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Long-term health consequences of PCOS

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The prevalence of cardiovascular risk factors, insulin resistance/diabetes and/or uterine pathology appears to be increased in women with polycystic ovarian syndrome (PCOS), although more outcome studies are necessary to determine incidence. Data pertaining to some of the potential long-term health consequences associated with PCOS are summarized. Medline, Current Contents and PubMed were searched for studies from the time of our original interest in this issue in 1980 to the present. The review is limited to published human data. The current literature indicate that women with this syndrome cluster risk factors for premature morbidity and mortality. Large multi-site co-operative studies are necessary to evaluate the long-term health outcomes.

Keywords: cardiovascular risk/diabetes/endometrial cancer/PCOS

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Introduction

In current practice, women with polycystic ovarian syndrome (PCOS) are frequently screened for diabetes/insulin resistance, hypertension, abnormal cholesterol/triglycerides (TG), other coronary-prone behaviour and/or abnormal uterine bleeding. Whether or not women with this syndrome are at increased risk for disease because of their PCOS status *per se*, independent of well-known determinants (obesity, diabetes, hypertension), is controversial. Controversy continues because research either involves sample sizes too small for meaningful inference, does not include the appropriate comparison group, or looks at mechanistic questions that focus on intermediate biological outcomes, not clinical events. Women with PCOS usually first seek care in their reproductive years. This is too early for the accumulative effects of some of the risk factors to culminate in disease. Educated to diagnose disease, physicians frequently focus on chief complaints. This also can lead to suboptimum screening. Without long-term health consequence data, the development of optimum cost-effective screening strategies remains elusive.

Three crucial questions need to be answered: (i) are known risk factors for premature morbidity and mortality more common in women with PCOS? (ii) Are women with PCOS at greater risk for events? (iii) Does modification of risk factors reduce events?

Criteria for assessment

Pertinent investigations are classified according to their level of evidence. For risk factors, a prospective longitudinal cohort study of long duration with limited loss to follow-up provides much more evidence than a retrospective study. Although a case–control study is less expensive, it can provide promising inferences. The design is frequently difficult to optimize and is prone to bias. Cross-sectional studies can generate hypotheses, but not determine causality. Panel design studies (a series of cross-sectional looks over time) can provide more inference. Matched case–control studies suffer from potential completeness of matching for known or unknown characteristics. Many hybrid studies are quite useful. The population studied determines in part the relevance/applicability. Particular attention to inclusion and exclusion criteria is important. Issues regarding validity include: (i) is there a well-defined, representative sample of patients assembled at a common early point in the course of the disease? (ii) Is patient follow-up sufficiently long and complete? (iii) Are objective criteria applied uniformly to both cases and controls in a blinded fashion? (iv) Do there subgroups have different prognoses? (v) Is confounding eliminated? Is interaction identified? (vi) Is there validation in an independent group of 'test-set' patients? (vii) Do independent studies validate the predictive power of prognostic factors? Epidemiological studies have the advantage of studying persons or groups in the community.

While there is no question that persons who volunteer for clinical trials differ from persons evaluated outside of the clinical

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Table I. Are women with PCOS at greater risk for abnormal glucose/diabetes?

Author/date	Patient population	Findings	Level of evidence
Dahlgren, 1992	33 PCOS, 132 age matched referents, S/P wedge resection.	Greater prevalence of physician-diagnosed diabetes in PCOS.	III
Ehrmann, 1999	122 PCOS.	Glucose intolerance in 45%, 35% had IGT, 10% type 2 diabetes.	IV
Legro, 1999	254 PCOS 14–44 years prospectively, 1 urban ethnically diverse ($n = 110$) 1 rural ethnically homogeneous ($n = 144$). Rural PCOS and 80 controls of similar weight, ethnicity, and age.	Prevalence of glucose intolerance: 38.6–31.1% IGT, 7.5% diabetes. Non-obese PCOS: 10.3% IGT and 1.5% diabetes.	III, IV

S/P = status post; IGT = impaired glucose tolerance.

trial setting in a number of important characteristics, for therapeutic interventions, randomization is enormously powerful. Small clinical trial populations can be so restricted that generalization is hazardous. In this review the following levels of evidence are used: level I is a randomized study with low α and low β; level II is a randomized study with high α and β; level III is a non-randomized study with a concurrent control group (quasi-experimental design); level IV is a non-randomized study with historical controls; and level V is a case series.

For purposes of this review, PCOS status is designated as those women with signs/symptoms of menstrual irregularity and hyperandrogenism unless designated differently in the text. Because of space constraints, this review is limited to diabetes, coronary vascular disease (CVD) and endometrial cancer. Other endpoints, including ovary and breast cancer, are the subject of a forthcoming review.

Are risk factors more common in women with PCOS?

Coronary risk factors

High blood pressure, insulin resistance, dyslipidaemia

Whether or not women with PCOS are more prone to high blood pressure because of their PCOS status *per se*, remains unknown. Studies to date are conflicting (Wild, 2002). Women with PCOS appear to have lower high-density lipoprotein (HDL) cholesterol and higher TG independent of body weight (Wild, 2002) Most, but not all, studies report this profile. Obesity appears to aggravate insulin resistance and dyslipidaemia in patients with or without polycystic ovaries. Oligo/amenorrhoea and clinical or laboratory signs of hyperandrogenism are associated with insulin resistance.

Glucose, diabetes, hypertension

Well-designed cohort studies to determine the incidence of these endpoints in women with PCOS are not available. Cross-sectional studies assessing prevalence suggest that women with PCOS are at greater risk for premature development of diabetes mellitus (see Table I). Ehrmann characterized the prevalence of glucose intolerance in a large group of women with PCOS (Ehrmann *et al.*, 1999). A total of 122 women with clinical and hormonal evidence of PCOS had a standard oral glucose tolerance test with measurement of glucose and insulin levels. A subset of 25 was restudied with the aim of characterizing the natural history of glucose tolerance in PCOS. Glucose tolerance was abnormal in 55 (45%) of the original 122 women: 43 (35%) had impaired glucose tolerance and 12 (10%) had type 2 diabetes at the time of initial study. The women with type 2 diabetes differed from those with normal glucose tolerance in that they had a 2.6-fold higher prevalence of first-degree relatives with type 2 diabetes (83 versus 31%, $P < 0.01$) and were significantly more obese [body mass index (BMI) 41.0 $\pm$ 2.4 versus 33.4 $\pm$ 1.1 kg/m^2, $P < 0.01$].

