Invited Review / Davetli Derleme
doi: 10.18678/dtfd.1191606

Duzce Med J, 2022;24(S1):86-89
Düzce Tıp Fak Derg, 2022;24(S1):86-89

Non-Specific Medical Treatment Methods in Female Infertility

Kadın İnfertilitesinde Spesifik Olmayan Medikal Tedavi Yöntemleri

Dilek KAPLANOĞLU[1]
0000-0003-0980-960X
Abdullah TOK[2]
0000-0003-0998-5531

[1]Department of Obstetrics and Gynecology, Yüreğir State Hospital, Adana, Türkiye

[2]Department of Obstetrics and Gynecology, Division of Infertility, Kahramanmaraş Sütçü İmam University Faculty of Medicine, Kahramanmaraş, Türkiye

Corresponding Author
Sorumlu Yazar
Abdullah TOK
abdullahtok@windowslive.com

Received / Geliş Tarihi : 26.08.2022
Accepted / Kabul Tarihi : 12.09.2022
Available Online /
Çevrimiçi Yayın Tarihi : 19.10.2022

ABSTRACT

Infertility, which is defined as the inability to conceive despite one year of unprotected sexual intercourse, affects 15% of couples. Any patient with infertility by definition or at high risk of infertility may be offered an infertility evaluation. In women older than 35 years, this waiting period can be limited to 6 months, and then infertility evaluation can be started. In women older than 40 years, more urgent evaluation and initiation of treatment is the most important option. Evaluation of infertility must be done by experienced and trained physicians and necessary treatments must be followed by these physicians. Alternative treatment methods can be used in patients who do not respond after standard evaluation steps and generally accepted treatment options. Various supportive treatments come to the fore here. These options are used both to obtain better quality oocytes before treatment and to ensure that more follicles participate in stimulation. Antioxidants and metformin are the most commonly used agents before treatment in women who are thought to have insulin resistance, especially considering that oocyte mitochondrial DNA damage increases in advanced female age. On the other hand, agents such as growth hormone that should be used in a controlled manner by experienced specialists have been found effective in many publications. In the presented article, non-conventional treatment options for infertility are explained.
Keywords: Infertility; treatment; non-specific agents.

ÖZ

Korunmasız bir yıl cinsel ilişkiye rağmen gebe kalınamaması olarak tanımlanan infertilite, çiftlerin %15'ini etkilemektedir. Tanım gereği infertilitesi olan veya infertilite riski yüksek olan herhangi bir hastaya infertilite değerlendirmesi önerilebilir. 35 yaşından büyük kadınlarda bu bekleme süresi 6 ay ile sınırlandırılabilir ve sonrasında infertilite değerlendirmesine başlanabilir. 40 yaşından büyük kadınlarda daha acil değerlendirme ve tedaviye başlama en önemli seçenektir. İnfertilite değerlendirilmesi mutlaka deneyimli ve bu konuda eğitimli hekimler tarafından yapılmalı ve gerekli tedaviler bu hekimler tarafından takip edilmelidir. Standart değerlendirme basamakları ve genel olarak kabul edilen tedavi seçeneklerinden sonra cevap alınamayan hastalarda alternatif tedavi yöntemlerine geçilebilir. Burada çeşitli destek tedavileri öne çıkmaktadır. Bu seçenekler hem tedavi öncesi özellikle daha kaliteli oosit elde etmek için gerekse de hem de daha fazla folikülün stimülasyona katılmasını sağlamak için kullanılmaktadır. Özellikle ileri kadın yaşında oosit mitokondrisi DNA hasarı arttığı düşünüldüğünde, insülin direnci olduğu düşünülen kadınlarda antioksidanlar ve metformin tedavi öncesi en yaygın olarak kullanılan ajanlardır. Diğer yandan büyüme hormonu gibi deneyimli uzmanlar tarafından kontrollü bir şekilde kullanılması gereken ajanlar tedavide pek çok yayında etkin bulunmuştur. Sunulan makalede infertilite için konvansiyonel tedavi dışı seçenekleri anlatılmıştır.
Anahtar kelimeler: İnfertilite; tedavi; non-spesifik ajanlar.

INTRODUCTION

Despite the advances in infertility treatments, especially in the last two decades, additional treatments are still up-to-date, especially in patients with poor response. On the other hand, these options are frequently used in recurrent failures in in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) cycles and in the presence of poor oocyte/embryo quality. While these options are often tablets, gels, or injectable preparations for ovulation induction, they also include improving laboratory conditions in IVF/ICSI applications.

Basically, all these auxiliary methods that are used both in laboratory and clinically in the infertility treatment process and ultimately aim to achieve a healthy pregnancy are called "adjuvant therapy", also termed as an adjunct therapy or add-on therapy (1). In the presented article, adjuvant agents used in ovulation induction regimens will be briefly mentioned.

