Cardiovascular risk factors in young Czech females with polycystic ovary syndrome

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BACKGROUND: Polycystic ovary syndrome (PCOS) could be associated with a variety of signs of metabolic syndrome. The aim of our study was to compare the cardiovascular risk factors in PCOS women and in a control group selected from a random population sample.

METHODS AND RESULTS: 50 PCOS women with a mean (±SD) age of 30.7 ± 4.2 years, and 335 controls with a mean age of 29.9 ± 3.1 years selected from a random population sample of nine districts of the Czech Republic were compared for basic anthropometric characteristics, blood pressure, plasma lipids and fasting glucose. PCOS women had a significantly higher body mass index (BMI). After adjusting for BMI, PCOS women had higher blood pressure and LDL-cholesterol, and lower HDL and HDL-cholesterol/total ratio. Arterial hypertension was more prevalent in PCOS women than in controls. There was no difference in the prevalence of impaired fasting glucose between both groups. Impaired glucose tolerance was found in 11.8% of PCOS women. Diabetes mellitus was more frequent in PCOS families.

CONCLUSIONS: Czech PCOS women, even in their thirties, show a significantly worse cardiovascular risk profile than a control group selected from a random population sample. The differences cannot be explained by obesity.

Key words: dyslipidaemia/hypertension/impaired glucose tolerance/type-2 diabetes mellitus

Introduction

Polycystic ovary syndrome (PCOS) seems to be the most common endocrine disease in women of reproductive age, with the incidence reported to be about 4–6% in this age group (Knochenhauer et al., 1998). The association of PCOS with carbohydrate metabolism disorders was not investigated in more detail until the 1980s (Burghen et al., 1980). Insulin resistance (Dunaif, 1997) and impaired insulin secretion (Holte, 1998) are no doubt key components of PCOS. Apart from insulin resistance, PCOS women show other symptoms included in the so-called metabolic ‘syndrome X’ (Ruderman et al., 1998; McFarlane et al., 2001) such as visceral obesity, arterial hypertension, increased levels of plasminogen activator inhibitor-1 (PAI-1), endothelial dysfunction, and mixed dyslipidaemia. These features are particularly striking in PCOS women younger than their forties and become blunted in the older age groups (Talbott et al., 1998; Cibula et al., 2000). On the other hand, a surprisingly low incidence of PCOS has been demonstrated in a population of women diagnosed as having syndrome X (Korhonen et al., 2001).

Recently, two studies conducted in North American PCOS patients reported an increased frequency of impaired glucose tolerance (IGT) and Type-2 diabetes mellitus (DM 2) (Ehrmann et al., 1999; Legro et al., 1999b). Similar results were obtained in South Asia (Weerakiet et al., 2001). Although coronary risk factors in hyperandrogenic states have recently been given more attention (Wild et al., 1985; Conway et al., 1992; Dahlgren et al., 1992a; Talbott et al., 1995; Atiomo et al., 1998; Wild et al., 2000; Diamanti-Kandarakis et al., 2001; Paradisi et al., 2001; Yarali et al., 2001), to the best of our knowledge, there has been only one paper addressing carbohydrate metabolism disorders and other risk factors for coronary heart disease in European women with PCOS compared with a healthy random population sample (Elting et al., 2001).

The incidence of IGT and DM 2 has been clearly shown to be race-related, being highest in Hispanic and Afro-American populations. Similarly, there have been only a few papers focusing on the prevalence of arterial hypertension in PCOS women, with inconclusive results (Zimmermann et al., 1992; Holte et al., 1996; Sampson et al., 1996).

The aim of our study was to compare the prevalence of cardiovascular risk factors in young Czech PCOS women and in a control group selected from a random population sample in the Czech Republic.
Materials and methods

Cases
A group of 50 women aged 25–42 years [mean (± SD) age 30.7 ± 4.2] meeting the criteria proposed by the 1990 NICHD PCOS Conference (Dunaif, 1997)—oligomenorrhoea or secondary amenorrhoea and hyperandrogenaemia—i.e. elevation of the free testosterone index, or testosterone, or androstenedione above the upper limit of the normal range [the normal range in our laboratory being 0.40–2.65 nmol/l for testosterone, 43–95 nmol/l for sex hormone-binding globulin, (SHBG) and 1.6–5.4 nmol/l for androstenedione] with its clinical manifestations (hirsutism and/or acne and/or androgenic alopecia) were included. None of the patients was diagnosed as having thyroid dysfunction, hyperprolactinaemia or a non-classical form of late-onset adrenal hyperplasia. The patients did not take oral contraceptives for at least 3 months prior to examination.

