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The polycystic ovary syndrome: a position statement from the Polish Society of Endocrinology, the Polish Society of Gynaecologists and Obstetricians, and the Polish Society of Gynaecological Endocrinology

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Abstract
Polycystic ovary syndrome (PCOS) diagnosis and therapy still arouse a lot of controversy. Each year brings new information, so, having collected the experience of three scientific societies, we present contemporary recommendations concerning PCOS diagnostics and treatment. In adult female diagnosis, we still use the Rotterdam criteria, which is two out of three of the follwing characteristics: a) ovulation abnormality, b) clinical or biochemical hyperandrogenism, and c) polycystic ovaries. In the case of teenagers, diagnostic criteria are as follows: menstruation disturbances two years after menarche and clinical or biochemical hyperandrogenism. The presence of polycystically abnormal ovaries is not necessary. The consensus paper presents the threats resulting from imperfect diagnostic methods applied in PCOS (hyperandrogenism diagnostics, ultrasound examination of ovaries). Suggested therapy includes personalised schemes according to the dominant PCOS phenotype, i.e. metabolic, hyperandrogenic, or reproductive ones. **(Endokrynol Pol 2018; 69 (4): 328–336)**

Key words: *polycystic ovary syndrome; diagnosis of PCOS; PCOS phenotypes, personalised therapy*

Introduction

Polycystic ovary syndrome (PCOS) is a disease comprising all periods of a woman's life, starting from the foetal period, through pubescence and the reproduction period, until menopause. The full clinical impact can be observed during the female reproductive period. It results in ovulation disturbances, excess of androgens, and fertility disorders. Depending on the diagnostic criteria, PCOS prevalence is assessed as 6–13% of women of reproductive age [1, 2]. PCOS is a disease resulting from many genetic and environmental factors. A cascade of events leading to PCOS development has been widely recognised, including the following: intrauterine development disturbances, low birth weight, early pubarche, increased risk of obesity, metabolic syndrome, cardiovascular complications, and diabetes type 2. Insulin resistance as well as hyperinsulinaemia seem to play a key role in this course of events [2, 3].

AGEs — advanced glycation products — are environmental factors that have been recently attracting a lot of attention. Their concentration in the organism is strictly connected with the thermic effects of food preparation as well as a diet rich in protein and low in carbohydrates. In PCOS women, increased AGE concentration in blood serum was found regardless their body mass. The same observance was made in the case of AGEs and their receptors in ovary theca and granulose cells. AGEs stimulate insulin resistance, synthesis of inflammatory factors, as well as adipogenesis in fatty tissue [2, 4, 5]. Endocrine disruptors seem to be another important element of the process. They are widely used

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as plasticisers in food packaging, bottles, cosmetics, CD and DVD envelopes, electronics, dental sealants, contact lenses, water pipes, and car upholstery. Their major representative is bisphenol A (BPA). It is a chemical compound the structure of which is similar to diethylstilbestrol, which causes homeostasis disturbances that lead to hormonal function disturbances of many glands. Only recently, there have been many arguments for the role of BPA in PCOS pathogenesis [6–8]. The important role of glutathione S-transferase (GST) polymorphism as an early marker of PCOS development in adolescents was suggested [9].

All recommendations from scientific societies including the Androgen Excess and PCOS Society, Endocrine Society, European Society of Endocrinology, International Society of Gynaecological Endocrinology, as well as the European Society of Human Reproduction and Embryology suggest the need to modify the current diagnostic criteria of PCOS. Our standpoint considers the opinions of all experts representing the above societies. In their opinion, there is also the need for therapy personalisation resulting from the age of diagnosis and its phenotype.

Diagnosis

In respect of women in reproductive ages, we still recommend the diagnostic criteria accepted by ESHRE/American Society for Reproductive Medicine (ASRM) in Rotterdam in 2004, i.e. the presence of two out of three clinical symptoms such as ovulation disturbances (oligo-ovulation or anovulation), hyperandrogenism clinical and/or biochemical features, and polycystic ovarian morphology (PCOM) characteristics in ultrasound examination [10]. We suggest slightly different criteria for the recognition of above three distinctions.