Although the target in adjuvant treatments is oocyte, sperm, and endometrium, it is also included in methods that affect general body health. According to this, androgens, growth hormone, metformin, and antioxidants are used for ovarian response and oocyte quality, antioxidants and sperm selection practices are used for sperm count and quality, and estrogen, aspirin, heparin, immunity-oriented therapies (steroid, intravenous immunoglobulin (IVIG), anti-tumor necrosis factor (TNF) alpha, platelet rich plasma (PRP), general methods, and acupuncture are used to improve endometrial quality and implantation.

OVARIAN RESPONSE AND OOCYTE QUALITY

Androgens

Androgens play an important role in ovarian physiology. In particular, it acts as an estrogen precursor in the follicle within certain limits. Androgens in infertility are mostly used for women who respond poorly or are likely to do so in IVF/ICSI cycles. Dehydroepiandrostenedion (DHEA) is the most widely used androgen, especially in poor responders. It is also available without a prescription (2). It helps by increasing the amount of insulin-like growth factor-1 (IGF-1), which has a role in both providing an estrogen precursor and developing follicles. In this way, both the quality of the oocyte and the number of follicles that respond to the simulation increase. However, the fact that the patients were quite heterogeneous and included a limited number of cases in the studies questioned the reliability. In the Cochrane review, it was reported that a significant increase in the live birth rate was found with the use of DHEA (odds ratio, OR: 1.88, 95% confidence interval, CI: 1.30 to 2.71). However, it has also been suggested that there are not enough randomized controlled trials (RCTs) and therefore the data are insufficient. It is recommended to use 25 mg tablets 3x1 (75 mg/day) for at least 2-3 months before treatment. Androgenic side effects are negligible during use (3).

Testosterone is another agent used in clinical practice. It has a critical role in intra-ovarian follicle development and estrogen production. Since oral use is not active, it is recommended to use gel (12.5 mg/day) and patch (2.5 mg testosterone in the first 5 days of treatment). However, the use of this agent needs more research due to the lack of adequate RCTs (4).

Growth Hormone

It performs its main effect through the synthesis of IGF-1 in the follicle granulosa cells. It has a positive effect on both follicle growth and oocyte maturation (5). Although it is a subcutaneous use form, its use has been defined differently in different studies. Usages have been defined as 8 IU daily or 13 IU every other day or 2 IU daily. It is stated that it increases live birth in poor responders, especially at doses started before treatment (6). However, the small number of RCTs and the low number of cases in the presented studies prevent a definitive conclusion. On the other hand, there are articles stating that it only increases clinical pregnancies, does not increase the live birth rate, or there is no difference between clinical pregnancy and live birth rates. As a result, although it is frequently used in IVF (ICSI cycles), especially in poor responder patients, there are insufficient data to show that it especially increases live birth (7).

Metformin

It is an oral antidiabetic, insulin-sensitizing, agent that is frequently used against possible insulin resistance, especially in obese polycystic ovary syndrome (PCOS) patients. Blaming insulin resistance in the etymology of PCOS has led to the use of insulin sensitizers, especially for ovulation restoration (8). In the first studies on metformin, it was determined that 850 mg twice a day in IVF cycles did not make an additional contribution to the treatment. However, a decrease in the risk of ovarian hyperstimulation syndrome (OHSS) due to increased vascular endothelial growth factor (VEGF) with follicle development has been detected, especially in PCOS patients. Therefore, the main benefit of metformin in IVF cycles was stated in the Cochrane review as OHSS prevention (9). Although many studies have reported a decrease in abortion rates with the use of metformin, this has not been confirmed in large case series. Although spontaneous ovulation can be achieved with the use of metformin, its use as an ovulation agent is not recommended (10).

Antioxidants

Oxidative stress is destructive pathological agents that can damage cell wall lipid structures and DNA in all cells. Oocyte mitochondria, which have had low metabolic activity in oocytes since the intrauterine period, are more sensitive to oxidative stress since they do not have sufficient DNA protective mechanisms (11). Mitochondrial DNA damage may cause oocyte division and maturation problems. However, the point to be considered in the use of antioxidants is that low level oxidation is necessary for cell division and saturation, and it can have a reverse effect in aggressive use.

Many antioxidants are used in clinical practice. The most common are: L-arginine, melatonin, vitamin E, vitamin D, Myo-inositol, d-chiro inositol, and CoQ10. A Cochrane review compared the effects of these antioxidants with each other and with placebo (12). As a result, although the sources are of low quality publications, there has been a slight increase in both live birth (OR: 2.13, 95% CI: 1.45 to 3.12, and clinical pregnancy (OR: 1.52, 95% CI: 1.31 to 1.76) rates. CoQ10 has a special place in IVF/ICSI cycles. As it is known, the energy required for the cell is supplied from the electron transport chain together with the Krebs

cycle in mitochondria. CoQ10 is frequently used to prevent or reverse mitochondrial dysfunction, especially in elderly and poor responder patients (12). This re-functioning mitochondrion will have an important role in cell saturation, division, and granulosa cell function (13). Although positive opinions about CoQ10 are common, it was found in a recent meta-analysis that it increased the clinical pregnancy rate, especially in poor responder patients, and had no effect on live birth and abortion rates. Therefore, more standardized RCTs are needed for both antioxidants and CoQ10 use.

