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INVITED ARTICLE

Effectiveness of supplement ingredients on infertility treatment in advanced aged women

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Abstract

Aim: Despite the remarkable progress made in reproductive medical technology in recent years, there has been no improvement in overall pregnancy and birth rates for the rising number of infertile patients. This is thought to be due to the increase in intractable infertility with ovarian dysfunction, as the desired age of pregnancy has increased for women. The aim of this article is to review preclinical studies that used laboratory animals and other tools to examine the effectiveness of diverse supplement ingredients on age-related ovarian dysfunction as well as recent human clinical trials using supplement ingredients.

Method: We summarized the articles discussing the effectiveness of supplement ingredients on infertility treatment in advanced-aged women by searching PubMed, Cochrane, EMBASE, and Google Scholar databases until December 2022.

Results: Supplements are relatively inexpensive and convenient for patients, as they can be purchased at the will of the individual and from among multiple options. Although supplements have been demonstrated to have certain effects in animal studies, evidence of their effectiveness in humans is either lacking or insufficient for reaching a definite conclusion. This may be due to the lack of standardized diagnostic criteria for ovarian dysfunction and poor responders, unclear optimal dosages and duration of supplement intake, and well-designed randomized clinical trials.

Conclusion: Additional lines of evidence on the effectiveness of supplements in patients with ovarian dysfunction at an older age need to be accumulated in the future.

KEYWORDS
aging infertility, oocyte quality, ovarian dysfunction, oxidative stress, supplement ingredients

INTRODUCTION

The main function of the ovary is to produce the sex hormones necessary for follicular development and reproduction. Ovarian function begins to decline in females at approximately 35 years of age, and many women reach menopause when they are in their 50s.[1] The ovary is considered one of the earliest organs to show aging disorder compared with other organs. The ovarian aging is known to cause (1) a decrease in the number of residual follicles and (2) deterioration of oocyte quality, both factors of which reduce fertility and can cause infertility in advanced-age women.[2,3] In fact, aging women exhibit resistance to agents used for ovarian stimulation to promote follicular development, such as gonadotropic hormones (gonadotropin formulations) and anti-estrogen preparations, resulting in a decreased number of developing follicles.[4,5] Additionally, poor oocyte quality results in a low pregnancy rate and high rates of miscarriage and fetuses with chromosomal abnormality.[6] Hence, aging infertility has become a major problem in fertility treatment.

Maternal age has been elevating in developed countries in recent years. In Japan, the majority of patients undergoing advanced reproductive medicine, including in vitro fertilization (IVF), are approximately 40 years old, and the age has been elevating yearly with socioeconomical changes. Therefore, establishing effective

treatment for ovarian dysfunction has become an important issue. With this goal in mind, we had previously developed a new infertility treatment, in vitro activation for ovarian dysfunction patients with decreasing ovarian reserve and successfully applied it clinically.[7,8]

It has been shown that the age-related decline of oocyte quality involves mitochondrial dysfunction in the oocyte and the cytotoxicity of the active oxygen (oxidative stress) generated along with the mitochondrial dysfunction.[9,10] Additionally, aging oocytes were shown to induce increased embryonic aneuploidy owing to chromosome nondisjunction, resulting in a high early-miscarriage rate.[11,12] As a treatment for aging infertility, oocyte donation from young healthy donors followed by IVF-embryo transfer (ET) is now available in some countries. However, there has been no established treatment that can improve the quality of one's own oocytes. Thus, in infertility treatment, supplement ingredients with antioxidative and anti-aging effects have been used in attempts to restore the deterioration of oocyte quality, thereby aiming to improve the outcome of assisted reproductive technology. In this article, we reviewed preclinical studies that used laboratory animals and other tools to examine the effectiveness of diverse supplement ingredients on age-related ovarian dysfunction as well as recent human clinical trials using supplement ingredients.

DEHYDROEPIANDROSTERONE

Molecular mechanism of action

Dehydroepiandrosterone (DHEA), secreted by the adrenal cortex and follicular theca cells, is a precursor of testosterone and estradiol.[13] DHEA molecules in the blood, which are mostly in the sulfate form (DHEA-S), reach their highest level when women are in their 20s and then continue to decline with age, decreasing by approximately 50% when the person reaches their 40s.[14] Testosterone metabolized from DHEA induces the expression of follicle-stimulating hormone (FSH) receptors in granulosa cells in early-developing follicles and increases the sensitivity of follicles to FSH, thereby promoting the development of preantral follicles and oocyte maturation (Figure 1).[15,16] Additionally, DHEA has been reported to increase the blood level of insulin-like growth factor 1, which promotes granulosa cell proliferation and follicular development.[17] Moreover, it facilitates mitochondrial biogenesis by inducing metabolic reprogramming in cumulus cells.[18] These findings suggest that multiple mechanisms may be involved in the DHEA-mediated improvement of ovarian function.

