Objective assessment of hyperandrogenism and modern ideas on PCOS treatment

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Abstract

Approximately 5 to 10% of female population in child-bearing age suffer from polycystic ovary syndrome (PCOS). PCOS is the most common cause of infertility brought by the lack of ovulation. The criteria for identification of PCOS include: oligo- or anovulation, hyperandrogenism and typical USG image of polycystic ovaries when other secondary causes of hyperandrogenism are excluded. The etiology of the syndrome has not been identified. It seems that the factor that initiates the disorder may be the originally existing improper regulation of cytochrome P450-17alfa. Disordered regulation of inappropriate androgens’ metabolism remains strictly related to the elevated level of luteinizing hormone (LH) and hyperinsulinemia. It is believed that high concentration of insulin may have the impact on the hyperandrogenism. The most common clinical symptoms include: disorder of the menstrual cycle, hirsutism and acne. Approximately 30 to 60% of women suffering from PCOS are obese. Very often the increase of body weight in PCOS patients is related to more intense clinical symptoms than the ones observed in not obese women suffering from the same syndrome and having similar biochemical disorders. Modern recommendations as to the treatment of PCOS include the introduction of particular therapies in stages. The lack of satisfactory effects at a given stage of treatment authorizes to apply another method. The treatment should be started with the change of lifestyle to reduce body weight. At the next stage the ovulation is stimulated by clomiphene and then by gonadotropins or laparoscopic surgical methods. In special circumstances IVF should be taken into consideration. In individual cases particular stages of the treatment may be abandoned.

Key words: hyperandrogenism, ovary syndrome, infertility

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder found in approximately 5-10% of women in reproductive age. PCOS is the most common hormonal disorder in women in child-bearing age and the most common cause of infertility. The symptoms and intensity vary among different patients. The underlying causes of the syndrome remain unknown, however, it has been found that immunity to insulin, very often a secondary effect of obesity, is strongly associated with PCOS [1-4].

There are two valid definitions:

• In 1990, at the expert meeting sponsored by NIH/NICHD, the following findings were made as to the symptoms observed in PCOS patients:
  1) symptoms of the excessive amount of androgens (clinical and biochemical),
  2) oligo-ovulation,
  3) when other factors that could cause polycystic ovary syndrome have been excluded.

• The findings made in 2003, at the expert meeting sponsored by ESHRE/ASRM in Rotterdam, indicate that PCOS is recognized when two of the three criteria listed below are observed:
  1) oligo- or anovulation,
  2) symptoms of the excessive amount of androgens (clinical and biochemical),
  3) PCOS ovaries (by gynecological ultrasound) – at least 12 follicles with the diameter (2-9 mm) or ovaries’ volume larger than 10 cm³, and when other causes of PCOS have been excluded.

The Rotterdam definition is broader and it encompasses a larger number of patients, especially where excessive amount of androgens is not observed, whereas in NIH/NICHD definition the excess of androgens is the necessary condition. Critics claim that the results of tests carried out on patients with excessive androgens may not necessarily refer to patients without excessive androgens [5].

In 1935 Stein and Leventhal described for the first time the syndrome for women with following features: the lack of ovulation, abnormal hair growth of male type and enlarged, polycystic ovaries. The group included women who suffered from the most severe form of the syndrome and who were classified for surgical treatment, wedge resection of the ovary in order to restore fertility and normal menstrual cycle. The Stein-Leventhal syndrome was literally described in 1935 as a rare disorder. Currently, it is known that the symptoms connected with
ovarian capsular fibrosis are variable. There is a broad spectrum of clinical symptoms in PCOS patients including women with ovulatory cycles and at the same time women with largely intensified masculinization. Strict criteria stated by Stein and Leventhal take too little account of the dispersion of phenotype expression. As it became possible to carry out non-invasive USG examination, which initially had been done with trans-abdominal and then vaginal method, morphological diagnosis of polycystic ovaries has become easier and in some tests has been confirmed with post-surgical histological examination. The method which combines USG with biochemical examination presents a number of opportunities in diagnosis of PCOS patients. At present, PCOS includes a lot of disorders starting with intensified hyperandrogenism, which manifest itself in acne and hirsutism with normal menstrual cycles up to oligomenorrhea and amenorrhea menstrual disorders with significantly advanced hirsutism in obese women.

