



Reimbursement of metformin for polycystic ovary syndrome

Metformina w zespole wielotorbielowatych jajników

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Abstract

The latest list of reimbursed medicines includes, as a new addition, metformin for the treatment of polycystic ovary syndrome (PCOS), which is extremely important for practicing physicians. While this paper briefly summarises the current state of knowledge on PCOS, its main aim is to remind the reader about the effectiveness of metformin in women with PCOS in controlling glycaemia, increasing tissue sensitivity to insulin and affecting endothelial function, vascular inflammation, lipid profile and other risk factors of atherosclerosis, which suggests its cardioprotective effects. The paper also discusses the clinical effect of metformin relative to hyperandrogenism, menstrual cycle disorders and ovulation induction. The paper concludes with an algorithm for the diagnosis and management of PCOS. (*Endokrynol Pol* 2013; 64 (5): 409–414)

Key words: PCOS, metabolic abnormalities, metformin

Streszczenie

Ostatnia lista leków refundowanych uwzględniła po raz pierwszy metforminę w terapii choroby wielotorbielowatych jajników (PCOS), co jest niezwykle istotne dla lekarzy praktyków. W artykule skrótoowo podsumowano stan wiedzy na temat PCOS. Jednak głównym jego przesłaniem było przypomnienie efektywności terapii metforminą u kobiet z PCOS w kontroli glikemii, zwiększeniu wrażliwości tkanek na insulinę, wpływie na czynność śródbłonka, proces zapalny w naczyniach, profil lipidowy oraz inne czynniki ryzyka miażdżycy, co świadczy o jej działaniu kardioprotekcyjnym. Ponadto omówiono efekt kliniczny odnośnie hiperandrogenizmu, zaburzeń cyklu miesięczkowego oraz indukcji owulacji. Podsumowaniem artykułu jest zaprezentowanie schematu postępowania diagnostyczno-terapeutycznego PCOS. (*Endokrynol Pol* 2013; 64 (5): 409–414)

Słowa kluczowe: PCOS, zaburzenia metaboliczne, metformina

The latest list of reimbursed medicines has been a pleasant surprise: it now includes metformin when prescribed off-label to patients with prediabetes but also, importantly, when prescribed off-label to patients with PCOS. We finally have legal grounds for prescribing reimbursed metformin to women with PCOS, which was previously not possible, so we now have the green light.

I will now try to remind you why this is all so important and provide you with some new facts about the old, safe and inexpensive treatment with this medicine.

PCOS is one of the most common endocrinopathies in women of reproductive age. Its prevalence is estimated at about 6–10%, or even 15% when the diagnosis is based on the Rotterdam criteria [1]. Three sets of diagnostic criteria for PCOS currently exist. The first, proposed by the National Institutes of Health (NIH), combines menstruation disorders and chronic anovulation with hyperandrogenism [2]. According to the Rotterdam criteria, the diagnosis of PCOS may be

made if any two out of the following three abnormalities are present: 1) chronic anovulation; 2) clinical and/or biochemical hyperandrogenism; and 3) polycystic ovaries on pelvic ultrasound [3]. According to the criteria most recently proposed by the Androgen Excess and PCOS Society, the diagnosis of PCOS requires both the presence of clinical and/or biochemical signs of hyperandrogenism and the presence of menstruation disorders with chronic anovulation or a characteristic sonographic morphology of the ovaries [4]. Each set of the diagnostic criteria of PCOS additionally requires exclusion of other causes of hyperandrogenism, such as: congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting tumours, hyperprolactinaemia, acromegaly, and thyroid diseases (Fig. 1).

