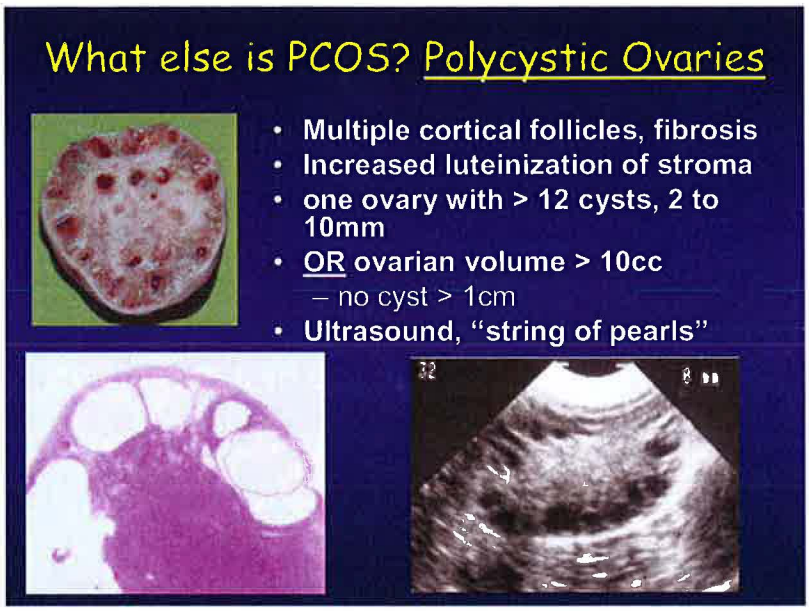
Introduction

Polycystic Ovarian Syndrome (PCOS) is a common disorder that occurs in at least 6-8% of women in the United States [1-3]. Using the Rotterdam consensus criteria could increase the prevalence of PCOS by at least 65%.[4] PCOS is characterized by irregular menses, hirsutism and/or elevated circulating testosterone concentrations and polycystic ovarian morphology.

A key feature of almost half of women with PCOS, whether or not they are obese, is the presence of insulin resistance.[5] Not surprisingly, PCOS is also associated with an increased prevalence of traditional risk factors for cardiovascular (CV) disease - obesity, hypertension, insulin resistance and dyslipidemia[2].



Using the Rotterdam consensus criteria could increase the prevalence of PCOS by at least 65%.[4]



But whether PCOS is a risk factor for CV disease above and beyond the metabolic syndrome now common in women without PCOS has been difficult to assess or conclude from existing studies. In addition, there are challenges in quantifying CV risk in these premenopausal, often overweight or obese women. This review will discuss these challenges in light of the current evidence available about CV events and surrogate markers of CV disease in women with PCOS.

Cardiovascular Events

The first report to raise concern for CV risk in women with PCOS was based on a calculated "risk" model without event identification. Based on the prevalence of CV risk factors among 30 Swedish women with PCOS after wedge resection, a 7-fold higher risk of MI was hypothetically predicted based on events observed in an unrelated control cohort. This risk for MI was driven by a much higher prevalence of hypertension (40% v. 11%, $p < 0.01$) and Type 2 Diabetes (DM) (15% v. 2.3% ($p<0.05$) in this small sample of women with PCOS compared to the control population-based cohort.[6] Despite the very speculative nature of this estimate, this was a provocative study that is still cited today as evidence for CV risk in women with PCOS.

Age group	Risk Rate	95% CI	p
40-49 18 PCOS	4.2	1.0 – 8.8	<0.05
50-61 12 PCOS	11.0	1.2 - 32.6	<0.05
All	7.4		<0.001

The first studies to analyze CV event and mortality data in women with PCOS were performed using the United Kingdom (UK) National Health Service Central Registry. PCOS was diagnosed through retrospective hospital record review by clinical evidence of ovarian dysfunction and ovarian pathology. Over a 50 year period, 1028 women were treated for PCOS in the UK, with the majority undergoing wedge resection. Standardized mortality rates (SMR) were calculated as a ratio of deaths among women with PCOS divided by deaths for age-matched women. Contrary to what the Dahlgren analysis predicted, there was no significant increase in the SMR for all causes [SMR 0.90, 95% confidence interval (CI) 0.69-1.17], ischemic heart disease (1.40, 95% CI 0.75 – 2.40), stroke (0.23, 95% CI 0.03-0.85) or DM (2.7, 95% CI 0.33-9.76). Despite 'the likelihood of severe disease in women with PCOS who required wedge resection surgery', there was no increased risk for women with PCOS up to the ages of 75.[7-9]