Hyperandrogenism in PCOS

Hyperandrogenism, understood as an elevated concentration of circulating active androgens in women, is one of the three diagnostic criteria for PCOS identification. Classical symptoms of hyperandrogenism include excessive, abnormal hair growth (hirsutism), typically male balding and acne. The severe form of hyperandrogenism may be singled out as virilization (virilism), which is characterized by enlarged clitoris, lower-sounding voice timbre and development of typically male musculature. In practice, this condition is very rare in PCOS patients and in fact it is more characteristic of androgen-secreting tumors [6].

Clinical evaluation of hyperandrogenism is a difficult issue, especially considering the assurance of maximum objectivity of the examination. Despite the fact that there is a number of clinical descriptions of PCOS at our disposal the use of different scales e.g. hirsutism evaluation scale cannot be very reliable. On the other hand the application of point scales for the measurement of symptoms’ intensity brings also other benefits for instance it allows to compare the intensity of symptoms and select appropriate treatment and it works well in scientific research. However, the prerequisite conditioning the application of the scales for measuring the intensity of symptoms is their sufficient reliability and acceptance granted by a broad circle of clinical specialists.

In case of PCOS, it has become common to use scales that refer to the intensity of hyperandrogenism, particularly for hirsutism, but also for acne and balding [7]. Nevertheless, the issue of selecting and applying a specific scale is related to the controversy.

Hirsutism

Hirsutism is defined as the excessive growth of thick hair in women in body and face locations, where hair growth is typical for men. Around 5-15% of women suffer from this condition, depending on the assumed definition of PCOS [8, 9]. Excessive and abnormal hair growth (i.e. in body locations where terminal hair is usually absent) is the most common clinical manifestation of hyperandrogenism [10]. It is estimated that in around 80-90% women who suffer from pathologically elevated androgens level hirsutism is observed [11]. In case of PCOS the frequency of hirsutism is estimated to be as high as 70% [14]. Despite the fact that some clinical specialists consider hirsutism mainly as a cosmetic problem, the presence of hirsutism is one of the most important factors that contribute to lower quality of life for women suffering from PCOS [12].

Clinical evaluation of the intensity of hirsutism is naturally to a large extent dependent on personal impression of patient and also medical doctor. Medical personnel should also take into account the possibility of different attitudes to hirsutism presented by individual patients. According to Espinos et al. [13] even when patients refer to the same scale of measurement as the physicians (in this case Ferriman and Gallwey scale), their self-assessment with regard to hirsutism differs significantly from the doctor’s assessment. It was proved in the same test that only the professional’s assessment made with the use of Ferriman-Gallwey scale correlates substantially with the intensity of hyperandrogenism [14].

It is worth to remember that age and ethnic background influence the intensity and pattern of hirsutism, mainly due to inherited factors (e.g. genetic differences in the activity of 5α-reductase) [15]. In women of Asian origin less intense terminal hair growth may be expected in comparison to women from other ethnic groups (e.g. coming from the Mediterranean Sea region or of Indian origin) [16].

As mentioned above, one of the biggest difficulties by the evaluation of hirsutism is the assurance of maximum objectivity of the examination. Currently, the main tool to provide objectivity is the application of Ferriman-Gallwey scale in daily practice. In the scale, which was proposed in 1961, the intensity of hirsutism is assessed on a scale ranging from 0 to 4 (where 0 means lack of terminal hair and 4 indicates hair growth characteristic of an adult male). Terminal hairs differ from original
hairs mainly with their length (> 0.5 cm), coarseness and pigmentation. In the originally developed Ferriman-Gallwey scale, 11 anatomical locations were taken into account and the sum of points given in the assessment of particular locations was the result indicating the intensity of hirsutism [17]. The widely accepted cut-off level for defining hirsutism is the sum equal to or higher than 8, however, the issue remains controversial. Some authors suggest to take the sum of 3 or 5 as the cut-off point. Many physicians also suggest various modifications of Ferriman-Gallwey scale. These modifications concern mainly the kind and number of body locations to be included in the scale. The most significant alteration was proposed by Ferriman himself, who concluded that the intensity of hairiness in the area of forearms and shins (so called "hormonal hair") is not in correlation with hair growth in the remaining nine body locations subject to assessment. Thus these two body locations had been excluded from the evaluation. Modified Ferriman-Gallwey (m F-G) scale at present is commonly used in clinical and scientific research.