In this referral population, the prevalence of impaired glucose tolerance and type 2 diabetes in women with PCOS was substantially higher than expected when compared with age and weight-matched populations of women without PCOS. Legro studied 254 PCOS women aged 14–44 years at two centres, one urban and ethnically diverse ($n = 110$) and one rural and ethnically homogeneous ($n = 144$) (Legro *et al.*, 2001). Rural PCOS cases were apparently compared with a convenience sample of 80 controls of similar weight, ethnicity and age. The prevalence of glucose intolerance was significantly higher in women with PCOS. Variables most associated with post-challenge glucose levels were fasting glucose, PCOS status, waist/hip ratio (WHR) and BMI. The authors suggested: (i) women with PCOS are at significantly increased risk for impaired glucose tolerance and type 2 diabetes mellitus at all weights and at a young age; (ii) the prevalence of both of these states of abnormal glucose metabolism was similar in two different populations of PCOS women.

Interestingly, the prevalence of PCOS appears to be higher in women with type 1 diabetes than in the general population. Escobar-Morreale studied 85 women with type 1 diabetes mellitus for symptoms and signs of hyperandrogenism (Escobar-Morreale *et al.*, 2000). In 68 women, serum androgen and other hormone concentrations were measured. PCOS was defined by the presence of menstrual dysfunction, together with clinical and/or biochemical evidence of hyperandrogenism, and exclusion of other aetiologies. Eighteen healthy women, menstruating regularly, served as controls for the androgenic profiles. Thirty-three patients (38.8%) presented as hyperandrogenic disorders (16 had PCOS and 17 had hirsutism without menstrual dysfunction). Type 1 diabetic patients with PCOS had increased serum total and free testosterone concentrations and androstenedione levels, but normal serum sex hormone-binding globulin (SHBG) and dehydroepiandrosterone sulphate (DHEAS) levels. Hirsute type 1 diabetic women without menstrual dysfunction had normal serum androgen levels. There were no significant differences between hyperandrogenic and non-hyperandrogenic type 1 diabetes mellitus women in clinical variables such as the duration

Table II. Are women with PCOS more prone to hypertension?

Author/date	Patient population	Findings	Level of evidence
Mattson *et al.*, 1984	20 PCOS versus 20 normal women.	BP higher in PCOS.	III
Zimmerman *et al.*, 1992	14 PCOS, versus 18 normal control similar age, race, BMI.	No difference in BP, LVH.	III
Conway *et al.*, 1992	102 lean and obese PCOS, 19 lean PCOS.	Lean PCOS higher insulin than normal, in addition, obese PCOS had higher BP.	III
Sampson *et al.*, 1996	24 non-obese PCOS irregular, menses, 26 PCOS by US, regular menses, 10 normal .	No difference: 24 h ambulatory BP, PCOS with menstrual disturbance, higher fasting insulin and PAI1.	III
Holte *et al.*, 1996	36 PCOS versus 55 controls matched for BMI.	Higher ambulatory mean arterial BP, higher daytime systolic BP. no difference in diastolic BP.	III
Fridstrom *et al.*, 1999	33 PCOS versus 66 normal.	Higher BP: 3rd trimester of pregnancy in PCOS, retrospective.	III
Dahlgren *et al.*, 1992	33 PCOS, 132 age matched referents, S/P wedge resection.	Greater prevalence of physician-diagnosed hypertension, PCOS.	III

BP = blood pressure; BMI = body mass index; PAI 1 = plasminogen activator inhibitor 1; LVH = low vascular hypertension; S/P = status post; US = ultrasound.

of diabetes, age at diagnosis of diabetes, conventional or intensive insulin therapy, mean daily insulin dosage or metabolic control. The authors point out that this prevalence is much higher than reported in the general population (Knochenhauer *et al.*, 1998; Diamanti-Kandarakis *et al.*, 1999). This higher prevalence than expected was reported earlier by Conn *et al.* and Kousta *et al.* in patients with type 2 diabetes using classic ultrasound criteria rather than the more widely accepted criteria of oligo/amenorrhoea with hyperandrogenism to define PCOS (Conn *et al.*, 2000; Kousta *et al.*, 2000).

Using case–control methodology, Dahlgren recruited women with PCOS from hospital clinics and obtained controls randomly from another population study (Dahlgren *et al.*, 1992). Thirty-three women aged 40–59 years with ovarian histopathology typical of PCOS at wedge resection 22–31 years previously and 132 age-matched controls were analysed. Clinical data was collected by questionnaire, supplemented with an interview in connection with a clinical examination that also included fasting venous sampling. The hormone data show a typical profile for PCOS. Compared with controls, women with PCOS had a marked increase in the prevalence of central obesity, high basal serum insulin concentrations, diabetes mellitus and hypertension. Other studies show varied results when comparing blood pressure and other markers of hypertension in PCOS patients and controls. These are shown in Table II.

Comment

Ehrmann's evaluation lacks follow-up of all patients (Ehrmann *et al*., 1999). At baseline, 45% of the women with PCOS had abnormal glucose tolerance. While one cannot determine causality from this type of study, the results suggest that the prevalence of abnormal glucose tolerance is high in PCOS. A small subset had a deterioration of glucose tolerance. The study by Legro is a prevalence study with concurrent and historical controls (Legro *et al*., 2001). Some women with and without PCOS were followed to determine if they developed carbohydrate deterioration. Whether or not the risk is equivalent in non-obese patients with PCOS is not clear. The issue of whether PCOS is truly a pre-diabetic state cannot be answered without a stronger evidence base that uses diabetes as an endpoint and PCOS status without body weight as a confounder.

