Review article

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Contemporary Therapeutic Principles in the Management of Patients with Polycystic Ovary Syndrome

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Abstract

Ovarian functional disorder is caused owing to an imbalance or disorder in the production of sex hormones, leading to irregularity in the menstrual cycles, as well as a reduced ability of conception or carrying to term. There are two types of ovarian dysfunction, i.e. primary, caused by the existence of ovarian pathophysiology, or secondary, which stems from thyroid or pituitary gland dysfunction. *Polycystic Ovarian Syndrome, or PCOS,* is an endocrine disorder of great complexity, and it was first described in 1935. The syndrome represents the most frequent cause of secondary amenorrhea and ovulatory dysfunction in reproductive-aged women. 'Syndrome' signifies a phenotype, or a set of clinical characteristics. Polycystic ovary syndrome involves classic phenotypes with specific characteristics that include the clinical signs of increased serum androgen concentrations, irregular periods, excessive androgen secretion , and infertility, as a consequence. What is more, the syndrome should be observed and treated as a metabolic disorder since it is closely associated with hyperinsulinemia and insulin resistance. A complex and individualized therapeutic approach is necessary to combat the complexity of the various disorders observed in various phenotypes. This review has been based on the literature research found in available databases. It presents a review of all the contemporary therapeutic options for managing patients suffering from polycystic ovary syndrome. Still, more studies are required to fully reveal the complex pathophysiology of the polycystic ovary syndrome. For this reason, this subject needs to be tackled in prospective epidemiological studies.

Key words: polycystic ovary syndrome, inositol, metabolic profile, insulin, LH, FSH

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Savremeni terapijski principi u lečenju pacijentkinja sa sindromom policističnih jajnika

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Savremeni terapijski principi u lečenju pacijentkinja sa sindromom policističnih jajnika

Apstrakt

Poremećaj funkcije jajnika je stanje u kome dolazi do neravnoteže odnosno poremećaja u stvaranju polnih hormona, a usled čega nastaju poremećaji u menstrualnom ciklusu i smanjena sposobnost začeća ili održavanja trudnoće. Poremećaj funkcije jajnika može biti primaran, usled patofiziologije na nivou jajnika ili sekundaran, kada poremećaj jajnika nastaje kao posledica poremećaja drugih žlezda kao što su hipofiza i štitna žlezda. Sindrom policističnih jajnika je složen endokrinološki poremećaj i prvi put je opisan 1935. godine. Predstavlja najčešći uzrok sekundarne amenoreje i najčešćim uzrokom ovulatorne disfunkcije kod žena u reproduktivnom periodu. Termin sindrom se odnosi na skup kliničkih karakteristika ili fenotip. Specifične karakteristike klasičnih fenotipova sindroma policističnih ovarijuma podrazumevaju kliničke znakove viška androgena, povišene koncentracije androgena u serumu, neredovne menstruacije i posledičnu neplodnost. Takođe, zbog česte udruzenosti sa insulinskom rezistenciom i hiperinsulinemijom se mora posmatrati i lečiti i kao metabolički poremećaj. Upravo iz te kompleksnosti različitih poremećaja koji se mogu videti u različitim fenotipovima i terapijski pristup je vrlo kompleksan i individualan. Ovaj pregledni rad je zasnovan na pretrazivanju sve dostupne literature u dostupnim bazama podataka i praktično daje prikaz svih danas dostupnih terapijskih opcija u lečenju pacijenata sa sindromom policističnih ovarijuma. Svakako potrebno je više istrazivanja da bi se razjasnila slozena patofiziologija sindroma policističnih ovarijuma, te su neophodne prospektivne epidemiološke studije na ovu temu.

Ključne reči: policistični ovarijalni sindrom, inozitol, metabolički profil, insulin, LH, FSH.