In the case of teenage girls, there is no one true consensus concerning diagnostic criteria of the syndrome. Many symptoms that in adult women are counted as pathognomic for PCOS are simply connected with physiological pubescence. Until recently, two criteria for diagnosing PCOS in youngsters were applied. The currently proposed European criterion includes four out of five of the following symptoms: ovulation disturbances, clinical and biochemical hyperandrogenism, insulin resistance, and polycystic ovaries. The other, American criterion embraces the presence of three symptoms: ovulation disturbances, clinical or biochemical androgenism, and polycystic ovaries [11]. In the latest consensus, Ibanez et al. [12] suggested modification of diagnostic criteria for PCOS in girls in the pubescence period. Our standpoint is convergent with the recommendations presented below.

In order to diagnose PCOS in adolescence, observation of the symptoms below is indispensable.

1. Irregular menstruation — especially oligomenorrhoea, primary and secondary amenorrhoea
2. Hyperandrogenism
   a) biochemical hyperandrogenism
   b) clinical hyperandrogenism

These symptoms should remain for at least two years [12]. If they last for less time, only the risk of PCOS is suggested, in order to avoid false positive diagnosis resulting from the pubescence period [13]. PCOM in ultrasound examination and/or cystic acne can be helpful but not necessary for diagnosis. It should be considered that PCOS development risk factors include early menarche, early pubarche, low birth weight, and obesity. Also, early diagnosis of the syndrome in the pubescence period is very important due to the risk of endometrium carcinoma development, cardiovascular diseases, or diabetes type 2 in life later stages [11, 13–17].

In hyperandrogenism-differentiating diagnostics the following endocrinopathy should be excluded:

1. Non-classical forms of congenital adrenal hyperplasia caused by 21-hydroxylase deficiency (for diagnosis we recommend estimation of serum 17-hydroxyprogesterone about 8.00 a.m. at follicular phase, and the dynamic test with ACTH as needed);
2. Cushing's syndrome (free cortisol estimation in urine collection and short dexamethasone test);
3. Acromegaly (morning GH concentration before and after glucose load);
4. Hypothyroidism (TSH estimation);
5. Hyperprolactinaemia (prolactin determination at follicular phase).

In the case of secondary amenorrhoea, a pregnancy test (β-HCG determination) must be performed [12, 13].

Ovary function assessment in PCOS

Disturbances in monthly menstruation regularity is found in 93% of PCOS women, including 68% of women revealing oligomenorrhoea, 21% with amenorrhoea, and 4% with primary amenorrhoea [12–14, 17–19]. Frequent menstruation in PCOS women in the time interval below 21 days or rare menstruations over 35 days most often occur with impaired or anovulation [13, 14, 16, 19]. The assessment of ovulation and menstruation in women in the reproductive period does not provide any problems — contrary to the pubescence period.

In adolescent PCOS diagnostics, several distinct diagnostic features should be considered, as compared to adult females. During the first post menarche year 85% cycles reveal anovulation, and in the third year still 59%

cycles proceed with no ovulation. One year after menarche regular menstruation is observed in only 65% of adolescents. Menstruations remaining irregular for over two years after menarche is a risk factor of menstruation disturbances in later periods of life [11, 14, 15, 17]. In the first post menarche year, bleeding more frequently than every 20 days and more rarely than every 90 days is considered abnormal and calls for diagnostics [13–15, 20]. After the first two years of menarche, in the majority of girls, the cycles are from 20 to 45 days. In turn, in subsequent years, irregular menstruations are those more frequent than every 20 days and rarer than every 45 days [15, 20]. Primary amenorrhoea is no menstruation up to the 16th year of life or no menstruation in the first 2–3 years of thelarche. Secondary amenorrhoea can be recognised when no menstruation is observed for longer than three months [15, 21].

In order to assess ovulation, we recommend the following menstruation regularity, ultrasound observation and blood serum progesterone estimation at luteal phase. Basal body temperature (BBT) may also be useful [2, 17].

Clinical and biochemical characteristics of hyperandrogenism

Hyperandrogenism and hyperandrogenaemia evoke a lot of controversy. In 93% of girls aged 16–18 years no correlation was observed between acne intensity and androgen levels in the pubescence period. In the group of girls with severe acne resistant to treatment, 40% will develop PCOS [17, 20]. Androgenic alopecia is a more reliable clinical marker of hyperandrogenism caused by androgen-secreting tumour; in PCOS it is very rare [17, 18, 20].

We recommended hirsutism as a more sensitive clinical marker of hyperandrogenism.