From a pathophysiology perspective, it seems intuitive that both obesity and PCOS status should confer risk for diabetes. These should be additive. When a woman becomes diabetic, she removes her selective gender advantage. It is unknown if women with PCOS and diabetes are as likely to die of CVD as non-PCOS diabetics. Wedge resection can theoretically change the natural history of disease progression. The histological diagnosis of PCOS was controversial, not standardized, and not uniformly recognized amongst pathologists 22–31 years previously. Caveats are the need for a well-designed questionnaire, the need for equal assessment in cases and controls, and a small number of persons where the exposure could not be ascertained (wedge resection). Theoretical models have been developed suggesting greater risk of myocardial infarction and/or diabetes in women with PCOS.

Blood pressure is often not determined with strict attention to detail and accuracy, such as the consistent use of calibrated instruments. Whether or not rates of hypertension increase differently over time in obese women with and without PCOS is a difficult question to study. Numerous factors affect blood pressure. These include genetics, physical inactivity, stress, salt loading, etc. Many of these have not been controlled for. Large cohort studies are also needed. Metabolic ward studies—where exercise and diet are accurately controlled—are needed in order to assess blood pressure differences, particularly when patients and controls are matched for body weight and age. Whether or not women with PCOS who are insulin resistant and not obese are more likely to develop hypertension over time also needs to be

determined. Obesity is a well known risk factor for hypertension and CVD (Kannel *et al.*, 1996). The risk goes up when each element of clustered risk factors is present. The risk with obesity, in women with or without PCOS, might be more than the 'sum of its parts' (Kannel, 2000).

What is the relation between glucose levels and cardiovascular events in persons without diabetes mellitus? PCOS is frequently associated with central obesity, and varying states of altered glucose metabolism ranging from minor deviations to overt hyperglycaemia with or without overt diabetes. It is a reflection of gender bias in publication that the majority of outcome studies pertinent to this question have only examined men. Coutinho provided a meta-analysis, with no attention to the presence or absence of PCOS (Coutinho *et al.*, 1999). He found an association between cardiovascular risk and fasting and postprandial blood glucose levels in non-diabetic patients. The analysis did not permit assessment of the independence of glucose level from other cardiovascular risk factors, but the findings may be important and relevant to the PCOS prediabetic and the diabetic with a PCOS spectrum.

The results of the UK Prospective Diabetes Study clearly showed that blood glucose control reduced the risk for vascular complications in patients with diabetes mellitus (UK Prospective Diabetes Study, 1998a). This clinical trial (UK Prospective Diabetes Study 1998b) also showed that blood pressure control was of even greater relevance in such patients. Large-scale clinical studies are underway to evaluate the importance of cholesterol reduction in patients with diabetes mellitus. These studies are attempting to highlight the multiplicative effects of cardiovascular risk factors. They are relevant to helping us predict this question for our PCOS patients. In persons who do not have overt diabetes mellitus, the combination of upper-body obesity, glucose intolerance, hypertriglyceridaemia, low levels of HDL cholesterol and hypertension has been associated with increased risk for CVD (Anonymous, 1999). Carbohydrate intolerance is prevalent with or without PCOS. It appears that women with PCOS are more likely to experience premature glucose abnormalities.

Obesity

Comment

Because the prevalence of obesity in women with PCOS appears to be high, data pertinent to obesity and CVD are reviewed. However, these landmark studies did not report whether or not their cohort members had PCOS.

The prospective cohort evaluated in the Nurses Health Study reflected that increased body BMI predicts mortality in women (Anonymous, 1996). During 16 years of follow-up, 4726 women died (881 of CVD, 2586 of cancer and 1259 of other causes). The age-adjusted relative risk (RR) for all deaths in all women was 1.0 with a BMI <19.0 kg/m^2, <1.0 in women with a BMI of 19.0–28.9 kg/m^2, and 1.3 in women with a BMI $\geqslant$32.0 kg/m^2. Compared with the reference group, women with no smoking history and a BMI $\geqslant$32.0 kg/m^2 had an RR for death from CVD of 4.1 (range 2.1–7.7) and an RR for death from cancer of 2.1 (1.4–3.2). Both weight gain ($\geqslant$10 kg after age 18 years) and a BMI of $\geqslant$22.0 kg/m^2 at age 18 years were predictors of overall mortality and death from CVD in middle adulthood. After controlling for the confounding effects of smoking and disease, there was a direct association between BMI and all-cause mortality and death from specific causes. The lowest mortality was in the leanest who never smoked and whose weight had remained stable since age 18 years.

The 5 year cohort Iowa Women's Health Study (Anonymous, 1993a) attempted to determine if BMI and WHR are risk factors for 5 year mortality in older women. A total of 1504 deaths occurred, 52% from cancer and 32% from CVD. Age-adjusted mortality rates were elevated in the leanest as well as the most obese for both never smokers and ever smokers, giving a J-shaped association for BMI and mortality. Risk for death was positively associated with WHR, increasing monotonically across each quintile of WHR.

In Gothenburg, Sweden (Anonymous, 1993b), 1462 women aged 38, 46, 50, 54 or 60 years were randomly selected from the community. Vital status was determined after 20 years. The main outcome measures were total mortality and death from myocardial infarction (MI). Of 1450 women, 12% who were followed for 20 years died, 26 (15%) from MI. Increased serum TG and abdominal adiposity were associated with increased risk for total mortality and death from MI. Increased cholesterol and general adiposity were not associated with risk for total mortality and minimally associated with death from MI. Women with PCOS often have the phenotype associated with increased abdominal girth.

Family history

Many women with PCOS have a high prevalence of relatives with the same disease (Givens, 1988b). They cluster hyperandrogenism (Legro *et al.*, 1998). Vascular risk factors or disorders are frequent causes of death in the families (Norman *et al.*, 1996a; Givens, 1988a; Diamanti-Kandarakis *et al.*, 1999; Fox, 1999). A dominant mode of inheritance or a multi-factorial complex trait is suggested (Lunde *et al.*, 1989; Kahsar-Miller *et al.*, 2001). The majority of the genetic investigations into PCOS tend to ignore those PCOS women with few affected relatives in the family. A study on the prevalence of diabetes (Fox, 1999) found that more families of women with PCOS had at least one member affected by type 2 diabetes (39.1% of the PCOS group and 7.6% of the controls). Both obese (54.8%) and non-obese (24.2%) women with PCOS had an increased prevalence of type 2 diabetes within their families, and paternal and maternal sides had similar proportions. Norman *et al.* found that hyperinsulinaemia (69%) and hypertriglyceridaemia (56%) were common in family members, as were polycystic ovaries in 79% of 24 females (Norman *et al.*, 1996b).

