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AN INTEGRATED APPROACH TO POLYCYSTIC OVARY SYNDROME: DIAGNOSIS, PHARMACOLOGICAL TREATMENT AND BEHAVIOURAL INTERVENTIONS

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ABSTRACT

Introduction and Objective: Polycystic ovary syndrome (PCOS) is an endocrine disorder affecting women of all ages. PCOS is one of the most common causes of anovulatory infertility, affecting up to 47% of patients. This work aims to present diagnostic methods, the importance of lifestyle management, and treatment methods in women with PCOS.
Review Methods: A literature review was conducted using the PubMed database to identify relevant articles related to polycystic ovary syndrome (PCOS) using keywords: "Polycystic Ovary Syndrome", "Polycystic Ovary Syndrome/diagnosis", "Polycystic Ovary Syndrome/therapy", "Phenotype", "Infertility", and "Life Style".
Brief description of the state of knowledge: PCOS typically presents with hyperandrogenism, polycystic ovarian morphology, and oligoovulation. It also affects metabolism, body weight, cardiovascular and mental health. Diagnosis is based on the modified Rotterdam criteria, which require two of three conditions: oligo/amenorrhea, hyperandrogenism, or polycystic ovaries, while excluding similar disorders. Treatment should be individualized and address infertility, menstrual disturbances, or androgen-related symptoms. Lifestyle interventions, including diet, regular physical activity, and weight control, are the first-line strategy in PCOS management.
Summary: PCOS requires early diagnosis and individualized treatment tailored to the patient's symptoms and reproductive goals. Lifestyle modifications, including diet and physical activity, play a key role in improving hormonal balance, metabolic health, and fertility outcomes in affected women.

KEYWORDS

Polycystic Ovary Syndrome, Polycystic Ovary Syndrome/Diagnosis, Polycystic Ovary Syndrome/Therapy, Phenotype, Infertility, Life Style

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Introduction.

PCOS, as an endocrinopathy, affects 6-10% of the female population. It is characterized by excess androgens, polycystic ovarian disease, and oligoovulation [1]. The first reports of PCOS appeared in 1935, when Stein and Leventhal observed hirsutism, obesity, amenorrhea, and polycystic ovaries in a group of patients [2]. This syndrome can lead to cardiovascular disease, dyslipidaemia, diabetes, cancers, psychiatric disorders, and infertility [3]. According to the researchers, abdominal obesity in women affected by PCOS may be partly responsible for androgen excess and lack of ovulation, as well as resistance to clomiphene citrate and ovulation stimulation with gonadotropins [4]. Insulin resistance occurs in 50% of women with PCOS, and abnormal phosphorylation of the insulin receptor is probably responsible for its development [5,6]. Studies indicate that the syndrome may be inherited, but it has not been possible to establish a clear mode of inheritance due to methodological difficulties. Risk factors may also include overweight, diabetes, and prenatal factors, including high birth weight in girls born to overweight mothers, congenital virilisation, and low birth weight [3]. The characterisation of the 4 PCOS phenotypes allows specific treatments to be tailored to the symptoms and complaints presented by PCOS patients. A distinction is made between: phenotype 1 (complete) characterised by polycystic ovarian morphology, hyperandrogenism and oligo/anovulation; phenotype 2 (classic) including anovulation and hyperandrogenism; phenotype 3 (ovulatory) including polycystic ovarian morphology and hyperandrogenism; phenotype 4 (non-androgenic) with polycystic ovarian pattern and anovulation [7].

Objective

This review aims to synthesize current knowledge on PCOS, with a particular focus on its diagnostic methods, lifestyle management, and available treatment options for clinical symptoms and infertility in women with PCOS.

Methodology

This literature review was conducted using the PubMed database to identify relevant and up-to-date scientific publications on polycystic ovary syndrome (PCOS). The search included the following keywords: “Polycystic Ovary Syndrome”, “Polycystic Ovary Syndrome/diagnosis”, “Polycystic Ovary Syndrome/therapy”, “Phenotype”, “Infertility”, and “Life Style”. Boolean operators (AND, OR) were applied to combine search terms and refine results.

