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Increased risk of non-insulin dependent diabetes mellitus, arterial hypertension and coronary artery disease in perimenopausal women with a history of the polycystic ovary syndrome

D.Cibula[1,5], R.Cífková[2], M.Fanta[1], R.Poledne[4], J.Zivny[1] and J.Skibová[3]

[1]Department of Obstetrics and Gynecology, General Teaching Hospital, Charles University, Apolinarska 18, Prague 2, 120 00, [2]Department of Preventive Cardiology, [3]Department of Statistics and [4]Laboratory for Atherosclerosis Research, Institute for Clinical and Experimental Medicine, Videnska 1958/9, Prague 4, 140 21, Czech Republic

[5]To whom correspondence should be addressed

The aim of the study was to determine the prevalence of non-insulin dependent diabetes mellitus (NIDDM), arterial hypertension, coronary artery disease and the risk factors for these diseases in perimenopausal women with a history of polycystic ovary syndrome (PCOS) treatment. A group of 28 women was selected from a large group of patients who had undergone wedge ovarian resection. A total of 752 controls was selected by age (45–59 years) from a random female population sample. There was no difference between the two groups in body mass index, waist circumference or waist–hip ratio. Both groups were found to have identical family histories of NIDDM, hypertension, and coronary artery disease and identical smoking habits. We did not find a difference between the mean concentrations of lipids and fasting glucose. The two groups did not differ in the proportions of women with elevated lipid concentrations. The prevalence of NIDDM and coronary artery disease was significantly higher in PCOS women. In conclusion, women in the general population have the same level of risk factors at perimenopausal age as PCOS women. Patients with markedly expressed clinical symptoms of PCOS made up a subgroup in the general population at high risk for developing NIDDM and coronary artery disease.

Key words: coronary artery disease/late risks/NIDDM/PCOS

Introduction

Polycystic ovary syndrome (PCOS) is the most frequent endocrine disorder in women, the most common cause of anovulatory infertility, oligomenorrhoea and hirsutism. The disorder affects almost 10% of women of fertile age (Yen, 1986). However, the exact prevalence is not known, as hyperinsulinaemia and insulin resistance are characteristic features of obese and non-obese women with PCOS. Up to 60% of lean women with PCOS exhibit fasting hyperinsulinaemia (Conway *et al.*, 1993). Obese and non-obese PCOS women have been shown to have β-cell dysfunction independent of obesity and glucose intolerance (Ehrman *et al.*, 1995; Dunaif *et al.*, 1996). Obesity, which is common in PCOS patients, together with insulin resistance and β-cell dysfunction, contributes to an increased risk for developing impaired glucose tolerance and non-insulin dependent diabetes mellitus (NIDDM).

Previous studies have demonstrated an atherogenic lipid profile (Talbott *et al.*, 1995, 1998; Robinson *et al.*, 1996; Rajkhowa *et al.*, 1997) and enhanced plasminogen activator inhibitor type 1 (PAI-I) production (Sampson *et al.*, 1996; Atiomo *et al.*, 1998) in PCOS patients. Peripheral insulin resistance, dyslipidaemia, and increased PAI-I activity are important risk factors for cardiovascular disease in these patients.

In addition to these theoretical considerations, there are only few data confirming an increased risk for certain diseases in PCOS women at a later age. To date, two studies (Dahlgren *et al.*, 1992, 1994) have focused on the risk of arterial hypertension and NIDDM in women in perimenopausal age with a history of PCOS. In a retrospective cohort study, a higher prevalence of NIDDM and hypertension was demonstrated in a group of 33 patients previously treated for PCOS, when compared to 132 age-matched controls. In the more recent study, a higher prevalence of hypertension and diabetes mellitus was shown in a group of 28 PCOS women, aged 43–62 years, matched by age and BMI (body mass index) to 56 controls. Recently, clinical evidence of an increased risk for atherosclerosis in women with PCOS was obtained (Guzick *et al.*, 1996). Sixteen women >40 years of age, with a history of treatment of PCOS, exhibited significantly greater intima/media thickness and a higher prevalence of plaque measured by carotid artery ultrasonography compared to 16 age-matched controls.

The aim of our study was to evaluate the prevalence of NIDDM, arterial hypertension and coronary artery disease (CAD), and the risk factors for these diseases in a group of women aged 45–59 years who had been treated for markedly expressed clinical symptoms of PCOS.