SPERM COUNT AND QUALITY

In men, unlike women, it is an important advantage to be able to see the germ cells directly with a test. In this way, possible pathologies can be recognized with higher accuracy. Here, number, movement, and morphology are the most important parameters to be evaluated. However, since the subject is female infertility, adjuvant treatments in male factor infertility will not be mentioned.

TO IMPROVE ENDOMETRIAL QUALITY AND IMPLANTATION

Even if the best embryo is obtained, successful live birth cannot be expected unless the appropriate endometrium and immunity required for implantation and growth are provided. For this purpose, preparing the endometrium for implantation and preventing the overreaction of immunity to a newly developing organism are other female fertility treatment options.

Estrogen can be used in the form of estrogen-priming, which helps to stabilize the irregularly developing follicular cohort as well as make the endometrium suitable for implantation, especially during freezing/thawing cycles (8). However, estrogen is not considered as an adjuvant treatment option and will not be reviewed here (14,15).

Aspirin is a non-steroidal anti-inflammatory agent that acts by inhibiting the enzyme involved in prostaglandin synthesis. The first indication for aspirin use is to prevent thrombus formation and to maintain thromboxane-prostacyclin balance. In this way, there was the idea that blood supply and embryo growth would continue. For this purpose, it is recommended that patients be started before treatment (8). However, further studies have shown that aspirin has no effect on live birth and clinical pregnancy except for more specific indications (16). Antiphospholipid antibody syndrome is a serious autoimmune pathology with pregnancy complications such as recurrent pregnancy loss and preeclampsia. It is thought that the use of low molecular weight heparin rather than its use alone in this group of patients may play a role in the treatment of infertility and the prevention of pregnancy complications (17,18). In the evaluation made by Zhang et al. (19), it was stated that the use of low molecular weight heparin only in addition to aspirin can be recommended in IVF/ICSI cycles in anticardiolipin ab positive patients. Similarly, in the Cochrane review, it was stated that aspirin alone did not improve outcomes in IVF/ICSI cycles (19).

Heparin has been evaluated in numerous studies, both with and without aspirin. It is very effective on trophoblastic invasion, especially in antiphospholipid antibody syndrome (8). On the other hand, its antithrombotic activity through the inhibition of factor Xa and thrombin formation in patients with thrombophilia allowed its use in these patients as well. Although bleeding is an important complication, it is not of clinical importance. On the other hand, heparin increases the rates of endometrial decidualization and implantation. It does this by decreasing the amount of insulin-like growth factor binding protein (IGFBP), increasing the amount of heparin-binding epidermal growth factor (HB-EGF), and increasing the expression of adhesion molecules such as E-cadherin (20-22).

Corticosteroids have been used in female infertility due to their anti-inflammatory and immunosuppressive effects. It is especially useful in patient groups who are thought to have immunological infertility in recurrent implantation failure. Because there is the idea that changes in Th1/Th2 balance and increases in uterine NK cell count may play a role in infertility in these patient groups (23). On the other hand, combined immunosuppression may increase implantation, as immunological factors often include thyroid or ovarian auto-antibodies. A total of 1879 couples were included in a Cochrane review and it was determined empirically that steroid initiation had no effect on IVF/ICSI cycle success, the clinical pregnancy rate (OR: 1.16, 95% CI: 0.94 to 1.44) or live birth rate (OR: 1.21, 95% CI: 0.67 to 2.19) (24).

CONCLUSION

Despite the lack of sufficient data, adjuvant treatments are currently used intensively in infertile women. Many of these treatments are far from sufficient scientific data. Clinicians should be especially vigilant in terms of the content and naturalness of these preparations. The use of experimental methods without sufficient clinical data will cause both safety and efficacy problems. Until adequate RCTs are available, nonspecific adjuvant treatments for female infertility seem to continue to be discussed.

Ethics Committee Approval: Since our study was a review, ethics committee approval was not required.

Conflict of Interest: None declared by the authors.

Financial Disclosure: None declared by the authors.

Acknowledgments: None declared by the authors.

Author Contributions: Idea/Concept: DK, AT; Design: DK, AT; Data Collection/Processing: DK, AT; Analysis/Interpretation: DK, AT; Literature Review: DK, AT; Drafting/Writing: DK, AT; Critical Review: DK, AT.

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