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REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Adjuvant therapy in assisted fertilization procedures

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SUMMARY

Introduction Despite continuous advances in assisted reproductive technologies (ART), their outcomes are limited. Before introducing adjuvant therapy to improve the *in vitro* fertilization (IVF) outcome, it is important to identify appropriate groups of patients, and avoid equal approach for everyone.

The objective of this paper was to review the available literature on the most commonly used adjuvant therapy aiming to improve the outcome of IVF. The guidelines of the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine were used, and the available literature was analyzed by searching the Medline – PubMed and Cochrane databases using appropriate keywords for each entity.

Discussion A review of the literature found no consistent evidence for the standard use of metformin in patients with polycystic ovarian syndrome, nor for use of dehydroepiandrosterone, testosterone, and growth hormone in patients with premature ovarian failure or those with poor response to stimulation. The standard usage of prednisone and aspirin in the general population of patients in ART is also not recommended. Recently, the significance of the oxidative stress has been emphasized, which is why the use of antioxidants in the form of supplementation (melatonin, vitamins C, A, E, coenzyme Q) might be important in improving reproductive outcomes.

Conclusion The modern approach to the problem of infertility has become strictly individual. The application of adjuvant therapy in order to improve the outcome of ART procedures requires an analytical and critical approach in each individual case.

Keywords: *in vitro* fertilization; outcome; adjuvant therapy; supplementation

INTRODUCTION

Despite continuous advances in assisted reproductive technologies (ART), there are ongoing efforts to improve the outcomes of *in vitro* fertilization (IVF) procedures. The clinical pregnancies occur once in three to four IVF procedures, and one in five cycles ends with live birth [1].

Considering that the factors which affect procedure outcomes are presented long before the procedure actually begins, it is important to identify appropriate groups of patients, especially those who may develop ovarian hyperstimulation syndrome (OHSS) or may have inadequate response to stimulation, those with premature ovarian insufficiency, endometriosis, associated endocrine diseases, verified thrombophilia, etc. [2, 3]. Accordingly, a uniform approach for all patients should be avoided.

The aim of this paper was to review the available literature data on the most commonly used adjuvant therapy aimed at improving the IVF procedures' outcome.

We used European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine guidelines, and analyzed available literature by searching Medline – PubMed and Cochrane database using appropriate keywords for every entity.

METFORMIN

Prescribing metformin, especially in patients with polycystic ovary syndrome (PCOSy) is often based on the presumed existence of insulin resistance. It has not been shown that there is a significant improvement in the live birth rate (LBR) in PCOSy patients who used metformin before or during the IVF procedure, but the incidence of OHSS was lower [4]. Similar conclusions emerge from a recent meta-analysis that showed no association between metformin use in patients with PCOSy and clinical pregnancy rate (PR) and LBR in IVF [5]. However, the PR was significantly higher in those with a BMI greater than 26 kg/m^2, suggesting that insulin resistance might have been the part of total metabolic component, and the metformin usage was useful with consequent favorable outcomes of IVF [5, 6]. So, a complete endocrinological examination with the evaluation of metabolic status and insulin resistance should be recommended before the introduction of metformin as an adjuvant therapy in IVF patients.

Protocols with GnRH antagonists are recommended in patients with PCOSy, as they are safer [7]. However, a recent meta-analysis showed the lower LBR in PCOSy patients with metformin using the GnRH antagonist protocol [4]. ESHRE Guide to Ovarian Stimulation in IVF/ICSI procedures does not recommend the routine use of metformin in patients with PCOSy using GnRH

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antagonist protocols to improve IVF outcomes [7]. The use of metformin as an adjuvant therapy in overweight/obese PCOSy patients undergoing IVF leads to decrease number of retrieved oocytes and does not influence the LBR [8]. The use of metformin as an adjuvant therapy in patients undergoing GnRH agonist protocols did not have a significant effect on the IVF outcomes either [8] (Table 1).

Table 1. Metformin and inositol as adjuvant therapy in *in vitro* fertilization

Therapy		Description
Metformin	Tso et al. [4]	There is no conclusive evidence that metformin treatment before or during ART cycles improved live birth rates in women with PCOSy; lower risk of OHSS
	Wu et al. [5]	Metformin treatment was associated with a decreased risk of OHSS but had no association with the overall clinical pregnancy rate or live birth rate among women with PCOSy undergoing IVF/ICSI-ET
	Abdalmageed et al. [8]	Usage of metformin could decrease the number of retrieved oocytes in overweight and obese PCOSy patient undergoing IVF
Inositol	Merviel et al. [10]	MI, at a dose of 4 g per day (2 g twice per day), three months prior to ovarian stimulation, is effective in normalizing ovarian function, improving oocyte and embryo quality in PCOSy
	Laganà et al. [11]	During IVF, MI is effective in both PCOSy and non-PCOSy women in saving gonadotropins, but reduces efficiently length of controlled ovarian hyperstimulation only in PCOSy women