Preclinical studies

In a study on sheep at 24 months of age that had been unilaterally ovariectomized to reduce ovarian function, the subcutaneous administration of DHEA to the animals for 10 weeks improved follicular development and promoted the proliferation of granulosa cells, although there was no clear information about the dosage of DHEA.[19] In rats with diminished ovarian function induced by the administration of 4-vinylcyclohexenediepoxide following the unilateral ovariectomy, subcutaneous injections of DHEA at a dose of 60 mg/kg for 45 days significantly reduced the number of apoptotic follicles.[20] In another study, researchers cultured endometrial stromal fibroblasts obtained from aging females in 10 nM DHEA-supplemented medium for 8 days during decidualization

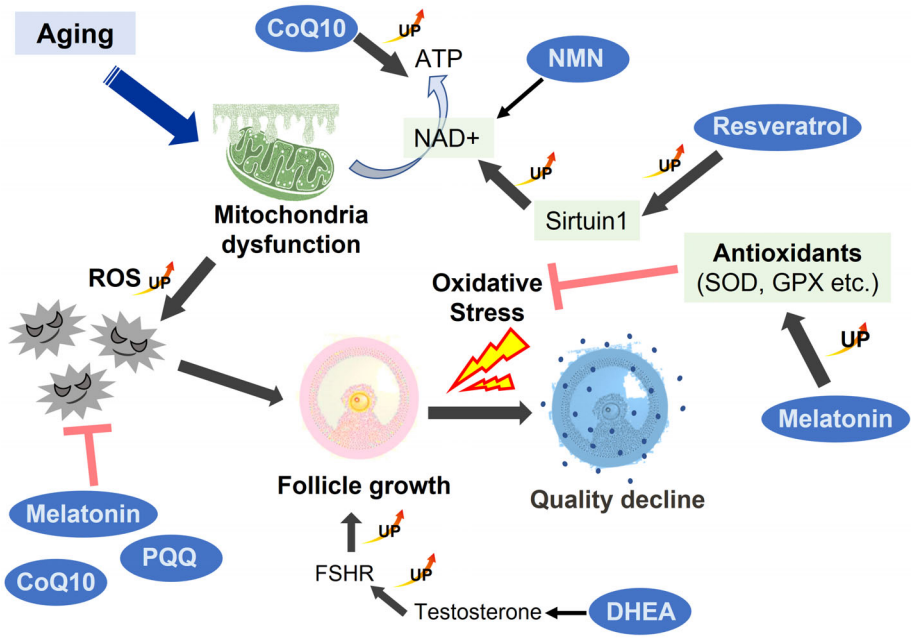

FIGURE 1 Putative molecular actions of different supplementary diets on restoring aging ovarian dysfunction. In aging ovarian follicles, ovarian function declines with aging mainly due to the decreases in mitochondrial function followed by the increases in cytotoxic reactive oxygen species. The accumulated oxidative stress deteriorates the intrafollicular environment, resulting in a decline in oocyte quality. This figure summarized the putative molecular actions of different supplementary diets against aging ovarian dysfunction. ROS, reactive oxygen species; SOD, superoxide dismutase; GPX, glutathione peroxidase.

induction, which resulted in increased expression of the decidualization marker insulin-like growth factor-binding protein-1 and the endometrial receptivity marker secreted phosphoprotein 1 compared with the levels in the control group.[21] Thus, DHEA is also expected to have an effect to promote embryo implantation.

Clinical studies

According to a meta-analysis of nine randomized controlled trials (RCTs) involving patients with ovarian dysfunction, the DHEA treatment group exhibited an increase in the clinical pregnancy rate and the number of retrieved oocytes, albeit there was no change in the birth rate.[22] By contrast, another meta-analysis of four RCTs led to the conclusion that DHEA supplementation had no effect on the clinical pregnancy rate.[23] With regard to oocyte quality, although there have been reports showing the IVF outcomes after DHEA treatment in RCTs, the results are contradictory as one study demonstrated an increase in the number of fertilized oocytes,[24] whereas another reported no such increase.[25] Thus, no consensus has been reached. Additionally, in a prospective observational study involving 31 patients with premature ovarian insufficiency (POI), DHEA treatment for 12 months resulted in no change in the number of antral follicles and the blood level of anti-Müllerian hormone and there was no improvement in ovarian function, suggesting the low effectiveness of DHEA supplementation in women with severe ovarian dysfunction.[26] Some clinical trial results suggested the effectiveness of DHEA in ameliorating ovarian dysfunction in humans, including its improvement of oocyte quality. However, few studies have examined the effect on birth rate, and a lack of improvement in the clinical pregnancy rate has also been reported, indicating that further studies on the effectiveness of DHEA in aging infertility are required.