Twin studies, though infrequent (Jahanfar *et al.*, 1995), include a group of 19 monozygotic (MZ) and 15 dizygotic (DZ) twin pairs identified from the Australian national twin register. Ultrasound, clinical and biochemical parameters defined PCOS. Eleven pairs (five MZ, six DZ pairs) were scan-discordant (i.e. one twin had ultrasound evidence of polycystic ovaries and the co-twin did not). Model fitting suggested that fasting insulin, androstenediol glucuronide and BMI were all significantly influenced by genetics. This suggests that PCOS is not the result of a single autosomal genetic defect. PCOS may be an X-linked disorder or the result of polygenic factors. However, fasting insulin, androstenediol glucuronide and BMI did appear to be under significant genetic influence. Lipid values have been compared in discordant twins for PCOS (Jahanfar *et al.*, 1997). Ultrasound, clinical and biochemical findings defined polycystic ovaries. The MZ intraclass correlation exceeded that of the DZ twin pairs for all the lipid variables. The

heritability estimates for lipoprotein a, apolipoprotein (Apo) B, total cholesterol and HDL cholesterol were 0.95, 0.56, 0.48 and 0.54 respectively. The intraclass correlation coefficient for TG was not significantly different between MZ and DZ twins. Maximum likelihood analysis indicated that at least 10% of the variance of TG concentration was genetic.

Comment
Large family studies of women with PCOS that evaluate genetic determinants are needed. It seems likely that environmental factors are important in developing the PCOS phenotype in those with genetic propensity. Intrauterine and extrauterine factors may be important.

Coagulation

In the same cohort as above, Dahlgren measured fibrinogen, von Willebrand factor antigen, factor VII procoagulant activity, factor VII antigen and plasminogen activator inhibitor (PAI-1) as well as serum insulin and serum TG (Dahlgren *et al.*, 1994). There was a strong positive correlation between TG, basal insulin, abdominal obesity, PAI-1, fibrinogen and von Willebrand factor among women with PCOS and also in the non-PCOS controls. Fibrinogen and factor VII antigen were higher in controls, but the mean values of most haemostatic variables were not different. Women with altered metabolic profiles had affected haemostatic factors, but PCOS status *per se* did not confer separate altered haemostatic variables.

Comment
Measuring coagulation factors as a surrogate endpoint is difficult. The true relevance for risk of coronary events is unclear because of family history, situational context and differences in having a defect and having an event. Thrombotic–anti-thrombotic interaction dynamics are complex. The concept of TG alterations associated with differences in clotting profiles is important to cardiovascular risk in a mechanistic sense.

Anovulation/oligoamenorrhoea/abnormal uterine bleeding

In a prevalence study, DeVoto studied 101 women <35 years of age who presented with oligomenorrhoea persisting 5 years after menarche or lasting >2 years after a period of normal menstrual cycles (DeVoto *et al.*, 1998). Ovulation was measured by assaying serial plasma progesterone levels. Eighty-nine percent had anovulatory oligomenorrhoea. The main causes were polycystic ovarian disease (51%) and hypothalamic dysfunction (31%). Thirty percent of women with secondary amenorrhoea had polycystic ovarian disease and 14% had hyperprolactinaemia. Women >20 years, with >10 years since the onset of puberty, had a high frequency of polycystic ovarian disease and a lower prevalence of hypothalamic dysfunction. Using ultrasound to identify polycystic ovaries, Adams *et al.* found polycystic ovaries in 26% of women with amenorrhoea, 87% with oligo/amenorrhoea and 92% with idiopathic hirsutism—that is, hirsutism but with regular menstrual cycles. Fewer than half of the anovulatory patients with polycystic ovaries were hirsute, but in 93% of cases there was at least one endocrine abnormality to support the diagnosis of polycystic ovaries: raised serum concentrations of LH, an increased ratio to FSH, or raised serum testosterone (T) and/or androstenedione (A).

In her study, Dahlgren found that oligomenorrhoea was more common among the subjects with PCOS (Dahlgren *et al.*, 1992). Infertility, hirsutism and oligomenorrhoea were more common, but there was a considerable spontaneous restitution of cyclic regularity with time. Women with PCOS were more likely to have had a hysterectomy and they entered menopause later compared with controls. In a small case–control study (Allen *et al.*, 1997), the hypothesis was tested that oligo-ovulatory ovulation is associated with hyperandrogenism in the absence of other clinical signs of androgen excess. Thirty-two consecutive non-hirsute oligo-ovulatory women and 37 eumenorrhoeic controls were evaluated. All study subjects underwent a physical exam and blood sampling in the follicular phase of the menstrual cycle. Mean free T was higher and SHBG lower in oligo-ovulatory patients compared with controls. The oligo-ovulatory patients were subdivided according to severity of menstrual abnormalities into those with cycles <45 days ($n = 19$, oligo-ovulatory-short) and ⩾45 days ($n = 13$, oligo-ovulatory-long). Oligo-ovulatory (long and short) patients had similar mean DHEAS, A and total T levels; but mean free T was higher and SHBG lower in oligo-ovulatory-long patients compared with either oligo-ovulatory-short or controls. Five of 13 (38%) oligo-ovulatory-long patients had at least one abnormal androgen value compared with one of 19 (5%) oligo-ovulatory-short patients. Approximately 40% of non-hirsute oligo-ovulatory women with cycle intervals ⩾45 days demonstrated at least one abnormally elevated androgen level, suggesting that they may have a discrete form of PCOS.