Considerable controversy surrounds the definition of PCOS and the diagnosis of PCOS and of its main components. There is no single diagnostic criterion for this syndrome. There is no straightforward relationship between the severity of clinical and biochemical signs



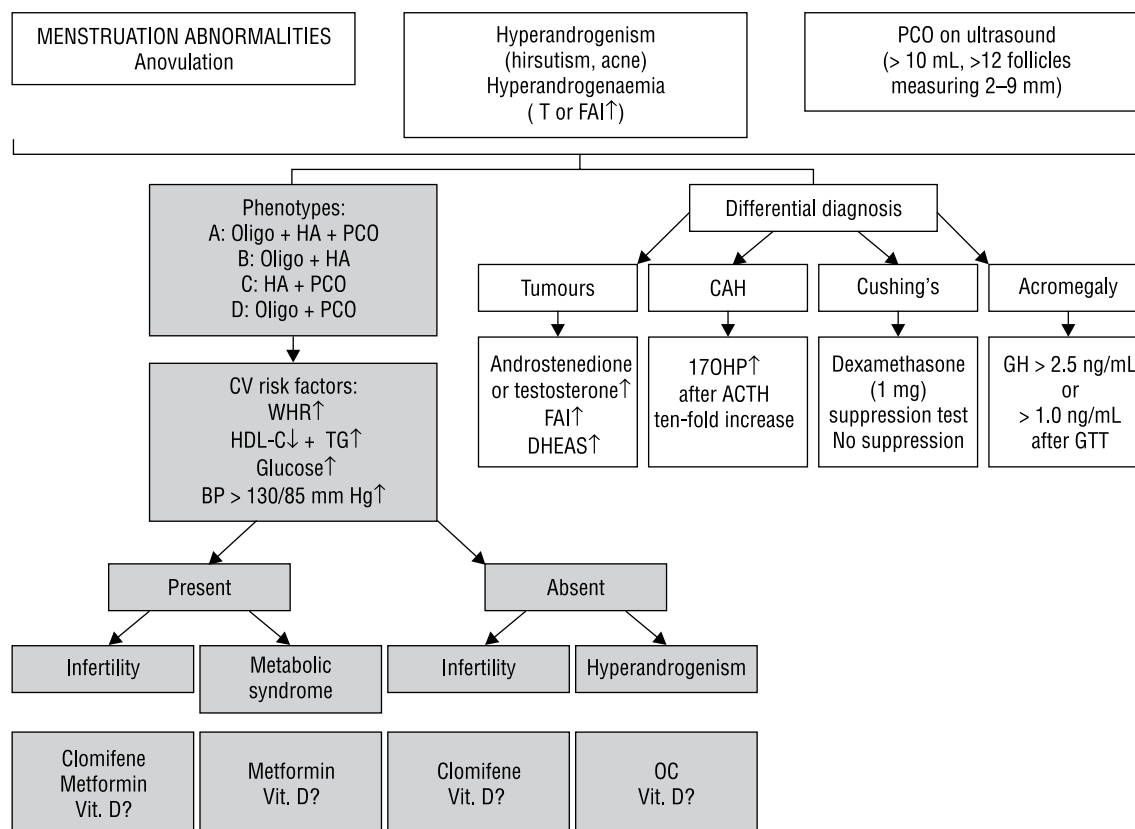


Figure 1. An algorithm for the diagnosis and management of PCOS

Rycina 1. Schemat postępowania diagnostyczno-terapeutycznego w PCOS

of hyperandrogenism. The clinical signs of hyperandrogenism, particularly hirsutism, are believed to be more useful in the diagnosis of PCOS than hyperandrogenaemia. On the other hand, hirsutism may be absent in women with elevated androgen levels, such as in Asian women, which is most likely due to ethnic factors. In addition, polycystic ovaries are found only in 50% of hirsute women [5]. Measurement of free testosterone levels is recommended to demonstrate hyperandrogenaemia. Assessment of total testosterone levels may not be sufficient, as they are within the reference range in about 14% of women with PCOS [5]. If free testosterone cannot be determined, the free androgen index (FAI) may be used. The FAI is a ratio of total testosterone level in nmol/l to sex hormone binding globulin (SHBG) level in nmol/l multiplied by 100%.