Ovarian Dysfunction

Ovarian dysfunction, otherwise known as ovarian functional disorder, is a condition caused by the disorder or imbalance in sex hormone production, leading to a reduced conception possibility, irregular menstrual cycles and an inability to carry to term. Ovarian dysfunction may primarily occur as a result of ovarian pathophysiology. Its secondary manifestation is a result of the dysfunction of diferent glands, such as the pituitary glands or thyroid glands (1). In essence, ovarian dysfunction is an imbalance in the secretion of estrogen and progesterone, which could lead to altered ovulation, a changed menstrual cycle, or a disrupted uterine function during pregnancy (2).

First described in 1935, *Polycystic Ovarian Syndrome, or PCOS,* is a highly complex endocrine disorder. It represents the most common cause of ovulatory dysfunction and secondary amenorrhea in women who are at a reproductive age. Considering the fact that the syndrome's etiology is still unknown, the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine developed a set of diagnostic criteria in Rotterdam in 2003, which was when the Rotterdam Criteria were established. Two out of the following three criteria need to be present for making the polycystic ovary disease diagnosis: oligo-anovulation, clinically manifested by the menstrual cycle disorder, biochemical or clinical hyperandrogenism, or a polycystic ovarian morphology detected with the use of ultrasound. In addition to the occurrence of at least two of the aforementioned criteria, it is necessary to exclude other etiologies, such as hypothalamic-pituitary dysfunction, congenital adrenal hyperplasia, androgen-secreting tumours and the Cushing syndrome. The Rotterdam criteria are universally recognized in the

diagnosis of polycystic ovarian disease, and are also widely accepted by gyneacological, pediatric, endocrinological, and cardiological associations (3, 4).

The disorder is complex and is characterized by hirsutism, infertility, , obesity, as well as different types of menstrual dysfunctions, such as amenorrhea, oligomenorrhea and anovulation. Polycystic Ovarian Syndrome is frequently associated with bilaterally enlarged ovaries, which contain atretic follicles, instead of cysts. This condition is characterized by enlarged ovaries, infertility, menstrual issues, a high male hormone level, acne, excess facial and bodily hair, and obesity. Women who have polycystic ovaries are at an increased risk of high blood pressure, diabetes, cardiac diseases and endometrial cancer (5).

The clinical symptom complex involves the presence of multiple ovarian cysts, amenorrhea or oligomenorrhea, anovulation, and is frequently followed by abnormal hair growth on the body (hirsutism), infertility obesity and insulin resistance (6, 7). It has been proved that patients suffering from this syndrome are at an increased risk of cardiovascular diseases and carbohydrate metabolism disorders, as well as of developing dyslipidemia, obesity and insulin resistance. Thus, Polycystic Ovarian Syndrome represents a significant metabolic entity, in addition to being an endocrinological one.

Pathophysiological Aspects of Polycystic Ovarian Disease

The pathophysiological aspects of polycystic syndrome are still not fully understood. There are three theories concerning the pathogenesis of PCOS: 1) disordered ovarian steroidogenesis theory, 2) insulin resistance theory, and 3) hypothalamus-pituitary axis theory (8). Previous findings idnicate that the syndrome may have a genetic component causing PCOS development (a mother who suffers from polycystic ovarian syndrome during pregnancy has a higher androgen level, inducing changes in the ovaries of the female fetus, which leads to the possibility of the girl developing her mother's symptoms later in life), as

well as exogenous factors, such as obesity, that may also play a key role in the development of PCOS (9). It has been noted that the levels of androstenedione in ovarian theca cells are twenty times higher in women suffering from PCOS than in healthy women. Moreover, the levels of 17α-hydroxyprogesterone (17OHP) and progesterone are also increased. This local ovarian hyperandrogenism is caused by the increased transcription of genes encoding steroid enzyme cytochrome P450-11A1, cytochrome P450-17α-hydroxylase/17-20 lyase and 3β-HSD in PCOS theca cells (10). CytochromeP450-17α-hydroxylase is the key enzyme in androgen synthesis both in the adrenal glands and in theovaries. Anovulatory and ovulatory cycles also have increased androgen synthesis in polycystic ovarian theca cells. Thus, it cannot be the only reason for anovulation (11). Furthermore, increased LH secretion and excess androgen production are noticeable both in normal-weight women and in obese ones, though they are present in women suffering from PCOS, leading to elevated levels of insulin, which has not been implicated in the pathogenesis yet. Considering the fact that ovarian theca cells are sensitive to insulin, a vicious circle is formed, since obesity development is stimulated by ovarian androgen hyper-production. All these processes in which insulin resistance seems to be the critical point result in the polycystic appearance of ovaries (12).

