Polycystic Ovary Syndrome – An Endocrine and Metabolic Disorder Throughout Life

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The etiology and pathogenesis of polycystic ovary syndrome (PCOS) is still a matter of controversies, but it is apparent that hyperinsulinism and insulin resistance (IR) are major determining factors in the development of ovarian hyperandrogenism and chronic anovulation. The consequences of the PCOS extend beyond the reproductive axis. Follow up studies have shown an increase in the incidence of type 2 diabetes mellitus and other elements of metabolic syndrome in PCOS and increased cardiovascular risk, too. It is possible that PCOS and type 2 diabetes mellitus are different clinical manifestations of the same IR syndrome, with their phenotypic differences. It is even more compound as PCOS is not a homogenous group of patients. It is reflected in the diagnostic criteria of PCOS by the Rotterdam PCOS Conference as the diagnostic criteria identify 4 phenotypes of PCOS. The PCOS phenotypes differ in the degree of hyperandrogenism, but differences in hyperinsulinism and obesity have not been studied yet. Management of PCOS depends on the principal goals of the patients (treatment of infertility, diminishing signs of hyperandrogenism, prevention of long term metabolic consequences), but the management should be individualized according to the phenotypes as well. The value of the insulin sensitizer therapy (e. g. metformin, myo-inositol), statins and/or lifestyle modification await further evaluation and it should be integrated in the spectrum of therapeutic options.

A challenging task for the future is to assess the individual risk of PCOS patients according to phenotypes and to elaborate personal steps for prevention.


Key words: PCOS, phenotypes, lifelong disorder, metabolic risk, management

Introduction

Polycystic ovary syndrome (PCOS) is probably the most prevalent endocrinopathy in women and the most common cause of anovulatory infertility [1]. More recent studies, although based on modified criteria of PCOS, also report high prevalence from 4–9% in the female population of fertile age [2, 3]. Polycystic ovaries (PCO) seen by ultrasound is an even more frequent finding. According to some large studies the prevalence of PCO in healthy volunteer populations may range up to 33% [4]. Women representing symptoms of oligo-amenorrhea with hyperandrogenism have polycystic ovaries in 87% of the cases [1]. Inspite of the high prevalence and thorough investigations, its etiology is still unsettled. There are theories supporting a primary hypothalamic-pituitary defect, a primary ovarian steroidogenic defect, a primary adrenal steroidogenic defect and a primary defect of insulin resistance [5–8]. It has been proven that hyperinsulinemia and insulin resistance play a key role in the pathophysiology of hyperandrogenism and probably the pathogenesis of PCOS [5, 9]. Whatever the pathogenesis of PCOS, the endpoint is an ovary secreting excessive amount of androgens in a hyperinsulinemic, insulin resistant patient. According to the common genetic basis and the characteristic hyperinsulinemia and insulin resistance PCOS patients are at risk for type 2 diabetes, whereas growing evidence suggests that a significant fraction of the younger patients with type 2 DM women also demonstrate signs of PCOS [10].

These findings suggest that PCOS is not only an endocrine problem of young, first of all infertile women, but it exerts a life long effect on the endocrine and metabolic milieu that turns to general, metabolic disorder in the perimenopausal years.

Clinical Discussion

Diagnosis of PCOS and its Phenotypes

Although PCOS has been defined clinically, biochemically, and by ultrasound, it is a heterogenous disorder that was evident already from the first description of PCOS by Stein and Leventhal [11]. Among the 7 women described in the original report, a variety of clinical symptoms were observed, such as obesity, hirsutism, acne, amenorrhea, all of them associated with polycystic ovaries. Most of the patients with ultrasound characteristics of PCO have a clinical or biochemical feature consistent with the ultrasound diagnosis and they are likely to face the problems of hyperandrogenism, subfertility and later on metabolic disorders. As for the predominantly North American view, the 1990 National Institute of Health (NIH) conference on PCOS recommended that diagnostic criteria should include biochemical evidence of hyperandrogenism and ovarian dysfunction without regarding the morphological diagnosis of PCO by ultrasound as an essential part of the diagnosis [12]. The Rotterdam Consensus on diagnostic criteria for PCOS in 2003 [13] attempted to bridge the gap between the predominantly American biochemical marker-based diagnosis and the predominantly European reliance on ultrasound as a sine qua non. According to the Rotterdam criteria PCOS can be diagnosed if 2 out of 3 criteria (oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, polycystic ovaries) are present, and other etiologies can be excluded. Using the possible combination of these three criteria, four different phenotypes of PCOS may be identified [14] (Fig. 1):