Comment
In general, epidemiological investigations of the prevalence of menstrual aberration associated with PCOS have suffered with small numbers, study designs that cannot conclude causality, differences in definition of what constitutes PCOS, anovulation, abnormal bleeding and referral bias. The exact prevalence of anovulation or menstrual regularity in women with PCOS is unknown, but appears to be common. The step towards consensus definition of PCOS to narrow the definition to include only those with oligo-amenorrhoea and androgen excess is recognition of the frequency of ovulatory abnormalities in women with PCOS. Many authors disagree with this more narrow definition (including this author). However, for the purposes of this review this narrow definition is the default, because without some consensus the heterogeneity issue can overwhelm the more important message. That message is that we need an evidence-based approach to provide meaningful progress in how to screen, treat and understand these syndromes. Prolonged anovulation, particularly in association with obesity, appears to be a significant risk factor for endometrial cancer in premenopausal women. The combination of obesity, diabetes with or without hypertension and prolonged amenorrhoea appears to be a clinical scenario affording an additive and possibly multiplicative risk for endometrial cancer (see below).

Are women with PCOS at greater risk for events?

Comment
This is a much more difficult question to answer. Large investigations pertinent to women and heart disease or endome-

Table III. Are women with PCOS more prone to dyslipidaemia?

Author/date	Patient population	Findings	Level of evidence
Wild, 1985	29 PCOS versus 30 controls.	Higher TG, lower HDL in PCOS.	III
Wild, 1988	13 PCOS, 13 controls matched for BMI.	Higher TG, VLDL, lower HDL cholesterol in PCOS.	III
Slowinska-Srzednicka, 1991	49 glucose tolerant women. Lean and obese PCOS versus normal.	Lower HDL_2 and higher Apo B in obese, non-obese PCOS. Obese PCOS, higher TG, VLDL, lower HDL cholesterol.	III
Wild *et al.*, 1992	47 hirsute versus 17 controls.	Higher TG, VLDL, Apo C-III, AI/AII, lower HDL.	III
Talbott *et al.*, 1995	206 PCOS and controls, voters' registration tapes and directories of households. Subjects matched by age, race and neighbourhood.	Increased TG, decreased total HDL and HDL_2, increased total cholesterol and LDL levels.	III
Velazquez, 2000	18 Hispanic PCOS versus 9 controls.	Lean and obese PCOS increased TG post fat load	III
Legro *et al.*, 2001	195 PCOS versus 62 controls.	PCOS lean and obese. Higher LDL	III

TS = triglycerides; HDL = high density lipoprotein; LDL = low density lipoprotein; PCOS = polycystic ovarian syndrome; BMI = body mass index; VLDL = very low density lipoprotein; Apo = apolipoprotein.

trial cancer, e.g. Framingham, the Nurses Health Study etc., ignored signs or symptoms of hyperandrogenism associated with aberrant menses. They did not, in their original study design, determine PCOS status in their cohort members. Retrospective attempts have been made. These are post-facto and thus have less credence. Post-hoc analysis can only generate hypotheses. The true prevalence of women with PCOS in these cohorts cannot be determined. The Gothenburg study offered some insight. It found that central obesity and high TG are risk factors for death from MI. This is a common characteristic of women with PCOS. In contrast, generalized adiposity or high cholesterol were associated with minimal risk of death from MI, not total mortality (Bengtsson *et al.*, 1993). Classic risk factors that women with PCOS commonly display, such as diabetes, hypertension and dyslipidaemia, are prevalent and predict a poor outcome for women enrolled in these studies. One cannot determine the converse either. Are women with PCOS, because of their uniqueness, actually protected and therefore at reduced risk in spite of clustering coronary vascular risk factors?

Given this dilemma, many have decided that it is much easier to assess risk factors and/or intermediate biological surrogate endpoints. A surrogate endpoint is a laboratory measurement or physical sign used to substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives. The following are often used: glucose, insulin, diabetes, lipids, obesity, coagulation and image studies to assess atherosclerotic burden. This is in contrast to a clinical outcome: coronary artery disease with symptoms, MI, stroke, death (both total mortality and CVD mortality) or endometrial cancer. The hazards of assessing an intermediate outcome as a surrogate marker for the true outcome are well known. A correlate does not a surrogate make. Below are often-used surrogates that attempt to predict the risk of an event.

Dyslipidaemia

PCOS and normal women have been evaluated by comparing lipoprotein lipid and androgen profiles. PCOS had higher androgens and menstrual irregularity, higher TG and lower HDL cholesterol (Wild *et al.*, 1985). While PCOS women were heavier, they had higher blood pressue, were more sedentary and had diets higher in saturated fat and lower in fibre. Lipoprotein lipid and androgen profiles (Wild and Bartholomew, 1988) were compared in women with and without PCOS, matched for percentage ideal body weight. Patients with PCOS had significantly higher TG, very low density lipoprotein (VLDL) cholesterol, and HDL cholesterol. Differences in body weight did not explain differences in lipoprotein lipid patterns. Slowinska-Srzednicka studied obese and non-obese women with PCOS and compared them with lean and obese controls (Slowinska-Srzednicka *et al.*, 1991). Lower levels of HDL_2 cholesterol and higher Apo B were found in obese and non-obese PCOS patients. In obese women with PCOS, this was associated with lower levels of HDL cholesterol and Apo A-I, higher TG and VLDL. In an independent study group (Wild *et al.*, 1992) higher TG, VLDL cholesterol and lipoprotein C-III levels, lower HDL_2, and Apo A-I/A-II ratios were found. Correlation studies with and without ovarian suppression with GnRH analogue suggested that this pattern was more related to insulin resistance than to hyperandrogenism.

Talbott recruited women with PCOS by using records from a large reproductive endocrinology practice (Talbott *et al.*, 1998). Women with PCOS had significantly increased BMI, insulin, TG and decreased total HDL and HDL_2 cholesterol levels, and increased total and fasting low density lipoprotein (LDL) cholesterol levels, as well as higher WHR and higher systolic blood pressures. Talbott next reported on the same cohort, expanded in number (Talbott *et al.*, 1998). Women with PCOS had substantially higher LDL and total cholesterol levels at each age group <45 years, after adjustment for BMI, hormone use and insulin. Over age 40 years, little difference was found between the groups. Among cases and controls (<40 years), PCOS predicted LDL cholesterol, total cholesterol and TG. These authors suggested LDL-cholesterol increased with age in the controls. Elevated small dense LDL levels seem to be common (Pirwany *et al.*, 2001) and appear to be related to insulin resistance. Velazquez found greater TG response to a fat load in women with PCOS (Velazquez *et al.*, 2000). A study by Legro found higher LDL

levels in PCOS patients (Legro *et al.*, 2001). Interestingly, in the Legro study, by current National Cholesterol Education Guidelines, HDL levels were abnormally low in obese PCOS patients and obese controls. Not all studies have assessed dietary intake of saturated fats, alcohol, smoking and exercise. Not all analyse results using similar categories of weight, age and dietary information. How the controls are obtained is frequently not described. These studies are summarized in Table III.