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Material and methods

Cases

A group of 61 women aged 45–59 years, who had undergone wedge ovarian resection in our department (1960–1981) for typical clinical and morphological symptoms of PCOS, were included in the study. All patients were Caucasian. At the time of surgery, all women met the following criteria: (i) oligomenorrhoea (menstrual period >45 days) or amenorrhea from menarche, (ii) hirsutism (Ferriman–Gallwey

score >8), (iii) anovulatory infertility and (iv) typical appearance of the ovaries described during surgery (enlarged ovaries with thickened tunica albuginea and multiple small-diameter follicles under the surface). A questionnaire was sent to all 61 women. Thirty-three questionnaires were not delivered because of a change in home address. All the women receiving the questionnaire returned it completed. The data of 28 women who responded are evaluated in our study.

Biochemical assays. Blood glucose was measured using hexokinase method (Glucose HK-UV test; Olympus Diagnostica GmbH, System Reagents, Listmechan, Co. Clare, Ireland), serum cholesterol and triglycerides were analysed using CHOD-PAP and GPO-PAP-based kits respectively (Oxochrom cholesterol 2500; Oxochrom Triacylgycerol T 500 respectively; Oxychrome, Lachema a.s., Czech Republic), high density lipoprotein (HDL)-cholesterol was determined by an immunoinhibition method (HDL-C Direct, Wako Chemicals GmbH, Neuss, Germany).

Controls

A control group of 752 women was selected; the women were aged 45–59 years and were selected from 3209 women representing a random population sample (1% of permanent residents of nine districts of the Czech Republic) aged 25–64 years to be screened for cardiovascular risk factors. The overall response rate was 64.4%.

Biochemical assays. Laboratory tests were performed in a WHO Regional Lipid Reference Laboratory (Institute for Clinical and Experimental Medicine, Prague, Czech Republic). Glucose was analysed enzymatically (Lachema, Brno, Czech Republic). Serum cholesterol and triglyceride concentrations were measured by a fully automated (Cobas Mira S autoanalyzer; Hoffman-La Roche, Basel, Switzerland) enzymatic method (reagents from Boehringer Mannheim, Germany and Hoffmann-LaRoche). HDL-cholesterol was determined by the same method after precipitation of serum lipoproteins with sodium phosphotungstate and magnesium chloride (kits from Boehringer Mannheim, Germany). Low density lipoprotein (LDL)-cholesterol was calculated using the Friedewald formula (LDL-cholesterol = total cholesterol – HDL cholesterol – triglyceride/2.19 mmol/l; Friedewald *et al.*, 1972).

Clinical investigations

All women had their family history taken with regard to hypertension, NIDDM and CAD in their parents. Each patient had her height and weight taken and her BMI was calculated; waist and hip circumferences were measured in the standing position at the levels of the umbilicus and spina iliaca anterior superior and the waist–hip ratio (WHR) was calculated. Venous blood samples were drawn from an antecubital vein after an overnight fast and glucose, total cholesterol, HDL-cholesterol and triglyceride concentrations were estimated. Blood pressure readings were taken twice in the sitting position after 10 min rest and the average of both determinations was calculated. Arterial hypertension was defined as a blood pressure ⩾140/90 mm Hg at clinical examination or by current use of antihypertensive medication. CAD was defined as follows: chest pain evaluated as definite or possible angina, a history of definite or possible myocardial infarction, a history of transluminal percutaneous coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG). NIDDM was defined as a fasting glucose concentration ⩾7.0 mmol/l at clinical examination or current medical treatment of NIDDM. All cases and controls were seen by a specialist in cardiology or internal medicine.

Statistical methods

Statistical analysis was performed using the χ^2 test with Yates' correction and Student's two-sample *t*-test. Gaussian distribution of data was identified in all variables except triglycerides and fasting glucose. Therefore these variables were logarithmically transformed. A two-way analysis of variance together with Bonferroni's method of multiple comparison was used to evaluate differences between pre- and post-menopausal subgroups. The study was approved by the Local Ethics Committees.

Table I. Characteristics of women suffering from polycystic ovary syndrome (PCOS) and control women

	PCOS *n* = 28	Controls *n* = 752
Age*	51.9 ± 4.64	51.0 ± 4.21
BMI* (kg/m^2)	28.0 ± 4.21	28.2 ± 5.42
Waist circumference (cm)*	89.2 ± 11.79	88.1 ± 13.10
WHR*	0.8 ± 0.05	0.83 ± 0.07
Parental coronary disease (%)	39	32
Parental NIDDM (%)	29	33
Parental hypertension (%)	39	37

*Mean values ± SD.
BMI = body mass index; WHR = waist–height ratio; NIDDM = non-insulin dependent diabetes mellitus.
There were no significant differences between the two groups.