MELATONIN

Molecular mechanism of action

Melatonin, a hormone produced by the pineal body and whose secretion is regulated by the light–dark cycle and photostimulation, is involved in the regulation of circadian rhythms, such as those of sleep, wakefulness, and body temperature. Melatonin also acts directly as a free radical scavenger, having a strong antioxidative effect against reactive oxygen species (Figure 1).[27] Additionally, melatonin exerts an indirect antioxidative effect by increasing both the enzyme activity and mRNA expression of the antioxidative enzymes superoxide dismutase (SOD) and glutathione peroxidase via melatonin receptors (MT1, MT2) (Figure 1).[28] It has been reported that melatonin may exert a direct antioxidative effect in the ovary and prevent ovarian dysfunction induced by aging, based on its presence in human follicular fluid and the expression of its receptors in oocytes and granulosa cells.[29,30] Moreover, it has been shown that the prevention of ovarian dysfunction by melatonin may involve multiple mechanisms, including the activation of sirtuin, which is involved in DNA repair, maintenance of telomere length, and mitochondrial function, in addition to the antioxidative effect.[30]

Preclinical studies

In mammals other than humans, the addition of melatonin to the culture medium for the in vitro maturation (IVM) of immature oocytes was shown to promote the maturation of oocytes as well as the development of fertilized oocytes into blastocysts.[31,32] Additionally, mouse (6 months old) eggs cultured in the presence of 10 μmol/L melatonin indicated an improvement in mitochondrial function.[33] In one study, the supplementation of melatonin in the drinking water to mice (2–3 months old) for 12 months (equivalent to 10 mg/kg/day) resulted in the suppression of age-related decreases in the number of litters, the number of residual follicles in the ovary, and the blastocyst formation rate.[34] This study also showed an improvement in mitochondrial function, a decrease in the production of active oxygen, and an increase in adenosine triphosphate (ATP) production with melatonin supplementation in the ovary. Another study using MT1-knockout mice suggested that both the MT1 and adenosine monophosphate-activated protein kinase signaling pathways in oocytes are important for the effect of melatonin to improve ovarian function in aging mice.[35] Therefore, these reports indicated two possibilities: (1) the addition of melatonin to the culture medium for the IVM of oocytes improves maturation, fertilizing capacity, and embryonic development; and (2) long-term intake of melatonin can ameliorate the age-related deterioration of oocyte quality and suppress the decrease in the number of follicles.

Clinical studies

In a double-blinded RCT involving 66 women with diminished ovarian reserve (DOR), daily intake of 3 mg melatonin from the fifth day of menstruation to oocyte retrieval ($n = 32$) in combination with ovarian stimulation followed by IVF-ET increased the number of mature oocytes and good morphological embryos compared with those parameters in the control group ($n = 34$), but there was no change in the clinical pregnancy rate.[36] There have been no other RCTs for melatonin involving patients with DOR or POI. Another study of 56 patients with previous unsuccessful IVF-ET and a fertilization rate of below 50% reported that daily intake of melatonin

(3 mg/day) from the fifth day of menstruation to oocyte collection significantly improved the fertilization rate.[37] Currently, some studies have reported that melatonin intake improves the treatment outcome of IVF-ET in infertile patients, but evidence of its effectiveness for aging infertility is limited.

COENZYME Q10

Molecular mechanism of action

Coenzyme Q10 (CoQ10), also known as ubiquinone, is a fat-soluble compound that is synthesized mainly in vivo and is known to be present in human follicular fluid.[38] As an essential component of the mitochondrial electron transport system, CoQ10 functions as a coenzyme for enhancing the efficiency of ATP synthesis (Figure 1). It also acts as a free radical scavenger, exerting an antioxidative effect against the active oxygen generated in the process of ATP production (Figure 1). Because the CoQ10 content in organs declines with age,[39] supplementation with CoQ10 for improving mitochondrial function via both its antioxidative effect and increased ATP production is expected to delay ovarian dysfunction.

