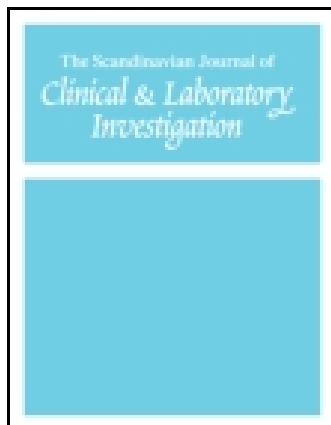


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ORIGINAL ARTICLE

Polycystic ovary syndrome: Metabolic consequences and long-term management

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*Department of Law, Society and Sport Sciences, University of Palermo, Palermo, Sicily, Italy***Abstract**

Young women with polycystic ovary syndrome (PCOS) present an increased risk for type II diabetes and cardiovascular diseases. The prevalence of altered glucose tolerance ranges between 20 and 35 % in patients while the prevalence of type II diabetes ranges between 2 and 8 % and seems related to body weight and ethnic group. Moving from the young fertile age to the 40s and the menopause the prevalence of type II diabetes continues to increase compared to the general female population and may reach 10–16 % of PCOS women. However, prevalence of altered glucose tolerance does not increase. Also cardiovascular risk is increased in a large part of young PCOS women but this risk tends to be normalized with age because of the reduction of ovarian androgen secretion and occurrence of ovulatory cycles in at least one third of PCOS women approaching menopause. It may explain the discrepancy between cardiovascular (CV) risk during young age and observed number of CV events. Long-term management should be directed to aggressively treat obesity and altered glucose tolerance. In non-obese patients with normal glucose tolerance it may be wise to wait until the age of 40 before deciding a long-term management of CV risk.

Key Words: *Polycystic ovary syndrome, cardiovascular risk, glucose tolerance, lipids*

Introduction

Because polycystic ovary syndrome (PCOS) is associated with insulin resistance, metabolically active obesity and androgen excess, young women with PCOS present an increased risk of type II diabetes and cardiovascular diseases.

Impaired glucose tolerance has been found in about 20–35 % of young PCOS women whereas type II diabetes is present in 7–8 % of American PCOS women and in about 2–3 % of Mediterranean PCOS women [1,2]. The prevalence of diabetes type II in these populations may be related to differences in body weight and severity of insulin resistance. However, also in countries with a relatively low prevalence of altered glucose tolerance and type II diabetes, the risk is many times higher in PCOS women than in control women of a similar age. Thus, meta-analyses have revealed an odds ratio of 2.5 for altered glucose tolerance and of 4.0 for type II diabetes in PCOS women aged 20–39 years compared with age- and BMI-matched controls [3].

Cardiovascular risk is also increased. The prevalence of risk factors, e.g. metabolic syndrome and

different patterns of dyslipidemia is increased in women with PCOS of reproductive age. In the US, metabolic syndrome is present in up to 40–50 % of young PCOS women [4] and again, also in countries with lower prevalence of metabolic syndrome, this aggregation of CV risk is much more common than in controls of similar age [5]. Atherogenic dyslipidemia (i.e. low HDL-cholesterol, elevated triglyceride concentrations and lower LDL particle size) [6] is very common in women with PCOS but increased LDL and total cholesterol concentrations have been also found and may be present in up to 30 % of the patients [7]. Finally, several markers of clinical and subclinical atherosclerosis, including carotid intima-media thickness and coronary artery calcium have been found to be altered.

Metabolic consequences in older PCOS women

In the general population, prevalence of decreased glucose tolerance and type II diabetes increases with age [8]. Therefore, and because some studies showed

a high conversion rate of altered glucose tolerance into diabetes, it was calculated that a large number of PCOS women would become diabetic with aging. Similarly, because metabolic syndrome and cardiovascular risk increase with age [9], it was hypothesized that PCOS patients would have a high prevalence of cardiovascular morbidity and mortality [10]. However, the data that are emerging from follow up do not confirm, at least in the expected proportion, these initial suggestions.

Metabolic consequences in PCOS women of late reproductive or postmenopausal age

Initial studies indicated a high conversion rate from altered glucose tolerance to type II diabetes [11] and suggested a very high prevalence of diabetes in aging PCOS women.