Table II. Proportions of smokers, obese women, women with increased BMI and women with elevated lipid concentrations in PCOS women and controls

	PCOS		Controls	
	Number *n* = 28	%	Number *n* = 752	%
Smokers	7	25	210	28
BMI >28.9	10	36	301	40
WHR >0.85	5	18	269	36
Total cholesterol >5.2 (mmol/l)	20	71	536	71
HDL-cholesterol <1.0 (mmol/l)	2	7	50	7
LDL-cholesterol >3.7 (mmol/l)	16	57	327	44
Triglycerides >1.9 (mmol/l)	7	25	207	28

There were no significant differences between the two groups.
HDL = high density lipoprotein; LDL = low density lipoprotein.

Results

Although the only criterion for the selection of the control group was the age range, both the groups did not differ in the anthropometric parameters assessed (BMI, waist circumference, WHR) (Table I). Similarly, there were no differences between the two groups in the proportions of obese women (BMI >28.9) and women with an increased WHR (WHR >0.85) (Table II). The groups did not differ in the incidence of NIDDM, hypertension, and CAD in their parents (Table I). The proportions of smokers were almost identical in PCOS patients and in the control group (Table II).

Table III gives a comparison of the mean values of blood pressure, lipids, and fasting glucose. The mean diastolic or systolic blood pressure was not significantly different. The groups of PCOS women and controls did not differ in the numbers of those with newly diagnosed hypertension during clinical examination in our department (28.6 versus 32%

Table III. The mean values ± SD of blood pressure, fasting glucose and lipids in PCOS women and controls

	PCOS $n = 28$	Controls $n = 752$
SBP (mm Hg)*	132.1 ± 23.10	129.2 ± 17.76
DBP (mm Hg)**	79.7 ± 10.91	81.9 ± 9.80
Glucose (mmol/l)	6.1 ±1.94	5.8 ± 1.39
Total cholesterol (mmol/l)	6.0 ±1.03	5.9 ± 1.20
HDL-cholesterol (mmol/l)	1.4 ± 0.32	1.5 ± 0.37
LDL-cholesterol (mmol/l)	3.9 ± 1.05	3.7 ± 1.07
Triglycerides (mmol/l)	1.5 ± 0.63	1.6 ± 0.93

*Systolic blood pressure.
**Diastolic blood pressure.
There were no significant differences between the two groups.

respectively). The fasting glucose concentrations among PCOS and control subjects did not differ significantly. In 33% of women of either group, the diagnosis of NIDDM was not established until indicated by fasting glucose concentrations (≥7.0 mmol/l). The PCOS and control groups did not differ significantly in the proportion of women with fasting glucose concentrations of 6.11–6.99 mmol/l (impaired fasting glucose) (17.6 versus 10.4% respectively).

A comparison of the groups did not reveal a significant difference in the mean serum concentrations with regard to a single parameter of the lipid profile (Table III). There was no difference between the groups of PCOS women and controls in the proportion of subjects with elevated total cholesterol (>5.2 mmol/l) (71.4 versus 71% respectively), LDL-cholesterol (>3.7 mmol/l) (57.1 versus 44.3% respectively), or triglycerides (>1.9 mmol/l) (25 versus 27.5% respectively) (Table II). At least one parameter of the lipid profile was increased in 78.6% of PCOS women and in 76.2% of controls.

While only 35.7% of women in the PCOS group were post-menopausal, the corresponding value for the control group was 60.2% (i.e. 433/719, excluding 33 women for whom records not available; see below). There were no significant differences between post-menopausal PCOS women and controls in the mean age of menopause (48.7 ± 4.16 versus 47.8 ± 4.61 respectively) and the mean number of post-menopausal years (5.2 ± 2.53 versus 5.5 ± 3.95 respectively).

Because of the different proportions of post-menopausal women in the two groups, each group was subdivided into pre- and post-menopausal subgroups. A reliable history of menopause was not available in 33 controls; therefore they were excluded from further analysis. Again, no differences were found in anthropometric parameters, mean blood pressure, lipids and fasting glucose between the four tested subgroups (Table IV).

