Prevalence of diabetes mellitus, hypertension and cardiac complaints in a follow-up study of a Dutch PCOS population

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The aim of this study was to investigate the prevalence of diabetes mellitus, hypertension and cardiac complaints in a Dutch population with polycystic ovarian syndrome (PCOS) and to compare the results with the prevalence of these conditions in the Dutch female population, as retrieved from the Netherlands Health Interview Survey of Statistics Netherlands. A total of 346 PCOS patients were interviewed by telephone, with a mean age of 38.7 years (range 30.3–55.7) and a mean body mass index of 24.4 (range 17.5–55.8). Diabetes occurred in eight (2.3%), hypertension in 31 (9%) and cardiac complaints in three (0.9%) of the women. The prevalence of diabetes and hypertension differed significantly from the prevalence of these conditions in the Dutch female population (both $P < 0.05$). In PCOS women aged 45–54 years ($n = 32$) the prevalence of diabetes was four times higher ($P < 0.05$) and of hypertension 2.5 times higher ($P < 0.01$) than the prevalence of these conditions in the corresponding age group of the Dutch female population. Hypertension also occurred significantly ($P < 0.05$) more in the younger (35–44 years) PCOS group ($n = 233$), but this age group was significantly more obese ($P < 0.01$) when compared with figures of obesity of the Dutch female population. In conclusion, our data show that in a follow-up study of a relatively lean PCOS population, the prevalence of diabetes mellitus and hypertension was increased when compared with the Dutch female population, especially in women aged 45–54 years.

Key words: diabetes/hypertension/polycystic ovarian syndrome

Introduction

A great deal of attention has been paid lately to metabolic disturbances in polycystic ovarian syndrome (PCOS) and their consequences in later life. Several authors observed peripheral insulin resistance in obese as well as in lean women with PCOS (Chang *et al.*, 1983; Dunaif *et al.*, 1989; Conway *et al.*, 1992; Morales *et al.*, 1996). However, not all patients with PCOS are insulin resistant and certainly the degree of insulin resistance is related to the degree of obesity (Rittmaster *et al.*, 1993; Acien *et al.*, 1999).

Two recent prospective studies reported on the prevalence of diabetes mellitus and impaired glucose tolerance in two obese PCOS populations in the USA (Ehrmann *et al.*, 1999; Legro *et al.*, 1999). Diabetes was found in 10 and 7.5% and impaired glucose tolerance in 35 and 31.1% respectively. Also in non-obese PCOS patients, i.e. those with a body mass index (BMI) of <27 kg/m^2, diabetes was found in 1.5% and impaired glucose tolerance in 10.3% (Legro *et al.*, 1999). In contrast, an Italian study of a less obese PCOS population did not find diabetes and only found impaired glucose tolerance in 15% of

the obese (BMI >25 kg/m^2) and hyperinsulinaemic PCOS women but not in lean normo- or hyperinsulinaemic patients (Ciampelli *et al.*, 1999).

Hyperinsulinaemia and insulin resistance not only increase the risk of diabetes mellitus but were also found to be correlated with the occurrence of hypertension, hypertriglyceridaemia and decreased high-density lipoprotein (HDL)–cholesterol and, hence, are involved in the aetiology of cardiovascular diseases (Reaven, 1988; Despres *et al.*, 1996; Yip *et al.*, 1998).

In a Swedish follow-up study of 33 PCOS women aged 40–59 years, the prevalence of diabetes mellitus and hypertension was found to be greatly increased when compared with age-matched controls (Dahlgren *et al.*, 1992a). The risk of myocardial infarction in this group was calculated to be seven times higher than for age-matched controls of the general population (Dahlgren *et al.*, 1992b). However, a recent epidemiological study did not find a higher mortality rate in general or from cardiovascular diseases in women who had been classified as having PCOS in the past (Pierpoint *et al.*, 1998).

In the above-mentioned studies, the diagnosis of PCOS has been made by the combination of chronic anovulation and hyperandrogenaemia or on the basis of histological evidence of polycystic ovaries in the past. The aim of this study was to investigate the prevalence of diabetes mellitus, hypertension and cardiac complaints in a follow-up study of our PCOS population, which is defined as having oligo- or amenorrhoea in combination with an elevated LH concentration, in relation to the prevalences of these conditions in the general Dutch female population.