A subsequent analysis of this same UK cohort evaluated a subgroup with questionnaires and physical exams in 1999 to confirm the diagnoses of PCOS and any CV risk factors or disease. Interestingly, only 26 of 345 people evaluated were excluded based on the absence of clinical symptoms. Otherwise, most women were still anovulatory after wedge resection. With a smaller sample size, the primary outcomes changed to presence of DM and CV disease. Both groups were overweight but not obese with a mean BMI of 26.6 in the PCOS group and 25.9 in the control. Adjusted for BMI, only the increased OR for cerebrovascular disease (3.4, 95% CI, 1.2 -9.6) was

significant.[8] With an additional 2 years of CV events and deaths from the original cohort, the SMR attributable to DM was 4.60 (95% CI, 1.25-11.77).

Underlying cause of death	ICD code	No. of deaths	SMR (95% CI)
All causes	ICD-7/8/9 1–999	70	93 (72–117)
Cardiovascular disease	ICD-7400–468 & 330–334 ICD-8/9390–429	17	78 (45–124)
Coronary heart disease	ICD–7420 ICD-8/9410 –414	14	122 (67–205)
Cerebrovascular disease	ICD-7330–334 ICD-8/9430–438	2	35 (4–126)
Diabetes	ICD–7260 ICD-8/9250	4	460 (125–1177)

Based on the analysis from this UK cohort, PCOS may increase the risk for deaths from DM, but it is unclear that there is any additional risk of death from CV disease for PCOS status per se. At the very least, there was no replication of the dramatic increase in expected CV disease mortality initially suggested by the Dahlgren study.[8] Criticisms of this work include participation bias, with questionnaire or medical record data obtained in only 31% (319/1028) of the original cohort, and the younger age of the cohort. The average age of the original cohort was 56.7 (range 38-98), but they also excluded women over the age of 74 from the study. CV disease differences might not have been fully appreciated without the appropriate horizon when CV death is more common and where differences might be more easily seen. Also, women undergoing wedge resection are those interested in fertility treatment; often, patients with the more severe forms of PCOS did not seek fertility treatment and did not undergo wedge resection. PCOS diagnosis was ascertained from pathology-confirmed tissue; therefore, this data excludes individuals not undergoing surgery.

An analysis of menstrual cycle irregularity in the Nurses' Health Study is often used as an indicator of potential risk given that this study was longitudinal and given the large proportion of women with PCOS who contribute to the pool of women with menstrual irregularity. [10]. Although androgen excess was not explored, PCOS is one of the most common causes of oligomenorrhea.[11] The Nurses' Health Study could analyze risk with over 1000 CV events.

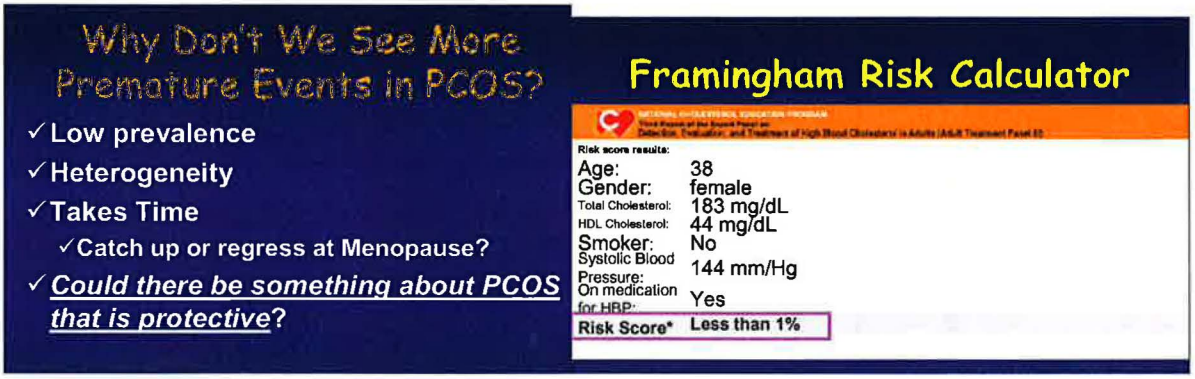
TABLE 2. RRs for CHD as a function of menstrual cycle regularity at ages 20–35 yr