Discussion

Diagnosis

The key to relieving PCOS symptoms and preventing complications is early diagnosis. The doctor can make a preliminary diagnosis based on the symptoms reported by the patient (such as hyperandrogenism, menstrual irregularities) and the image of polycystic ovaries on ultrasound. The first criteria for diagnosing PCOS were created in 1990 by the National Institute of Child Health and Human Development. To make a diagnosis, both criteria must be met: chronic anovulation, clinical and/or biochemical signs of hyperandrogenism, and other pathologies that may resemble PCOS must be excluded [8]. In 2003, in Rotterdam, the Netherlands, scientists from the European Society of Human Reproduction (ESHRE) and the American Society for Reproductive Medicine (ASRM) attempted to create new diagnostic criteria known as the "Rotterdam criteria". They require 2 of 3 criteria: oligomenorrhea/amenorrhea, hyperandrogenism, and polycystic ovarian morphology on ultrasound, and exclusion of other aetiologies [8,9,10]. The Androgen Excess Society (AES) established criteria in 2006, emphasizing the role of hyperandrogenism in the diagnosis of PCOS. To make the diagnosis, the criteria had to be met: hirsutism and/or biochemical hyperandrogenism, oligo/anovulation and/or polycystic-appearing ovarian morphology (PCOM) [8].

Currently, to diagnose PCOS in adults, two of the following criteria are required (Modified Rotterdam Criteria): oligo/anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries on ultrasound. At the same time, other disorders that may simulate PCOS must be excluded. The diagnosis of oligo/anovulation requires ovulatory cycles >35 days or the presence of <8 menstrual periods per year. In a patient with strongly suspected PCOS with regular menstrual cycles or an unclear menstrual pattern, serum progesterone measurement is used to assess ovulation. Biochemical hyperandrogenism is diagnosed by finding elevated levels of total testosterone, free testosterone or a calculated free testosterone index. In the case of normal total and free testosterone results, androstenedione and dehydroepiandrosterone sulfate (DHEAS) levels may be considered. Clinical hyperandrogenism is assessed using the modified Ferriman-Gallwey scale (cut-off from ≥4 to ≥8 depending on the population). PCOM can be diagnosed when there are ≥20 follicles

per ovary and/or an ovarian volume of ≥10 cm3 per ovary on transvaginal ultrasound using a transducer frequency of 8 MHz or higher [8]. In adults, serum anti-müllerian hormone (AMH) levels can also be used, but it is important to remember that their levels depend on age, weight, contraceptive use, ovarian procedures, and the day of the menstrual cycle [11]. An ultrasound examination is not necessary to make the diagnosis in cases where oligo/anovulation and hyperandrogenism coexist. In adolescents, both oligo-ovulation and hyperandrogenism are required, although ultrasound is not recommended for diagnosis [8,12]. According to the most recent recommendations, all women with PCOS should have an assessment of cardiovascular risk factors, obstructive sleep apnoea, depression, anxiety disorders, and have their glycaemia determined by performing an oral glucose load test (OGTT) with 75 g glucose. In case of difficulty performing an OGTT, fasting glucose and/or glycated haemoglobin (HbA1c) determination may be considered [11].

Lifestyle management

The cornerstone of PCOS treatment is lifestyle management, including diet, exercise, and achieving a healthy body weight. These should be followed both before and during drug treatment [13]. A systematic review comparing the effects of lifestyle modification (LSM) and metformin in people with PCOS revealed that LSM and metformin had similar efficacy in improving menstrual regularity and pregnancy outcomes. Serum testosterone level was the only factor for which metformin proved superior to LSM. The combination of LSM and metformin appears to have the most beneficial effect on fasting serum insulin levels, while there is no expected effect on lowering BMI [14]. A study comparing the effects of lifestyle modification with pharmacological treatment (metformin, clomiphene citrate, metformin + clomiphene citrate) showed that favourable hormonal parameters (testosterone, SHBG, serum insulin) were significantly improved in the lifestyle modification group compared with pharmacological treatment [15]. Lifestyle changes may also affect the sexual aspects of the lives of people with PCOS. A study by Weiss et al. found that intensive LSM alone, as well as in combination with oral contraceptive pills, significantly improved sexual function (increased FSFI score) and reduced sexual stress (lower FSDS-R scores) [16]. A study in a mouse model of PCOS showed that the balance of macronutrients in the diet can affect reproduction. In the mouse model, a diet low in protein and medium in carbohydrate and fat improved ovulatory dysfunction [17]. According to the recommendations, none diet is superior, so balanced diets tailored to individual needs, in line with population guidelines, are recommended. The first line of treatment for PCOS is weight reduction in those with a body mass index (BMI) of ≥25 and weight maintenance in those with a BMI of <25 through a reduced calorie intake and exercise. It is emphasised that the superior role of limiting caloric intake over changing the ratio of specific macronutrients. In addition, a psychological aspect should also be considered to ensure adherence to lifestyle changes [13]. Physical activity in people with PCOS affects weight reduction and the regulation of many organs and systems. By increasing insulin sensitivity, it lowers blood sugar levels and the risk of type 2 diabetes, and by lowering total cholesterol and LDL cholesterol, it reduces the risk of cardiovascular disease and Non-Alcoholic Fatty Liver Disease (NAFDL). It also reduces oxidative stress, regulates menstrual cycles, restores ovulation, improves the LF/FSH ratio, lowers testosterone levels and the free androgen index (FAI) [18]. International guidelines for the management of PCOS have not demonstrated an advantage of one form of physical activity over another. Any activity using population-based physical activity guidelines positively affects health, so balanced physical activity tailored to personal preferences and abilities is recommended. For adults (18-64 years), physical activity should be at least 250 minutes per week of moderate-intensity exercise or 150 minutes per week of high-intensity exercise and muscle-strengthening exercises at least 2 days per week (not consecutive) to achieve a moderate body weight and prevent weight gain. For adolescents, at least 60 minutes of moderate to high-intensity physical activity at least three times a week is recommended [11].