Materials and methods

This study was part of a larger follow-up study of a cohort of ageing polycystic ovary syndrome patients called the APOS study (Elting *et al.*, 2000). It was performed under the guidelines of the Helsinki Declaration of 1975 (revised version 2000) and approved by the committee for ethics of research involving human subjects of the Vrije Universiteit Medical Centre.

Patients and study design

All patients registered as having PCOS in the out-patient clinic of the Division of Reproductive Endocrinology and Fertility of the Vrije Universiteit Medical Centre, Amsterdam, The Netherlands, were traced retrospectively. The patients were referred to the clinic for oligo- or amenorrhoea and/or hirsutism and/or infertility. The diagnosis of PCOS was confirmed by screening the medical charts for the combination of oligo- or amenorrhoea and an increased LH concentration, determined at least 2 weeks after and 3 weeks before a menstrual bleeding, in the presence of a normal FSH concentration. Prior to 1988, LH or FSH were elevated when >12 IU/l (polyclonal radioimmunoassay; Amerlex, Amersham, UK) and after 1988 LH was elevated when >6.5 IU/l and FSH was normal when <10 IU/l (monoclonal assay; Maia, Serono, Geneva, Switzerland, and Amersham immunometric assays).

All patients of this study participated in a telephone questionnaire. The design of the questionnaire and the data on the menstrual cycle patterns of these patients have been reported elsewhere (Elting *et al.*, 2000).

Questionnaire

The questionnaire was divided into several question categories, e.g. PCOS signs (menstrual cycle pattern, hirsutism and BMI), marital status and level of education, ethnic origin, smoking and alcohol intake and a category asking for the occurrence of diabetes mellitus, hypertension and cardiac complaints (serious heart disease or cardiac arrest). The phrasing of the questions in the last category was similar to that of the questions of the Netherlands Health Interview Survey of Statistics Netherlands (Statistics Netherlands, 1996). The Health Interview Survey studied, among other conditions, the prevalence of chronic conditions in the Dutch population. For instance, the patient was asked whether she had diabetes mellitus, and, if she answered positively, she was asked whether a check-up or treatment had been performed by the general practitioner (GP) or by a specialist and whether medication had been used in the last year. In our questionnaire, the women were asked about the occurrence of the condition in first degree family members. The same sequence of questions was followed for hypertension and cardiac complaints. The questions on marital status and level of education were categorized in the same way as in the Health Interview Survey.

In this report, the data on diabetes mellitus, hypertension and cardiac complaints in PCOS patients were compared with the figures of the Dutch female population (1989–1993) as retrieved from a publication of the Health Interview Survey (Van der Wulp, 1996). The proportion of obese (BMI >27 kg/m^2) women in the PCOS population was compared with the proportion of the Dutch female population (1989–1993), as retrieved from another Health Interview Survey publication (van Baal, 1996).

Statistical analysis

A step-forward logistic regression analysis was used to find the variables predicting diabetes mellitus, hypertension or cardiac complaints in our PCOS population. To compare the proportion of these conditions between three BMI groups (lean, overweight and obese) in the PCOS population and the proportion of affected first degree family members of patients with and without the condition, a two-sided Fisher's exact test was used. The comparison of the prevalence of diabetes mellitus, hypertension and cardiac complaints in PCOS patients was compared with the prevalence of these conditions in the Dutch female population using the χ^2 test with continuity correction. Because of the small numbers, the exact 95% confidence intervals were obtained for the prevalence of the conditions studied in the PCOS population (Geigy and Diem, 1960). For the Dutch female population, the ~95% confidence intervals (prevalence $\pm 1.96 \times SE$) were calculated. For all tests, $P < 0.05$ was considered to be statistically significant. Statistical analysis by computer was performed by SPSS/PC 7.5 (Statistical Package for the Social Sciences).