	Menstrual cycle regularity ages 20–35 yr				P trend
	Regular	Usually regular	Usually irregular	Very irregular	
Total CHD					
No. of cases	810	327	184	96	
Person-yr	715,293	264,924	126,406	49,292	
Age-adjusted RR (95% CI)	1.0	1.02 (0.90–1.16)	1.25 (1.07–1.47)	1.67 (1.35–2.06)	<0.001
Multivariate[a] RR (95% CI)	1.0	1.02 (0.89–1.16)	1.22 (1.04–1.44)	1.53 (1.24–1.90)	<0.001
Nonfatal CHD					
No. of cases	562	210	132	60	
Age-adjusted RR (95% CI)	1.0	0.95 (0.81–1.11)	1.30 (1.07–1.60)	1.50 (1.15–1.96)	0.001
Multivariate[a] RR (95% CI)	1.0	0.96 (0.82–1.12)	1.27 (1.05–1.54)	1.38 (1.06–1.80)	0.005
Fatal CHD					
No. of cases	248	117	52	36	
Age-adjusted RR (95% CI)	1.0	1.17 (0.94–1.46)	1.16 (0.86–1.56)	2.04 (1.44–2.89)	0.001
Multivariate[a] RR (95% CI)	1.0	1.12 (0.90–1.40)	1.11 (0.82–1.50)	1.88 (1.32–2.67)	0.005

[a] Adjusting for age, body mass index, cigarette smoking, menopausal status/postmenopausal hormone use, parential history of MI before age 60 yr, parity, alcohol intake, aspirin use, multivitamin use, vitamin E supplement use, physical activity level, and history of oral contraceptive use.

The adjusted relative risk (RR) for CV events was 1.53 (95% CI 1.24–1.90) for women with the most irregular cycles. This is similar to that seen in the retrospective UK cohort study. A positive dose-response effect was seen from usually irregular to very irregular, with an increasing risk for all, nonfatal and fatal CV events. However, when adjusting for the additional risk factors of hypertension, DM and cholesterol, the RR was attenuated and only significant for women with the most irregular cycles 1.34 (95% CI 1.08–1.66).[10] Because menstrual irregularity was also associated with increased risk for insulin resistance and diabetes in this same cohort [12], menstrual irregularity may be less a surrogate for PCOS than for insulin resistance. Interestingly, the estimated RR of 1.5 for menstrual irregularity is comparable to the 1.6 to 2.0 hazard ratios for CV events from the metabolic syndrome in two large population studies.[13,14]

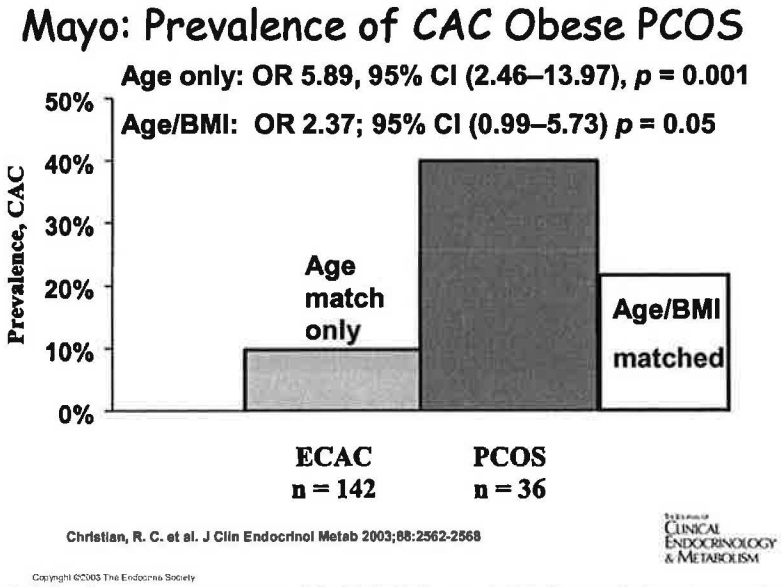
Why don't we see more premature events in PCOS? The difficulty in studying CV events in women with PCOS derives from the low prevalence of CV events in premenopausal women. Three studies of post-menopausal women undergoing coronary angiography found an increase risk of coronary occlusion or CV events in women with androgen excess and/or irregular menses or polycystic ovaries.[15-17] These results must be viewed with caution because it has not been established whether polycystic ovaries or elevated androgens during the post-menopause correctly identify women with PCOS during their reproductive age. Androgen excess in women with PCOS normally decreases during the menopausal transition[18,19] and polycystic ovaries may regress.[20] On the other hand, many would argue that unbiased ascertainment of recall for symptoms of hirsutism is reasonably accurate. They suggest that older women can report accurately whether or not they were more hirsute than their peers given the importance of androgen excess to female identity. There is a clear need for future studies to prospectively evaluate and determine the risk for CV disease and events for women with PCOS through the menopausal transition and beyond.