Acne

Acne is another, next to hirsutism, cosmetic problem encountered by PCOS patients. Androgens have the ability to stimulate the production of sebum in sebaceous gland which creates optimal environment for the colonization of bacteria inter alia Propionibacterium acnes [18].

Despite the fact that acne is considered as a significant symptom of the syndrome there is a lot of controversy as to the frequency and intensity of this dermatological symptom in PCOS patients. The frequency of acne in PCOS patients has been determined to occur in a broad range from around 20 to 40% [19, 20]. The precise figure remains unknown as there are no large population research available. Moreover, the majority of research is based on the definition of PCOS, which differs from the modern one and at the same time refers to different groups of patients.

Another problem refers to the evaluation of acne intensity in PCOS. The systems used for classification of acne intensity (photographic methods, Leeds technique, methods based on counting) are reliable and are applied in dermatology to facilitate therapeutic decisions and the evaluation of responses to treatment [21]. These scales, however, are rarely used by gynecologists, so our knowledge on the intensity of acne in PCOS is limited.

Balding

For most physicians it is obvious that typically male balding (i.e. thinning hair in the area of the top of a head usually with the head frontline maintained) is related to hyperandrogenism. This thesis has also strong historical grounds as balding in women with PCOS in the past was considered as a typical feature of the syndrome. Nevertheless, modern research on the occurrence of balding in PCOS patients yield very inconsistent results. The frequency varies in different publications from 5% to as much as 50%, which questions the assumption that balding is more frequent (or more intense) in PCOS patients. The application of different methods for the evaluation of balding is a significant cause for such big discrepancies with regard to the frequency of balding. It should also be noted that the methods developed to assess hair loss objectively are rarely used by gynecologists.

Balding as the only symptom of PCOS is very rare. In one of the research on women with hyperandrogenism manifested exclusively with balding only 10% of the participants were diagnosed with PCOS [23].

It should be concluded that this symptom has low sensitivity and specificity in the identification of hyperandrogenism in PCOS. It is well documented that balding occurs more frequently in women with excessive androgens, however it is also well known that there is no clear correlation between hyperandrogenemia and hair loss. This fact is understandable as we are aware that the most significant hormonal stimulus for a hair follicle is 5alpha-dihydrotestosteron (DHT). DHT is mostly synthesized in skin papilla and its effect on the skin is mainly paracrine [24].

In the evaluation of women with balding other possible causes of this symptom should be taken into account. Particularly, one should consider environmental factors (pollution, irritation caused by hair care cosmetics), inherited features (family history of premature hair follicle loss) and dietary (including zinc or iron deficiency, malnutrition) [25].

Hyperandrogenemia

It is estimated that in 60 to 80% of patients diagnosed with PCOS elevated serum androgens concentrations are found. It should be emphasized that a number
of issues concerning the occurrence of hyperandrogenemia in PCOS patients remain disputable.

No agreement has been reached as to the following questions: which androgens should be marked, when exactly to measure their concentration and how to interpret the result, and most of all there is still controversy over the selection of analytical techniques [26]. The last problem in recent years has become the most important issue in the discussion over the appropriate evaluation of hyperandrogenemia in PCOS.

Similarly to other hormones transported in circulation in a protein-bound form, only the unbound ones (free) circulating hormones are active. Therefore, the main indicator of hyperandrogenemia is the identification of free testosterone (fT). Moreover, it is known that the concentration of fT is often elevated in PCOS patients. Consequently, the identification of fT in blood serum is considered as the most sensitive biochemical marker in PCOS diagnosis [19]. One of two groups of methods may be used to identify the concentration of fT or total testosterone and sex binding hormone globulin (SHBG).