Preclinical studies

It was reported that the IVM of immature oocytes obtained from infertile aging patients (>38 years of age) in the presence of 50 μmol/L CoQ10 increased the rate of oocyte maturation and reduced post-meiotic chromosomal aneuploidy.[40] Similarly, compared with the granulosa cells obtained from younger infertile women, those from older infertile patients (≥39 years of age) exhibited a functional decline in the mitochondrial electron transport system, but this was restored after culture by the addition of CoQ1 (a soluble analog of CoQ10).[41] It was also indicated in a mouse study that long-term intake of CoQ10 may prevent age-related ovarian dysfunction, with the subcutaneous administration of 22 mg/kg for 15 weeks shown to improve fertility, suppressing the age-related decreases in ovulation number and litter size.[42] Therefore, CoQ10 likely restores oocyte quality by improving the mitochondrial function of granulosa cells and oocytes, and its long-term intake may prevent ovarian dysfunction.

Clinical studies

The effect of CoQ10 supplementation on patients scheduled for IVF-ET treatment (169 women) was investigated in a RCT, with patients with DOR (<35 years of age) comprising the control group.[43] The amount of gonadotropin required for ovarian stimulation was significantly lower in the group administered 600 mg CoQ10/day for 60 days (76 participants) than in the control group (93 participants). Moreover, the fertilization rate and the number of good morphological embryos, in addition to the number of oocytes collected, were significantly higher in the CoQ10-supplemented group. Although not significant, the pregnancy and birth rates per ET and per treatment cycle were also higher in this group, indicating that CoQ10 may ameliorate the deterioration of oocyte quality. However, there have been no other clinical studies targeting aging patients with ovarian dysfunction, and the accumulation of additional evidence is required to ensure the effectiveness of this antioxidant in humans.

RESVERATROL

Molecular mechanism of action

Resveratrol is a natural polyphenol found in grape skin, red wine, and peanuts. This compound exerts an antioxidative effect by activating sirtuin 1 (SIRT1, an NAD^+-dependent histone deacetylase) and promotes the neogenesis and functional enhancement of the mitochondria (Figure 1). Resveratrol is expected to prevent ovarian dysfunction via SIRT1 activation in granulosa cells and oocytes.[44]

Preclinical studies

In one study in which IVM was performed on immature oocytes at the germinal vesicle stage, collected from 64 women (38–45 years of age) undergoing intracytoplasmic sperm injection, the addition of 1 μmol/L resveratrol to the culture medium resulted in an increase in mitochondrial function and a decrease in the proportion of oocytes with abnormal spindle formation and chromosome distribution compared with the group without resveratrol supplementation.[45] In that study, in vitro culturing of oocytes collected from aging mice (48–52 weeks of age) were also examined. The group cultured in medium containing 1 μmol/L resveratrol showed increases in the rates of oocyte maturation, fertilization, and embryos reaching the blastocyst stage as well as in the transcript levels of SIRT1 and the antioxidative enzymes SOD, glutathione peroxidase 4 and catalase.[45] In another study, the administration of 30 mg/L resveratrol in drinking water to mice at 2–3 months old for 12–14 months increased the number of follicles in the ovary relative to that in the control group and also increased the litter size when those females were mated with males, suggesting that the long-term administration of resveratrol may prevent ovarian dysfunction.[46] Recent our study demonstrated increases in the implantation and live pups rates and decreases in the abortion rate as short as 1 week after resveratrol treatment in aging mice at 47 weeks of

age fed with diet (6 g per day) containing 0.04% (w/w) resveratrol. We also showed positive correlations between serum resveratrol levels and the rates of pregnancy and live pups as well as transcript levels of Sirtuin family including Sirt1, Sirt3, Sirt4, Sirt5, and Sirt7 as potential downstream anti-aging effectors in ovaries. Furthermore, our study showed the restoration of mitochondrial function in oocytes by a short-term (1 week) resveratrol treatment.[47]

Clinical studies

To date, no clinical trials have investigated the effect of resveratrol on ovarian dysfunction in aging women. However, one clinical study examined the effects of a daily intake of 200 mg resveratrol during the luteal phase after ET (102 participants, 204 cycles) and reported a decrease in the clinical pregnancy rate and an increase in the miscarriage rate.[48] Because resveratrol has the effect of suppressing endometrial decidualization in humans,[49] its intake may require precautions, such as the avoidance of use at the time of implantation.

