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CURRENT METHODS TO REALIZE THE REPRODUCTIVE FUNCTION IN PATIENTS WITH POLYCYSTIC OVARIAN SYNDROME AND CHRONIC ENDOMETRITIS

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Abstract

Literature review indicates that both polycystic ovary syndrome (PCOS) and chronic endometritis (CE) have a significant role in implantation disorders, one of the main causes of infertility and unsuccessful outcomes of assisted reproductive technologies.

Study aim was to analyze the literature on current methods to recover reproductive function in patients with polycystic ovary syndrome and chronic endometritis.

Materials and methods. The review analyzed scientific literature published in the past decade, as well as relevant research publications available in the online databases, which were searched using the key words "polycystic ovary syndrome", "endometritis", "comorbidity", and "infertility".

Results. While the evidence of positive effects of lifestyle changes on fertility is inconclusive, weight loss is a first-line treatment option recommended for women with PCOS. International guidelines for women with anovulatory PCOS consistently recommendas a second-line option gonadotropin therapy to induce ovulation if oral first-line induction ovulatory therapy, including aromatase inhibitors and selective estrogen receptor modulators,

fails. In regards to the treatment of CE, research supports the use of antibiotic therapy which increases the incidence of pregnancy in women with CE and repeated unsuccessful implantation, infertility of unknown ethoilogy or recurrent miscarriage.

Conclusions. Current methods of restoring reproductive function in patients with PCOS and chronic endometritis include a wide range of non-pharmacological and pharmacological treatments of PCOS in combination with antibiotic therapy of chronic endometritis, but their effectiveness remains low, which requires the use of assisted reproductive technologies.

Key words: **polycystic ovary syndrome; chronic endometritis; comorbidity; infertility; treatment.**

Introduction

Infertility affects 40% of women with polycystic ovary syndrome (PCOS) [1]. Among the risk factors for infertility against the background of PCOS are overweight, which is diagnosed in 90% of patients, and is an independent factor that reduces the effectiveness of infertility treatment and causes a higher risk of miscarriage [2]. Another factor that is closely correlated with infertility is age. Psychological and emotional state is also a notable factor in reducing female fertility [3]. Thus, an open discussion of fertility problems is considered to be playing an important role in the treatment of infertility comorbid with PCOS [4, 5].

At the same time, studies have shown that the incidence of chronic endometritis (CE) in infertile patients ranges from 0.2 to 46% [6]. In several studies, CE diagnosis ranged from 2.8 to 67.6% of patients with infertility and implantation failure [7–13]. It is generally understood that CE, even if not clinically manifested, reduces the effectiveness of both natural and assisted reproductive technologies, in addition to being a contributing factor in the development of obstetric and neonatal complications [14].

In summary, literature review indicates that both PCOS and CE play a substantial role in the failure of implantation processes as one of the main causes of infertility and unsuccessful rounds of assisted reproductive technologies.

Study aim was to analyze the literature on current methods of reproductive function in patients with PCOS and chronic endometritis.

Materials and methods

The review examined research publications from the last decade, including highly cited papers indexed in online databases, which were selected after a search with keywords "polycystic ovary syndrome", "endometritis", "comorbidity", and "infertility".

Results and discussion

While the evidence for lifestyle changes to restore fertility remains inconclusive, weight loss is recommended as a first-line treatment option for women with PCOS [15]. A healthy diet and regular physical activity help to reduce insulin resistance and hyperandrogenism, as well as balance hormonal and lipid profiles [16, 17]. Some studies suggest that weight loss in infertile women with both overweight and PCOS is be associated with sporadic ovulation and a better response to ovulation-stimulating treatment, as well as with an increase in pregnancy and live birth rates [18, 19]. For instance, a decrease in body weight of only 5% from baseline can restore regular menstruation and improve the response to drugs for ovulation and fertility [20]. In addition, sustained physical activity can improve fertility results by modulating the hypothalamic-pituitary-gonadal axis[21].