A modified Ferriman-Gallwey scale (mF-G) is applied to assess hirsutism because the observation of hair in nine areas of the body in the scale from 0 to 4 is not objective. This ratio largely depends on ethnic factors. For Caucasian females, a value over 7.0 indicates hirsutism, for Mediterranean area inhabitants it amounts to 9.0–10.0, and for Asian women it is only 2.0. It was proven that such assessments made by a patient, nurse, and doctor may vary one from another in the same patient [22]. Moderate hirsutism may appear in 50% of women without any characteristics of biochemical hyperandrogenism, similarly to those revealing biochemical hyperandrogenism in whom clinical features cannot be observed [23, 24]. In a meta-analysis including 6251 PCOS women, 75% of them revealed significant hirsutism and only 50% of them represented increased serum concentration of total testosterone [23]. This may indicate no direct relationship of simultaneous coexistence of these two characteristics. These facts stand for imperfectness of the above diagnostic parameter, so in the case of observed hirsutism, determination of blood serum androgen concentration is required.

Nonetheless, there are no objective standards that consider both age and ethnic factors on determining free and total testosterone concentrations. Dissimilar distribution of testosterone concentrations in female age groups was demonstrated [24–27]. In girls and premenopausal women the testosterone concentration should not exceed 0.55 ng/ml whereas in postmenopausal women it should not be higher than 0.35 mg/ml [25, 26]. Designation should be carried on with the use of high-pressure chromatography with mass spectrophotometry. However, in everyday practice, this method is rarely applied due to the poor availability and high price of the equipment [2, 26]. Also, in females, in contrast to males, testosterone concentration is significantly lower, so immunoenzymatic or radioimmunoassay may overestimate the results, which was observed on comparing these concentrations with the ones elicited with the method of gas chromatography combined with mass spectrophotometry or high-pressure chromatography [2, 26]. For the same reason, and due to no standard of measurement method, free testosterone is considered useful in diagnostics. However, in our practice, the key method is designation of total testosterone and sex hormone binding globulin (SHBG) and then calculation of the free androgen index (FAI) using the following formula: FAI = total serum testosterone concentration [nmol/l] x 100/SHBG [nmol/l] [16].

A value of this index over 5.0 suggests hyperandrogenaemia [2, 16, 26].

In PCOS diagnostics, determination of anti-Mullerian hormone (AMH) is not recommended due to lack of standardisation and low sensitivity of this method, and due to no cut-off value accepted as a standard [2, 12]. AMH concentrations in the group of PCOS women are higher than in the group of healthy women and are well correlated with antral follicles in an ovary [28]. The concept was postulated in PCOS diagnosis to apply AMH concentration convertible with the number of antral follicles found in ultrasound examination. This postulate, however, was not taken into account in establishing diagnostic criteria of any of the scientific associations mentioned here.

In turn, in hyperandrogenaemia diagnostics, complete profile determination of androgens is recommended, i.e. serum testosterone, SHGB, free testosterone, androstenedione, 17-hydroxyprogesterone, and dehydroepiandrosterone sulphate (DHEAS) [25].

Morphology of polycystic ovaries

Former visualising diagnostic criteria have been widely criticised, and the presently proposed ones are strictly connected with technological development of ultrasound equipment. In the experts' opinion, those most often criticised were also most commonly applied, e.g. Rotterdam criteria dealing with ovary ultrasound image qualification coexisting with PCOS. Rotterdam conference arrangements ESHRE/ASRM (2003) presumed to be diagnosed, polycystic ovaries should present at least one out of two of the characteristics presented below:

minimum 12 ovarian follicles with 2–9 mm diameter and/or increased volume (> 10 ml) gonad with no dominant follicle or corpus luteum.

In our new recommendations the Rotterdam criterion concerning ovary volume remains the same, and an ovary with volume > 10 ml is considered abnormal. However, there are some divergences related to the other parts of the ultrasound criterion — the number of follicles qualifying the ovary to the PCOM group. In many reports, there have been demands to increase the number of follicles to 19. After available literature analysis in the latest recommendations of the Androgen Excess and PCOS Society (Task Force 2014), due to more and more excellent ultrasound equipment, our societies recommend increasing the diagnostic criterion of antral follicle number in polycystic ovary to 25 in women aged 18–35 years with the same cut-off point of gonad volume of 10 ml [29, 30].

In accordance with the above agreement, the number of 25 follicles should be obligatory for contemporary examinations made with the use of a vaginal head. For more dated equipment (endovaginal heads below 8 MHz frequency or transdermal heads), avoiding this criterion is acceptable; however, the volume criterion should be observed.

