

## Long term health consequences of polycystic ovarian syndrome: a review analysis

Daniilidis A, Dinas K

2<sup>nd</sup> Department of Obstetrics and Gynecology, Hippokratia General Hospital, Thessaloniki, Greece

### Abstract

Polycystic ovarian syndrome (PCOS) is the commonest endocrinopathy among women of reproductive age with an estimated prevalence of about 10%. Type 2 diabetes, cardiovascular disease, endometrial cancer, breast cancer and ovarian cancer are some of the most important emerging issues regarding syndrome's influence in women's future well being. The aim of this review is to provide clear and up to date information, based on clinical evidence, in order to advise clinicians about the late consequences of the syndrome. Hippokratia 2009; 13 (2): 90-92

**Key words:** Polycystic ovarian syndrome (PCOs) and cancer, cardiovascular risk and PCOs, diabetes and PCOs

**Corresponding author:** Angelos Daniilidis, 9 Smirnis street, 56224, Evosmos, Thessaloniki, Greece, e-mail: ange1972@otenet.gr, fax:00302310559711

The polycystic ovarian syndrome (PCOS) is considered to be a gynecological condition, about which evidence and knowledge is rapidly evolving. It is the commonest endocrinopathy among women of reproductive age with an estimated prevalence of about 10%<sup>1</sup>. Traditionally it is regarded as an endocrine condition presenting with a constellation of symptoms among which anovulation, hyperandrogenism, obesity and acanthosis nigricans are the most common. According to the new Rotterdam criteria formulated by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine two out three criteria have at least to be met in order to fit the diagnosis of PCOS<sup>2,3</sup>. These criteria are anovulation, androgen excess and polycystic ovarian morphology in ultrasound assessment<sup>2,3</sup>. Although, to date, most attention of the clinicians has been paid to the management of specific symptoms linked to PCOS, it is becoming more and more obvious that due to the complexity of the syndrome, a number of metabolic and other implications of women's health will have to be confronted in the near future. PCOS seem to have a long prodrome phase with detectable abnormalities throughout the life cycle of affected women. Approximately, 25% to 30% of women with PCOS will show impaired glucose tolerance by the age of 30 and 8% of affected women will develop type 2 diabetes annually<sup>4</sup>. Women with PCOS are seen to have more extensive coronary artery disease by angiography<sup>5</sup>. Hypertension is also observed more frequently in these women<sup>3</sup>. Chronic anovulation predisposes women to endometrial cancer and emerging evidence associates more and more PCOS with ovarian and breast cancer<sup>6</sup>.

The aim of this review is to provide clear and up to date information, based on clinical evidence, in order to advise clinicians about the late consequences of the syndrome.

### Impaired glucose tolerance and diabetes

It is well known that obesity is observed in about 60% of women with PCOS. The central distribution of fat though is not dependent to BMI and actually is associated with higher insulin concentrations. Independent of obesity, the presence of a defect in insulin action which amplifies LH stimulated androgen secretion from thecal cells, has been well established. The key underlying abnormality that leads to later development of impaired glucose tolerance appears to be insulin resistance<sup>7</sup>. It is reported that more than 20% of obese women with PCOS will have impaired glucose tolerance after the age of 30<sup>4,8</sup>. Evidence demonstrates that the prevalence of type 2 diabetes in women diagnosed with PCOS is 7 times higher than controls (15% to 2% respectively)<sup>8,9</sup>. Insulin resistance combined with abdominal obesity is thought to account for the higher prevalence of type 2 diabetes in PCOS<sup>6</sup>. However, the risk of developing type 2 diabetes is also increased in non-obese women with PCOS<sup>10,11</sup>. Thus PCOS is an independent risk factor for type 2 diabetes in middle age<sup>5,12</sup>. The majority of women under 45 with type 2 diabetes are also diagnosed with PCOS. Thus it is not surprising that there is a concomitant increased risk of gestational diabetes to these women<sup>4,13</sup>. The risk is believed to be much greater in women with PCOS who are also obese and who need ovulation induction in order to conceive<sup>10</sup>. Also women with gestational diabetes have been found with high prevalence of PCOS after pregnancy<sup>13,15</sup>.