PCOSy – polycystic ovarian syndrome; ART – assisted reproductive technologies; OHSS – ovarian hyperstimulation syndrome; IVF – *in vitro* fertilization; ICSI-ET – intracytoplasmic sperm injection – embryo transfer; MI – myo-inositol

INOSITOL

Inositols, classified as insulin sensitizers, are also recommended for the treatment of PCOSy [9]. The latest research has shown that myoinositol in a dose of 4 g daily (2 g twice a day), three months before ovarian stimulation is effective in normalizing ovarian function and obtaining quality oocytes and embryos in patients with PCOSy [10]. The meta-analysis confirmed the beneficial effect of inositol, even in relation to the gonadotropin doses [11]. Oral myoinositol supplementation can reduce the amount of gonadotropins used in both women with PCOSy and those without PCOSy, but it reduces the duration of stimulation only in the PCOSy patients [11] (Table 1).

SUBCLINICAL HYPOTHYROIDISM

Thyroid disorders in patients with infertility are primarily autoimmune thyroid disease (prevalence 5–10%) and subclinical hypothyroidism (prevalence 5–7%) [12]. Subclinical hypothyroidism leaves a wide field of doubts regarding the use of therapy in patients preparing for the IVF procedures. The most of data on subclinical hypothyroidism and IVF outcomes suggest that there is no association with lower LBR or higher miscarriage rates compared to patients with TSH < 2.5 mIU/L [13]. Patients with PCOSy have a higher prevalence of elevated TSH and autoimmune thyroiditis. In these patients, TSH levels > 3.5 mIU/L are associated with adverse ART outcomes, and levothyroxine treatment may improve the LBR in patients when TSH levels are > 4 mIU/L [13]. The routine TSH assessment is recommended as a part of infertility evaluation, but screening of anti-TPO antibodies only if TSH levels are > 2.5 mIU/L [13]. Systematic treatment of all euthyroid women with TSH > 2.5 mIU/L and elevated levels of anti-TPO antibodies is not recommended [13]. Treatment decision should be made taking into account infertility factors such as POF, poor ovarian response, older age (> 35 years), history of recurrent miscarriages, or the presence of high levels of other thyroid antibodies [13].

DEHYDROEPIANDROSTERONE (DHEA)

The use of DHEA before the procedure and further during stimulation is mainly reserved for patients who are marked as "poor responders." A literature review does not reveal a sufficient number of large and well-designed RCT that would support either improvement of the ovarian response or the IVF outcomes in these patients. A randomized trial of 140 patients with poor ovarian response who received DHEA at a dose of 75 mg daily for 12 weeks showed a significantly higher number of obtained oocytes, a higher fertilization rate, and a higher PR [14]. On the other hand, in the randomized study of 52 patients also receiving DHEA at a dose of 75 mg daily for 12 weeks there was no improvement in ovarian response or LBR [15]. A larger meta-analysis that included 17 RCTs provided inconsistent conclusions regarding the effectiveness of DHEA therapy before initiating IVF [16] (Table 2).

TESTOSTERONE

Testosterone is mostly reserved for the "poor responders," but there is inconsistent evidence regarding the improvement of ovarian response and overall outcomes. An earlier Cochrane meta-analysis did not prove that the use of testosterone in patients with poor response leads to a higher LBR [16]. A recent meta-analysis of seven RCTs and 573 patients showed a positive effect of transdermal testosterone administration on the LBR, PR, total oocyte, and embryo count [17]. Due to conflicting results, larger RCTs are needed to confirm the true clinical efficacy of testosterone (Table 2).

GROWTH HORMONE (GH)

The use of GH is not exclusively reserved for patients with a poor response to stimulation, it is also used in those with a normal response. Heterogeneity of applied doses,

Table 2. Dehydroepiandrosterone, testosterone and growth hormone as adjuvant therapy in *in vitro* fertilization