The very definition of chronic anovulation is controversial. It is believed that fewer than 6–8 menstruations per year is an indicator of chronic anovulation. 43% of women with PCOS suffer from oligomenorrhoea (where the duration of menstrual cycles ranges from 35 to 199 days), 21% from secondary amenorrhoea (where the duration of menstrual cycles exceeds 199 days), and 7% from primary amenorrhoea [1–6]. It should, however, be noted that up to 32% of women ovulate spon-

taneously despite PCOS [6]. Sonographic diagnosis of polycystic ovaries requires the demonstration, in one or both ovaries, of 12 or more peripherally located follicles measuring 2 to 9 mm in diameter or an ovarian volume of more than 10 cm³. If a follicle measuring more than 10 mm in diameter is identified, the ultrasound scan needs to be repeated. It should be noted that about 30% of women with normal menstruation and with normal androgen levels may have polycystic ovaries, in which case the diagnosis of PCOS is not warranted.

The pathogenesis of PCOS has not been completely elucidated and is multifactorial, with genetic and environmental factors being implicated. Those genes thought to be involved in the pathogenesis of PCOS include genes associated with steroidogenesis, regulation of gonadotropin secretion, effects of insulin, obesity, factors regulating the body's energy expenditure, and genes associated with chronic inflammation [7]. A primary defect in the synthesis and metabolism of androgens in the ovaries resulting in an increased secretion of these hormones by the gonads is believed to be responsible for the development of PCOS. Neuroendocrine abnormalities leading to an increased secretion of luteinising hormone (LH) are also observed.

Numerous studies have demonstrated a pathogenetic association of PCOS with insulin resistance and hyperinsulinaemia. Insulin resistance is thought to be caused by defects in the insulin receptor and post-receptor components of the insulin signalling pathway. According to Dunaif et al., in about 50% of patients with PCOS, insulin receptor autophosphorylation is impaired [8]. Phosphorylation of serine residues of this receptor interferes with its function and with downstream signalling. Phosphorylation of insulin receptor substrate 1 (IRS-1), stimulated by tumour necrosis factor alpha (TNF- α) and leading to decreased activity of tyrosine kinase, may also play a role here [9]. Phosphorylation of serine residues may occur in cytochrome P450c17 and lead to increased activity of 17,20-lyase and 17 α -hydroxylase. Free fatty acids and proinflammatory cytokines are believed to cause excessive phosphorylation of serine residues in the insulin receptor and cytochrome P450c17 resulting in insulin resistance and hyperandrogenism in PCOS [10]. Vitamin D deficiency and polymorphisms of vitamin D receptor genes (*Cdx2*, *BsmI*, *FokI*, *Apal* and *TaqI*) have recently been implicated in the aetiology of the metabolic abnormalities in PCOS [11].

Insulin resistance in PCOS is mainly evident in the metabolic effects of insulin. Hyperinsulinaemia secondary to insulin resistance leads to an increased ovarian response to gonadotropins that is mainly manifested by overexpression of LH and IGF-1 receptors [12, 13]. Insulin increases the sensitivity of immature granulosa cells to LH, proliferation of thecal cells and the activity of enzymes required for androgen synthesis: 3 β -hydroxysteroid dehydrogenase, 17 α -hydroxylase, and 17,20-lyase [14–18]. Another mechanism whereby insulin resistance causes hyperandrogenaemia involves reduced synthesis of SHBG, which results in increases in the bioavailability of testosterone to peripheral tissues [19]. Hyperinsulinaemia may also increase the activity of the hypothalamic-pituitary-adrenal axis and, as a result, the secretion of androgens by the adrenal glands [20].

According to various studies, up to 70% of women with PCOS are resistant to insulin, with about 50% of them being obese [10, 21]. Insulin resistance and obesity are also associated with a number of other metabolic abnormalities observed in PCOS. The prevalence of metabolic syndrome is 2–4 times higher compared to healthy controls [22, 23]. Abnormalities of carbohydrate metabolism observed in women with PCOS include an increased frequency of impaired glucose tolerance and of type 2 diabetes mellitus compared to controls matched for age and body mass index (BMI) [24]. Women with PCOS are also at a ten-fold higher risk of gestational diabetes than women in the general