### Cardiovascular disease and hypertension

Hyperinsulinemia appears to be the main reason for the increased cardiovascular risk of women with PCOS. There is a pancreatic b-cell dysfunction, in the absence of impaired glucose tolerance, which is inversely correlated

to SHBG (sex hormone binding globulin) concentration, leading to hyperandrogenism and chronic unopposed estrogen secretion. There are two mechanisms by which insulin resistance in PCOS contributes significantly to higher incidence of cardiovascular disease in these women. One mechanism is the direct atherogenic action and the other mechanism is the adverse effect of the lipoprotein profile<sup>11</sup>. Women with PCOS are seen to have more extensive coronary artery disease by angiography<sup>7</sup>. Impaired glucose tolerance and diabetes caused by PCOS are known risk factors for cardiovascular disease. The lipoprotein profile in women with polycystic ovaries is significantly distorted. They usually have high concentrations of serum triglycerides and total and low-density lipoprotein cholesterol<sup>16</sup>. On the other hand the levels of high density lipoprotein (HDL) and particularly HDL2 subfraction are suppressed<sup>17,18</sup>. In addition serum plasminogen activator inhibitor-I concentrations are also elevated<sup>15</sup>. The last could lead to impaired fibrinolysis and thus affect directly vascular tissue causing changes associated with coronary heart disease. The evidence is thus mounting that there is indeed an increased risk for women with PCOS of developing cardiovascular disease.

Regarding hypertension there seems to be a direct relationship between insulin plasma levels and blood pressure<sup>19,20</sup>. The prevalence of treated hypertension is three times higher in women with PCOS between the age of 40-59 years in comparison with controls. The incidence of preeclampsia in obese women with PCOS conceiving compared to the general pregnant population is 4 times higher<sup>20</sup>. It seems that significant risk factors for developing atherosclerotic conditions, hypertension and myocardial infarction, are present at an earlier age than women without PCOS<sup>21</sup>.

### Endometrial cancer

Recent interest in the long term risks of PCOS has also focused on its possible associations with endometrial cancer. Prolonged anovulation which characterizes the syndrome is considered to be the main mechanism responsible for continual unopposed secretion of oestrogens and consequent increased risk of endometrial carcinoma<sup>5,22</sup>. The known factors which increase the risk of developing endometrial cancer are obesity, long-term use of unopposed oestrogens, nulliparity, infertility, hypertension and diabetes<sup>9,15</sup>. Most of these factors are known also to be associated with PCOS. Endometrial hyperplasia may be a precursor to adenocarcinoma. A precise estimate rate of progression is practically impossible to be determined, but it is estimated that 18% of cases of adenomatous hyperplasia will progress to cancer in the following 2 to 10 years. In women with PCOS intervals between menstruation of more than three months may be associated with endometrial hyperplasia and later carcinoma<sup>5,22</sup>. Evidence from a big study in which 1270 women with chronic anovulation participated, the excess risk of endometrial cancer was identified to be 3.1(95%

CI, 1.1-7.3)<sup>23</sup>. However a more recent appraisal of the evidence for association between PCOS and endometrial cancer was inconclusive<sup>24</sup>. The true risk of endometrial carcinoma in women diagnosed with PCOS has not been clearly defined yet.

### Ovarian cancer

There has been much debate and concerns about the risk of ovarian cancer in women with anovulation, particularly because of the extend use of drugs for induction of ovulation to these patients. Several lines of evidence might suggest that there is a connection between PCOS and increased risk of ovarian cancer. The risk appears to be increased in nulliparous women (multiple ovulations), with early menarche and late menopause. Without any evidence based data to support this theory, it may be that inducing multiple ovulations in women with infertility will increase their risk. So, although women with PCOS are expected to be in low risk groups for developing ovarian cancer due to their life time reduced ovulation rate, by using ovulation induction treatments and inducing multi-follicular ovulations theoretically an imbalance to their risk for ovarian cancer will be technically created.

There are only a few studies addressing the possibility of association of polycystic ovaries and ovarian cancer with conflicting evidence. Large Danish studies suggest that infertility on its own increases the risk of borderline and invasive ovarian tumors<sup>25,26</sup>. Another study linking clomiphene and ovarian cancer suggests that the relative risk for ovarian cancer for women with PCOS is 4.1 compared to controls<sup>27</sup>. The large UK study though concludes that the standardized mortality rate for ovarian cancer is only 0.39 (95% CI 0.01-2.17)<sup>28</sup>. Even more recent evidence about association between polycystic ovarian syndrome and ovarian malignancy are still conflicting but generally reassuring<sup>29</sup>.

### Breast cancer

Obesity, hyperandrogenism and infertility are features known to be associated with the development of breast cancer. However studies failed to show any significant increase in the risk of developing breast cancer in women with PCOS (RR1.2;95% CI0.7-2.0)<sup>5,11</sup>. On the other hand though, it seems that there is a positive association between PCOS and the presence of family history of breast cancer. In a study of 217 women the proportion of women with positive family history of breast cancer was significantly higher in women with PCOS compared with controls<sup>30</sup>.

### Conclusion

There is great need for research into several issues regarding the complexity of PCOS and their true negative late impact on woman's health. The real challenge will be after acquiring evidence based knowledge regarding the late consequences to adopt safe strategies in protecting woman's health during her all life.

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