Treatment

PCOS affects many aspects of patients' lives, including metabolism, mental health, physical appearance, fertility or general health. Therefore, the choice of treatment should be individually tailored to the patient's needs and problems, taking into account their procreative plans.

Main medications and treatments used in PCOS:

- Oral Contraceptive Pills (OCPs)
- Clomiphene citrate
- Aromatase inhibitors
- Gonadotropins

- Laparoscopic Ovarian Diathermy
- In Vitro Fertilization or In Vitro Maturation
- Metformin
- Myoinositol
- Anti-androgens
- Hair Removal Methods (Electrolysis, Photoepilation, Eflornithine hydrochloride)

The primary treatment for women who have no plans to conceive are oral contraceptive pills. They alleviate the symptoms of hyperandrogenism, provide contraception, and regulate the menstrual cycle. The oestrogen component increases the concentration of sex hormone binding globulin (SHBG), which has the effect of lowering the concentration of free androgens. In the meantime, the progestogen component is responsible for preventing endometrial hyperplasia [19]. The specific composition of the preparations has not been determined, but low doses (<50 μg) are preferred. Attention should also be paid to the degree of androgenicity of the progestogens used in OCPs, choosing those with low androgenicity (such as noretyndrone, desogestrel, norgestimate) or with anti-androgenic effects (cyproterone acetate (CPA), drospirenone, dienogest) [19,20]. According to systematic reviews, drospirenone and CPA show comparable efficacy in improving clinical and hormonal parameters, as well as lipid and insulin metabolism in women with PCOS [21]. In the fight against hirsutism, OCPs containing drospirenone seem to be highly effective and reduce excessive hair in just 6 cycles of use, but according to the guidelines, the various OCPs formulations used in PCOS show similar efficacy against excessive hair [12,22]. Based on the findings of World Health Organisation guidelines, preparations containing 35 μg of oestrogen in combination with cyproterone (CPA) should only be considered as second-line therapy in cases of severe forms of acne or hirsutism [23].

A serious problem for those struggling with PCOS is infertility, often resulting from a lack of ovulation. In such cases, ovulation-inducing drugs are used, among which clomiphene citrate (CC) is the drug of first choice. It is an oestrogen receptor modulator that acts as an agonist and antagonist. Its anti-estrogenic action in the hypothalamus and pituitary gland blocks the negative feedback mechanism. It affects the increased secretion of pulsatile gonadotropin-releasing hormone (GnRH) from the hypothalamus, followed by endogenous gonadotropins from the pituitary gland, leading to follicular growth [24,25]. Treatment is started on the second day of the cycle at a dose of 50 mg/day for 5 days, and the dose can be increased if there is no response in two cycles. If there is no treatment effect at 100 mg/day, a change of treatment should be considered. Side effects include visual disturbances, hot flashes, breast tenderness, dizziness, and nausea [26]. The use of CC is associated with an 11% risk of multiple pregnancy, so ovarian response to treatment should be monitored by ultrasound during therapy [26,27].

A drug for women who do not respond to ovulation induction with CC or are resistant to CC is letrozole, which belongs to the aromatase inhibitors [26]. It binds reversibly to the aromatase enzyme, resulting in a decrease in estrogen levels. This leads to increased secretion of folliculotropic hormone (FSH) by the pituitary gland and stimulation of ovulation [28]. Letrozole has a higher pregnancy rate, shorter time to attempt conception, and a lower risk of multiple pregnancies compared with CC [29,30]. Side effects include gastrointestinal distress, weakness, hot flashes, headache, and back pain [26]. In the Legro et al. study, treatment was started at a dose of 2.5 mg/day, which was increased by 2.5 mg if there was no response, with a maximum dose of 7.5 mg/day, resulting in a cumulative ovulation rate of 61.7% [31].