Biochemical assays
After a 12–14 h fast, 34 PCOS patients had the oral glucose tolerance test (oGTT) using 75 g of glucose, with blood collections for glucose determination using the glucose oxidase method (Beckmann, Fullerton, USA) at 0, 60 and 120 min; the evaluation was made using the revised World Health Organization (WHO) criteria (Alberti and Zimmet, 1998). A baseline venous blood sample was used to determine total cholesterol, HDL-cholesterol and triglycerides, all of which were assessed by photometry (Ecoline 25; Merck Vitalab Eclipse, Darmstadt, Germany). Hormonal analysis was undertaken between days 1–5 of the spontaneous menstrual cycle, with testosterone, androstenedione, dehydroepiandrosterone-sulphate (DHEAS) and SHBG determined as stated previously (Vrbikova et al., 2001). The mean (±SD) hormonal levels in our PCOS women were: testosterone 2.67 ± 1.12 nmol/l; androstenedione 7.1 ± 3.0 nmol/l; and SHBG 33.1 ± 14.4 nmol/l.

Controls
A control group of 335 women aged 25–34 [mean (± SD) age 29.9 ± 3.1] years was made up from a randomly selected (1%) population sample of permanent residents of nine districts of the Czech Republic in the 1997–98 period as part of a cross-sectional survey of cardiovascular risk factors (Cifkova et al., 2000). As there are no data on IGT in the Czech general population, we used results of oGTTs obtained during a worksite screening project for thyroid dysfunction and carbohydrate metabolism disorders undertaken, in the late 1980s, among Škoda car factory employees in Mladá Boleslav. The group of females examined comprised 54 individuals of similar age and body mass index (BMI) as the population random sample (age 34 ± 3 years; BMI 24.3 ± 3.8 kg/m²).

Biochemical assays
Blood glucose was determined by an enzymatic method (Lachema, Brno, Czech Republic). Total cholesterol and triglycerides were determined enzymatically (reagents from Boehringer Mannheim, Germany, using a Cobas Mira S autoanalyzer, Hoffman-La Roche, Basel, Switzerland); HDL-cholesterol was determined using the same method after precipitation.

Clinical investigations
All women were asked about the history of diabetes in their first- and second-degree relatives. BMI, as a measure of relative weight, was calculated as weight divided by height squared (kg/m²). Two blood pressure (BP) readings were obtained in sitting patients after a 10 min rest; the mean was determined from two values and was used for further analysis. BP values ≥140/90 mmHg or a history of antihypertensive use was defined as hypertension.

The study was approved by the Local Ethics Committees of both institutions.

Computations and statistical methods
LDL-cholesterol was calculated using Friedewald’s formula (LDL-cholesterol = total cholesterol minus HDL-cholesterol minus triglycerides/2.19).

Statistical analysis of discrete variables was performed using the χ²-test. Continuous variables were analysed using Student’s two-sample t-test. A highly skewed variable (triglycerides) was analysed after logarithmic transformation. A two-tailed P < 0.05 was considered statistically significant. As cases and controls differed significantly in BMI, we adjusted BP values, lipid parameters and fasting blood glucose values for BMI and analysed them using analysis of co-variance (ANCOVA).
Results
When comparing PCOS women with controls, we found the former to have significantly higher BMI (P < 0.001), systolic (P < 0.01) and diastolic BP (P < 0.001) (Table I). Arterial hypertension was significantly more prevalent in PCOS patients compared with controls (22 versus 2.1%; P < 0.001). Total cholesterol, triglycerides and fasting blood glucose did not differ significantly between the two groups. HDL-cholesterol was significantly lower in PCOS patients compared with controls (P < 0.001) as was the HDL-/total cholesterol ratio (P < 0.001). LDL-cholesterol was significantly higher in PCOS than in controls (P < 0.001) (Table II). After adjusting the BP values, lipid parameters and fasting blood glucose for BMI, the significance for differences between PCOS and controls remained the same as for the unadjusted values.

The oGTT was performed in 34 PCOS women. One patient had a history of DM 2 and was treated with insulin. IGT was found in four (11.8%) out of the 34 PCOS women and was thus more common than in a control group of Škoda car factory employees (0 versus 11.8%; P < 0.05). Impaired fasting glucose (IFG) was found in two (4%) out of the 50 PCOS patients, both of them with normal oGTT. On the other hand, IFG was diagnosed in nine individuals (3.2 versus 4%; NS) of the random population sample. Compared with controls, PCOS patients reported DM more often in their relatives (54.5 versus 19.7%; P < 0.001).