Since 70% of women with PCOS are diagnosed with anovulation or oligoovulation, ovulation induction is essential for the treatment of infertility in women with PCOS.

Clomiphene citrate is a selective estrogen receptor modulator (SERM), which traditionally was considered the first treatment of choice for ovulation induction in women with PCOS. Current guidelines suggest the use of clomiphene citrate as a second-line therapy to improve ovulation and pregnancy in women with PCOS with anovulatory infertility and no other infertility factors (conditional recommendation) [15]. It acts as an antiestrogen by blocking estrogen receptors in the hypothalamus, leading to an increase in the release of the gonadotropin-releasing hormone (GnRH) and, subsequently, increased production of the anterior pituitary follicle-stimulating hormone (FSH) and luteinizing hormone (LH), stimulating complete follicle maturation. The antiestrogenic action can also affect the endometrium and cervical mucus, inhibiting endometrial proliferation, which could potentially inhibit implantation [22]. Tamoxifen acts similarly to clomiphene citrate and is used to treat anovulation in patients who do not respond to clomiphene citrate. Due to the effect of tamoxifen on the uterine mucosa, studies of combined clomiphene and tamoxifen administration have shown a marked increase in pregnancy [23].

Letrozole is an inhibitor of aromatase, the enzyme converting androgen to estrogen, and it is the most commonly used selective third-generation nonsteroidal inhibitor for ovulation induction [24]. Letrozole inhibits the secretion of estradiol by the ovaries. This

results in increased both the secretion of FSH by the pituitary gland and the sensitivity of follicles to FSH, with subsequent improvement in ovulation rate [25]. Since letrozole, compared to clomiphene citrate, has a relatively short half-life (approximately 45 hours), there is no adverse effect on estrogen target tissues [26].

International guidelines maintain the recommendation to use gonadotropin therapy for ovulation induction in women with anovulatory PCOS as a second-line option for those patients who do not respond to first-line oral induction ovulation therapy, including aromatase inhibitors and selective estrogen receptor modulators [15].

In patients with PCOS, gonadotropins are associated with an increased risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies. Exogenous FSH stimulates the proliferation of granulosa cells and follicle growth. Different gonadotropin preparations are equally effective, without significant variability in the frequency of live births, clinical frequency of pregnancy, frequency of multiple pregnancies, frequency of miscarriages or incidence of OHSS [27, 28].

In combination gonadotropin therapy with metformin, Bordewijk et al. found a higher cumulative level of live births compared to FSH alone, while there was insufficient data on the incidence of multiple pregnancies and other adverse events [29]. Similarly, Palomba et al. demonstrated that the introduction of metformin significantly increases the number of live births and the frequency of pregnancies, while at the same time reducing the frequency of miscarriages [30].

Metformin is a biguanide insulin sensitizer, commonly used as the first-line antihyperglycemic agent to treat Type 2 diabetes. In the ovaries, metformin reduces androgen production by the theca cells by reducing the activity of ovarian cytochrome P450c17a and the expression of steroidogenic acute regulatory protein [31, 32]. Ovarian hyperandrogenism is responsible for premature follicular atresia and anovulation, so metformin may in theory stimulate ovulation [33].

A meta-analysis by Panda et al. showed that orlistat, an anti-obesity drug that reduces the absorption of fat in the gut, is more effective than metformin in reducing body weight, LDL cholesterol, total cholesterol and insulin resistance [34]. Another meta-analysis to evaluate the efficacy and safety of glucagon-like peptide-1 (GLP1) receptor agonists showed that GLP1 receptor agonists were also more effective than metformin in improving insulin sensitivity and reducing BMI, suggesting that these medications may be a good choice for obese PCOS patients, especially those with insulin resistance [35].