Controversy related to the increase in the number of follicles concerns mainly the improvement of ultrasound system resolution and better visualising. The application of previous criteria with the use of outdated high-resolution equipment resulted in PCOS overdiagnosis, especially in young girls [30].

PCOS phenotypes

Taking into account many opinions, we recommend identification of PCOS women in the aspect of ovulation dominant disturbances, hyperandrogenism, and metabolic problems, which prevail both in pubescence and menopausal periods. The therapy should be personalised with respect to the dominant PCOS phenotype of the patient. Taking into account phenotypes adopted in ESE consensus, metabolic, hyperandrogenic, and reproductive phenotypes should be considered [2].

Metabolic phenotype

This PCOS phenotype is predominant, and metabolic disturbances accompany abdominal obesity. Females with this phenotype reveal fertility disorders, hyperandrogenism, and PCOM, which is described as classical phenotype [2]. Abdominal obesity, which is detected in 50–80% of PCOS women, is the main reason for metabolic problems observed in 30–35% females in the form of glucose tolerance impairment and in 8–10% of females in the form of diabetes type 2 [31]. Insulin resistance was diagnosed in 40–70% of PCOS females, and it is observed in obese females with visceral obesity phenotype and BMI over 25 kg/m^2 as well as in non-obese females with metabolic phenotype and normal body weight (BMI below 25 kg/m^2) [2, 10, 20, 32]. In these groups, abnormal fat accumulation is noted not only in adipose tissue but also in muscles and liver. Also, increased visceral fat deposit is observed, and this is the reason for insulin resistance [31, 33]. Very often, in this phenotype, in females, non-alcoholic fatty liver is diagnosed, which is accompanied by an increase in the significant cardiometabolic index — the lipid accumulation product index (LAP) — to over 34.5 [34]. About 70% of PCOS females reveal lipid management disturbances in the form of increased triglycerides concentration (> 150.0 mg/dl) and HDL-cholesterol decreased concentration (< 50.0 mg/dl) [34, 35]. In PCOS females, regardless of their obesity, lipogenesis in fatty tissue as well as lipolysis stimulation are disturbed [2, 35–37]. Fatty tissue is resistant to catecholamine-induced lipolysis, and adipocytes in PCOS females, which are stimulated by androgens, show larger sizes and increased production of pro-inflammatory factors. This results in more prominent insulin resistance than is observed in the BMI-matched healthy females [2, 20, 33]. To diagnose insulin resistance, 75 g glucose load test is recommended to determine the insulin level and HOMA-IR index, calculated with the use of the following formula:

HOMA-IR = fasting glucose level (mmol/l) x fasting insulin level (mIU/l) / 22.5.

Normal fasting glucose values are included in the range 3.9–5.5 mmol/l and insulin levels below 25.0 mIU/l [2, 20]. Also, free radical production was observed along with oxidation stress in PCOS women [2]. This set of factors increases the risk of cardiovascular diseases.

Hyperandrogenic phenotype

In this PCOS phenotype, biochemical and clinical hyperandrogenism symptoms are dominant [2, 10, 20, 23, 24]. Similarly to metabolic phenotype, they may be accompanied by fertility impairment, PCOM, and metabolic problems. hyperandrogenism clinical

symptoms do not always occur along with biochemical hyperandrogenism [2, 10, 20–24].

In the case of local treatment-resistant acne or hirsutism, in girls, a blood serum androgen profile is recommended [2, 11, 14, 16, 20]. In about 46% of PCOS females, hyperandrogenism is accompanied by hyperandrogenaemia, i.e. increased serum total testosterone level and FAI over 5.0 [18]. In the case of doubled value of serum total testosterone concentration above normal limits, adrenal or ovary tumour should be excluded. The serum DHEAS estimation is necessary as well as MRI or CT of the abdominal cavity [2, 38]. In the case of normal DHEAS concentration, diagnostics should consider hyperthecosis accompanied by insulin resistance and ovary tumour. In ovarian tumour, increased testosterone concentration is the result of excessive LH stimulation, so in differentiation diagnostics, GnRH agonists can be applied. It should be remembered that in hyperthecosis and in ovarian virilising tumours, hormone secretion is LH-dependent and a visualising examination will be differentiating [2, 38, 39]. In very rare cases, the above concentration of total testosterone can relate to increased concentration of SHBG in blood serum caused by iatrogenic factors (tamoxifen, raloxifene) or hepatic cirrhosis [2]. In these females free testosterone concentration and FAI will stay in normal limits. A slight increase of testosterone level may be of adrenal origin — late-onset 21-hydroxylase deficiency adrenal hyperplasia or Cushing's disease. In differentiating diagnostics, 1 mg overnight dexamethasone suppression test or analogue ACTH stimulation prove effective [2, 20]. In about 20–60% of PCOS females, increased concentration of DHEAS was observed, which denotes the presence of an adrenal component in hormonal disturbance formation. The reason for functional adrenal hyperandrogenism is receptor stimulation for LH that are present in adrenal glands as well as the influence of hyperinsulinaemia on adrenal glands, which is analogous to the effect on ovarian thecal cells. This condition is frequently observed in PCOS women in the menopausal period [40, 41].