population [25]. Studies investigating metabolic abnormalities in PCOS have shown that the affected women have abnormalities of lipid metabolism manifested by decreased HDL-cholesterol levels and increased LDL-cholesterol and triglyceride levels [10]. Vascular wall abnormalities, such as an increased intima-media thickness [26] or the presence of calcium deposits in arterial walls, both indicative of an increased cardiovascular risk, have also been reported in patients with PCOS. The presence of endothelial dysfunction, an early marker of ischaemic heart disease in patients with PCOS, has been demonstrated in studies investigating abnormalities of vascular dilation relative to blood flow (flow-mediated dilation, FMD) [28, 29]. FMD has been shown to correlate positively with the insulin resistance index HOMA and negatively with the insulin sensitivity index QUICKI. There have also been reports of elevated levels of chronic inflammation markers, prothrombotic factors and factors associated with oxidative stress, such as: C-reactive protein, homocysteine, paraoxonase-1, fibrinogen, plasminogen activator inhibitor-1 (PAI-1), interleukin-6, TNF- α , and nucleic factor kappa-B (NF- κ B) [30–37].

In conclusion, patients with PCOS have multiple cardiometabolic risk factors: obesity, insulin resistance, atherogenic lipid abnormalities, elevated levels of chronic inflammation markers and elevated levels of fibrinolysis markers. In order to prevent premature atherosclerosis, cardiovascular disease and type 2 diabetes mellitus in PCOS it is therefore necessary to treat these risk factors. Non-pharmacological interventions, namely lifestyle modifications and increased physical activity, should be at the forefront. However, these interventions may not always be effective if employed alone. A recent metaanalysis has shown that while lifestyle modifications can reduce body mass, total testosterone levels, fasting insulin levels, hirsutism as assessed using the Ferriman-Gallwey score, and the waist-to-hip ratio (WHR), they do not affect BMI, SHBG levels, FAI, fasting glucose levels or lipid profile [24].

An important role in the management of many aspects of PCOS, particularly in the management of the metabolic abnormalities in the course of the disease, is therefore played by pharmacological treatment, particularly by treatment with drugs that increase insulin sensitivity, with metformin being the most important one.

Metformin belongs to the biguanide class of drugs. Although it has been available for more than 50 years, it continues to be widely used in clinical practice and its indications are expanding. The principal effect of metformin is to decrease insulin resistance. In addition, metformin exerts a pleiotropic protective effect on the cardiovascular system, which effect cannot be solely

explained by improved glucose levels. Metformin decreases hepatic synthesis of glucose (gluconeogenesis), decreases absorption of glucose from the intestines and increases peripheral uptake and metabolism of glucose. An important effect of metformin at the cellular level is to increase the activity of the enzyme AMP kinase, which plays a crucial role in the regulation of carbohydrate and lipid metabolism [38]. AMP kinase affects, among other processes, the function of the glucose transporter GLUT4 and free fatty acid oxidation, which may result in decreased lipolysis in adipocytes [39].

Despite previously published reports of body mass reduction in patients treated with metformin, recent metaanalyses have not confirmed weight-reducing efficacy of metformin [40, 41]. Metformin seems to have a neutral effect on body mass, although it may cause redistribution of fat from the active visceral adipose tissue to the metabolically inactive subcutaneous fat [42]. Metformin treatment beneficially affects lipid profile by decreasing total cholesterol, LDL-cholesterol and triglyceride both in patients with type 2 diabetes mellitus and in non-diabetic patients [41, 43]. Numerous studies have shown beneficial antiatherosclerotic effects of metformin, such as improved endothelium-dependent vasodilation [44], decreased levels of endothelial activation markers, sVCAM-1 and E-selectin, decreased levels of PAI-1 [45], decreased levels of CRP [46], suppressed monocyte adhesion to cultured vascular wall cells and suppressed monocyte conversion to foam cells [47]. Metformin may also exert an antioxidant effect by decreasing the formation of advanced glycation end-products (AGE) [48].