However, follow up studies have produced confusing results (Figure 1). In one Italian study where initial prevalence of type II diabetes in young PCOS women was low (2.5 %), the prevalence of this disorder increased strongly with age and became 16.9 % at a mean age of 45.9 years [12]. In a similar Swedish study, 84 women with PCOS in their 40s had a prevalence of type II diabetes of about 8.3 % (with 2.4 % having type I diabetes) [13]. Interestingly, in this study, altered glucose tolerance had a prevalence of 16.9 % suggesting that few new patients present altered glucose metabolism with age. In our large follow-up study, altered glucose tolerance was not assessed but prevalence of type II diabetes increased from 1 to 3.8 % moving from the 20s to 40s years of age [14]. While the prevalence of type II diabetes in our population of PCOS women in their late reproductive age was similar to that reported in an Italian population of similar age; if calculating only patients who at that age had classic (hyperandrogenism and chronic anovulation) PCOS symptoms, the prevalence was 7 %.

Only one small study has reported data in older postmenopausal women who were affected by PCOS during their reproductive age [15]. This study found normalization of the prevalence of type II diabetes with aging (60–70 years) in PCOS women [15].

More studies, including different subsets of women with PCOS and prolonged follow-up until late postmenopausal age, are needed. Data are too few for permitting assessment of the prevalence of type II diabetes and altered glucose tolerance in PCOS women of late reproductive age. However, available data seem to suggest that prevalence of type II diabetes in PCOS increases during reproductive age probably because many patients with altered glucose tolerance become diabetics during their 30s or 40s. This risk may be higher in obese or very obese patients. However, prevalence of altered glucose tolerance does not seem to increase and in some way may tend to become normalized suggesting that no new alterations of glucose metabolism appear with

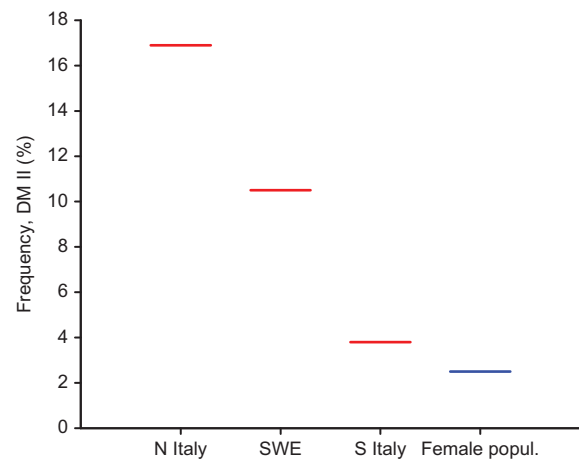


Figure 1. Prevalence of type 2 diabetes in women with pcos and in female population during late reproductive age.

age in patients who had normal glucose metabolism during their young age. Ultimately, it may mean that the total prevalence of diabetes is similar in the PCOS and in the general population but women with PCOS become diabetic at a younger age.

Cardiovascular consequences in women of late reproductive or postmenopausal age

Although cardiovascular risk is clearly increased in young women with PCOS, long-term studies examining the prevalence of cardiovascular diseases among women with PCOS gave no or only a slightly increased number of events of cardiovascular morbidity and mortality [14,16–18]. Several factors may contribute to reduce the cardiovascular risk in aging PCOS women. One of these factors may be related to changes in ovarian androgen production that occur with increasing age. In fact, ovarian androgen secretion starts decreasing as early as age 30 and continues decreasing until the menopause [19]. Interestingly, in the study by Shaw et al. [18], the cardiovascular mortality was related to postmenopausal androgen concentrations of women who had PCOS during their fertile age. It suggests that the patients who maintain the highest androgen levels during their late reproductive age and after the menopause may have a larger number of cardiovascular events.

An additional factor may be the occurrence of ovulatory cycles with age in many PCOS women (at least 30 %) [14,19]. In our follow-up study, lipid parameters, mainly low-density lipoprotein (LDL) cholesterol concentration, increased with aging, but not in women who attained ovulatory cycles [14].