Surrogates for CV Disease

Given the low prevalence of CV events in premenopausal women, surrogate markers for CV disease have been evaluated in PCOS women. Coronary artery calcification (CAC) has been established as a predictor of pathologically diagnosed atherosclerosis and angiographically determined coronary artery disease.[21,22] Peripheral measures of CV disease, including carotid intima-media wall thickness (IMT) and peripheral endothelial reactivity have also been validated as predictors of CV events.[23,24]

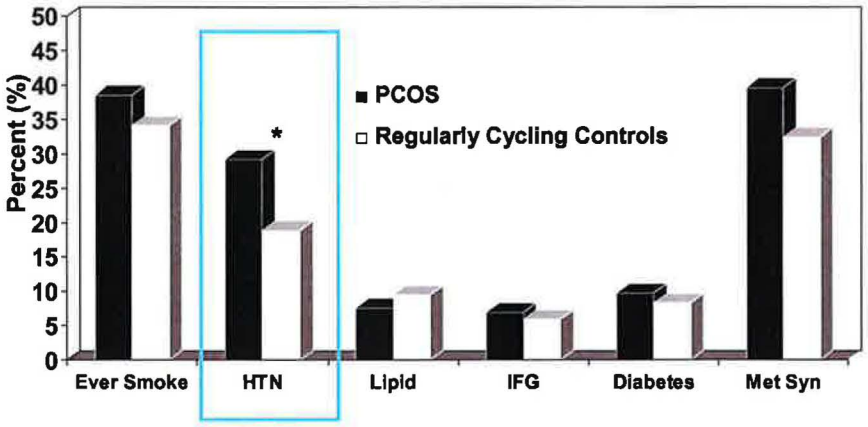
Coronary Artery Calcium Whether or not women with PCOS have a higher prevalence of CAC is debatable when considering two critical limitations to measuring CAC in young women. It is known that the overall prevalence of any detectable CAC is low among young women (5.1 % of women ages 33 to 45).[25] With three published studies measuring CAC with approximately 60 or fewer women with PCOS, only large differences could be confidently appreciated.[26-28] Second, accounting for obesity is especially important in defining and interpreting positive CAC scores. In obese persons, x-ray scatter from adjacent soft tissue is known to increase the false-positive rate. In the Dallas Heart Study, repeated scans among the same individuals demonstrated the highest degree of potential false-positives with CAC scores below 10, especially among the obese.[29] For that reason, a CAC score of 10 was used to define a positive versus negative scan. Reviewing all three studies in women with PCOS, the majority of the CAC scores were less than 10. The significant influence of BMI on CAC is illustrated in the first study that failed to find significant differences between 36 women with PCOS and control groups matched for BMI (OR 2.37, 95% CI 0.99–5.7, $p = 0.05$).[26] Even when comparing this PCOS group to a second population sample with a lower BMI and a lower prevalence of detectable CAC, the difference in prevalent CAC were not significant after adjusting for BMI.[26]



A second study of 24 obese women with PCOS and BMI-matched controls illustrates both limitations of studying CAC in PCOS. The range of CAC scores was only 0-9.3 in the PCOS group, and BMI was the only significant predictor of CAC among all women

with CAC (n=10) compared to women without CAC (n=38) (p=0.027).[27] In the third study of 61 women with PCOS and BMI-matched controls both groups were overweight, but not obese.[28] After adjustment for age and body mass index, the OR for CAC among women with PCOS achieved borderline significance (OR 2.31, 95% CI 1.00-5.33, p=0.049) but was no longer was significant after adjustment for insulin, triglyceride and high density lipoprotein concentrations. Therefore, the influence of obesity both technically and mechanistically should reduce enthusiasm for the assumption that CAC and coronary atherosclerosis is greater among women with PCOS rather than among women who are obese or who have the metabolic syndrome.

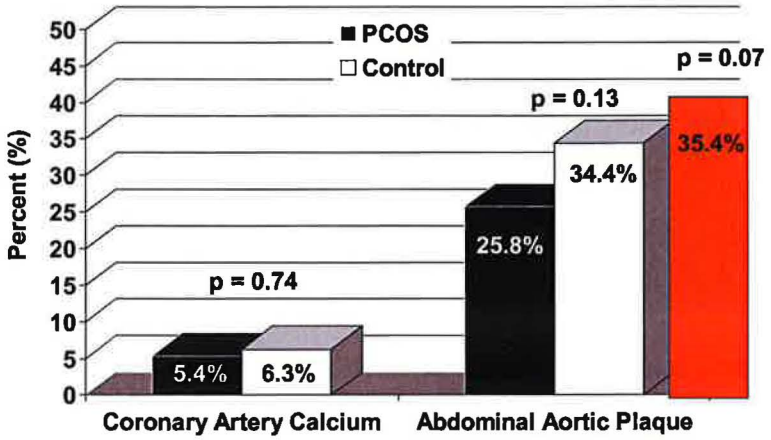
DHS: Cardiovascular Risk Factors
PCOS and Regularly Cycling Controls



* p = 0.03

Chang, AY et al. *Endo Suppl*;147(298): 2006.