Reproductive phenotype

In this phenotype, irregular (rare) menstruation with disturbed ovulation or no ovulation and secondary amenorrhoea are dominant problems. Very often it seems to be primary impairment folliculogenesis problems resulting in infertility. Polycystic ovaries are characteristic for these disturbances. In turn, total testosterone concentration remains within normal limits, and slightly increased FAI value is rarely observed. However, hirsutism or acne are not present, and some cases reveal overweight/obesity [2, 10, 16].

Personalised therapy

In clinical practice, there are cases that cannot be clearly identified in respect of the dominant phenotype. In such cases, the assessment of metabolic disturbances should be a priority. In the case of metabolic phenotype, lifestyle modification is recommended — increased physical activity, reduction diet (1200–1400 kcal for six months in order to reduce body mass) [2, 20]. Body mass reduction by 5–10% significantly influences tissues sensitivity to insulin; however, it cannot be maintained for a long time. It is achieved in 15% of cases only, so pharmacotherapeutic support is necessary [2, 20, 42]. For achievement of long-term effect, metformin application is very important because it reduces glucose production, inhibits glycogenolysis and gluconeogenesis, increases muscular sensitivity to insulin, improves glucose peripheral uptake and consumption, and delays its intestinal absorption [43]. Metformin seems to exert a positive effect upon AGE concentration, visceral fat deposit reduction, and improvement of liver condition in women with non-alcoholic fatty liver [2, 20, 44]. In PCOS females, besides its favourable influence upon carbohydrate management, metformin presents a beneficial impact on lipid management, reducing concentrations of serum total cholesterol, triglycerides, and LDL-cholesterol fraction [2, 16, 20]. However, there are reports that do not reveal any significant changes in the lipid profile after metformin treatment. The majority of studies comprise small groups of patients and short time of treatment [2, 16, 45, 46]. There are no long-term observations of homogenic groups of PCOS females in whom metformin was applied, although it has been used in PCOS therapy since 1994 [2].

Usually, metformin is applied in PCOS patients in doses of 850–1750 mg/daily, and in significantly obese females the dose may be increased to 2500 mg/daily [1, 2, 16, 46, 47]. Apart from its influence on metabolic parameters, metformin modifies hormonal management by increasing oestrogen secretion, decreasing androgen production in ovary and adrenal glands, as well as SHBG production growth [1, 2, 16, 45–47]. While using metformin, in order to avoid possible side effects in the form of dyspeptic symptoms, the therapeutic dose should be reached gradually starting from a dose of 500–700 mg/daily and increasing it every few days. At present, metformin is registered in Poland as a PCOS therapy drug. In the case of PCOS females, metformin is recommended as a first-line treatment with comorbid diabetes and as a drug supporting lifestyle modification with inter-current glucose intolerance, insulin resistance, and/or cardiometabolic disturbances. The therapy results in easier reduction of fatty tissue, BMI drop,

menstruation frequency increase, and sustained patient motivation to carry on with the introduced changes [2, 16, 20, 48, 49]. In PCOS metabolic phenotype with increased clinical hyperandrogenism, positive clinical effects are achieved in metformin administration as the second-line drug in combination with low-dose contraception therapy [2, 16, 50, 51]. Metformin is not the first-line drug in oligo-ovulation, hyperandrogenisation, or infertility in PCOS females.

