

# Primary and secondary prevention of metabolic and cardiovascular comorbidities in women with polycystic ovary syndrome

*Prevenção primária e secundária de co-morbidades metabólicas e cardiovasculares em mulheres com síndrome do ovário policístico*

## Editorial

### Current concepts on polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is a very common endocrine disease, affecting women of reproductive age. The prevalence of PCOS varies according to the diagnostic criteria used, with estimates ranging from 9% in women of reproductive age according to NIH criteria up to 18% with Rotterdam criteria<sup>1,2</sup>.

Evidence indicates PCOS is a polygenic disease in which the individual susceptibility is also determined by environmental risk factors, including lifestyle. In essence, PCOS is characterized by androgen excess and chronic anovulation. However, the clinical presentation is heterogeneous among patients and may change in the same women along the years<sup>2-4</sup>. Most common signs and symptoms include hirsutism, irregular menstrual cycles and infertility. In the last two decades it has become also clear that PCOS women often present insulin resistance and increased risk for metabolic syndrome, type 2 (T2) diabetes, dyslipidemia and hypertension.

Currently, the diagnosis of PCOS is confirmed according the Rotterdam Consensus<sup>5</sup>, an expansion of the former NIH criteria<sup>6</sup>. Proposed Rotterdam criteria for PCOS include two out of the following three: the presence of clinical and/or biochemical hyperandrogenism, oligomenorrhea/anovulation and the polycystic ovary appearance (PCO) on ultrasound. In turn, the Androgen Excess and PCOS Society<sup>7</sup> considers that androgen excess is a central event in the pathogenesis and development of PCOS and that this criterion should be present for the diagnosis of PCOS. In any case, other androgen excess disorders, such as non-classic congenital adrenal hyperplasia (NC-CAH), Cushing's syndrome, androgen secreting tumors, hyperprolactinemia, thyroid diseases, drug-induced androgen excess should be excluded as well as the other causes for oligomenorrhea or anovulation<sup>5-7</sup>.

Recently, the Expert Panel from a NIH Evidence Based Methodology Workshop on PCOS reinforced the use of the wider Rotterdam criteria<sup>8</sup>. In consequence, new phenotypes had arisen in addition to the classic phenotype, in which patients present hyperandrogenism and oligomenorrhea with or without PCO on ultrasound. These new phenotypes are the

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“ovulatory phenotype”, that means hyperandrogenism and PCO in an ovulatory woman and the “non-hyperandrogenic phenotype”, in which there is oligomenorrhea and PCO, without overt hyperandrogenism<sup>2,5,8</sup>.

Concerning ovarian morphology, PCO has been defined as an ovarian volume higher than 10 cm<sup>3</sup> and/or the presence of multiple small follicles<sup>5</sup>. In this sense, with the recent improvements on ovarian imaging the current follicle number threshold value is being reevaluated and will probably be increased from the prior follicle number of 12 or more follicles of 2–9 mm<sup>9–11</sup>.

## Metabolic disturbances and cardiovascular risk factors in women with polycystic ovary syndrome

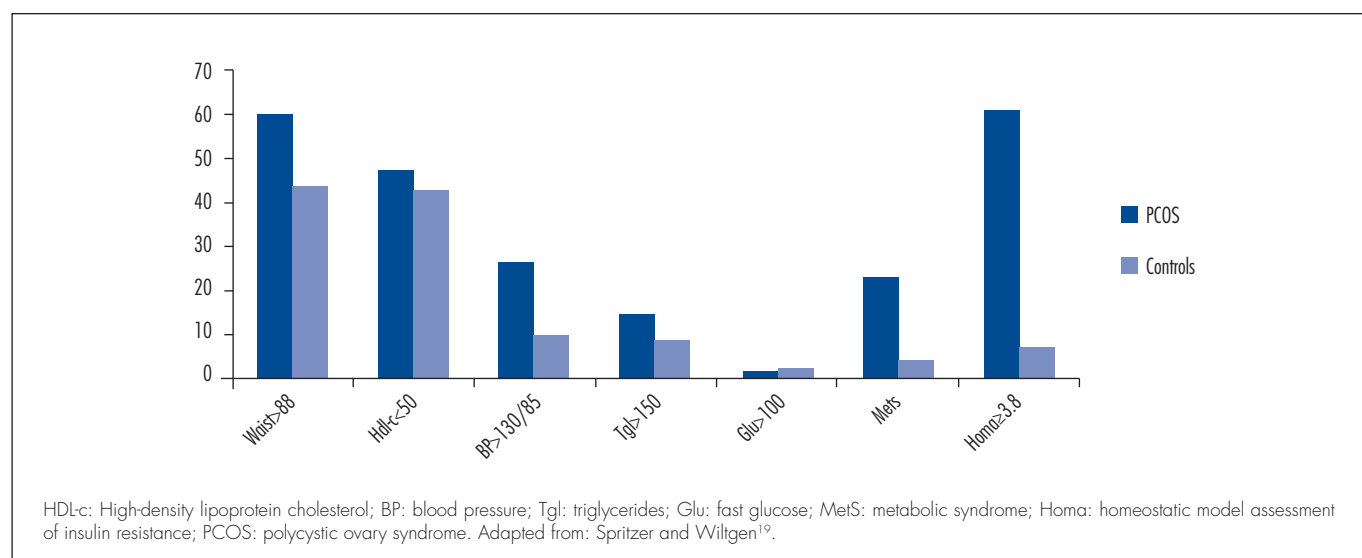
Obesity is a common characteristic of PCOS with a prevalence of around 50% according to different populations<sup>12</sup> and may exacerbate the metabolic and reproductive disorders associated with the syndrome<sup>13–15</sup>. In addition, PCOS women present higher risk for T2 diabetes and metabolic syndrome and sub-clinical atherosclerosis<sup>9,16–18</sup> (Figure 1)<sup>19</sup>. Metabolic syndrome is defined, for women, by the presence of three out of five criteria: waist circumference >88 cm, fast glucose >100 mg/dL, systolic blood pressure >130 and/or diastolic blood pressure >85 mmHg, HDL-c <50 mg/dL and triglycerides >150 mg/dL<sup>20</sup>. Interestingly, despite presenting higher prevalence of cardiovascular risk factors, definitive evidence for increased incidence of cardiovascular events later in life is lacking in the PCOS population. Studies with small sample sizes, relatively short periods of follow-up, highly selected