Different polycystic ovarian disease phenotypes can be seen in clinical practice. Phenotypes A and B are classical phenotypes, although type A is characterized by hyperandrogenism, anovulation and polycystic ovaries, whereas type B does not necessarily possess such a specific ovarian morphology. A combination of hyperandrogenism and ovarian polycystic morphology is the characteristic of phenotype C, also known as the hyperandrogenic ovulatory phenotype. Finally, the characteristic of phenotype D, or the normoandrogenic anovulatory type, is the ovarian polycystic structure and anovulation.

The abnormal values of gonadotropin-releasing hormone (GnRH) in women suffering from PCOS lead to the hypersecretion of luteinizing hormone (LH) prior to ovulation. Then,

oocyte ovulation failure is caused by the perturbation in the LH. This is one of the reasons why women with PCOS encounter menstrual issues. Some women suffering from PCOS have irregular ovulations, while others do not experience these at all. Such ovulatory issues decrease the fertility in patients suffering from PCOS. In addition, anovulation may result in the continuous increase in estrogen levels, subsequently leading to the increased endometrial thickness and the suppression of follicle stimulating hormone production. Progesterone also plays a role in endometrial protection against the effects of estrogen, so it cannot be produced in women experiencing anovulation. All these factors might lead to the development of endometrial hyperplasia, which elevates the risk of possible progression to endometrial cancer in women suffering from PCOS (13).

PCOS also features increased levels of circulating insulin/ hyperglycemia/hyperinsulinemia, produced in the β-cells of the pancreas. Hyperglycemia is believed to be caused by lifestyle or environmental factors (diet and obesity), and that it eventually progresses to PCOS. Hyperinsulinemia stimulates the anterior pituitary, thus releasing LH and ovarian thecal cells, which leads to the production of ovarian androgen. In addition, it stimulates the hypothalamus to release adrenocorticotropic hormone (ACTH) for the induction of adrenal androgen. Insulin inhibits the synthesis of insulin-like growth factor binding protein 1 (IGFBP-1) in the granulosa cells of the ovaries, resulting in the increased bioavailability of insulin-like growth factor 1 (IGF-1), and consequently to the increased secretion of ovarian androgen. In addition, insulin is also able to increase the activity of cytochrome enzyme P450 17A1, which is an enzyme that synthesizes androgen in the ovaries. Furthermore, insulin inhibits the production of IGFBP-1 in the liver and elevates free IGF-1 which stimulates ovarian androgen synthesis. The production of sex hormone-binding globulin (SHBG) in the liver is also limited by insulin, which increases free testosterone levels, leading to hyperandrogenism (14, 15).

Meanwhile, high levels of testosterone, being one of the androgen hormones subtypes, and androgen receptor changes, such as the ones in the beta-3 adrenergic receptors and the alpha-2 (α2) adrenergic receptors, facilitate catecholamine-induced lipolysis in visceral adipose tissues. As a results, high levels of fatty acids accumulate in the liver, leading to obesity, which could eventually lead to complications, such as cardiovascular diseases (16).

Preventive and Therapeutic Strategies

In order to treat PCOS adequately, medication needs to be applied for the purpose of increasing tissue insulin sensitivity (a decrease in insulin resistance – *insulin sensitization agents*) (17, 18). Dependent on the fertility status and the clinical manifestation of the disease, there are different types of current treatment protocols in managing PCOS. These may include oral hormonal contraceptives, lifestyle modification, ovulation induction protocols, application of leptin, the ovarian hippocampal signal path block, inositol or resveratrol treatment (19, 20). Most therapeutic protocols are efficient in lleviating certain symptoms, but have no effect on others.