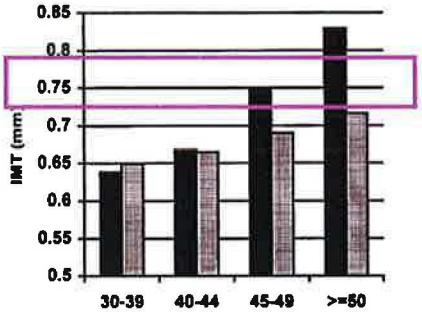
No Difference in the Prevalence of Atherosclerosis.
PCOS and Regularly Cycling Controls



Chang, AY et al. *Endo Suppl*;147(298): 2006.

Carotid Intimal Media Thickness (IMT) PCOS has been more consistently associated with greater carotid IMT in older[30] and younger women[31-33] and higher carotid atherosclerotic plaque index scores.[20] When no difference was seen in one study, the overweight and obese controls had a higher than normal carotid intimal medial thickness.[34] Multivariable models have found that the associations of PCOS with carotid IMT were attributable to insulin resistance and dyslipidemia.[32,35] Interestingly, along with positive associations with insulin resistance, two studies found that the adrenal androgen, dehydroepiandrosterone sulfate, was *inversely* associated with carotid IMT in PCOS.[33,34]

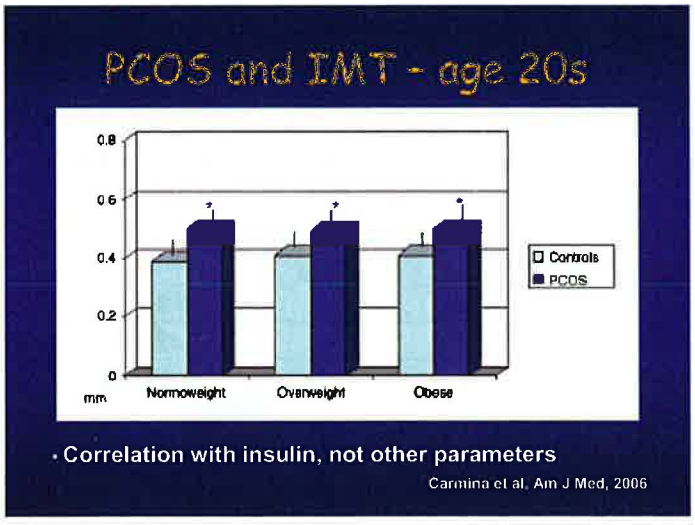
Mean CIMT in PCOS cases, controls by age



(Cases = solid, Controls = hatched) (PCOS X age interaction p =.031)

Talbott, E. O. et al. Arterioscler Thromb Vasc Biol 2000;20:2414-2421

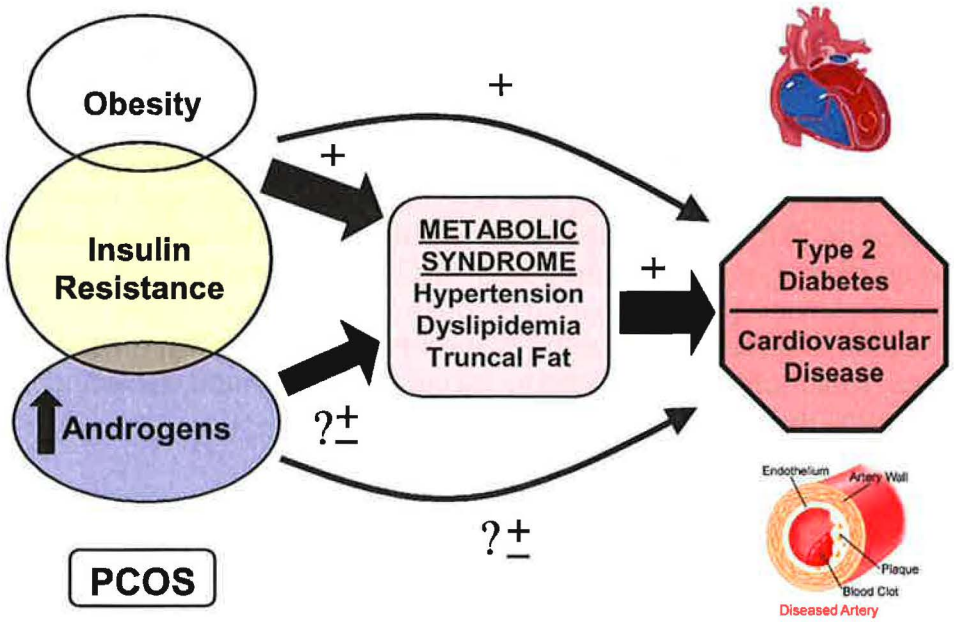
Arteriosclerosis, Thrombosis, and Vascular Biology