Comment

Each of these studies is cross-sectional. Concurrent controls were in a clinical research centre or in the community. Patients were age-matched in one of the Talbott studies. They were ethnically matched in the Legro study. In most studies, PCOS women had a characteristic profile of lower HDL cholesterol (and lower Apo A1), and higher TG and VLDL; and in some instances, higher Apo B and small dense LDL cholesterol. Some found increased LDL. Dyslipidaemia is present in different populations at different sites throughout the world. None of the lipid values is extreme. However, most heart attacks occur in women without extremely altered lipid values. Most studies found significant associations with insulin levels as a marker for insulin resistance in non-diabetic women. Poorly controlled diabetes is associated with altered lipid metabolism and at times markedly abnormal lipid profiles.

Vascular lesions

Coronary artery

Angiography

Women coming to coronary artery catheterization for past signs and symptoms of androgen excess (Wild *et al.*, 1990) have been studied for a history of significant hirsutism and acne. These signs and symptoms were more common in those women with confirmed coronary artery disease (CAD). WHR was associated with hirsutism and with coronary artery disease. The strongest associations were found in older women (≥60 years). Birdshall conducted a prevalence study of women referred for coronary angiography for assessment of chest pain or valvular disease (Birdsall *et al.*, 1997). Women who had bilateral oophorectomy were excluded. Quantitative angiography determined the extent of the lesions. Polycystic ovaries were present in 42% of women and coronary lesions were associated with hirsutism, previous hysterectomy, higher free T, TG and C-peptide levels, and lower HDL cholesterol levels. Women with PCOS had more extensive CAD (see Table IV).

Comment

In these studies, the surrogate outcome, confirmed coronary artery lesion, was blindly matched with the clinical data to avoid interpretation bias. Evaluating consecutive patients without regard to the outcome helps avoid bias of ascertainment. With adequate numbers, it is unlikely there would be an uneven distribution of risk factors. Patients were referred to angiography for chest pain, or suspected CAD or valvular disease. Angiography is not without risk. Unfortunately, this tool examines the arteriosclerotic burden relatively late in the evolution of this disease process. We now know that less advanced lesions might actually be more likely to culminate in heart attacks and sudden death than the ones best determined by angiography. The Birdshall study has the advantage and disadvantage of ultrasound (many investigators argue that a polycystic ovary is a sign, not a diagnosis). Those with the ultrasound diagnosis were more likely hirsute. Oophorectomy is associated with premature coronary heart disease and this may be true in women with or without PCOS. These studies establish the prevalence in women coming to angiography on each service (we cannot rule out some factor biasing referral, although there is no reason to believe that this is operative).

Electron beam computed tomography (EBCT)

Christian determined the prevalence of sub-clinical CAD by EBCT in a cohort of women with PCOS aged 30–45 years, matched to two ovulatory controls by age and BMI (Christian *et al.*, 2000) (see Table IV). Women and men who had previously undergone EBCT for the Rochester Family Heart Study served as additional historical community controls. The study concluded that prevalence of coronary artery calcification in premenopausal women with PCOS is significantly greater than that of community-dwelling women [odds ratio (OR) = 5.5] and is similar to that of men of comparable age.

Comment

This non-invasive study has the advantage of evaluating premenopausal women with PCOS before events have occurred. Coronary calcium scores do not perfectly predict coronary artery events; however, there is a strong relationship when corrected for age and gender. PCOS seems to be associated with greater prevalence of coronary calcium, independent of the well known risk factors for CAD, as early in life as the premenopause age.

Carotid artery

Ultrasound

Guzick studied premenopausal women age ≥40 years with a history of clinical PCOS and a total testosterone concentration ≥2.0 nmol/l (Guzick *et al.*, 1996). Intima-media thickness (IMT), plaque, BMI, fasting insulin and lipid levels were assessed. IMT was greater for PCOS. In spite of a major limitation of small sample size, the data suggested that women with PCOS have an increased risk of subclinical atherosclerosis in their 40s. Talbott *et al.* extended these studies and analysed for potential associations with risk factors (Talbott *et al.*, 2000) (see Table IV). They found that among PCOS cases compared with controls, 7.2% (nine of 125) of PCOS cases had a plaque index of ≥3 compared with 0.7% (one of 142) of similarly aged controls ($P = 0.05$). Overall and in the group aged 30–44 years, no difference was found in the mean carotid IMT between PCOS cases and the controls. Among women aged ≥45 years, the PCOS cases had significantly greater mean IMT than did the control women (0.78 ± 0.03 versus 0.70 ± 0.01 mm, $P = 0.005$). This difference remained significant after adjustment for age and BMI ($P < 0.05$). The authors felt that these results suggested: (i) lifelong exposure to an adverse cardiovascular risk profile in women with PCOS may lead to premature atherosclerosis; and (ii) the PCOS–IMT association is explained in part by weight and fat distribution and the associated risk factors. There may be an independent effect of PCOS unexplained

Table IV. Coronary/carotid vessels

Author/date	Patient population	Findings	Level of evidence
Wild, 1990	102 consecutive patients undergoing angiography.	PCOS more likely positive, hirsutism, acne, waist/hip. With CAD.	III
Birdshall, 1997	143 consecutive patients undergoing angiography, <60 years, pelvic US. No one with oophorectomy.	PCOS in 42%, associated with hirsutism; prior hysterectomy; higher free testosterone, TG, and C-peptide ; lower HDL cholesterol. PCOS more CAD.	III
Christiansen. 2000	EBCT 30–45 years. PCOS, and NL, historical community controls, age- and BMI-matched, women ($n = 175$) and men ($n = 154$), prior EBCT.	Coronary calcification more prevalent PCOS odds ratio 2.52, versus community-dwelling women odds ratio 5.5 similar age, equivalent to men.	III-IV
Guzick, 1996	Carotid US 16 PCOS premenopausal women, 16 age-matched controls.	Intima-media thickness greater PCOS, 5 cases, 2 controls -plaque (NS).	III
Talbott, 1998	46 PCOS versus 59 controls carotid scanning.	Carotid artery index worse in PCOS: correl. age, BMI, diastolic BP, LDL. III	
Talbott *et al.*, 2000	125 PCOS versus 142 controls. Risk factors.	No difference in mean control IMT between PCOS and controls. In women >45 years PCOS significantly higher IMT than controls.	III

CAD = coronary artery disease; US = ultrasound; EBCT = electron beam computed tomography; PCOS = polycystic ovarian syndrome; NL = normal; IMT = intima-media thickness; TG = triglyceride; NS = not significant.

by the above variables related to the hormonal dysregulation of this condition.