Lifestyle Changes

According to epidemiological data, insulin resistance is present in approximately 60-80% of the women suffering from polycystic ovarian syndrome. What is more, approximately 95% of obese women show insulin resistance, diabetes and increased cardiovascular risk (21). The first-line treatments for PCOS management in these patients are lifestyle changes. In this sense, it is recommended that a restrictive diet be administered, i.e. there should be a reduced daily caloric intake. The recommended intake should be in the range of 1,200-1,500 kcal/day, followed by a minimum of 30 minutes of moderate physical activity five times per week. The purpose of the lifestyle changes should be the reduction of the body mass index,

lower alcohol and cigarette consumption for the purpose of reducing insulin resistance and regulating menstrual cycles (22). In the randomized studies to date, certain authors have investigated the effects of diet and physical activity, demonstrating that there was a significant improvement in the ovary functions in obese patients suffering from polycystic ovarian syndrome after four months of lifestyle changes. The mentioned patients experienced a 6% reduction in the body mass index by implementing dietary changes, 3% achieved this by exercising, and 5% did so through combined treatments. It has also been established that the testosterone level was reduced in 69% of the patients. Such investigations have shown that a reduced dietary intake, combined strategies, and moderate physical activity are effective in improving the reproductive function in obese and overweight patients suffering from polycystic disease. Furthermore, a reduced body mass index has significantly contributed to the pregnancy rates and live birth rates in patients suffering from polycystic syndrome.

Oral Contraceptive Therapy

The chief therapeutic option in the management of polycystic ovarian syndrome is oral hormone contraceptive therapy. Oral contraceptive pills represent the key treatment when combating polycystic ovarian syndrome. There are currently three oral contraceptive pill types: progesterone-only medication, combined estrogen-progesterone medication and contraceptive pills for extended or continuous use. Contraceptive pills are the most commonly prescribed forms of contraception both in America and world-wide. Nevertheless, oral contraceptives may be utilized for the treatment of other conditions, especially menstrual cycle disorders, such as irregular periods, menstrual pain, endometriosis-related pain, fibroids and menstrual migraines. Certain combination pills brands have obtained official FDA

approval for acne treatment. Although the majority of women take OCPs to prevent pregnancy, 14% use them for reasons unrelated to birth control (23-26).

Progestogen negative feedback acts on the hypothalamus in order to slow gonadotropin-releasing hormone pulse frequency. This, in turn, lowers the secretion of follicle-stimulating hormone (FSH) and the decrease in the luteinizing hormone (LH) (27, 28). Should a follicle not develop, no estradiol level increase occurs (as the follicle produces estradiol). Progestogen negative feedback and the lack of estrogen positive feedback regarding LH secretion terminate the LH increase mid-cycle. No developed follicle and no LH surge to release the follicles prevent ovulation. Since estrogen slows down FSH secretion, it does have a certain effect on follicle development inhibition owing to its negative feedback on the anterior pituitary gland, though it is not as pronounced as the progesterone effect. All this chiefly affects the reduction of very high luteinizing hormone levels. Moreover, certain types of oral contraceptives possess extremely potent antiandrogens, such as chlormadinone acetate or cyproterone acetate.

Ovulation Inductors

One of the criteria in patients suffering from polycystic syndrome is the ovulatory or anovulatory disorder, and an effective treatment for anovulatory disorder is the ovulation induction (29). Ovulation induction drugs are clomiphene citrate, a selective estrogen receptor modulator; letrozole, an aromatase inhibitor; and gonadotropin. The usual initial dose of clomiphene is 50 mg/day, for a period of 5 days, from cycle day 2 to cycle day 5. Ovulation usually occurs 5-10 days once the treatment has been completed. The dosage can be gradually increased to 250mg/day provided ovulation is not achieved. In the event that ovulation still fails to occur, the said patient is considered to be clomiphene resistant. Approximately 15% of the patients suffering from PCOS fail to react to treatment. For this

reason, they are regarded as clomiphene resistant. Clomiphene resistance risk factors include insulin resistance, obesity, elevated serum androgen levels, and old age (30).