– Type A: Hyperandrogenism, chronic anovulation and polycystic ovaries
– Type B: Hyperandrogenism and chronic anovulation
– Type C: Hyperandrogenism and polycystic ovaries
– Type D: Chronic anovulation and polycystic ovaries
The Rotterdam criteria except all the four phenotypes, but not all the phenotypes meet the criteria of other definitions. According to the NIH criteria only Type A and B are acceptable, because the presence of polycystic ovaries are not needed for the diagnosis of PCOS. Later on the American Androgen Excess Society (AES) in 2006, and the Androgen Access and PCOS Society in 2009 pointed out that PCOS is a hyperandrogenic disorder meaning that Type A,B, and C are the phenotypes of PCOS [15]. After all we should rely on four phenotypes as the Rotterdam criteria are the most widely accepted at least in Europe. The existence of the four phenotypes raises several questions that are not fully answered for the time being: prevalence of the phenotypes, degree of severity they represent, short and long term consequences of PCOS depending on the phenotypes.

**Prevalence and Severity of Phenotypes with Regard of Hormonal and Metabolic Consequences**

As the prevalence of the PCOS itself depends on the criteria used the prevalence of the phenotypes also represent a relatively wide range [14, 16]: the most frequent is type A (44–65%) followed by type B (8–33%), then type C (3–29%), and the less frequent is type D (0–23%). It hasn’t been completely clarified what kind of severity is represented by the different phenotypes concerning hormonal and metabolic disturbances. Endocrine differences, first of all the degree of hyperandrogenism is characteristic for three types (A, B, C) of PCOS. It is in connection with the hyperinsulinism, because in type D, where there is no hyperandrogenism, hyperinsulinism is not characteristic [16].

Long term metabolic risk in PCOS patients was established already in patients diagnosed by the NIH criteria. According to several studies it has been proved that PCOS patients in their perimenopausal years will have higher prevalence of type 2 diabetes, hypertension, dyslipidemia, obesity, cardiovascular diseases – the so called “metabolic syndrome” [17–19]. There is an overlapping between the symptoms and characteristics of PCOS and type 2 diabetes [19] that is summarized in Table 1.

**PCOS and the Risk of Type 2 Diabetes**

Dunaif and co-workers [20] were the first to report higher ambient glucose levels and greater than expected frequency of glucose intolerance among PCOS patients compared with normal women. Later, retrospective studies of postmenopausal women with a history of PCOS demonstrated that 15% had type 2 diabetes mellitus, compared with a 2.3% prevalence among age-matched controls [21, 22].

Thirty to 40% of women with the PCOS have impaired glucose tolerance, and as many as 10% have type 2 diabetes by their fourth decade [23]. Glucose tolerance also changes over time. Women without PCOS and baseline impaired glucose tolerance (IGT) have a low conversion risk of 6% to type 2 diabetes over approximately 3 years, or 2% per year. The effect of PCOS, given normal glucose tolerance baseline, is more pronounced with 16% conversion to IGT per year [24]. These findings support that women with PCOS should be periodically rescreened for diabetes due to worsening glucose intolerance over time.

Insulin resistance alone cannot fully explain the predisposition to and development of type 2 diabetes among patients with PCOS. Most women with PCOS are able to compensate fully for their insulin resistance, but a substantial proportion (particularly those with a first-degree relative with type 2 diabetes) have a disorder and insufficient beta-cell response to meals or glucose challenge [23]. A family history of diabetes is present with significantly greater frequency among women with PCOS who had IGT or type 2 DM compared with those with normal glucose tolerance [25].

Before the development of frank glucose intolerance, defects in insulin secretion may be latent and revealed only in circumstances that augment insulin resistance, as with the development of gestational diabetes in pregnancy [26], or glucose intolerance associated with glucocorticoid administration [23].