The prevalence of NIDDM, hypertension and CAD among PCOS subjects and controls is shown in Table V. Hypertension was diagnosed in 50% of PCOS women and in 39% of controls (not significant), the diagnosis of NIDDM was established in 32% of women with PCOS and in 8% of controls ($P < 0.001$), CAD was diagnosed in 21% of PCOS women and in 5% of controls ($P < 0.001$). Thus, only the difference between the prevalence of hypertension in the two groups did not reach statistical significance.

Discussion

In the past, our department has been heavily involved in the treatment of PCOS. The large patient group allowed us to select patients meeting strict criteria for the clinical diagnosis of the syndrome.

The higher prevalence of central obesity, manifesting itself as a greater waist circumference or a higher WHR, in PCOS women of fertile age has been repeatedly reported in the literature (Lapidus *et al.*, 1984; Talbott *et al.*, 1995). The volume of visceral fat is an important risk factor for the development of cardiovascular disease. Although age range was the only criterion for selecting the control group, our controls did not differ from PCOS women in mean BMI, waist circumference and WHR. Our results indicate that, in older age, there is a trend for the difference between PCOS women and the general population in these anthropometric parameters to minimize.

Only 35.7% of women with a history of PCOS, compared to 58.2% in the control group, were post-menopausal ($P < 0.05$). This is in agreement with the previous studies (Dahlgren *et al.*, 1992, 1994). We can speculate that the number of ovulations during life or an impaired process of apoptosis could play a role in determining the age of the menopause.

It was previously reported that women with PCOS have higher very low density lipoprotein (VLDL; Robinson *et al.*, 1996) and lower HDL concentrations (Wild *et al.*, 1985). This was later confirmed to be independent of weight (Wild *et al.*, 1988). Recently, a large study of 206 women with PCOS confirmed higher total cholesterol, LDL-cholesterol and triglycerides, and lower HDL-cholesterol concentrations after adjustment for BMI (Holte *et al.*, 1994).

Compared to controls, there was no difference in the mean values of any of the lipid parameters. The proportion of women with elevated lipid concentrations likewise did not differ between the two groups. We thus confirmed the data reported by a previous elegant study (Talbott *et al.*, 1995), which found that PCOS women <40 years of age had substantially higher LDL and total cholesterol concentrations after adjustment for BMI and insulin concentrations, and which observed only minor differences between PCOS women and controls in the >40 years group. Although there were some methodological differences in biochemical assays in our study, both laboratories were standardized with the Center for Disease Control (Atlanta, GA, USA).

One of the parameters possibly determining serum lipid concentrations, blood pressure and body fat distribution is decreasing oestrogen production in menopause. Because of the unequal proportion of postmenopausal women, each group was subdivided to reflect the history of menopause. Again, there were no differences found between the tested subgroups in the above parameters.

An increased prevalence of impaired glucose tolerance and NIDDM in women with PCOS has been demonstrated in many

Table IV. Mean values ± SD of BMI, waist circumference, WHR, blood pressure, fasting glucose and lipids in pre-menopausal and post-menopausal PCOS women and controls

	PCOS		Controls	
	premenopausal $n = 18$	postmenopausal $n = 10$	premenopausal $n = 286$	postmenopausal $n = 433$
BMI (kg/m^2)	27.6 ± 4.66	28.8 ± 3.33	27.4 ± 5.5	28.9 ± 5.33
Waist circumference (cm)	87.3 ± 12.82	92.7 ± 9.26	85.2 ± 13.38	90.2 ± 12.54
WHR	0.8 ± 0.05	0.83 ± 0.06	0.81 ± 0.07	0.84 ± 0.07
SBP (mm Hg)*	128.9 ± 21.77	138.0 ± 25.44	125.9 ± 17.59	131.5 ± 17.55
DBP (mm Hg)**	79.3 ± 12.07	80.5 ± 9.0	80.3 ± 10.34	82.9 ± 9.31
Glucose (mmol/l)***	5.9 ± 1.75	6.3 ± 2.33	5.6 ± 1.05	5.9 ± 1.5
Total cholesterol (mmol/l)	5.9 ± 1.2	6.0 ± 0.67	5.6 ± 1.09	6.2 ± 1.22
HDL-cholesterol (mmol/l)	1.3 ± 0.33	1.5 ± 0.29	1.5 ± 0.36	1.5 ± 0.39
LDL-cholesterol (mmol/l)	4.1 ± 1.17	3.8 ± 0.84	3.4 ± 0.99	3.9 ± 1.1
Triglycerides (mmol/l)***	1.5 ± 0.64	1.6 ± 0.66	1.4 ± 0.78	1.8 ± 0.99

*Systolic blood pressure.
**Diastolic blood pressure.
***Logarithmically transformed.
There were no significant differences between any of the groups.