There is also evidence of beneficial effects of metformin in non-alcoholic fatty liver. An improvement in liver function tests (decrease in liver aminotransferase levels), a decrease in liver fat and an increase in insulin sensitivity have been shown in patients with non-alcoholic fatty liver treated with metformin [49]. Another potential action of insulin is its antitumour effect. Observational studies have shown a reduction of cancer-related mortality in patients with type 2 diabetes mellitus treated with metformin [50].

Metformin is used in the treatment of many components of PCOS, with type 2 diabetes mellitus, impaired glucose tolerance and insulin resistance being the principal indications. Numerous publications have also reported positive effects of metformin on other cardiometabolic risk factors present in PCOS. These effects include improved endothelial function [51, 52], improved levels of inflammation markers [52, 53] and improved coronary reserve [54]. A metaanalysis has shown a decrease in LDL-cholesterol levels in patients with PCOS treated with metformin [41] and an observational study has revealed a dose-dependent (1,500

mg vs 2,550 mg) body mass reduction in women with this condition [55].

Although a reduction in androgen levels by metformin has been reported in several studies [56, 57], this biguanide is not very effective in reducing the severity of hirsutism in PCOS. Most studies have shown no evidence of hirsutism-reducing activity of metformin [58, 59], which is why this drug is not used in the management of hyperandrogenism. The principal role in the treatment of menstruation disorders is played by oral contraceptives. The possible contraindications to oral contraceptives in women with PCOS should, however, be borne in mind. These agents may further exacerbate insulin resistance and increase cardiovascular and thrombotic risk, which is why it is beneficial to combine them with metformin. However, according to recent studies, oral contraceptives do not increase metabolic risk in women with PCOS [57].

The reported percentage of women in whom metformin regulates their menstrual cycle varies between 23% and 90%, while the results of studies investigating the impact of this drug on ovulation and pregnancy rates remain inconclusive. According to some studies, metformin increases ovulation and pregnancy rates from 5% to 18%, while according to other studies, similar effects may be obtained by lifestyle modifications and weight reduction [60]. A Cochrane review has shown that metformin treatment may result in a four-fold increase in the ovulation rate and a three-fold increase in the pregnancy rate versus placebo or no treatment, although these results did not reach statistical significance [58]. According to the most recent consensus statements, the addition of metformin to clomifene in the treatment of infertility in women with PCOS results in no evident benefit [61]. An important issue in PCOS is the increased risk of miscarriage of up to 30–50% in women with this condition. During pregnancy, the levels of glyodelin and IGFBP-1 fall, and these abnormalities are worsened by hyperinsulinaemia. By stimulating glyodelin secretion, metformin may reduce the incidence of early miscarriage in women with PCOS [62, 63].

Metformin treatment in patients with PCOS not only improves glycaemic control and tissue sensitivity to insulin but also — as a result of its effects on endothelial function, vascular inflammation, lipid profile and other risk factors of atherosclerosis — exerts cardioprotective effects and may reduce cardiovascular risk. Patients with PCOS are a heterogenous group in terms of phenotypes distinguished on the basis of specific clinical presentations necessary for the diagnosis. This classification distinguishes the 'classic' phenotype in which all the three criteria required for diagnosis are present (oligomenorrhoea, hyperandrogenism and polycystic

ovaries [phenotype A]) and three other phenotypes which are combinations of two of the criteria required for diagnosis (oligomenorrhoea and hyperandrogenism [phenotype B]; hyperandrogenism and polycystic ovaries [phenotype C]; oligomenorrhoea and polycystic ovaries [phenotype D]). Taking this classification into consideration, the most common metabolic abnormalities were observed in the 'classic' phenotype [21].

Figure 1 illustrates an algorithm for the diagnosis and management of PCOS which takes into account the recommendations of the ESHRE/ASRM (Amsterdam, 2012). In the diagram, the starting point for therapeutic interventions is the presence of cardiovascular risk factors, i.e. obesity, abnormalities of carbohydrate metabolism, abnormalities of lipid metabolism, and hypertension.

Please do not forget to measure vitamin D levels in patients with PCOS. I hope you find the diagram useful in your everyday practice.

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