Therapy		Description
DHEA	Kotb et al. [14]	DHEA increases the number of oocytes, fertilization rate, fertilized oocytes, and clinical pregnancy rate and ongoing pregnancy rate in women with POR according to the Bologna criteria; DHEA was well tolerated by the patients and was associated with less COH days and gonadotropins doses
	Narkwichean et al. [15]	Pre-treatment DHEA supplementation, although statistical power in this study is low, did not improve the response to controlled ovarian hyperstimulation or oocyte quality or live birth rates during IVF treatment with long protocol in women predicted to have poor OR
	Nagels et al. [16]	In women identified as poor responders undergoing ART, pre-treatment with DHEA or testosterone may be associated with improved live birth rates; the overall quality of the evidence is moderate
T	Nagels et al. [16]	There was no evidence that the use of testosterone in patients with poor response leads to a higher LBR
	Noventa et al. [17]	Transdermal testosterone administration had positive effect on the LBR, PR, total oocyte and embryo count
GH	Zhu et al. [18]	GH treatment may not improve live birth rate in expected poor responders
	Li et al. [19]	GH addition can significantly improve the clinical pregnancy rate and live birth rate; furthermore, the GH addition time and collocation of medications may affect the pregnancy outcome

DHEA – dehydroepiandrosterone; T – testosterone; GH – growth hormone; IVF – *in vitro* fertilization; COH – controlled ovarian hyperstimulation; ART – assisted reproductive technologies; LBR – live birth rate; PR – pregnancy rate

as well as insufficient studies results are the limiting factor for recommending the standard use of GH in IVF [7]. A retrospective study (about 3000 patients) suggests that the use of GH, even in those with a poor response may be without the expected success [18]. However, there are indications that adjuvant GH therapy before and during stimulation improves the LBR in patients with expected poor response to stimulation [19] (Table 2).

PREDNISONE

Immune system plays a central role in providing endometrial receptivity, so it can be responsible for both embryo implantation and recurrent miscarriages [20]. The aim of corticosteroid therapy would be to reduce the aberrant populations of natural killer cells at the endometrium, to normalize cytokine expression, and/or to suppress endometrial inflammation [21]**.** A meta-analysis that included 16 RCTs with 2232 couples showed insufficient evidence that periimplantation glucocorticoid administration in IVF/ICSI cycles affects clinical outcomes [22]. A randomized study of 133 women who were positive for antinuclear antibodies (ANA) with a history of failed IVF implantation showed that combined treatment with prednisone 10 mg/day and aspirin 100 mg/day could improve the IVF outcome [23]. The current stand is that glucocorticoids are not indicated in women with recurrent miscarriages or repeated unsuccessful IVF procedures, unless autoimmune antibodies are evident. Their use in the absence of autoimmunity does not improve the implantation rate and may pose a potential risk to the outcome of a healthy pregnancy [21].

ASPIRIN

The use of aspirin as adjuvant therapy in IVF was also investigated a lot, but suggested doses and the therapy duration are quite different. They vary from 75, 80 to 100 mg per day, and can be applied until the final maturation of the follicles, up to 12 weeks of gestation or even until the advanced period of gestation [7]. A recent meta-analysis involved 13 RCTs and indicated that low doses of aspirin may improve PR in IVF/ICSI, with a recommended dose of 100 mg/day [24]. However, recent ESHRE recommendations point out that there is no clear evidence that adjuvant aspirin administration before or during ovarian stimulation improves the ovarian response in the context of oocytes count, as well as PR and LBR in the general population of patients and the patients with poor response in IVF/ICSI cycles [7].

ANTIOXIDANTS

A possible role of oxidative stress in IVF outcomes has recently been investigated [25]. The ART exposes both oocytes and embryos to high levels of free radicals during cell and embryonic culture [26]. High levels of oxidative stress in the follicular fluid are associated with poor oocyte maturation and embryo quality [26]. Mitochondrial dysfunction that is characterized by high levels of accumulated free radicals is the key cause of oxidative stress and oxidative stress-induced cell aging [27]. Antioxidants such as melatonin, coenzyme Q, vitamins A and E may be crucial for increasing the reproductive capacity by improving mitochondrial function. The recent meta-analysis which included five RCTs showed that oral supplementation of coenzyme Q increases PR in infertile women undergoing ART procedure, without influence on the on LBR or miscarriage rates [28]. The addition of micronutrients may have a significant effect on the redox status of the follicular microenvironment and, consequently, on the favorable outcome of IVF [29].

MELATONIN

Melatonin regulates various physiological processes, including circadian rhythms, apoptosis, and autophagy, and protects cells from oxidative stress [30]. Studies suggest that melatonin concentration in the follicular fluid is associated with oocytes maturation rate and embryo quality in women undergoing IVF [31]. Melatonin treatment with at least 3 mg/day can significantly increase its concentration in serum but also in the follicle fluid [32]. Recent

meta-analysis suggests that melatonin treatment significantly increases PR in ART, with an increase in total number of mature oocytes and quality embryos, but without a significant effect on LBR [33].