Peripheral Vascular Function Multiple studies have reported impaired peripheral vascular function by different techniques mediated by both endothelium-dependent and -independent mechanisms.[31,32,36-39] Similar to the carotid data, the differences could also be explained by insulin resistance[32,34,38,39] or dyslipidemia.[37,38] In contrast, the association of androgens and peripheral vascular dysfunction is variable. In two studies,

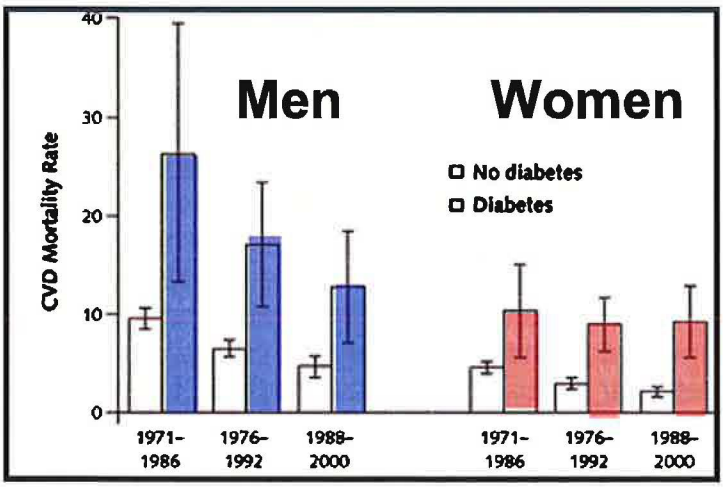
there was no association,[38] while one study demonstrated a positive correlation of endothelial dysfunction with elevated free testosterone.[39]

What can we learn from surrogate markers? It is easier to start answering the opposite question, what do we fail to learn from surrogate markers in PCOS. In the case of CAC, the low prevalence of detectable CAC in premenopausal women and the impact of obesity significantly limit the ability of this measurement to provide meaningful information about disease and risk unless much larger groups of women are studied and longitudinal CAC progression, CV disease and event data can be obtained. At the very least, CAC is unlikely to provide useful information at the individual level for women with PCOS. Although the peripheral vascular disease data may be the most consistent in favor of a greater amount of disease in women with PCOS, these measurements have not been validated as predictors of CV events in women with PCOS. Peripheral vascular disease in PCOS might not necessarily predict coronary atherosclerosis just as other CV risk factors - hypertension, dyslipidemia and diabetes - can affect different vascular beds with different degrees of risk for stroke, myocardial infarction and peripheral vascular disease.[40] It has been demonstrated that women in particular may demonstrate greater variability in the presence of atherosclerosis among vascular beds.[41] Finally, the peripheral vascular disease data raise an additional important question –*if there is a greater burden of CV disease, is it mediated more directly by the associated risks of obesity, insulin resistance, the metabolic syndrome or the androgens?* As illustrated in Figure 1, insulin resistance both underlying PCOS at an early stage and augmented by the development of obesity and higher risk depots of adipose tissue. The answer to this question has important implications for prevention and treatment strategies to lower the risk for CV disease in women with PCOS.



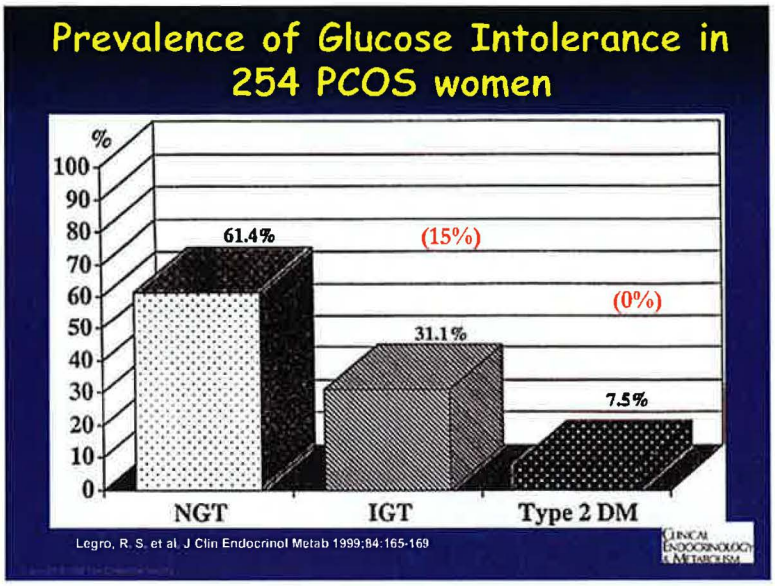
Diabetes, A Cardiovascular Disease Equivalent

