

The Existence of a Male Equivalent of the Polycystic Ovary Syndrome – the Present State of the Issue

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Abstract: The polycystic ovary syndrome (PCOS) in women belongs to the most frequent endocrinopathies. This syndrome is characteristic by a hormonal and metabolic imbalance. It seems to be a kind of an oligogenic disease resulting from the interaction among several key genes and environmental effects. Considering the genetic basis of this syndrome there is no reason why the syndrome could not occur in men as well, be it with a different symptomatic expression. Premature baldness before the age of thirty used to be suggested as a symptom of the male PCOS equivalent. Yet there still seems to be rather a meagre attention devoted to the endocrinological changes in men in the specialised literature, although there do exist genealogical studies on the occurrence of alopecia or glucose metabolic disorder in male members of the families where a considerable number of females were affected by PCOS.

Polycystic ovary syndrome

Definition

PCOS accounts for frequent endocrinopathies in women with the occurrence between 5 to 10 per cent [6, 33]. Estimated frequency of PCOS depends of course on how we define the term and that is no easy task. The polycystic ovary syndrome represents a set of symptoms given by hormone and metabolic changes neither of which is determined exactly. The syndrome described in 1935 by Stein and Leventhal was characterised by morphologically polycystic ovaries, clinical disorders of female cycle and fertility, by hyperandrogenic symptoms and obesity. Later definitions of the polycystic ovary syndrome are based on the coexistence of anovulation and hyperandrogenism. Women diagnosed with this syndrome often suffer from obesity yet a group of rather lean patients with PCOS is known too.

In 1990 the following PCOS definition was proposed: hyperandrogenemia and chronic anovulation after excluding the non-classical block of the steroid 21-hydroxylase, hyperprolactinemia or androgens producing neoplasm [2]. The joint conference of the European Society for Human Reproduction and Embryology (ESHRE) and American Society for Reproductive Medicine (ASRM) in Rotterdam in May 2003 [25] agreed that PCOS should be diagnosed when at least two of the following three criteria are met: 1) oligomenorrhea and/or anovulation, 2) clinical or biochemical symptoms of hyperandrogenemia, 3) sonographic finding of polycystic ovaries. PCOS continues to be understood as a syndrome having more than one symptom.

According to this definition the typical morphological changes in ovaries may or may not be present. These changes mean that at least 10 and more follicular cysts of 2–8 mm in diameter are laid subcapsularly in combination with increased stroma. The basis of the changed ovarian morphology is the presence of a great number of growing follicles in various stages of their development. The cause is probably a disruption in the downfall of the growing follicles rather than the increased acceleration of primordial follicles recruitment. Polycystic ovaries are present in

majority of the PCOS patients. However, the same morphological changes often occur with other types of endocrinopathies, for example with hypothyroidism or hyperprolaktinemia, as well as in healthy women with regular menstruation cycle and physiological androgen concentration. Although some authors consider the presence of the polycystic ovaries as the principal diagnostic criterion, its specificity in relation to PCOS is very small. Therefore, this definition distinguishes between the endocrine and metabolic syndromes and mere morphological changes, which were described repeatedly in women with completely normal androgenic spectrum [2].

Hyperandrogenemia is the basic laboratory finding with PCOS. Yet the examination of the androgen production in the organism requires verifying of the level of all main androgens. With testosterone we must closely observe not only the overall levels of the hormone but the share of biologically active components too. As the free biologically active testosterone level depends on the SHBG level, it is necessary to calculate the free testosterone index ($FAI = [(testosterone / SHBG) \times 100]$), or use another suitable method. For a PCOS diagnosis it is a prerequisite to find an increase at least of one of the hormones (total or free testosterone, androstenedione, dehydroepiandrosterone or its sulphate). There is often a moderate increase in the androgen precursor level too, 17 α -hydroxyprogesterone. In the case of the increased value of one of the androgens up to the limit it is important to observe if the values of other androgens move closer to the lower or higher border of the reference range. However, a higher level of some of the androgens is not specific for PCOS only and it is therefore necessary to exclude other hyperandrogenic conditions (non-classical form of the congenital adrenal hyperplasia, ovarian and adrenal tumours producing androgens). Low concentration of SHBG is a very frequent finding in women with PCOS. Yet despite normal testosterone level ranges in these patients the real concentration value of the active, bioavailable androgens, is higher. With PCOS the LH to FSH ratio often shifts to higher values in favour of LH. This is neither specific nor sensitive indicator but it is an important and easily

Table 1 – Increased risk of various diseases in males with androgen alopecia

Disease	odds ratio	95% reliability range	reference
Benign prostate hyperplasia	3.23	1.81–5.79	Oh et al. 1998
Prostate gland carcinoma	1.50*	1.12–2.00	Hawk et al. 2000
Ischemic heart disease	1.36	1.11–1.67	Lotufo et al. 2000
Hyperinsulinemia	1.91	1.02–3.56	Matilainen et al. 2000
Obesity	2.90	1.76–4.79	Matilainen et al. 2000
Hypertension	2.09	1.14–3.82	Matilainen et al. 2000
Dyslipidemia	4.45*	1.74–11.34	Matilainen et al. 2000

*relative risk

available indicator in the case PCOS is suspected. Blood withdrawal for gonadotrophin determination should be carried out in morning hours and in the early follicular phase.