In recent years, due to the role of insulin resistance and hyperinsulinaemia in PCOS pathogenesis, inositols have been incorporated into the treatment (myo-inositol and D-chiro-inositol) — sugar alcohols engaged in a non-classical way of transmitting the signal by insulin [52]. In PCOS treatment, they are expected to improve sensitivity to insulin and induce ovulation cycle. However, there is no reliable evidence for the efficiency of inositols, hence there is no recommendation for these preparations in PCOS treatment. Analogues of glucagon-like peptide-1 (GLP-1) applied in obesity treatment give promising effects in body-mass reduction. However, high costs restrict the availability of this therapy in Poland. A good effect of metformin and liraglutide combined therapy in PCOS females is observed [2, 53].

In the therapy of PCOS hyperandrogenic phenotype, two-component contraceptive therapy is recommended, preferably with progestogen of anti-androgenous activity [2, 10, 11, 13, 16, 20]. Contraceptive drugs are most often used in the form of pills, patches, or intrauterine devices. It provides the effect of regular menstruation with decreased heaviness, which can be a real problem in girls and young PCOS women. The first biochemical effects are observed after three months of therapy whereas clinical results appear after six months [2, 10, 13, 16, 20]. The oestrogen component of contraceptive pills increases the SHBG concentration and progestogen inhibits LH secretion and 5α-reductase. Additionally, progestogens of strong anti-androgenous activity, e.g. drospirenone or cyproterone acetate, are characteristic for their similar efficacy in clinical and biochemical hyperandrogenism reduction, but they also produce frequent side effects [2, 10, 13, 16, 20]. Usually, the pill oestrogen component is the drug containing 35 μg ethinylestradiol, which reduces hirsutism. The pill containing 20 μg of ethinylestradiol has similar efficacy. Its application is worth considering due to lower risk of metabolic and cardiovascular side effects [2, 10, 12, 13, 20]. Due to their oestrogen component, contraceptive pills are contraindicated in patients with venous thrombosis, migraines, as well as in smokers. Also, in the case of hyperandrogenism, the contraceptive pill is recommended in girls only in pubescence (stage 4–5 of Tanner's scale). In long-term use of levonorgestrel and ethinylestradiol, thrombotic complications are significantly less frequent than in the case of drospirenone and ethinylestradiol application [2, 10, 12, 20]. The goal of monthly bleeding regulation should be achieved with the use of progestogen treatment in the cycle second phase [2, 10, 12, 20]. Anti-androgenous drugs (flutamide) are not registered in PCOS treatment in grown up females or in teenage girls. In the case of very intense hyperandrogenism, in grown up females, cyproterone acetate doses are 50–100 mg for 10 days in a cycle or finasteride 5 mg/daily [2, 10, 20]. In girls, these drugs are contraindicated. However, there were some trials to apply them in very intense hyperandrogenism [12]. Anti-androgenous activity is also characteristic for spironolactone — a potassium saving diuretic that inhibits production of androgens, their binding with hair follicle receptor, and 5α-reductase activity [2, 15, 54]. In adult PCOS females, spironolactone reduces clinical and biochemical hyperandrogenism. Its application side effect, especially in the first days of therapy is tachycardia and low arterial blood pressure. Blood serum potassium check-up are recommended as well as simultaneous incorporation of a contraceptive. The dose for adult females is 100–200 mg/daily in two doses. In teenage girls, the starting dose of 25 mg/daily is suggested [2, 15, 54]. Hirsutism reduction effect can be observed only after six months of spironolactone application. The length of therapy in PCOS women and girls has not been specified yet [13, 15]. The therapeutic schedule in hyperandrogenic phenotype depends on the patient type:

a) pubescence girls — in the case of intense hirsutism — low-dose contraceptive therapy is recommended; in the case of biochemical hyperandrogenism — metformin — is recommended;
b) normal BMI and hirsutism — low-dose contraceptive therapy;
c) obese women with hirsutism — combined therapy: low-dose contraception and metformin;
d) menopausal woman with hirsutism revealing insulin resistance — metformin and anti-androgens,
e) woman with hirsutism and glucose intolerance — combined therapy — low-dose contraception and metformin.