Letrozole is an aromatase inhibitor of the third-generation, which blocks androgen to estrogen conversion in the ovarian follicle, peripheral tissue and the brain, which creates a positive feedback loop with the estrogen of the hypothalamus-pituitary-ovary axis, leading to an endogenous GnRH release, promotes FSH secretion and stimulates the growth of follicles. The usual Letrozole dose is 2.5-5mg/day over a period of five days, starting on days 4-8 of the menstrual cycle (31). Recently conducted studies indicate that selective estrogen receptor modulator clomiphene will be replaced as the first-line ovulation treatment with a letrozole aromatase inhibitor, which possesses a unique advantage for ovulation promotion in obese patients suffering from PCOS. Simultaneously, not only does letrozole exhibit less harmful effects on the cervical mucus, but it can also reduce ovarian hyperstimulation or other adverse effects, such as multiple pregnancies, and these are the unique safety advantages of the drug.

Androgens

Excessive androgen secretion in patients suffering from PCOS is in correlation with the biological synthesis and excessive androgen secretion of theca cells as well as reticular adrenal zone cells secreting testosterone. Women suffering from PCOS, hyperinsulinemia or insulin resistance have increased adrenal and ovarian gland functions. An effective androgen treatment is not free of side-effects, especially in patients suffering from PCOS who are not undergoing treatment and who are at risk of developing cardiovascular disease. Regardless of whether a woman is obese or not, high testosterone levels are in direct correlation with hypotension, hyperglycemia and subclinical atherosclerosis. Oral contraceptives are currently the first choice in excessive androgen secretion treatment, although the combination of

glucocorticoid (GCR) and norethindrone receptors in the polycystic syndrome will reduce the activity of fibrinolysin, another testosterone derivate and a recently revealed marker , but which has an antiandrogenic activity without any GCR receptor affinity. This derivate is expected to represent a new oral contraception form in the future, but it is being tested in clinical trials at present (32, 33).

Insulin-sensitizing Agents

Clinically, 60–80% patients suffering from PCOS exhibit differing insulin resistance levels. A body of evidence suggests that biguanide metformin, an insulin-sensitizing agent, leads to the decrease of elevated testosterone levels through the reduction of glycogen production, thus improving glucose metabolism and inhibiting follicular membrane cells. Moreover, metformin could restore ovulation in aproximately 30-50% of the women suffering from PCOS as well as regulate their menstrual cycles, but it was not as effective as clomiphene was when it came to fertility and pregnancy rates (34, 35).

Metformin can be classified as an anti-diabetic drug which improves insulin resistance. The mentioned drug represents the first-line treatment for type 2 diabetes, although it has been used in the pharmacotherapy of PCOS over the recent years (36). The basic action mechanisms encompass the inhibition of gluconeogenesis and glycogenolysis, in which results in the reduction of hepatic glucose production, consequently increasing the peripheral tissue's insulin sensitivity. Slowing down the intestinal absorption of glucose represents another relevant mechanism of metformin's action, since the consequently decreased glucose amount is absorbed into the bloodstream. Literature contains description of the therapeutic effects of metformin in patients suffering from polycystic ovarian disease, as well as the cases of the improved ovarian function of such patients. Conversely, certain

studies indicate that metformin does not lead to weight loss, as well as that the patients are resistant to the improvement of the lipid status (37, 38).

Vitamin D Deficiency

Literature data cites a correlation between the serum 25 (OH) vitamin D levels and sex hormone binding globulin levels. This may be employed as a parameter for the diagnosis of endocrine abnormalities or PCOS metabolism. In patients that suffer from a vitamin D deficiency, vitamin D supplementation increases insulin secretion and insulin sensitivity. At the same time, vitamin D supplement decreases the overall androgen and testosterone levels, which is why it is expected to be an option treatment for PCOS (39, 40).