clinic populations, potential confounding due to effects of treatment at baseline and changing clinical phenotype over time are some reasons why further strict long-term prospective studies focusing on cardiovascular outcomes and clinical trials assessing changes on risk factors are needed in women with PCOS<sup>21</sup>.

Likewise, it has been shown that insulin resistance and their clinical consequences are more prevalent in PCOS women with the classic phenotype and to a lesser extent with the ovulatory phenotype<sup>16,22,23</sup>. In turn, the non-hyperandrogenic phenotype seems to function as a separate group, being metabolically similar to non-PCOS women<sup>8,23</sup>.

## Primary and secondary prevention of metabolic and cardiovascular comorbidities in women with polycystic ovary syndrome

Beyond the management of hirsutism and reproductive abnormalities, concerns arise regarding how to prevent and treat prevalent metabolic and cardiovascular comorbidities in PCOS women. In this context, it is important to underline the central role of insulin resistance on the pathophysiology of metabolic syndrome and on cardiovascular risk in these women. However, while being a common trait, insulin resistance is not a universal feature of PCOS<sup>19,24</sup>. In addition, the focus of treatment should be their clinical consequences instead of the insulin resistance *per se*, such as metabolic syndrome, abdominal adiposity (waist circumference higher than 88 cm) as well as impaired fasting glucose (IFG, fasting glucose between 100 and 125 mg/dL), impaired glucose tolerance (IGT, 2 h post-glucose between 140 and 199 mg/dL) and T2



**Figure 1.** Prevalence of insulin resistance, metabolic syndrome and their isolated components in 91 women with polycystic ovary syndrome and controls, paired by age and body mass index.

diabetes (fasting glucose equal or higher than 126 and/or 2 h post-glucose equal or higher than 200 mg/dL)<sup>2,24,25</sup>.

Lifestyle change is the first-line non-pharmacological therapy to lessen cardiovascular and metabolic risks, mainly in overweight or obese PCOS women, and should combine behavioral (reduction of psychosocial stressors), dietary, and exercise management<sup>26-28</sup>. Lifestyle modification has been already proved to be effective in reducing the incidence of diabetes in persons at high risk<sup>29</sup>.

Nevertheless, in many cases it will be necessary to add a drug to lifestyle change. Pharmacological therapy should address specific goals, such as to treat dyslipidemia, metabolic syndrome, pre-diabetes or T2 diabetes, high blood pressure or severe obesity with statins, insulin-sensitizing, antihypertensive and anti-obesity agents, respectively. Bariatric surgery is an additional option for PCOS women with severe obesity or obesity with metabolic comorbidities<sup>2,9</sup>.

The most widely insulin-sensitizing agent used for women with PCOS presenting metabolic syndrome, obesity or impaired glucose tolerance is metformin, in great part because of its impact on diabetes prevention in pre-diabetic subjects<sup>30</sup>. Besides its actions on glucose balance, reducing hepatic glucose output and increasing peripheral insulin action, metformin also directly

inhibits ovarian androgen secretion<sup>2,31</sup>. In line with the current knowledge, metformin seems to minimize cardiovascular and metabolic risks in PCOS by improving insulin sensitivity, lowering blood glucose and androgen levels<sup>2,28,32</sup>. These effects are stronger if combined with lifestyle intervention<sup>2,28</sup> and appear to be dose dependent, although this issue is not completely consensual<sup>33,34</sup>. While metformin is not effective to treat hirsutism it can improve menstrual disturbances and has been regarded as a second-line treatment for women with PCOS with contraindications for using contraceptive pills<sup>9,35</sup>.

Therefore, primary and secondary prevention of metabolic and cardiovascular comorbidities in PCOS involves firstly, an accurate and individualized clinical assessment of any PCOS woman. Obesity or normal-weight with familiar history of diabetes, presence of clinical manifestations of insulin resistance such as acanthosis nigricans or central adiposity and the screening for metabolic and cardiovascular risk factors, mainly hypertension, dyslipidemia or dysglycemia (IFG, ITG or T2 diabetes), are clearly recommended. Secondly, according to the risk profile, treatment goals should be tailored to each individual PCOS women, covering both metabolic risks as well their main complaints related to menstrual disturbances, hirsutism or infertility.

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