Also prevalence of metabolic syndrome that in the general population is strictly related to age, did not increase with age in PCOS patients [14]. In our population, prevalence of metabolic syndrome was about 7 % in young patients and remained the same in the 40s (Figure 2). It was the consequence of

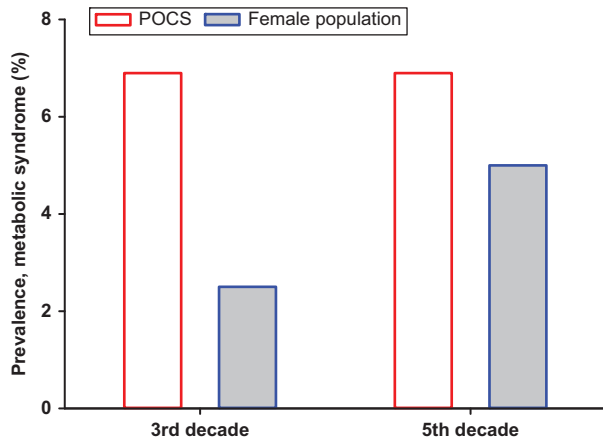


Figure 2. Prevalence of metabolic syndrome in pcos women of different reproductive age

different changes in metabolic syndrome parameters with waist circumference but also an increasing HDL-cholesterol concentration with age.

All these factors determine a generalized reduction of cardiovascular risk in PCOS women when they approach menopause. Although the population of PCOS women remain heterogeneous with some women presenting normalization of cardiovascular risk and others remaining with a substantial risk (Table I), the final consequence is probably a much lower number of events than that initially anticipated.

Treatment

The emerging data on changes in metabolic and cardiovascular risk with age in PCOS have complicated our approach to long-term management of young PCOS women. What should we do? Treat all young women with PCOS who present a risk or wait until the age of 40 to concentrate the treatment in women who do not normalize or substantially improve their risk?

No clear answer exists to these questions and many more and more prolonged follow-up studies are needed. However, a rational approach may be to limit the treatment to only young patients presenting more severe metabolic involvement. In fact, data on prevalence of type II diabetes with age seem to indicate a high risk of conversion from altered glucose tolerance to overt diabetes in obese patients. Therefore, obesity and altered glucose tolerance should always be actively treated also during young age.

Patients who are not obese but present increased cardiovascular risk may probably wait until the age of 40. At that age, a careful analysis of CV risk should

be performed and all patients with increased CV risk should be actively treated.

The recent AEPCOS Statement gives some useful recommendations [20] for long-term management of PCOS women that may be summarized thus:

Obesity

- Pharmacological treatments are not recommended.
- Bariatric surgery may be used in patients at risk with a BMI > 40 kg/m² or in patients at high risk with a BMI > 35 kg/m².

Dyslipidaemia

- Patients with atherogenic dyslipidaemia.
- No treatment for isolated low HDL-cholesterol or high triglycerides concentrations.
- Patients with atherogenic dyslipidemia may be treated by metformin.
- Alternatively, statins may be used.
- The combination metformin + statins does not give additional (sybiotic) results.
- Patients with increased LDL-cholesterol or non-HDL-cholesterol concentrations.
- Lipid goals depend on the degree of risk.
- Statins should be used to reduce LDL- and non-HDL-cholesterol concentrations.
- Metformin is not effective against LDL-cholesterol concentration.
- In certain conditions, fenofibrate, nicotinic acid or omega-3-fatty acids may be added to statins.

Hypertension

- Pharmacotherapy is indicated for BP > 140 systolic or /90 mmHg diastolic.
- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are generally preferred.
- Both ACE and ARB are contraindicated in pregnancy and require contraception.

Altered glucose tolerance

- Metformin should be used.
- In certain conditions, pioglitazone treatment may be considered.

Table I. Changes of CV risk factors in PCOS with aging.

	P-glucose	P-cholesterol	P-HDL-cholesterol	P-non HDL-cholesterol	P-LDL-cholesterol
Remain anovulatory	+	++	++	++	++
Become ovulatory	No	+	++	No	No

Questions and answers

Q (Ferrari): Are there any genetic markers useful in PCOS?

A (Carmina): There are some genes related to PCOS; one described is the receptor for LH and was found in China but not in USA and different receptors have been identified. It seems that the receptor for LH is different in western countries than in the Far East. Two other genes described are DENND1A and THADA but their functions are unknown and are described in many populations. There is a common genetic background but with a strong influence of environment.

Q (Young): Is there any influence of the type of diet prescribed for weight loss in PCOS?

A (Carmina): The type of diet does not have much influence. There is a study from Australia which showed that diet may have an influence the results are not very strong. Decreasing the calories seems to be the important factor.

Comment (Diamanti): In general, low calories are good and also the time when you eat: It is better to eat early in the day and not eat meals late in the day.

Declaration of interest: The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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