Chronic anovulation or irregular menstruation cycle is another PCOS diagnostic criterion for PCOS patients. Here we can anamnestically find oligomenorrhea since menarche or secondary amenorrhoea. The menstruation cycle with the bleeding interval extends to over 35 days and even more. Majority of menstruation cycles are of the anovulation type. However, ovulation may occur accidentally too and therefore spontaneous pregnancy is possible in the PCOS patients. It is necessary to exclude thyreopathies and prolactinomas. Moderate hyperprolactinemia occurs in 20–30% patients with PCOS [2].

Obesity is also a part of the PCOS patient's clinical sing. It is described in 20–80 per cent of patients and considerably modifies the disease clinical sing. In the differential diagnosis it must be differentiated from the Cushing syndrome. Hirsutism and acne, sometimes including androgenic alopecia, are further symptoms. Various theories on pathophysiology of PCOS presuppose some defect on the hypothalamus-hypophysis – ovary axis, in the ovarian or adrenal steroidogenesis [14] or in the insulin sensitivity. Unfortunately none of the theories is capable of explaining the PCOS pathogenesis in a complex way [2]. PCOS carries various risks, some of which are related to the female reproduction functions (infertility, pathological pregnancy, with an expected risks of increased carcinoma of endometry and ovary) while some are general (disrupted glucose tolerance or diabetes mellitus of the second type, hypertension, increased risk of cardiovascular diseases) [2, 29].

PCOS and insulin resistance

Over 20 years proofs have been documented on relations between IR and PCOS. In PCOS women hyperinsulinemia is a result of the combination of IR, compensatory higher insulin secretion and reduced insulin clearance in the liver. It has been noted that the PCOS patients have lower insulin sensitivity in comparison with controls, but these data are found in small groups of patients only and they are rather loosely related to BMI. The problem is whether IR depends or not on BMI in patients with PCOS. No exact prevalence of IR with PCOS has been known so far [2, 23, 33]. Recently, it was shown that that lean PCOS women are not more insulin resistant than healthy controls. Insulin hypersecretion, on the other hand, is present even in lean PCOS women [34]. Published data [3] offer evidence that a substantial subgroup of women with PCOS have insulin sensitivity comparable with healthy controls if matched carefully for potential confounding factors.

Women with PCOS have a higher risk of developing type 2 DM [16, 32]. Studies on isolated adipocytes and cultures of PCOS patients' skin fibroblasts show reduced effects of insulin when stimulating glucose transportation. Metabolic

processes in fibroblasts are intact, except the insulin signalisation. Skeletal muscles of the women with PCOS are resistant to insulin *in vivo*, whereas *in vitro* cultivated muscle cells show a normal sensitivity to insulin in accord with the main role of the other factors when creating the insulin resistance in tissue. Excessive serin phosphorylation of the insulin receptor or down regulation of signal proteins can play a role in the IR pathogenesis of PCOS. Hypothetical serine kinase affecting the insulin effect remains so far unknown. Any explanation of the differences in insulin effects in the insulin receptor and insulin signal transportation with PCOS, which could link all the current information, is so far lacking [2, 32].

Measurement of insulin resistance

To measure organism's sensitivity to insulin we use its effects on glucose metabolism *in vivo*. The most exact methods are the so-called direct methods with the euglycemic hyperinsulinemic clamp being the golden standard.

As the clamp methodology is relatively elaborate and expensive, it is applied mostly in clinical studies [2]. The insulin tolerance test and intravenous glucose tolerance test represent other direct methods. These two tests are mutually comparable [18]. The intravenous glucose tolerance test has a similar information value as the euglycemic clamp [3].

Suitable for epidemiological studies are indices of insulin sensitivity deduced from the fasting glycemia and fasting insulinemia. Among the most frequently used is the Homeostatic Model Assessment (HOMA) calculated as a product of fasting glycemia (mmol/l) and the average of three values of fasting insulinemia (mIU/l) divided by the constant of 22.5. There is another possibility, as e.g. the fasting glucose to insulin ratio (FGIR), which is a ratio of fasting glycemia (mg %) and insulinemia (mIU/l) [2].