Table V. Prevalence of coronary artery disease (CAD), non-insulin diabetes mellitus (NIDDM) and hypertension in the PCOS and control groups

	PCOS $n = 28$		Controls $n = 752$		*P*-value
	Number	%	Number	%	
Coronary artery disease	6	21	38	5	$P < 0.001$
NIDDM	9	32	60	8	$P < 0.001$
Arterial hypertension	14	50	290	39	NS

NS = not significant.

studies (Dunaif *et al.*, 1987; Harris *et al.*, 1987; Dahlgren *et al.*, 1992, 1994; Holte *et al.*, 1994). However, the relative contribution of insulin resistance and β-cell dysfunction to the pathogenesis of NIDDM has been controversial; it has been postulated (Ehrmann, 1997) that only women with PCOS who have an additional defect, such as hypersecretion of insulin, tend to develop NIDDM.

Some studies showed data confirming an increased risk for hypertension and CAD in PCOS women. An increased risk for arterial hypertension in women with a history of PCOS at older age has been repeatedly demonstrated (Dahlgren *et al.*, 1992, 1994). Higher daytime systolic arterial mean blood pressure, which persisted after adjustment for BMI, insulin sensitivity and body fat distribution, in women with PCOS of fertile age has also been documented (Holte *et al.*, 1996). A New Zealand study demonstrated a high prevalence of sonographically verified polycystic ovaries in women with documented coronary artery disease (CAD) (White *et al.*, 1994). A higher incidence of hirsutism in women with CAD compared to women without this finding was demonstrated using coronary arteriography (Wild *et al.*, 1990).

Cardiovascular disease patterns show an East–West gradient with the highest mortality rates in Eastern Europe, including the former Czechoslovakia (Sans *et al.*, 1997). In agreement with this expectation, the prevalence of NIDDM, arterial hypertension, and CAD was high in our control group. When comparing our controls (752 women) to the control group in the study of Dahlgren *et al.* (120 women), our study showed a markedly higher prevalence of NIDDM (8 versus 2.3%) as well as that of hypertension (39 versus 11%). Despite this high incidence of NIDDM in the Czech population, the prevalence of NIDDM (but not hypertension) was significantly higher in the group of PCOS women. The incidence of NIDDM and CAD in our women with a history of PCOS was four times that of a control group representing the Czech female population. The difference was not statistically significant regarding the incidence of hypertension. One in two women with PCOS was diagnosed to have hypertension, one in three met the criteria of NIDDM and one in five was being treated for CAD. At the same time, there was no difference between the two groups in the family histories of the diseases studied and smoking habits.

In conclusion, the group of women with PCOS did not differ from the large control group in their basic anthropometric criteria (BMI, WHR, waist circumference), family history, or proportions of smokers. The identical lipid profiles between these groups were most probably the consequence of a deteriorating status in a population of older age. Despite the identical risk for the development of the diseases studied, the prevalence of NIDDM and CAD was significantly higher in PCOS women. Our results confirm that women with markedly expressed clinical symptoms of PCOS make up a subgroup in the general population, at high risk for the development of NIDDM and CAD.

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References

Atiomo, W.U., Bates, S.A., Condon, J.E. *et al.* (1998) The plasminogen activator system in women with polycystic ovary syndrome. *Fertil. Steril.*, **69**, 236–241.

Conway, G.S. and Jacobs, H.S. (1993) Clinical implications of hyperinsulinaemia in women. *Clin. Endocrinol.*, **39**, 623–632.

Dahlgren, E., Johansson, S., Lindstedt, G. *et al.* (1992) Women with polycystic ovary syndrome wedge resected in 1956 to 1965: a long term follow-up focusing on natural history and circulating hormones. *Fertil. Steril.*, **57**, 505–513.

Dahlgren, E., Janson, P.O., Johansson, S. *et al.* (1994) Hemostatic and metabolic variables in women with polycystic ovary syndrome. *Fertil. Steril.*, **61**, 455–460.

Dunaif, A. and Finegood, D.T. (1996) Beta-cell dysfunction independent of obesity and glucose intolerance in the polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.*, **81**, 942–947.

Dunaif, A., Graf, M., Mandeli, J. *et al.* (1987) Characterization of groups of hyperandrogenic women with acanthosis nigricans, impaired glucose tolerance, and/or hyperinsulinemia. *J. Clin. Endocrinol. Metab.*, **65**, 499–507.