The American Heart Association and American Diabetes Association consider the diagnosis of Diabetes (DM) a CV disease equivalent to a prior MI based on population-based cohort studies that equate CV risk in patients with DM to that of persons without DM who have already experienced a CV event.[42-44] For premenopausal women in general, the diagnosis of DM heralds a dramatic change in CV risk. The CV risk associated with DM essentially erases the CV protection usually experienced by premenopausal women.[45] Moreover, CV deaths for women with DM have increased 23% in the past 30 years, despite the declining CV mortality rates experienced by men.[46]



With the UK PCOS cohort identifying the highest SMR among women with PCOS attributable to DM, clearly prevention of diabetes should be an important target for CV risk identification and reduction.

With the known association of PCOS with insulin resistance, independent of obesity, a higher prevalence of prediabetes and DM is not surprising. Although there is some variability in reports of the prevalence of pre-diabetes and DM among women with PCOS, most studies agree that women with PCOS have a higher prevalence of impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and DM, especially among the obese. The magnitude of the difference between women with PCOS and controls varies, which can be attributed to variations in methods, including diagnostic testing, age groups and body size.



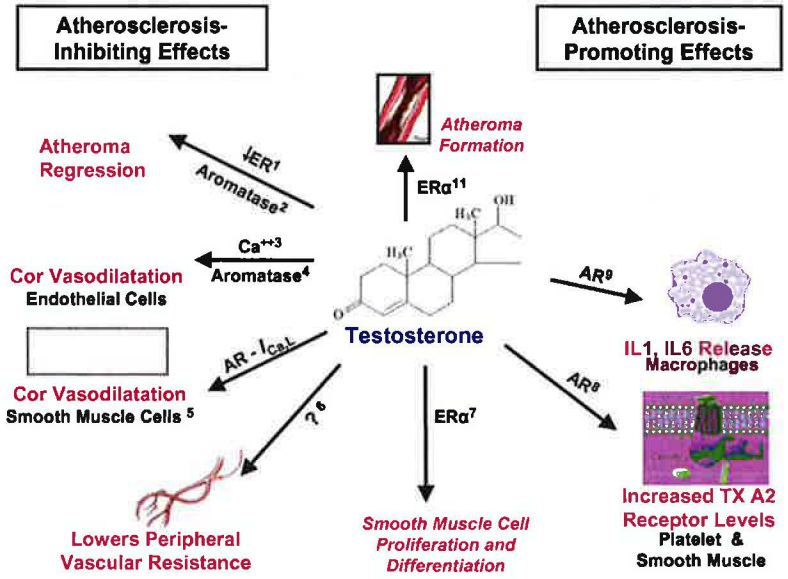
One prospective controlled study established a significantly higher prevalence of both IGT (30.0 %) and DM (4.0 %) in obese women with PCOS compared to controls (15.7 % IGT, 0% DM).[47] Another uncontrolled study demonstrated similar rates among women with PCOS (35% IGT, 10% DM).[48] But do women with PCOS convert to DM at higher rates?

Conversion rates for women with PCOS in the United States who have IGT have been reported to be anywhere from 6% over 3 years to 13.4% over 8 years, in older women.[48,49] In smaller samples, rates of 29% (4 of 14) over 2 years and 54% (7 of 13) after 6 years have been reported [50]. In comparison, conversion rates of 25% and 66% over 5 and 10 years in the high risk Pima Indian population [51], and 50% over 5 years in Latina women with a previous history of gestational diabetes have been reported. [52] Conversion rates for normoglycemic women vary from 9% to IGT [50], and 40% IGT. [48,53] Collectively, this data may support high rates of conversion from IGT to DM and normal glucose tolerance to IGT, but the rates are not higher than other at-risk populations. This data is also hampered by lack of defining presence or absence of PCOS status according to race in the populations referred to. Finally, with the RR of developing DM 6.90 (95% CI4.35–10.94) over 8 years in women with the metabolic syndrome (established in much larger cohorts though also among older women), focusing on assessment of the metabolic syndrome and prevention of conversion to DM is clinically very meaningful for women with or without PCOS.