Results

Questionnaire

The response to the questionnaire was 80% (404 out of 506); 73% (369 out of 506) agreed and 7% (35 out of 506) refused to participate. After a drop out of 23 patients for different reasons (Elting *et al.*, 2000), 346 PCOS patients with a mean age of 38.7 years (range 30.3–55.7) and a median BMI of 24.4 (range 17.5–55.8) were interviewed. The first visit had been 12 years ago on average (range: 1.7–31.6). Patients answered to having hirsutism in 56.6% (196 out of 346) of cases.

Eight (2.3%) of the 346 PCOS women had diabetes mellitus (one had diabetes since childhood), 31 (9%) had hypertension, 3 (0.9%) had cardiac complaints. One of the latter three women (0.3%) had had a cardiac arrest. The combination of two of the three conditions occurred in 2 (0.6%) women, one had diabetes and hypertension and one had hypertension and cardiac complaints. None had all three conditions. Treatment and follow-up by the general practitioner (GP) was carried out in two (25%) of the women with diabetes and in 25 (80.6%) with hypertension. The others, and the three (100%) with cardiac complaints, were monitored by a specialist. All patients with diabetes used medication, five used insulin and three used oral hypoglycaemic agents. In all, 17 (54.8%) women with hypertension and 100% of women with cardiac complaints used medication. Of the patients with diabetes, 37.5% (three out of eight) had first degree family members with diabetes. For the women without diabetes this was 22.8% (77 of 338) ($P = 0.39$). Hypertension in first degree family members of patients with hypertension was 74.2% (23 out of 31) in contrast to 41% (129 out of 315) of the patients without hypertension ($P < 0.01$). The three patients with cardiac

complaints did not have first degree family members with cardiac complaints (not significant, when compared with the women without the condition).

Lean, overweight and obese patients

Of the 346 PCOS women, 194 (56.1%) had a BMI <25 kg/m^2 (defined as lean), 39 (11.3%) had a BMI $\geqslant 25$ and <27 kg/m^2 (overweight) and 113 (32.7%) had a BMI $\geqslant 27$ kg/m^2 (obese). Diabetes occurred in 1% (two out of 194) of the lean, 5.1% (two out of 39) of the overweight and in 3.5% (four out of 113) of the obese women. The prevalence of hypertension was 5.2% (10/194) in the lean, 2.6% (one out of 39) in the overweight and 17.7% (20 out of 113) in the obese women ($P < 0.01$). Cardiac complaints occurred in one lean and in two obese women.

Regression analysis

A step-forward logistic regression analysis with the variables age, BMI, hirsutism, marital status, level of education, ethnic origin, smoking and alcohol intake and their interactions showed that the interaction of age with BMI was the most significant variable in predicting diabetes mellitus ($P < 0.01$) and hypertension ($P < 0.01$). For hypertension, the interaction of hirsutism with age was a second significant predictor ($P < 0.01$) and the interaction of hirsutism with BMI a third ($P < 0.05$). Cardiac complaints were not predicted by either of the variables. When a step-forward regression analysis was performed without interactions between the variables, age was the only significant variable ($P < 0.05$) predicting diabetes. For hypertension, age was the first ($P < 0.01$), BMI the second ($P < 0.01$) and hirsutism ($P < 0.05$) the third significant variable.

Comparison with Dutch female population

The 345 PCOS patients were divided in three age groups: 30–34 years ($n = 80$), 35–44 years ($n = 233$) and 45–54 years ($n = 32$) to compare the prevalence of these conditions in these groups with the corresponding age groups (25–34, 35–44 and 45–54 years) in the Dutch female population of 1989–1993 (Table I). One PCOS patient was excluded because she was the only one aged >55 years. Hypertension occurred significantly more often in PCOS women aged 35–44 years ($P < 0.05$) and 45–54 years ($P < 0.01$). A significantly higher prevalence of diabetes ($P < 0.05$) was found in women with PCOS aged 45–54 years. When comparing the prevalence of these conditions in the total group of 345 PCOS patients with their prevalence in the combined age group 25–54 years of the Dutch female population, a significantly higher occurrence of diabetes and hypertension was found in the PCOS women (both $P < 0.05$).