The next-line treatment for women refractory to CC or in whom treatment has proved ineffective and who experience a lack of ovulation in the absence of other causes of infertility is gonadotropin therapy. They can also be used as a first-line treatment for lack of ovulation, provided ultrasound monitoring of ovulation stimulation is carried out [12]. To avoid ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies, low-dose stepwise treatment regimens are recommended, starting with a dose of 50-75 IU [26,32]. In addition, no significant differences between gonadotropin preparations have been shown, so the most cost-effective preparation is recommended [26,33]. During therapy, ultrasound monitoring of the number of growing follicles should be performed, and if three or more follicles greater than 14 mm in diameter are present, hCG should not be given [26].

Laparoscopic ovarian diathermy (ovarian drilling) is an alternative treatment method for women refractory to CC. The method involves stressing multiple channels in the surface and lining of the ovary using monopolar or bipolar electrocoagulation or a laser. Due to the risk of peri-ovarian adhesions, it is recommended to perform as few openings as possible, 4 points of diathermy using 40 W power is preferred [34,35]. However, due to the invasive nature of the procedure, it should be performed in cases where there are also other

indications for laparoscopy. The advantages of this method of treatment are the lower risk of multiple pregnancy and OHSS, as well as the lack of need to monitor follicular development with ultrasound [34,35,36,37]. The effect of treatment is to reduce LH and testosterone levels, especially in patients with initially high LH levels [35]. In a study by Debras et al. pregnancy following laparoscopic ovarian diathermy was achieved in at least 47.4% of patients. The average time to natural childbirth is 4.5 months after ovarian drilling. Factors that increase the chances of proving the peak of therapy are: BMI <25 kg/m², a period of infertility of less than three years, age less than 35 years, and number of antral follicles less than 50 [38].

If ovulation stimulation fails or there are other causes of infertility, the third line of treatment is IVF (in vitro fertilisation) or IVM (in vitro maturation). IVF in patients with PCOS is associated with a higher risk of OHSS. Factors that increase the risk of this complication include a high number of antral follicles, while baseline serum E2 levels correlate strongly with the severity of OHSS [39]. To reduce the risk of OHSS, a GnRH antagonist protocol is recommended, which is safer compared to GnRH agonist protocols [26,40]. In addition, lifestyle changes, weight loss, and inositol supplementation appear to increase the chance of pregnancy and reduce the risk of OHSS [41]. Due to the lower risk of OHSS, IVM is an alternative to IVF for patients with PCOS. In this case, a short gonadotropin stimulation protocol is used, without the hCG trigger [42].

Metformin is used to treat metabolic disorders in PCOS. Through its action, it sensitises tissues to insulin, lowering insulin levels. In addition, it has a beneficial effect on lowering testosterone levels [12,43,44]. RCTs have shown the effect of metformin in increasing pregnancy and ovulation rates, as well as menstrual frequency in women with PCOS, regardless of BMI [45]. In women with PCOS refractory to CC, it was shown that the use of 2x850 mg daily metformin for 8 weeks before ovulation induction with gonadotropins allowed lower doses of gonadotropins with better pregnancy outcomes. In addition, the risk of multiple pregnancy and ovarian hyperstimulation was lower [46]. Studies comparing the efficacy of metformin and myo-inositol showed no significant differences. Both drugs were shown to reduce BMI, improve insulin sensitivity, and regulate menstrual cycles. However, their effects on hirsutism and acne have not been observed [47]. Metformin can be used in infertile women with anovulation without other risk factors, if CC and letrozole are not possible, to improve ovulation rates and increase the chances of pregnancy [26]. The combination of metformin and physical activity in women with PCOS helps to lower BMI, reduce subcutaneous fat, and regulate menstruation [44].