Shifting Paradigms

- There is no clear evidence linking PCOS with increased disease or events
- An intriguing paradox –
  - *despite an increase in CV risk factors & insulin resistance since adolescence, little evidence for events, CV disease, diabetes*

Potential Mechanisms: Testosterone in CV Disease

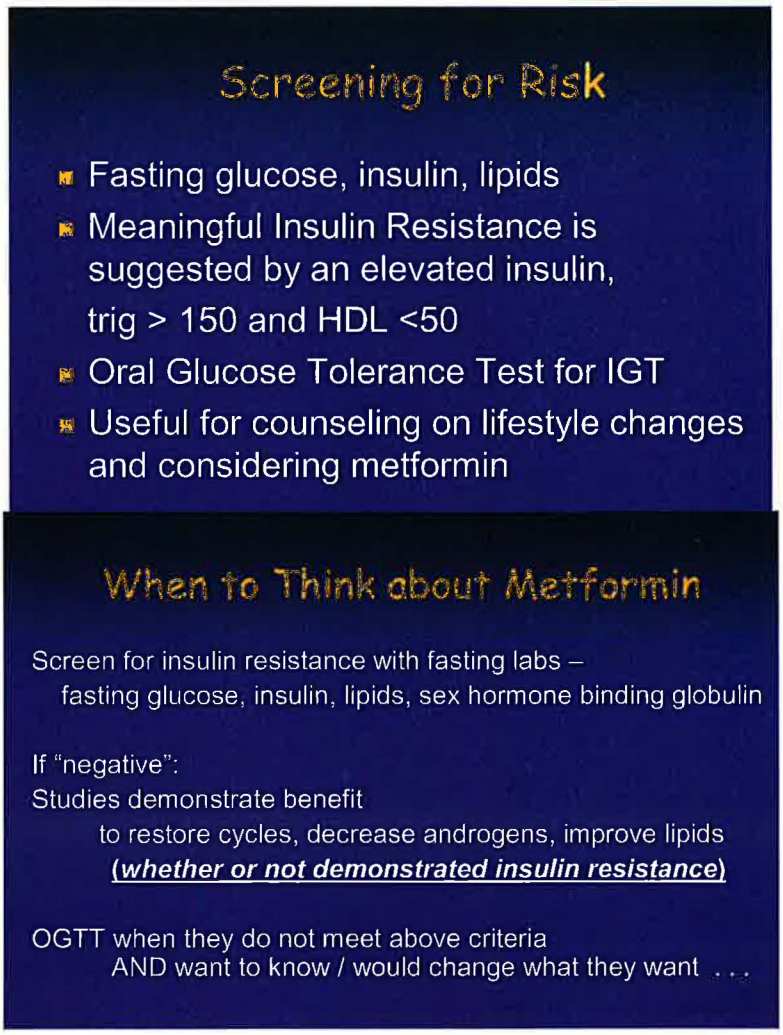


Assessment and Treatment

How and when should we screen for insulin resistance and diabetes in women with PCOS?

This question remains unresolved. The ADA lists presence or absence of PCOS as a reason to screen. We are now seeing many obese children, and many have PCOS. The decision regarding when to screen more aggressively (and at what intervals) seems to be a bit of a moving target and will rely on further evidence that earlier treatment will lower the rate of conversion to diabetes or change management.

Until a large multi-center longitudinal cohort study can clarify the incidence of CV events and the impact of DM for women with PCOS, women with PCOS should be counseled that their risk for developing DM and the metabolic syndrome appears to be increased. The best estimate for CV event risk and mortality likely approximates those who have the metabolic syndrome – a relative risk of 1.5-2.0 or a 50 to 100% increase in events - with the development of DM more importantly escalating risk to a 4-fold lifetime risk of death. The risk may be even higher for older obese and morbidly obese women with PCOS.



Summary/Future Directions

The challenge in this area is that obesity, insulin resistance and DM may be in the causal pathway for developing CV disease in women with PCOS. This makes the ability to sort out these confounders impossible when we try to determine in cross-sectional segmental looks whether PCOS status per se confers CV disease risk independent of the obesity, insulin resistance, metabolic syndrome and DM pathways. Therefore, until we learn more, the most urgent target to lower the risk for CV disease in women with PCOS is the prevention of obesity and subsequent diabetes. Surrogate markers for CV disease should be interpreted with a great deal of caution when extrapolating to CV death inference. They may be helpful however in teasing apart the potential mechanisms for the development of CV disease in women with PCOS.

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