In conclusion, patients with PCOS, regardless of ethnicity, appear to have 5- to 10-fold greater risk for type 2 diabetes mellitus, compared with the case of age and weight-matched women [10, 13]. Additionally, a family history of diabetes and the presence of obesity are important predictors for the development of type 2 DM [10].

**Prevalence and Severity of PCOS among Patients with DM**

If type 2 DM is a frequent finding among PCOS women, and both conditions are characterized by IR, type 2 diabetic patients must have a greater risk of having PCOS than normal women. There is a growing evidence to support this notion, although there have been few studies addressing this point for the time being. In a group of premenopausal type 2 diabetic women polycystic ovaries were seen by sonography in 82% of the cases, and clinical signs of PCOS were present in 52% [27]. In another study the prevalence of PCOS among premenopausal
type 2 diabetic women was 26.7% [28], much higher than the 4–9% prevalence in unselected population of reproductive-aged women [3, 4]. Women with previous GDM also show a higher prevalence of polycystic ovaries (41%), hirsutism and irregular menstrual cycles, and a higher body mass index than the controls [26]. According to a small study, women with type 1 diabetes mellitus may also have higher prevalence of hyperandrogenic disorders, including PCOS (18.8%) and hirsutism [29]. The body mass index was not different among these type 1 diabetic women with or without hyperandrogenic disorders.

Concerning the above mentioned studies, the prevalence of PCOS seems to be significantly higher among reproductive-aged women with type 2 (and probably type 1) DM, resulting in additional reproductive and endocrinologic abnormalities in these women.

**PCOS Phenotypes and the Metabolic Risk**

Increased metabolic and cardiovascular risk is assumed to be characteristic for PCOS patients [18, 30]. A challenging question for the future is to settle which phenotypes exert higher cardiovascular and metabolic risk. Hyperandrogenism itself seems to be a significant risk factor meaning that type A, B and C represent higher risk. Hyperandrogenism not only in adults, but also in adolescent girls represents an increased metabolic risk independent of obesity [31]. Identification of two or three components of metabolic syndrome correlates with the testosterone level in adolescent PCOS girls, although the prevalence of metabolic syndrome is independent of the body mass index, lipid profile and serum insulin level of these young patients. Other studies show that hyperandrogenism correlates with obesity, because sex hormone binding globuline (SHBG) is decreased in obese patients and obesity itself generates increased testosterone level. Obesity means secondary subtypes of PCOS phenotypes, but its clinical significance needs further evaluation. The type of the elevated androgen is also important: PCOS patients with increased androstenedione level have higher metabolic risk [14].

As insulin resistance is a prominent feature of PCOS, and women with this disorder are at increased risk for the development of other diseases that have been linked to insulin resistance, namely type 2 DM and furthermore, metabolic syndrome the correlation of insulin resistance with the different PCOS phenotypes would be an important contribution to the metabolic risk. Very few studies address this correlation. According to a Chinese study PCOS phenotype does not correlate with the degree of insulin resistance [32]. However, no tests of insulin resistance are necessary to make the diagnosis of PCOS, although they may be considered if additional risk factors for insulin resistance, such as a family history of diabetes, are present. There is currently no clinical test for detecting insulin resistance for the everyday use in the general population, but in a recent study the routine measurement of HOMA-S (homeostasis model assessment) was recommended for identifying insulin resistant PCOS women with a view of targeting them with insulin-sensitizing agents [33]. According to the Rotterdam Consensus [13], instead of measuring IR, criteria have been developed for defining a metabolic syndrome in women with PCOS, that is clinically more relevant and useful.

**Table 1. Common Pathophysiological and Clinical Characteristics of Polycystic Ovary Syndrome (PCOS) and Type 2 Diabetes Mellitus (DM) (for details see text)**