Discussion
Recent research has shown that PCOS is not only a gynaecological condition affecting women of reproductive age but, also, a comprehensive syndrome with a variety of associated metabolic disorders (insulin resistance, hyperinsulinaemia and dyslipidaemia) (Taylor, 1998; Amowitz and Sobel, 1999). In addition to a higher prevalence of DM 2 (Legro et al., 1999b), coronary heart disease (CHD) was suggested to be more common (Dahlgren et al., 1992a) in these women. Nevertheless, recent epidemiological studies did not confirm increased morbidity and mortality rates from CHD in PCOS patients (Pierpoint et al., 1998; Wild et al., 2000). Only an increased risk for cerebro-vascular events was demonstrated (Wild et al., 2000) in PCOS. These discrepancies have not been explained so far.

Coronary risk factors in hyperandrogenic states have been given more attention over the last decade (Wild et al., 1985; Conway et al., 1992; Dahlgren et al., 1992b; Talbott et al., 1995; 1998; Atiomo et al., 1998; Wild et al., 2000; Diamanti-Kandarakis et al., 2001; Paradisi et al., 2001; Yarali et al., 2001). A more adverse lipid profile (higher total and LDL-cholesterol) was found in young American PCOS women compared with the healthy population (Talbott et al., 1995). Our search of the relevant literature did not produce a single report of a study directly examining coronary risk factors (including glucose tolerance) in Caucasian PCOS patients compared with apparently healthy individuals selected from a random population sample. We took advantage of our control group selected from a 1% random sample of permanent residents of nine districts of the Czech Republic in the 1997–98 period as part of a study designed to survey cardiovascular risk factors (Cifkova et al., 2000). These nine districts cover 11.2% of the total area of the Czech Republic and are inhabited by 9.9% of the country’s population. As the respondent rate never fell below 60%, the sample is considered to be truly representative and the results allow generalization.

As there are no data on IGT in the Czech general population, we used data obtained during a worksite screening project for thyroid dysfunction and carbohydrate metabolism disorders undertaken, in the late 1980s, among employees in the Škoda car factory in Mladá Boleslav. IGT was not found in this particular group of female employees comprising 54 individuals (mean age 34 ± 3 years; mean BMI 24.3 ± 3.8 kg/m²). However, we cannot exclude the error of small numbers and, obviously, this was not a random population sample. In addition to that, the Škoda car factory female workers were mostly from rural areas and smaller communities whereas the controls included almost equal proportions of individuals from small communities and larger towns/cities. One of the nine districts of the Czech Republic involved in the screening for cardiovascular risk factors was the city of Pilsen (currently with a population of 160 000).

Our PCOS patients have an IGT prevalence of ~10%. This is rather low compared with USA or Asian PCOS patients with a prevalence of ~35% (Ehrmann et al., 1999; Legro et al., 1999b; Weerakiet et al., 2001). The higher prevalence of IGT in the USA and South Asia is probably the result of interaction of various ethnic backgrounds and environmental factors (especially obesity, as the average BMI was about 30–36 kg/m² in these studies compared with 29.2 kg/m² in Czech PCOS subjects).

DM 2 may develop as a clinically silent condition. It is not unusual to meet patients at the time of diagnosis of DM with advanced micro- and macrovascular complications, which not only impair the quality of life but also have a negative predictive value in these patients. These complications may already be present at the stage of IGT. There seems to be no threshold level of blood glucose; the association between the risk for cardiovascular disease and blood glucose seems to be present even across blood glucose values regarded as the normal range (Coutinho et al., 1999). The increasing prevalence of DM 2 in the population has recently led to attention focusing on its early diagnosis. To simplify screening for impaired glucose metabolism, the American Diabetic Association (ADA) (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997) proposed to determine fasting blood glucose instead of performing the oGTT. The ADA defined fasting blood glucose levels of 6.11–6.99 mmol/l as IFG. However, various authors have repeatedly criticized the introduction of the concept of IFG to replace performing the oGTT. Some reports pointed to the low concordance of these two diagnostic criteria (Burke et al., 1998). This is presumably due to the fact that, as IGT/DM develop, post-prandial blood glucose levels tend to rise (apparently as a result of inadequate insulin secretion following stimulation) earlier than fasting blood glucose (Gerich, 1998). In our series, no woman diagnosed as having IGT using the WHO criteria, was shown to have IFG according to the ADA.
Further investigations, preferably prospective studies, are needed to elucidate the exact effect of BMI and the incidence of cardiovascular events in PCOS in the next decades.

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