Comment

Carotid change is a surrogate marker for potential CAD and stroke. Arteriosclerotic changes do not necessarily translate into more events. Lesion progression can theoretically stop with vigorous prevention. Women with PCOS appear to be more likely to have carotid disease early in life compared with non-PCOS controls.

Endothelial dysfunction

In a cross-sectional study of young women, using the brachial artery, Mather *et al.* could not find more frequent endothelial dysfunction in women with PCOS in spite of insulin resistance and hyperandrogenism (Mather, 2000).

Comment

Dysfunctional endothelium is an early step in atherosclerosis. Measures of sheer stress in capacitance and resistance vessels might be a useful clinical tool as an indicator of endothelial dysfunction (Sica, 2000). Endothelium governs a broad range of critical vascular functions and adapts to local requirements in a rapid temporal fashion. Dysfunction is present when its properties, either in the basal or stimulated state, are recast in a fashion inappropriate to the preservation of organ function. When the endothelium is operationally intact and its various functions are summed, the overall effects realized include physiologically appropriate vasodilatation as well as the effective dampening of proinflammatory and procoagulant processes. Newly available technologies allow endothelial function to be studied longitudinally. The number of factors that can affect endothelial function are legion. Measurements at the periphery seem to correlate well with coronary measurements (Anderson *et al.*, 1995). There are data in men indicating that endothelial dysfunction correlates with subsequent events (Al Suwaidi *et al.*, 1999; Schachinger, 1999). Although controversial, a number of interrelated variables involved in insulin resistance including dyslipidaemia, dysglycaemia and hyperinsulinaemia may play a role in progression to CVD—all are thought to involve endothelial dysfunction in different vascular beds (Leiter, 1999). Balletshofer found associations between endothelial dysfunction and insulin resistance in normotensive and normoglycaemic first-degree relatives of patients with type 2 diabetes mellitus (Balletshofer *et al.*, 2000). Evaluating endothelial function in patients with PCOS and family members is a promising tool. Determining the positive/negative predictive value of this testing in women in general, and in women with PCOS in particular, is needed.

Circulatory death

Pierpoint *et al.* reported their findings in women with PCOS diagnosed in the UK between 1930 and 1979 (Pierpoint *et al.*, 1998). Hospital records were used. Women were followed historically for an average of 30 years, and had standardized mortality ratios (SMRs) calculated to compare the death rates with national rates. The all-cause SMR was [0.90 (0.69–1.17)], 59 deaths. Fifteen were from circulatory disease [SMR 0.83 (0.46–1.37)]. Of these, 13 were from ischaemic heart disease [SMR 1.40 (0.75–2.40)] and two were from other circulatory disease [SMR 0.23; 0.03–0.85]. There were six from diabetes mellitus compared with 1.7 expected [OR = 3.6 (1.5–8.4)]. Breast cancer was the most common cause of death [SMR 1.48, 13 deaths (0.79–2.54)]. The authors concluded that women with PCOS do not have markedly higher than average mortality from circulatory disease, although the condition is strongly associated with diabetes, lipid abnormalities and other cardiovascular risk factors. They hypothesized that the characteristic endocrine profile of women with PCOS may protect against circulatory disease in this condition.

Table V. Endometrial cancer (EC)

Author/date	Patient population	Findings	Level of evidence
Potishman, 1996	Case–control	High androstenedione associated with 3.6- and 2.8- fold increased risks among premenopausal and post-menopausal women after adjustment for other factors (P for trend = 0.01 and < 0.001).	II
Niwa, 2000	Case–control	Irregular menses, PCOS and obesity in the EC patients <40-years significantly higher than the controls ER ($P < 0.05$) and PR ($P < 0.01$) were more frequently recognized in the EC of premenopausal than post-menopausal patients. Over-expression of p53 was detected in 27.2% of the post-menopausal EC group, found in 7.1% of the premenopausal EC group.	II

PCOS = polycystic ovarian syndrome; ER = estrogen receptor; PR = progesterone receptor.

Comment

Diagnosis in this study was primarily from ovarian wedge material. Clinical indices—androgen excess and abnormal menses—were not reported. Many would point out that a polycystic ovary is a sign, but not a diagnosis. The differential diagnosis for this phenotypic expression is wide. Indications for wedge resection were often liberal and inconsistent. The procedure is no longer performed. Androgen and estrogen milieu change after wedge resection. Optimally, PCOS patients without resection and controls should be observed until later years when cardiovascular disease is prevalent. The authors suggest that because these patients underwent wedge resection they should be more severe. However, the main indication for wedge resection historically was for fertility not severity. Often women with severe metabolic disturbances were not good candidates for wedge resection. Of all patients, many records were not available. This can lead to differential recall bias. Regional differences in CVD rates are well known. SMRs came from national data and cases were therefore not matched regionally. Difficulties with using death certificate data are well known. In spite of these limitations, there was no increase in premature CVD deaths. It is also striking that deaths from diabetes were markedly elevated. A random selection of PCOS women and community controls with more complete retrieval would reduce potential biases about known and unknown factors.