In both PCOS patients and in the Dutch population, the prevalence of diabetes mellitus and hypertension significantly increased with age (for all: $P < 0.05$). Cardiac complaints in PCOS women did not increase with age in contrast to the data of the Dutch population.

In the total population (men and women of all ages) of this publication of the Health Interview Survey, 62.5% were checked for hypertension by the GP and 73.7% used medication. For cardiac complaints, medication was used in 89% and

for diabetes in 83% of this total population. These total (men and women) figures showed significantly more of all three conditions in lower educated people and more hypertension and diabetes in widows and widowers.

Information on the BMI of the female population was not given in this publication of the Health Interview Survey. Another publication of the same Health Interview Survey (van Baal, 1996) reported the proportions of obese (BMI $\geqslant 27$ kg/m^2) women in each year of the period 1989–1993. The pooled data of this period showed that obesity occurred in 13% of the female population aged 20–44 years and in 25.9% of women aged 45–64 years. When the PCOS women in this study were divided into comparable (as far as possible) age groups of 30–44 years ($n = 313$) and 45–56 years ($n = 33$), significantly more obesity was found in the younger age group (32.9%, $P < 0.01$) but not in the older age group (30.3%).

Discussion

The results of this study show that in our PCOS population (defined by oligo- or amenorrhoea and an elevated LH concentration), the total prevalence of diabetes and hypertension was significantly increased when compared with the Dutch female population. When stratifying to age group, it was found that this was based on a higher occurrence of diabetes in women aged 45–54 years and of hypertension in women with PCOS aged 35–54 years in comparison with the corresponding age groups of the Dutch population. Cardiac complaints (defined as serious heart disease or cardiac arrest) clearly did not differ between the two populations but this could be explained by the low prevalence of this condition prior to 60 years of age. A limitation of this study is that information was restricted for the control population of Statistics Netherlands. For example, the incidence of women with PCOS in the Dutch population study was not known. Theoretically, this might falsely elevate the prevalence of the conditions studied in the control group.

In the age group of 45–54 years, consisting of 32 PCOS patients, the prevalence of diabetes was four times higher and of hypertension 2.5 times higher than the prevalence of these conditions in the Dutch population. The proportion of obese ($\geqslant 27$ kg/m^2) PCOS women in this age group was not significantly different from the proportion in the Dutch female population. These findings are comparable with the follow-up study in Sweden of 33 PCOS women aged 40–59 years where it was found that diabetes had a 6.5-times higher prevalence and treated hypertension a 3.5-times higher prevalence when compared with age-matched controls (Dahlgren *et al.*, 1992a). In the current study, a two times higher prevalence of hypertension in a larger ($n = 233$) and younger (35–44 years) PCOS group was also observed. However, this could be due to obesity, because this younger PCOS group was significantly more obese than the corresponding age group of the Dutch female population.

We addressed the question of whether, in fact, not all of the differences found could be related to obesity rather than to PCOS itself. When lean, overweight and obese PCOS patients in our study population were compared, we found a significantly

Table I. Prevalence of diabetes mellitus, hypertension and cardiac complaints in 345 polycystic ovarian syndrome (PCOS) subjects compared with the prevalence in the Dutch female population ($n = 8950$) between 1989 and 1993 (Statistics Netherlands)

	Diabetes		Hypertension		Cardiac complaints	
	%	95% CI	%	95% CI	%	95% CI
25–34 years						
PCOS ($n = 80$)	1.3	0.0–6.8	3.8	0.8–10.6	0.0	0.0–4.5
Dutch population ($n = 3421$)	0.4	0.2–0.6	3.5	2.9–4.1	0.2	0.1–0.3
35–44 years						
PCOS ($n = 233$)	1.7	0.5–4.3	8.2*	5.0–12.5	0.9	0.1–3.1
Dutch population ($n = 3157$)	0.7	0.4–1.0	4.6	3.9–5.3	0.4	0.2–0.6
45–54 years						
PCOS ($n = 32$)	9.4*	2.0–25.0	28.1*	13.8–46.8	3.1	0.1–16.2
Dutch population ($n = 2372$)	2.3	1.7–2.9	11.1	9.8–12.4	0.9	0.5–1.3
Total						
PCOS ($n = 345$)	2.3*	1.0–4.5	9.0*	6.2–12.6	0.9	0.2–2.6
Dutch population ($n = 8950$)	1.0	0.8–1.2	5.9	5.4–6.4	0.7	0.5–0.9