GLP-1 Polycystic Disease Management Agonists

Available GLP-1 therapy studies regarding the excess body weight management in women suffering from PCOS indicate that liraglutide and exenatide are effective in body weight reduction, either in the form of monotherapy or combined with metformin. Several studies have shown that androgen levels could be modestly decreased and that menstrual frequency may be increased. Still, the limited data do not clearly present the obvious effect on blood pressure and lipid metabolism, with the most common side-effect being nausea, though it does not affect the efficacy of the drug or the treatment (4).

Anti-androgen Drugs

Other drugs used for polycystic ovarian disease management include the application of spironolactone, which reduces triglycerides and increases the ‘good’ cholesterol levels; flutamide reduces serum total cholesterol, LDL and triglyceride levels; orlistat and acarbose reduce the digestion of polysaccharides in the GI tract.

Hirsutism, as one of the clinical entities, is one of the consequences of elevated circulating androgen levels. Flutamide has proven to be a relevant anti-androgen, although it could also lead to the improvement of the lipid profile. It is a nonsteroid antiandrogen which mediates its effect through the inhibition of androgen hormones in the target tissues. When compared with metformin effects and dietary modifications, flutamil considerably reduces androgenes (42).

Spironolanctone is another antiandrogen utilized in the pharmacotherapy of PCOS. In addition to the antiandrogenic effect, it has an antimineralocorticoid effect. However, treatment which involves solely spironolactone does not yield significant results, but combined with lifestyle changes, this medication results in reduced insulin resistance.

Assisted Reproduction Therapy

The third-line treatment of patients experiencing fertility issues involves assisted reproduction technology (ART). This therapy chiefly includes artificial fertilization (IUI), oocyte *in vitro* maturation (IVM), *in vitro* fertilization-embryo transfer (IVF-ET), and intracytoplasmic sperm injection (ICSI). IUI is adequate for patients suffering from PCOS who can achieve successful ovulation upon the conducted ovulation induction, and may combine the male factor, immunological factor or cervical factor. In accordance with the latest ASPM research, the delivery rate remained stable after IUI, at 8.5% (8.3% in 2011) after husband/partner's sperm (IUI-H) and 12.0% (12.2% in 2011) after donor's sperm (IUI-D). Twin and triplet delivery rates related to IUI cycles were 9.0%/0.4% and 7.2%/0.5% after the treatment with husband's and donor's semen. Conventional IVF-ET ovarian stimulation is used to collect a considerable number of follicles by utilizing the GnRH agonist, which is both costly and also poses a risk of ovarian hyperstimulation. It has also been observed in the

study that, although IVM was lower than the ones in conventional IVF pregnancy, IVM is the simpler and safer ART method.

Surgical Treatment

As described by Stein and Leventhal in 1935, ovarian wedge resection was the first surgical treatment which was intended for anovulation correction in patients suffering from PCOS (44). Such a treatment could reduce endogenous androgen production and elevate the secretion of FSH, thus achieving natural ovulation. However, the approach has been discontinued owing to the considerable loss in ovarian tissue postoperative adhesion formations.

Inositols

Insulin signal transduction follows three main pathways: *phosphatidylinositol (PI) 3-kinase (PI-3-K) pathway*, *mitogen-activated protein kinase (MAPK) pathway*, and *protein kinase C (PKC) pathway*.

Clinical studies have showed that inositol reduces insulin levels in circulation, improves serum androgens, and regulates certain metabolic disorders (hypertriglyceridemia and elevated blood pressure) in the women suffering from PCOS who have a body mass index lower than 26 kg/m^2 (45, 46). A study investigating inositol efficacy (47) on the regulation of metabolic parameters and hormone levels at a dose of 500 mg per day, when administered to overweight patients (BMI>26), showed a notable reduction in the LH, LH/FSH ratio, testosterone, androstenedione, fasting glucose, basal insulin, as well as the insulin ratio and body weight. During OGTT, insulin concentration is also significantly improved when it comes to the insulin maximal response and the insulin AUC (*Area Under*

Curve) (48-50). These changes were observable in the whole study group, particularly in patients whose family history involved the occurrence of diabetes. Finally, the LH response during the GnRH test was also reduced upon the initiation of the inositol treatment.