VITAMIN D

Vitamin D is important for oocyte development, production of Anti-Mullerian hormone (AMH), ovarian steroidogenesis, endometrial receptivity, etc. [34]. Chu et al. [35] reported that deficiency of vitamin D could be an important treating condition in women undergoing fertility treatment. A meta-analysis of nine cohort studies found that vitamin D deficiency was associated with decreased LBR in IVF/ICSI [34].

LUTEAL PHASE SUPPORT

There is a broad consensus that the use of progesterone (Pg) is recommended for the luteal phase support in IVF [7, 36, 37, 38]. Cochrane meta-analysis showed a higher LBR in patients receiving progesterone compared to those without it, with no differences in the applied doses or administration routes (vaginal, parenteral) [39]. Generally speaking, the recommended dose is 100 mg of micronized Pg 2–3/day, and dydrogesterone for oral administration [7]. The use of estrogen (E2) for the luteal phase support is quite widespread. The ESHRE guideline emphasize that E2 application is not necessary, as it does not improve IVF outcomes (PR, LBR) nor does it reduce the possibility of OHSS [7]. Meta-analysis of van der Linden et al. [39] supports this recommendation. On the other hand, RCT of Gizzo et al. [40] showed the advantage of higher doses of progesterone with mandatory addition of E2 in the short protocols with antagonist, or when E2 ≤ 5 nmol/l and endometrial thickness less than 10 mm. There were no clearly demonstrated benefits of E2 administration when the long protocol with agonists was used, particularly in patients older than 35 years [40]. The addition of human chorionic gonadotropin to support the luteal phase is similar in efficacy to Pg, but should be used with caution, especially when it is used for the final maturation of follicles due to the risk of OHSS [7, 39]. The analysis of a GnRH agonists' single application as an adjuvant to progesterone therapy six days after oocyte aspiration is also interesting, where studies have shown favorable cycle outcomes. However, there is still no evidence good enough for its safe use, considering the possible risk of OHSS [7, 39].

CONCLUSION

The modern approach to the problem of infertility has become strictly individual. In this context, the application of adjuvant therapy aimed at improving the IVF procedure outcomes requires an analytical and critical approach in each individual case. Although generalization is not recommended, a review of the literature shows that the use of inositol in the population of both PCOSy and non-PCOSy patients, and the use of antioxidants in all categories of patients with the problem of infertility can improve the IVF outcome. Additional evaluations of adjuvant DHEA, testosterone or growth hormone therapy in the group of patients with premature ovarian insufficiency and/or poor response to stimulation are needed. Endocrinological and/or immunological therapy should only be used when all diagnostic procedures were conducted with the proper patient evaluation.

NOTE

The authors declare that the article was written according to the ethical standards of the Serbian Archives of Medicine as well as ethical standards of medical facilities for each author involved.

Conflict of interests: None declared.

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Адјувантна терапија у поступцима асистиране фертилизације

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САЖЕТАК

Увод Без обзира на континуирани, вишедеценијски напредак у асистираним репродуктивним технологијама, ограничени су домети у погледу побољшања успешности њихових исхода. Пре укључивања адјувантне терапије са циљем унапређења исхода вантелесне оплодње важно је идентификовати одговарајуће групе пацијенткиња и избегавати једнак приступ за све.

Циљ овог рада је преглед доступне литературе о најчешће коришћеној адјувантној терапији у циљу побољшања исхода поступака вантелесне оплодње. У ту сврху коришћене су смернице Европског удружења за хуману репродукцију и ембриологију и Америчког удружења за репродуктивну медицину, а такође је анализирана доступна литература претраживањем база података *Medline – PubMed* и *Cochrane* уз коришћење одговарајућих кључних речи за сваки ентитет.

Дискусија Прегледом литературе нису нађени конзистентни докази за стандардну примену метформина код пацијенткиња са синдромом полицистичних јајника, као ни дехидроепиандростерона, тестостерона и хормона раста код пацијенткиња са превременом оваријалном инсуфицијенцијом или оних код којих се очекује лош одговор на стимулацију. Стандардна примена преднизона и аспирина у општој популацији пацијенткиња уведених у поступке вантелесне оплодње такође се не препоручује. У последње време истиче се значај оксидативног стреса у поступцима асистираних репродуктивних технологија, због чега примена антиоксиданата у виду суплементације (мелатонин, витамини *C*, *A*, *E*, коензим *Q*) може имати значаја у побољшању репродуктивних исхода.

Закључак Савремени приступ проблему инфертилитета је постао строго индивидуалан. У том контексту и примена адјувантне терапије са циљем побољшања исхода процедура асистираних репродуктивних технологија захтева аналитички и критички приступ у сваком индивидуалном случају.

Кључне речи: вантелесна оплодња; *IVF/ICSI*; исход; адјувантна терапија; суплементација