Apart from pharmacological treatment, in women and girls with hirsutism, local cosmetic treatment may be applied. Removal of excessive hair with laser and photo epilation (contraindicated in youngsters) as well as eflornithine (α-difluoromethylornithine) creams are quite effective [2, 10]. Using a laser in teenage patients usually requires parental consent and depends on the rules applied in beauty parlours. Eflornithine chlorexidine, a drug inhibiting ornithine

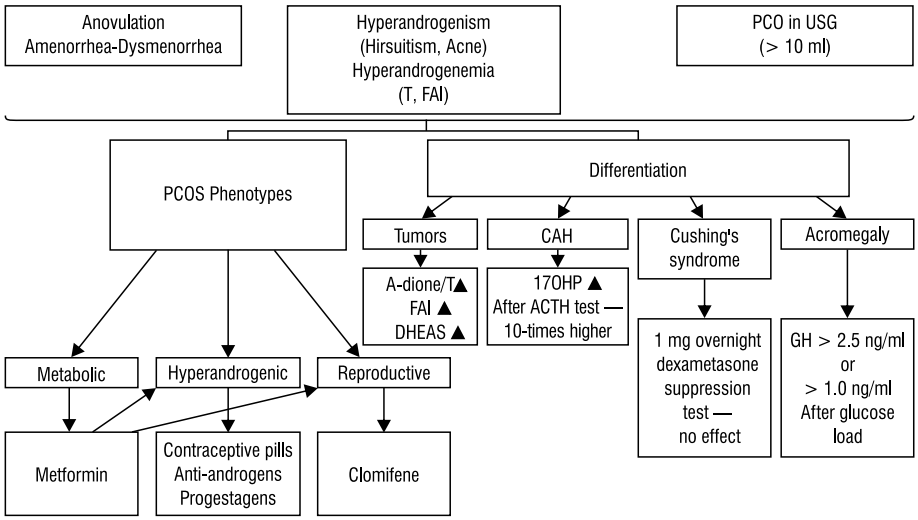

Figure 1. *Diagnostic and therapeutic scheme in PCOS*

decarboxylase in skin, protects from hair growth and proves very effective in moderate hirsutism. However, it is not available in Poland. The effects of treatment are observed in about 75% of patients after 4–8 weeks of treatment [2].

In reproductive phenotype, disturbances or lack of ovulation are presented, and they can be accompanied by hyperandrogenism or PCOM. The goal of therapy is ovulation restoration. In obese women, body mass reduction is recommended by changing the lifestyle and diet, giving up smoking, and supportive therapy application (metformin) [2, 10, 16, 20]. Another step is to induce FSH secretion, which is indispensable for follicle growth. The first-line drug is clomiphene citric acid, which used to be regarded as anti-oestrogenic but now is described as a selective modulator of oestrogen receptor [55]. Physiologically, it reveals antagonistic activity to oestrogen receptor; however, in the case of low concentration of endogenous oestradiol, it reveals agonistic activity. Application of clomiphene citric acid results in reduction in the number of oestrogen receptors both in pituitary gland and in hypothalamus and impairs negative feedback evoked by oestradiol. It results in GnRH secretion and pituitary gland stimulation along with FSH secretion increase, which in turn stimulates follicle growth and maturation [2, 55, 56]. The efficacy of the therapy (ovulation) is estimated at 75–80%, whereas the percentage of pregnancies is 40–60%. The recommended dose amounts to 50–150 mg/daily starting from the 2nd–4th day of the spontaneous or induced cycle (for 5 or even 10 days) for three to a maximum of six months [2, 10, 11, 55, 57]. In cases resistant to clomiphene, ovulation induction can be achieved with the use of exogenous FSH. There is an increased risk of ovary hyperstimulation and multiple gestation in PCOS women [55]. The recommended initiative dose is 37.5–50 IU/daily followed by its gradual increase by 50%, which reduces the risk of hyperstimulation [56]. When clomiphene application fails, letrozole may prove useful. It belongs to the group of reversible competitive inhibitors of aromatase, which block peripheral conversion of testosterone to oestrogens in tissues. Letrozole induces ovaries to produce oestrogens and evokes ovulation. Letrozole is recommended in 2.5–7.5 mg doses daily starting from day 2–3 until day 6–7 of the cycle, which should provoke ovulation on about 14th day of the cycle [58]. In the case of clomiphene citric acid resistance as well as other failures in ovulation induction in the PCOS female algorithm, surgical intervention (ovaries cauterisation) should be considered [59]. Several studies revealed that, as well as a lower percentage of multiple gestation and hyperstimulation syndrome cases, laparoscopic cauterisation is characterised by lower costs than ovulation stimulation with gonadotropins. A diagnostic and therapeutic scheme is presented below including the discussed criteria (Fig. 1).

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