Inositol is a newer insulin sensitizer and belongs to the B vitamin family. In patients with PCOS, it has positive effects on menstrual cycle regulation (normalises cycle length), carbohydrate metabolism, and symptoms of hyperandrogenism (reduces serum total and free testosterone, androstenedione, and increases SHBG levels) [48]. There are nine stereoisomers, of which myo-inositol (MI) and D-chiro-inositol (DCI) are mainly used in PCOS. The two compounds, despite belonging to the same group, play different roles in the body. MI is involved in cellular glucose uptake by stimulating GLUT-4 transporter translocation to the cell membrane and is involved in FSH signalling in the ovaries. On the other hand, DCI is responsible for glycogen synthesis and contributes to the reduction of circulating androgens, improving insulin sensitivity. The interaction of the two compounds allows the reduction of LH and testosterone levels and the improvement of the LH/FSH ratio [49]. Both inositol isomers show no advantage over metformin in reducing hyperandrogenism, improving glucose metabolism, and pregnancy rates, but cause fewer side effects than metformin [48]. For inositol treatment to be effective, its isomers must be used in the right proportions. To restore ovulation and improve other symptoms of PCOS, a 40:1 MI/DCI ratio is recommended [49].

Anti-androgens (finasteride, flutamide, cyproterone acetate, spironolactone) are an option for the treatment of hirsutism in patients with PCOS. They act by inhibiting 5α-reductase activity, competing for intracellular androgen receptors in target tissues, or by inhibiting androgen synthesis by the ovaries and adrenal glands [50]. All anti-androgens can cause feminisation of male foetuses if the patient becomes pregnant, so contraception is mandatory [49]. Spironolactone, an aldosterone antagonist and androgen receptor inhibitor, can also inhibit 5α-reductase. To achieve the desired effect in the treatment of hirsutism, a dose of 100 to 200 mg/day should be used [50]. It can cause fatigue, orthostatic hypotension, dizziness, and the use of high doses alone causes irregular menstrual cycles [20]. The addition of OC allows for a better effect, preventing irregular menstrual cycles and providing contraception [50]. Finasteride (inhibits dihydrotestosterone production) has a low risk of side effects, but is equally or less effective against hirsutism than spironolactone [20]. Flutamide is a non-steroidal selective anti-androgen without progestogen or anti-gonadotropic effects. It can cause irregular menstruation, and doses of 750 to 1,500 mg daily can be significantly toxic to the liver [50]. CPA is a progestogen antiandrogen well tolerated by female patients; however, asthenia, loss of libido, mastalgia, headache, and nausea may occur. In addition, in high doses, it may affect adrenal function. The addition of ethinylestradiol to treatment is highly effective in the treatment of hirsutism and acne [20,50].

Cosmetic interventions have also found their way into treatment to combat excessive hair. These include electrolysis, approved by the FDA as a treatment for hirsutism. This method can be used for any hair colour, but has the disadvantages of being painful and costly. The second method is photoepilation, which uses light to destroy hair follicles. Despite its high cost, it is quicker and less painful than other methods. Topical treatment uses eflornithine hydrochloride to reduce excessive facial hair by reducing the rate of hair growth. It can be used in combination with laser treatment [49].

Conclusions

Polycystic ovary syndrome is a common endocrine-metabolic disorder, already manifesting itself in young women and affecting many organ systems. Infertility, which occurs in a significant proportion of patients, is one of the main reasons for patients presenting to their doctor. Early diagnosis, using the Rotterdam Criteria, taking into account the patient's symptoms, ultrasound image, and laboratory tests, plays a key role in the fight against PCOS. Treatment, started as soon as possible after diagnosis, should be tailored to the symptoms presented by the patient and to her reproductive plans. Diseases and disorders coexisting with PCOS, such as insulin resistance or lipid disorders, should also be taken into account. Individualised treatment can improve metabolic disorders, menstrual disorders, as well as infertility, and the first intervention should be lifestyle management. Women should be encouraged to be physically active, follow a diet, and restore a normal body weight, thus improving hormonal and metabolic parameters, restoring ovulation, and regulating menstrual cycles.

Disclosure

Author's contribution Statement: Conceptualization: Aleksandra Dzwonkowska; Methodology: Aleksandra Dzwonkowska, Paulina Redel; Software: Aleksandra Dzwonkowska, Paulina Redel; Check: Aleksandra Dzwonkowska, Paulina Redel; Formal analysis: Aleksandra Dzwonkowska, Paulina Redel; Investigation: Aleksandra Dzwonkowska, Paulina Redel; Resources: Aleksandra Dzwonkowska, Paulina Redel; Data curation: Paulina Redel, Writing - rough preparation: Aleksandra Dzwonkowska; Writing - review and editing: Aleksandra Dzwonkowska, Paulina Redel; Visualization: Paulina Redel; Supervision: Aleksandra Dzwonkowska, Paulina Redel; Project administration: Aleksandra Dzwonkowska.

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