CI = confidence interval.
*$P < 0.05$.

higher existence of hypertension, but not of diabetes in obese women. Regression analysis showed that the combination of the variables, age and BMI, was superior to one of these risk factors alone in predicting diabetes as well as hypertension. For hypertension the third predictor, i.e. hirsutism, was restricted to the combination of hirsutism with age and BMI. In the Dutch female population, the prevalence of diabetes and hypertension significantly increased with age. Unfortunately, this particular reference study mentioned no conclusions with respect to the influence of body weight on the prevalence of these conditions (Van der Wulp, 1996).

It is concluded that, for every Dutch woman, the risk of diabetes mellitus and hypertension increases with age regardless of having PCOS. However, it was found that being obese and hirsute further increases the risk of hypertension in PCOS patients. These findings suggest a co-existence of hyperinsulinaemia and hyperandrogenaemia, at least in some of our patients. Hyperandrogenaemia was found to cause a male lipid spectrum and thus create a metabolic environment prone to development of cardiovascular diseases (Mattsson *et al.*, 1984; Wild *et al.*, 1985; Talbott *et al.*, 1995). Insulin might also play a role by stimulating the process of atherosclerosis (Godsland and Stevenson, 1995).

For diabetes mellitus, obesity is only an additive risk factor to age in our PCOS population. This is consistent with extensive studies done in insulin resistance in PCOS and to its independence of obesity (Chang *et al.*, 1983; Dunaif *et al.*, 1989; Conway *et al.*, 1992, Morales *et al.*, 1996). A unique, but not precisely known, blockade in the post-insulin receptor signalling pathway was suggested to cause this insensitivity for insulin in PCOS (Ciaraldi *et al.*, 1992; Dunaif, 1995; Book and Dunaif, 1999).

Comparison of the total prevalence of diabetes in this study (2.3%) with other studies that measured the prevalence of diabetes and impaired glucose tolerance by an oral glucose tolerance test showed that a higher prevalence of diabetes (10 and 7.5%) was found in two younger US populations (Ehrmann

et al., 1999; Legro *et al.*, 1999). This could be explained by the higher degree of obesity of these populations or by the fact that there are undiagnosed cases in our PCOS population. In another European PCOS population which had a proportion of lean PCOS patients (43.6% with a BMI <25 kg/m^2) comparable with that of the current study (56.1% lean patients), the authors did not find any patients with diabetes (Ciampelli *et al.*, 1999). This agrees with our results because these patients were aged as the youngest age group in the current study, in which we found only one patient with diabetes.

In the current study, it was found that PCOS patients with hypertension had significantly more first degree family members with hypertension when compared with the affected first degree family members of women without hypertension. This might suggest a genetic basis for hypertension in this population.

It was not possible to confirm the association of a low educational level and a widowed status with diabetes and hypertension as was found in the total Dutch population. This could be due to the difference in sample size between the two studies or the fact that these figures of the Dutch population were only available for the total sample of the study (men and women of all ages) in contrast to the PCOS women aged 30–55 years.

A serious limitation of this study is that the populations were not individually matched for age and BMI. Further investigations, preferably prospective studies, are needed to elucidate the exact influence of BMI and the occurrence of cardiovascular events in the next decades of life of these PCOS patients. Any possible effect of the choice of treatment (clomiphene citrate and/or gonadotrophins) in our population was not investigated.

In conclusion, the data show that in a follow-up study of a relatively lean PCOS population, diagnosed as having oligo- or amenorrhoea and an elevated LH concentration in the past, the prevalence of diabetes mellitus and hypertension is

increased when compared with the Dutch female population, especially in women aged 45–54 years.

Acknowledgement

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