The uptake of free inositol by tissues occurs through a membrane-dependent sodium-inositol cotransporter for which myo-inositol shows a 10 times greater affinity than DCI does. Myo-inositol (MI) and DCI mediate inositolphosphoglicane (IPG), and have the function of second messengers. Then, these mediators are internalized and modify intracellular metabolism and enzymatic activity, mimicking insulin activity (51). Myo-inositol is the most common inositol isomer in human body. It decreases body weight and leptin secretion, but it increases HDL cholesterol (52).; DCI is synthesized by an insulin-dependent epimerase, which converts myo-inositol into DCI. The deregulation of epimerase activity affects the MI/DCI ratio, as in PCOS, where a defect in the use of myo-inositol may compromise FSH and insulin signaling. There is a specific MI/DCI ratio related to the function of each organ (52). For this reason, high levels of DCI have been observed in glycogen storage organs. In the ovaries, DCI is responsible for the excess production of insulin-dependent testosterone, whereas myo-inositol enhances the FSH activity through the anti-Mullerian hormone (AMH). Myo-inositol has been found in follicular fluid (53) and it seems to improve oocyte and embryo quality.

The role of myo-inositol and/or DCI supplementation has been studied in women with PCOS undergoing assisted reproduction technologies (ART) for the purpose of improving embryo quality, oocyte quality and pregnancy chances (54,55). When applied three months prior to the initiation of ovarian stimulation, myo-inositol reduces the FSH doses required for a follicular response, decreases the concentration of estradiol on the ovulation induction day, by which it lowers the risk of ovarian hyperstimulation (56) and the number of cancelled cycles. Simultaneously, the quality of the ovary cells and the embryo is increased.

Women suffering from PCOS are four times more likely to develop diabetes than women not suffering from this disorder (57). These women are also at a higher risk of gestation diabetes (GD), which occurs in pregnancy. One study made an estimate that the mentioned risk is greater by almost 20% (58). Different research has shown that the MI supplementation intake might decrease GD and blood glucose in in women suffering from PCOS and in overweight women (59). One study in gyneacological endocrinology indicated that the number of GD cases in pregnant women suffering from PCOS using MI was 17.4%, when compared to 54% in the women who were not using MI (60).

Clinical practice involves the use of D-chiro-inositol (DCI) for the induction of ovulation in women suffering from polycystic ovarian syndrome (61). Data obtained recently have confirmed the fact that the molecule acts via two different mechanisms that lead to potentially different outcomes. On the one hand, when viewed from the metabolic perspective, insulin signaling is improved by DCI , which restores the physiological level of insulin in resistant individuals. On the other hand, it decreases the expression of steroidogenic enzyme aromatase, at a cellular level, which is responsible for androgen to estrogen conversion. DCI was first described as a molecule and mediator mimicking insulin. Afterwards, its role was discovered as an aromatase modulator in steroidogenesis (62).

Insulin sensitizing achieved through MI and DCI plays a crucial role in patients suffering from PCOS, which is seen as a decrease in the homeostatic model assessment (HOMA) index. Both mentioned isomers are useful in insulin resistance treatment (63).