Given the development of insulin resistance in patients with PCOS, inositol (hexahydroxycyclohexane) may be an effective treatment option, with two stereoisomeric forms of myoinositol (MI) and D-chiroinositol (DCI) each playing a corresponding biological role as insulin sensitizing agents [22, 36]. In the ovaries, MI mediates glucose uptake and FSH signaling, while DCI improves insulin-induced androgen synthesis [22, 37]. Depletion of MI and overabundance of DCI in the ovaries due to increased epimerase activity can impair the quality of oocytes [38]. Pundir et al. found a significant improvement in ovulation rate and normalization of menstrual cycles with the use of inositol [39]. In additiont MI supplementation was shown to restore spontaneous ovulation with subsequent increase in conception rates, both alone and in combination with gonadotropins [40]. Currently, international guidelines suggest considering inositol as an experimental therapy for PCOS.

Given the crucial role of insulin resistance and oxidative stress in the pathological mechanisms of PCOS, the combination of inositol and alpha-lipoic acid is a promising therapeutic approach without significant adverse effects on women with PCOS [41]. Alpha-lipoic acid is a powerful scavenger of free radicals and a natural cofactor of mitochondrial dehydrogenase complexes. Research findings show that alpha-lipoic acid activates 5' adenosine monophosphate-activated protein kinase (AMPK), which lowers triacylglycerol levels and improves endothelial function [42]. When used alone or in combination with inositol, alpha-lipoic acid improves glucose control, insulin resistance, and ameliorates metabolic and endocrine disorders in patients with PCOS [43-45]. Both inositol and alpha-lipoic acid can improve metabolism and endocrine parameters by acting as both insulin sensitizers and antioxidants [46–48].

Currently under study is the effectiveness of a combined preparation *Sinopol*, which is a new three-in-one formula containing alpha-lipoic acid (400 mg), myoinositol (1000 mg) and folic acid (200 mcg). This combination of ingredients is designed to decrease endocrine and metabolic imbalances associated with insulin resistance and reproductive health in women with PCOS [49–52]. Since there are no identifiable side effects of any of these components when used for therapeutic purposes, in recent years research focus has shifted to identify new natural compounds and combinations as alternative treatments of PCOS, in particular, the combinations of inositol with monacolins or bergamot flavonoids [53 - 56].

Worth mentioning among the plethora of various vitamin preparations is vitamin D. The deficiency of this vitamin in women of reproductive age ranges from 45 to 90% [57, 58]. One study found that vitamin D deficiency in women with PCOS who underwent ovarian stimulation for infertility treatment was associated with a significant reduction in ovulation,

pregnancy, and, ultimately, reduced likelihood of live births [59]. PCOS and vitamin D deficiency are also associated with insulin resistance [60].

Treatment of CE involves antibiotic therapy, which, in a number of studies, improved the incidence of pregnancy in women with CE and a history of repeated unsuccessful implantation [61-63], unexplained infertility [64] or recurrent miscarriage [65]. In addition, patients with CE who underwent antibiotic therapy showed improved incidence of live births, pregnancy and implantation compared to the patients with recurrent CE [63]; and in antibiotic treated CE patients the IVF outcomes were comparable to those of women without CE [63]. In women with repeated unsuccessful implantation, polyvalent treatment of inflamed endometrium often leads to a doubled implantation frequency and the number of live births in assisted reproductive technology programs [66]. In addition, in cases of recurrent miscarriage, there was an increase in the frequency of live births (7 to 56% after treatment) and the cumulative incidence of live births [65]. A study by Lewis et al. where CE was found in 40.7% of women, showed that treatment of CE significantly improved the rate of implantation in patients who underwent *in vitro* fertilization and embryo transfer [67].

Conclusions. Current approaches to restore reproductive function in patients with PCOS and chronic endometritis include a wide range of non-pharmacological and pharmacological treatment of PCOS in combination with antibiotic therapy for chronic endometritis, but their effectiveness remains low, which requires the use of assisted reproductive technologies.

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