<table>
<thead>
<tr>
<th>PCOS</th>
<th>Type 2 Diabetes Mellitus</th>
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<tbody>
<tr>
<td>Overlapping in genetic background with type 2 DM</td>
<td>Overlapping in genetic background with PCOS</td>
</tr>
<tr>
<td>Insulin resistance in 50–70% [9, 10]</td>
<td>Insulin resistance in 80–100% [10]</td>
</tr>
<tr>
<td>Risk of impaired glucose tolerance (IGT): 40% [23]</td>
<td>Risk of having polycystic ovaries: 82% [27]</td>
</tr>
<tr>
<td>Risk of type 2 DM: 10% [23] or 5- to 10-fold increased risk [10, 13]</td>
<td>Risk of having PCOS: 26–52% [38, 39]</td>
</tr>
<tr>
<td>Increased risk of metabolic syndrome („syndrome XX”) [13, 30]</td>
<td>Type 2 DM is a component of the metabolic syndrome [20]</td>
</tr>
<tr>
<td>Long term management includes: lifestyle modification, insulin sensitizers (metformin) [44, 45]</td>
<td>Management includes: lifestyle modification, insulin sensitizers, insulin if needed [48]</td>
</tr>
</tbody>
</table>

**Management of PCOS from the View of Phenotypes and Long Term Consequences**

Management of PCOS depends on the requirements of the patient. First line management may be managing hyperandrogenism, menstrual cycle disorder or infertility. A further therapeutic goal should be the prevention of the long term metabolic and cardiovascular disorders, diminishing the risk of type 2 diabetes and metabolic syndrome.

**Management of Hyperandrogenism**

Gestagens with anti-androgen properties in combined oral contraceptives are the most widely used medications to diminish the signs of hyperandrogenism (acne, hirsutism, alopecia). Inhibition of ovarian androgen secretion or administration of insulin sensitizers are further options.

The most effective and widely used anti-androgen is cyproterone acetate. In combination with ethinyl-estradiol it is an effective anticoncipient that decreases signs of hyperandrogenism and has a good cyle control as well [34]. However, we may infer that most of the combined oral contraceptives have anti-androgenic effect, because estrogen increases SHBG level, and on the other hand the 3rd and 4th generation gestagens (e.g. gestoden, desogestrel, drospirenone) have no androgenic activity, they do not decrease the beneficial effect of estrogens. There are few data how PCOS phenotypes may play a role in choosing a given hormonal contraceptive. In case of increased metabolic risk vaginal contraceptive ring, or an oral contraceptive pill combined with the insulin sensitizer myo-inositol may be recommended [35]. If only the signs of hyperandrogenism should be treated administration of insulin sensitizers alone...
(e.g. metformin) have also promising results [36].

Management of Infertility
There are medical and surgical therapeutic modalities for the treatment of PCOS related infertility, but there are no studies regarding the management options in the different phenotypes. In obese patients the reduction of BMI alone may lead to resumption of ovulation [37]. The gold standard of ovulation induction is clomiphene citrate, because it is simple and cheap. It induces ovulation in 80–90% of cases, but the pregnancy rate is much less favorable (30–50%). A further, but contradictory option is the use of insulin sensitizers (e.g. metformin, troglitazone, resiglitazone, myo-inositol and/or D-chiro-inositol) alone or in combination with clomiphene citrate. Hyperinsulinaemia and insulin resistance, characteristic for most of the PCOS patients, is reduced with this therapy that concludes in resumption of ovulation. Earlier studies and a Cochrane analysis [38, 39] indicated that metformin is more effective in ovulation induction than placebo and metformin combined with clomiphene citrate induces higher ovulation and pregnancy rate than clomiphene alone. The rationale of administrating metformin for ovulation induction was argued later on in 2007 by the Second PCOS Conference in Thessaloniki [40]. According to the recommendations of this Conference metformin is indicated in PCOS only if carbohydrate intolerance is diagnosed. A recent Cochrane analysis also questions the efficacy of metformin for ovulation induction [41].

According to recent studies patients may also benefit from lifestyle changes as a result of the metabolic and cardiovascular risk of PCOS patients, but the best result may be achieved probably by the combination of medical therapy and lifestyle modifications. The results may depend on the phenotype (degree of hyperandrogenism) and obesity as well.

For future studies it is needed to evaluate, if PCOS and type 2 DM are no more than different clinical manifestations of the same IR syndrome, and how effective are the insulin sensitizer drugs and/or lifestyle modifications in lifetime management of IR disorders, including PCOS.

A challenging task to the future is to assess the individual risk of PCOS patients according to phenotypes and to elaborate personal steps for prevention.

Conflict of Interest
The author declares no conflict of interest.

References:
PCOS throughout Life