PCOS Genetics

There is no doubt that an important role in the PCOS pathogenesis is played by genetic factors. This is manifested by a frequent familiar occurrence of this syndrome. The research in genetic causes, similarly as with the other complex syndromes, encounters many obstacles. Among the complications in the study of PCOS genetics are cited: rather unclear primary etiology, unclear phenotype definition, heterogeneity of the studied sets, unclear heredity type and complications in the completing sets (the problem of parent phenotype determination – how to characterise the postmenopausal woman with declining androgen synthesis, issue of the corresponding male phenotype) [2]. PCOS seem to be an oligogenic disease, which is a result of interaction of several key genes and environmental influences. When searching for the PCOS genetic basis there are many genes candidates described in the specialised literature. Among these gene candidates for PCOS are cited: genes taking part in the androgen biosynthesis and metabolism, in the effects of gonadotropins and folliculogenesis, effects of

insulin in the origins of obesity and in energy regulation [2]. So far there was no success in exposing the key genes in the PCOS etiopathogenesis, many promising results in further studies have not been confirmed. Recently some information has surfaced about another candidate gene for PCOS on the chromosome 19p13.2 [30].

One of the candidate genes is for polymorphism in the number of tandem repetitions (VNTR – Variable number of tandem repeat) of the insulin gene (INS) [7, 31, 35]. The VNTR areas are highly polymorphous loci in human genome and their alleles are differentiated according to the number of repetitions of the tandem-like repeating sequences of given size. INS VNTR is located at the end of the 5'-end of the insulin gene on the 11p15.5 chromosome and is the result of the repetitions of the 14–15 bp long sequences. Short alleles (containing 28–44 repetitions) are marked as alleles I and are often linked to DM1. Long alleles (containing 138–160 repetitions) are marked as alleles III and are linked to DM2, PCOS and also to lower weight at childbirth [35]. Latest studies suggest that INS VNTR does not play any key role in the PCOS development [24].

Searching for a PCOS male equivalent

The polycystic ovary syndrome (PCOS) is characterised by hormonal and metabolic imbalance originating on a genetic basis. The complexity of symptoms and the genetic basis give rise to a hypothesis on existence of a male PCOS equivalent [1, 11, 15, 27]. Premature hair loss before the 30th year of age has been suggested as one of the male symptoms of this syndrome. Although there is no lack of genealogical studies on the occurrence of androgenic alopecia and metabolic disorders in the families with PCOS [20] these symptoms have not been followed systematically in families with PCOS and in males suspected of having the PCOS male phenotype, there is a lack of systematic documentation on laboratory findings of the typical steroid disorder [28,] and gonadotropins and on the findings of the insulin resistance. A frequent deviation from normal values in men diagnosed with premature androgen alopecia represents, apart from androgens and gonadotropins, also the SHBG levels, which are frequently lower. It seems that the frequency of the polymorphism D327N of the SHBG gene is higher in these men too [36]. Though the topic of the male PCOS equivalent is now a subject of interest, it is evident that now we need a long term follow-up of a large population sample. At the same time an exact identification of the male PCOS phenotype might be facilitated by genetic studies [8].

The importance of the search for a male PCOS equivalent is ongoing on two levels: Exact specification could help in defining the PCOS with women and in a clearer demarcation of this nosologic notion from other close diagnoses as e.g. the Reaven syndrome X. The second level is the use in practical medicine. Literature cites PCOS as a risk factor for the origin of Type 2 diabetes mellitus, cardiovascular diseases, hypertension, obesity and others. Men are exposed to the same PCOS

risk as women. It is therefore important to detect and to characterise this risk subpopulation early, so that the patients could be informed about the proven risks, and to endeavour through preventive measures, i.e. by change in lifestyle and regular checks to reduce the development of potential complications in the future. These are the reasons why to learn about the possible metabolic consequences of the premature androgenic alopecia linked to the defective insulin sensitivity is so important for common medical practice as well.

The premature androgenic alopecia is known to be a risk factor of cardiovascular diseases, saccharide metabolism disorders [13, 17, 19, 9] and prostate gland carcinoma [10, 5, 12]. Established connections of the premature alopecia with some diseases are listed in the tab.1. Premature hair loss before 30 years of age has been proposed as one of the phenotype manifestations of the male PCOS equivalent. This premature baldness before men reach thirty years of age occurs in approximately 30 per cent of the male population [26]. The PCOS prevalence in women ranges, according to various studies, between 5 to 10 per cent. Hence it follows, assuming that the male PCOS equivalent does really exist, that only a part of the male patients, i.e. of those with the premature alopecia, could be considered to represent the male PCOS equivalent. It seems therefore necessary to find a subgroup among the male population with the premature hair loss which will show similar hormone changes as in PCOS women, i.e. disrupted insulin sensitivity, which is also often described in the PCOS women. Then these men could represent the PCOS equivalent [7]. Yet further studies are needed to elucidate the existence of the male PCOS equivalent and establish whether the men with the premature baldness do exhibit the male PCOS equivalent or whether it is more likely that it is closer to the X metabolic syndrome.

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