The identification of total testosterone in the blood serum covers the testosterone pool bound with SHBG, thus SHBG needs to be additionally marked. It should be remembered that in PCOS patients decreased serum level of SHBG is observed as a consequence of the interference between hyperinsulinemia and the synthesis of SHBG in liver [27]. A single marking of SHBG and fT concentration with the use of appropriate measurement method presents high diagnostic value in PCOS [28]. Furthermore, the concentration of SHBG is a good indicator of immunity to insulin, so it is a useful test also in the diagnostics of metabolic disorders in PCOS.

Among the available methods for marking fT the following can be mentioned: Radio Immuno Assay methods (RIA), equilibrium dialysis and chromatographic methods.

The RIA method is widely available, but it gives accurate results only when the level of free T is relatively high (e.g. in men). In case of women RIA does not reflect the testosterone level accurately, neither for free nor for bound testosterone [29]. In practice, the immunological method which works best is the direct double RIA of high quality. However, it is suggested that the coefficient of variation between the markings in this method be lower than 10% of the standard set by the laboratory that carries out the tests. The range of the standard should be determined locally in a carefully selected female population without elevated concentrations of androgens.

The direct methods for measuring the concentration of fT in the blood serum, such as equilibrium dialysis, are very precise and the results they yield correlate with the results of mass spectometry [30]. Still, these methods are not widely available mainly due to technical difficulties and expensiveness.

Another disputable issue in PCOS diagnosis is the significance of measuring androgens other than testosterone, such as androstendion, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S). It must be noted that currently there is no scientific evidence pointing to clinical significance of marking the concentration of androstendion. It is estimated that in around 10% of women with PCOS elevated concentration of this androgen is found, but it remains unknown, how this correlates with the clinical image of the syndrome [31].

It should be emphasized that the measurement of DHEA is not clinically useful. DHEA is found in circulation in low concentrations and what is more it is released in a pulsating way [32]. It is even more difficult to interpret the result of DHEA marking as its concentration is largely dependent on the emotional condition of a patient, because stress (e.g. connected with admission to hospital) may significantly increase the release of the hormone [33]. DHEA metabolite of the adrenal gland origin, i.e. DHEAS, is a much better marker of hyperandrogenemia in PCOS. Its secretion is relatively stable in a twenty-four hour as well as a monthly period of time and its concentration is sufficiently high to allow for its reliable marking. DHEAS is a marker of hyperandrogenemia of adrenal gland origin because it is mainly produced by the adrenal glands (> 95%). In PCOS, the elevated level of DHEAS is found in around 25-35% of patients and, although it is not a marker of ovary disfunction, the identification of elevated concentration of DHEAS is sufficient to diagnose hyperandrogenism [34].

PCOS treatment – modern ideas

The presented recommendations for treating infertility in PCOS have been based on therapeutical consensus developed in Saloniki by a group of ESHRE/ASRM experts in March 2007 [35].

More and more significance is given to the modification of the lifestyle of PCOS patients. In obese PCOS patients, treating obesity becomes of the utmost importance. It includes dietary treatment based on a permanent change of eating habits in opposition to the more and more negatively assessed and not recommended short-term reduction diets. Physical exercises play an
important role in this treatment, preferably selected individually for the patient’s capabilities. At present, pharmacological reduction of body mass is treated as an element ancillary to the dietary treatment. It is often hard to explicitly assess the risks and the effectiveness of pharmacological therapy due to the lack of population research on the pharmaceuticals. As the extreme method and one which fortunately is used in very rare cases one should mention the possibility of surgical intervention on the digestive tract [36].