Ehrmann, D.A. (1997) Relation of functional ovarian hyperandrogenism to non-insulin dependent diabetes mellitus. *Baillière's Clin. Obstet. Gynecol.*, **11**, 335–346.

Ehrman, D.A., Sturis, J., Byrne, M.M. *et al.* (1995) Insulin secretory defects in polycystic ovary syndrome. Relationship to insulin sensitivity and family history of non-insulin dependent diabetes mellitus. *J. Clin. Invest.*, **96**, 520–527.

Friedewald, W.T., Levy, R.I. and Frederickson, D.S. (1972) Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of preparative ultracentrifuge. *Clin. Chem.*, **18**, 499–502.

Guzick, D.S., Talbott, E.O., Sutton-Tyrrell, K. *et al.* (1996) Carotid atherosclerosis in women with polycystic ovary syndrome: initial results from a case-control study. *Am. J. Obstet. Gynecol.*, **174**, 1224–1232.

Harris, M.I., Hadden, W.C. and Knowler, W.C. (1987) Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in a US population aged 20–74 yr. *Diabetes*, **36**, 523–534.

Holte, J., Bergh, T., Berne, Ch. *et al.* (1994a) Serum lipoprotein lipid profile in women with the polycystic ovary syndrome: relation to anthropometric, endocrine and metabolic variables. *Clin. Endocrinol.*, **41**, 463–471.

Holte, J., Bergh, T., Berne, C. *et al.* (1994b) Enhanced early insulin response in relation to insulin resistance in women with polycystic ovary syndrome and normal glucose tolerance. *J. Clin. Endocrinol. Metab.*, **78**, 1052–1058.

Holte, J., Gennnarelli, G., Berne, C. *et al.* (1996) Elevated ambulatory daytime blood pressure in women with polycystic ovary syndrome: a sign of a pre-hypertensive state? *Hum. Reprod.*, **11**, 23–28.

Lapidus, L., Bengtsson, C., Larsson, B. *et al.* (1984) Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden. *Br. Med. J.*, **289**, 1257–1261.

Rajkhowa, Z., Neary, R.H., Kumptala, P. *et al.* (1997) Altered composition of high density lipoproteins in women with the polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.*, **82**, 3389–3394.

Robinson, S., Henderson, A.D., Gelding, S.V. *et al.* (1996) Dyslipidemia is associated with insulin resistance in women with polycystic ovaries. *Clin. Endocrinol.*, **44**, 277–284.

Sampson, M., Kong, Ch., Patel, A. *et al.* (1996) Ambulatory blood pressure profiles and plasminogen activator inhibitor (PAI-1) activity in lean women with and without the polycystic ovary syndrome. *Clin. Endocrinol.*, **45**, 623–629.

Sans, S., Kesteloot, H. and Kromhout, D. (1997) The burden of cardiovascular diseases mortality in Europe. *Eur. Heart J.*, **18**, 1231–1248.

Talbott, E., Guzick, D., Clerici, A. *et al.* (1995) Coronary heart disease risk factors in women with polycystic ovary syndrome. *Arterioscler. Thromb. Vasc. Biol.*, **15**, 821–826.

Talbott, E., Clerici, A., Berga, S.L. *et al.* (1998) Adverse lipid and coronary heart disease risk profiles in young women with polycystic ovary syndrome: results of a case-control study. *J. Clin. Epidemiol.*, **51**, 415–422.

White, H.D., Birdsall, M.A. and Farquhar, C.M. (1994) Association of polycystic ovaries with coronary artery disease (Abstract 686). *Circulation*, **90**, 686.

Wild, R.A. and Bartholomew, M.J. (1988) The influence of body weight on lipoprotein lipids in patients with polycystic ovary syndrome. *Am. J. Obstet. Gynecol.*, **159**, 423–427.

Wild, R.A., Painter, P.C., Coulson, P.B. *et al.* (1985) Lipoprotein lipid concentrations and cardiovascular risk in women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.*, **61**, 946–951.

Wild, R.A., Grubb, B., Hartz, A. *et al.* (1990) Clinical signs of androgen excess as risk factors for coronary artery disease. *Fertil. Steril.*, **54**, 255–259.

Yen, S.S.C. (1986) Chronic anovulation caused by peripheral endocrine disorders. In Yen, S.S.C. and Jaffe, R. (eds), *Reproductive Endocrinology. Physiology, Pathophysiology and Clinical Management*, 2nd edition. Saunders, Philadelphia, pp. 441–499.

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