Endometrial cancer

Two case–control studies are summarized in Table V. In the first study (Potischman *et al.*, 1996), high circulating levels of androstenedione have been associated with 3.6- and 2.8- fold increased risks of endometrial cancer among premenopausal and post-menopausal women respectively, after adjustment for other factors (P for trend = 0.01 and < 0.001). Risks related to other hormone fractions varied by menopausal status. Among post-menopausal women, reduced risk was associated with high SHBG levels and persisted after adjustment for obesity and other factors (OR = 0.51; 95% CI 0.27–0.95). High estrone levels were associated with increased risk (OR = 3.8; 95% CI 2.2–6.6), although adjustment for other risk factors (particularly BMI) diminished the effect (OR = 2.2; 95% CI 1.2–4.4).

The prevalence of endometrial cancer in young women appears to be increased in women with PCOS (Niwa *et al.*, 2000). To assess the risk factors for endometrial carcinoma (EC), a case–control study was performed with 136 Japanese women with EC and 376 healthy controls. Immunohistochemical analyses on p53, estrogen and progesterone receptors of EC patients were measured. Nulliparity, increased BMI, hypertension, diabetes mellitus, later age at menopause and personal cancer history were all seen predominantly in the EC group. The frequency of irregular menses, PCOS and obesity in the EC patients <40 years old was significantly higher than in the controls. Immunohistochemical expressions of estrogen receptor ($P < 0.05$) and progesterone receptor ($P < 0.01$) were more frequent in the EC of the premenopausal than in the post-menopausal patients. Over-expression of p53 was detected in 27.2% of the post-menopausal EC group, yet only found in 7.1% of the premenopausal EC group. The authors felt that these findings indicate that possible factors related to endometrial carcinogenesis are different in pre- and post-menopausal EC patients. Namely, untreated ovarian dysfunction such as PCOS with unopposed estrogenic action in the endometrium may be associated with development and growth of EC in younger women, yet abnormality of the p53 gene may be more concerned with the development of post-menopausal EC, independently of sex steroid influence.

Comment

In the USA, endometrial cancer is the most common invasive gynaecological cancer. Using registry data from the USA Surveillance, Epidemiology and End Results (SEER) Program (1986–1990), the age-specific incidence peaked at 70–74 years (n = 110.7 per 100 000). This was 2.85 times the rate reported at 50–54 years (n = 38.9 per 100 000). There is racial disparity. Endometrial cancer is more frequent in African Americans. Reproductive history, choice of contraception methods, hormone replacement therapy, obesity, dietary factors, age-specific prevalence of hysterectomy for other gynaecological conditions, quality of medical care and surveillance practices, genetic factors influencing susceptibility, and tumour-associated biological factors may all be important. The majority of risk factors and medical conditions associated appear to be related directly or indirectly to the levels and metabolic effects of the reproductive hormones, namely estrogens and progestogens. High endogenous unopposed estrogen appears to increase the risk of endometrial cancer. Their independence from other risk factors is inconsistent with this being a common underlying biological pathway through which all risk factors for endometrial cancer operate.

While PCOS appears to be a risk factor for endometrial cancer, and for some patients it appears to be a pre-diabetic state, the reader should be aware that the literature is conflicting as to whether or not diabetes is a risk factor for endometrial cancer independent of obesity (data not shown).

Women with PCOS frequently have abnormal uterine bleeding. Case reports suggest that in the setting of prolonged anovulation, endometrial cancer can develop in women with PCOS even in their teenage years. However, the true incidence of endometrial cancer in premenopausal women with PCOS is not known. Premenopausal endometrial cancer may have different risk factors associated with it than post-menopausal endometrial cancer. Obesity, body fat distribution and the biological relevance of the increased risk associated with higher androstenedione levels in both premenopausal and post-menopausal cancer patients (Potischman *et al.*, 1996) all need to be explored further in these types of studies. Women with PCOS commonly have increased circulating androstenedione.

Does modifying risk factors reduce CVD events?

Comment

This difficult question remains. The effects of an intervention on the surrogate must reliably predict the overall effect on the clinical outcome. It is a common misconception that if an outcome is a correlate for a true clinical outcome, it is a valid surrogate endpoint. Proper justification for such replacement requires that the effect of an intervention on the surrogate endpoint can predict the true effect on the clinical outcome. To do so, it must fully capture the net effect of treatment on the clinical outcome. There are many examples of treating surrogate endpoints that have caused more harm than good. A number of reasons include: (i) a therapy may affect the surrogate, not the disease; (ii) the converse may happen, and the disease risk may decrease without a change in the surrogate; or (iii) the intervention may affect an outcome independent of either the surrogate or the disease progression.

No studies have had the adequate power necessary to assess fully the net effects of therapy on the incidence of diabetes, coronary vascular morbidity or mortality, or anovulation with attendant risk in women with PCOS.

Is treatment of the risk factors in high-risk patients worth it? In current medical practice, not treating anovulation with the attendant potential risk of abnormal uterine bleeding and endometrial cancer seems unwise, particularly when excellent preventive therapy is very well studied and widely available. However, optimum treatment strategies that avoid aggravating the risk of diabetes yet protect against endometrial cancer need to be determined. Five α reductase inhibitors (Finasteride, Spironolactone, oral contraceptives, etc.) and insulin-sensitizing drugs are widely used to treat PCOS. Each is widely used based on mechanistic theory. Long-term safety data, with attention to effects related to overall clinical events, is for the most part non-existent.

Summary

There is little doubt that women with PCOS cluster risk factors for diabetes, CVD and endometrial cancer. Premature diabetes, circulatory disease and/or endometrial cancer in women with PCOS has major public health implications. The prevalence of PCOS in women in different populations or racial groups is not well understood. Whether having PCOS is an independent risk factor for each of these outcomes remains unclear. Most studies have been cross-sectional, they look at surrogate endpoints, and they assess prevalence. Case–control studies suggest that PCOS might be a risk factor for endometrial cancer. Cohort studies suggest that endometrial cancer is more common in obese diabetics, although the effects of these two separate classic risk factors is controversial. Whether PCOS is an independent risk for circulatory death remains unclear. Invasive and non-invasive studies have found more premature atherosclerosis in women with PCOS. Clinical trials that assess the net effects of any of the current treatments are needed. Whether the surrogate markers available are useful clinical indicators of meaningful outcomes in women with PCOS requires further investigation. Determining the sensitivity, specificity, positive and negative predictive value of screening tests is hampered because of the absence of adequate long-term event data.

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