Manganese pidolate *(IUPAC name: manganese(2+);(2S)-5-oxopyrrolidine-2-carboxylate)*

Manganese (Mn) is an essential intracellular activitiy nutrient; it functions as a co-factor for multiple enzymes, including glutamine synthetase (GS), arginase, pyruvate

carboxylase and Mn superoxide dismutase (Mn-SOD). Through these metalloproteins, Mn plays a critical role in the development, digestion, antioxidative defence, reproduction, immune response, energy production, and the regulation of neuronal activities. It is found in almost all tissues and is required for blood glucose regulation, digestion, reproduction, and homeostasis (64). Manganese is among the most abundant trace elements included in bone growth, cell energy, the immune system and the healthy metabolism of proteins, lipids and carbohydrates (65). Considering the fact that manganese represents an integral component for manganese catalase and MN-superoxide dismutase (SOD), pyruvate carboxylase and arginase, it helps to minimize oxidative stress by detoxing superoxide free radicals (66). The activities of the mentioned enzymes involve manganese in the metabolism of aminoacids, glucose and cholesterol, but its key role is to eliminate reactive oxygen species from the body, as well as bone tissue synthesis and immune response improvement. Preclinical studies have shown that a deficiency of manganese may reduce bone mineral density and impair very bone formation, while supplementation could improve both bone formation and mineral density (67). Studies conducted in patients who are at an average age of 69.3and suffering from osteoporosis have demonstrated that the levels of manganese were lower (20 mcg/L) in comparison with the healthy controls, at the mean age of 64.5 (40 mcg/L) (68). In another randomized clinical study involving postmenopausal women, manganese levels were correlated with bone mineral density (69).

In combination with vitamin K, manganese has a significant role in blood clotting and hemostasis. It is involved in carbohydrates, glucose and lipid metabolism in the role of a cofactor of several enzymes . In addition, manganese deficiency may affect carbohydrate metabolism, leading to glucose tolerance abnormalities. Therefore, the scientist has examined whether the status of manganese affects a risk of diabetes. A case-control cohort study in China has suggested a U-shaped association between type 2 diabetes and plasma manganese

levels. 1,614 adults with type 2 diabetes (mean age of 52.5 years) and 1,614 adults without diabetes (mean age of 54.7 years) participated in this study. In comparison with the middle tortile of plasma manganese concentration (4.21–6.84 mcg/L), those in the lowest tortile (≤4.21 mcg/L) were 1.89 times more likely to have type 2 diabetes, while those in the group with the highest tortile (≥6.84 mcg/L) were 1.56 times more likely to have type 2 diabetes (69).

Resveratrol

Resveratrol is a phytoalexin and a stilbene compound, synthesized by plants when they respond to stressful stimuli, which are frequently caused by infection. RSV can be found in red wine, sherries and ports , red grapes, peanuts, blueberries, itadori tea, as well as pistachios hops, and in cranberry and grape juices. An increased action of the glucose transporter in the cytoplasmic membrane seems to result in the anti-hyperglycemic effects of resveratrol. What is more, resveratrol enhances the levels of adiponectin, which could be a potential mechanism for insulin sensitivity improvement. (71). It is believed that resveratrol has beneficial effects on the cardiovascular system, since it has been found that it improves ischemic preconditioning and vasodilatation, both of which seem to be the result of endothelial NO synthase enzyme activation, and that it inhibits both vascular smooth muscle cell proliferation and platelet aggregation (70). Supplementation performed using a combination of resveratrol and alpha-lipoic acid exerted positive effects on the BMI, total and trunk adipose mass, as well as lean tissue mass, in obese women suffering from PCOS. Supplementation with the use of these dietary substances may be beneficial for glycemic control, weight loss, or both (71).

Conclusion

Pathophysiology of the polycystic ovarian syndrome is highly complex, but it has not fully been defined yet. Owing to a variety of pathophysiological mechanisms, it is accompanied by a wide spectrum of symptoms. This is why an individual approach is a basic principle in the treatment of patients who have polycystic ovaries. Namely, on the basis of the phenotype, characteristics of the phenotype, biochemical indicators, and specific symptoms, the treatment mostly involves different therapeutic combinations. Furthermore, during regular check-ups, it is common to realize that certain therapeutic option combinations have not completely realized our therapeutic goal. It is for this reason that novel combinations have to be considered. Such situations are not uncommon, but it must be taken into consideration that the treatment of patients with polycystic ovaries is a dynamic long-term process, and we trust that new therapeutic approaches will be available in the near future.

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