Direct therapeutical effect leading to the induction of ovulation should first of all include the application of clomiphene citrate. At present, it is considered the first drug at choice to induce ovulation. The argument for this therapy is low cost of the treatment, simple scheme of application, practically no contraindications, rare side effects and what should be emphasized most of all, the drug is very well known. It should not be forgotten though that basic rules for ovulation induction therapy should be followed, i.e. the required ultrasonographic control over ovulation. Failures of treatment with clomiphene citrate may unfortunately be expected in obese patients with hyperandrogenism and more than 35 years old. The administration is very simple and in its basic scheme it includes 50 mg dose daily for 5 days. The most frequently recommended administration scheme should be started from the 2nd, 3rd, 4th or 5th day of menstrual cycle and continued for 5 subsequent days. It is recommended that the stimulation scheme be repeated up to 6 cycles. Positive effect of the therapy, i.e. ovulation, is reached in 75% to 80% of patients. Unfortunately, only 22% of patients with ovulation confirmed ultimately get pregnant. One should also remember about possible undesired effects of clomiphene citrate. They are quite rare, still one should note hot flashes, headaches, visual disturbances most often occurring as scotomas. The syndrome of hyperstimulation of the ovaries is extremely rare.

Not long ago the opinion about supplementing the clomiphene citrate therapy with additional drugs was positive. At present, it should though be clearly stated that there is no evidence for beneficial effect of simultaneous application of metformin and dexamethasone in the ovulation induction therapy. Metformin may potentially have ancillary effect in patients with glucose intolerance. It should be remembered to stop taking metformin immediately after the patient is found to be pregnant [37].

Another alternative method of inducing ovulation are aromatase inhibitors. In this case the only obstacle to application of the therapy, apart from the lack of proper registration of the drug, is also the lack of unambiguous data on the effectiveness of aromatase inhibitors with regard to their effect on ovulation.

The next stage of PCOS treatment, when the treatment with clomiphene citrate is ineffective, is the stimulation protocol with the use of gonadotropins and GnRH analogues. The basic problem in this therapy is the lack of one best protocol for stimulation. There is still individualization of stimulation schemes based on gonadotropins. Nevertheless, what is being recently called for is the initial FSH dose of 37.5-50.0 IU/a day, contrary to previously propagated doses of 150 IU/a day. Another recommendation is to administer small FSH doses and when the follicle does not grow, the dose should be increased in subsequent days maximum by 50% of the previous FSH dose. And when the follicle grows, previous dose should be maintained. The therapy extends from 7 to 14 days. Such stimulation should be carried out for maximum 6 cycles. Permanent USG control is required. It is believed though that GnRH should not be used routinely. The benefits that should come from the observance of the above recommendations include the elimination of too fast peak concentration of LH. Still, stimulation protocols involving gonadotropins are characterized by much greater risk of hyperstimulation of the ovaries, higher risk of multiple pregnancy, uncomfortable use and high cost of therapy [38].

The following conditions constitute indications for surgical treatment: ineffective use of clomiphene citrate, constant high levels of LH, impossibility to remain under strict control during stimulation with gonadotropins and simultaneously required evaluation of the small pelvis in case when adhesions are suspected. Recommended laparoscopic techniques include electrocauterization or laser technique. The extent of the surgery depends exclusively on the size of the ovary. The biggest problem with surgeries is to avoid undesired side effect in the form of too extensive surgery leading consequently to premature termination of ovarian activity. It is believed that the only certain element guaranteeing the safety of the surgery is the experience of the surgeon.

Nevertheless, 50% of patients after laparoscopic treatment require further stimulation therapy. The most beneficial effects are obtained when clomiphene is administered after 3 months from the surgery and the stimulation with gonadotropins after 6 months from the surgery. The highest effectiveness of the therapy is guaranteed by the concentration of LH >10 IU/l, BMI between 20-25 and short period of infertility, preferably
up to 12 months. Recently often repeated key argument for laparoscopic treatment in PCOS is the cost of this treatment compared with gonadotropins.

Only in incidental cases of PCOS treatment in vitro fertilization is recommended to be taken into consideration. The lack of ovulation is not a sufficient reason for applying medically assisted reproductive techniques. Assisted reproduction techniques should be potentially considered for patients who are over 35 years old and in cases where additionally male factor coexists.

Modern recommendations for PCOS treatment include the introduction of particular therapies in stages. The lack of satisfactory effects of a given stage of treatment authorizes to use another method. The treatment should be started with the change of lifestyle aiming at the reduction of body mass, at the next stage stimulation of ovulation with clomiphene is applied, then gonadotropins or laparoscopic surgical techniques. Under special circumstances IVF should be considered. In individual cases particular stages of treatment may be abandoned.

References