NICOTINAMIDE MONONUCLEOTIDE

Molecular mechanism of action

In the body, nicotinamide mononucleotide (NMN) is metabolized by nicotinamide phosphoribosyltransferase to form nicotinamide adenine dinucleotide (NAD^+), which functions as an electron donor in mitochondria for the ATP production process and as a coenzyme for SIRT1. The administration of NMN is expected to replenish the age-related decrease in NAD^+ in the ovary and restore mitochondrial functions to improve ovarian functions through the activation of SIRT1 (Figure 1).

Preclinical studies

The intraperitoneal administration of NMN at a dose of 200 mg/kg to aging mice (64–68 weeks of age) was shown to restore the NAD^+ concentration in oocytes, increase the ovulation number, and suppress fragmentation of oocytes compared with these parameters in the controls.[50] Additionally, in the IVM of immature oocytes from aging mice, the use of a culture medium containing 1 μmol/L NMN was shown to increase the blastocyst formation rate relative to that in the non-supplemented group, suggesting that NMN can improve oocyte quality directly.[50] Furthermore, when aging mice (14–16 months old) that had been administered 0.5 g/L NMN in drinking water for 4 weeks were mated with males, their litter acquisition rate was increased and their litter size was larger than those of the control group, suggesting that NMN intake can improve fertility in aging mice.[51] However, all of the studies demonstrating the improvement in oocyte quality via NMN supplementation were conducted in mammals other than humans. Of note, the excessive dose of NMN showed lower fertility in aging mice compared with that in the non-supplemented controls.[50,51]

Clinical studies

No human studies examining the clinical significance of NMN on ovarian dysfunction have been reported to date.

PYRROLOQUINOLINE QUINONE

Molecular mechanism of action

Pyrroloquinoline quinone (PQQ), which was first discovered in bacteria, is a vitamin-like compound that functions as an oxidation–reduction coenzyme. With regard to its mechanism of action for ovary protection, PQQ was reported to act as a free radical scavenger, removing excessive active oxygen generated during the division of granulosa cells and suppressing apoptosis and mitochondrial degeneration (Figure 1).[52] Furthermore, in addition to its indirect antioxidative effects, such as through the induction of antioxidant gene expressions by nuclear factor erythroid 2 (Nrf2) activation.[53] PQQ was shown to promote mitochondrial neogenesis in a peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α)-dependent manner,[54] which may also contribute to the prevention of ovarian dysfunction.

Preclinical studies

The administration of PQQ in drinking water to mice (20 days of age) at a dosage of 2 mg/kg/day for 4 days, followed by equine chorionic gonadotropin, reduced the number of TUNEL-positive granulosa cells and increased that of preovulatory follicles relative to the numbers in the non-supplemented group.[52] Moreover, although the PQQ-supplemented group showed a significant increase in ovulation number, rates of fertilization, and blastocyst formation of oocytes obtained from PQQ-treated mice were comparable to those of the control group, indicating that the supplement has no adverse effect on oocyte quality.[52] Therefore, the administration of PQQ is expected to yield more oocytes under ovarian stimulation in humans.

Clinical studies

Clinically, a single oral intake of PQQ at a dose of 0.2 mg/kg has been shown to increase the blood

concentration of the compound and decrease that of thiobarbituric acid reactive substances, which are generated during the decomposition of lipid peroxides, suggesting that the antioxidative effect of PQQ is also effective in humans.[55] However, there have been no reports of studies examining its effectiveness in patients with ovarian dysfunction.

CONCLUSION

Aging women with ovarian dysfunction tend to exhibit resistance to ovarian stimulation by ovulation-inducing agents, such as gonadotropic hormones (gonadotropin formulations) and anti-estrogen preparations. Therefore, increases in the dose and frequency of use of gonadotropin preparations are often attempted, but with limited treatment effect, notwithstanding that the long treatment duration places a heavy financial and mental burden on the patients and their partners. Under such circumstances, patients often take supplemental diets in the hope of improving their fertility. Supplemental diets are relatively inexpensive and convenient for patients, as they can be purchased at the will of the individual and from among multiple options. However, as shown in this review article, although supplements have been demonstrated to have certain effects in animal studies, evidence of their effectiveness in humans is either lacking or insufficient for reaching a definite conclusion. This may be due to the lack of standardized diagnostic criteria for DOR and poor responders as well as unclear optimal dosages and duration of supplement intake. Therefore, additional lines of evidence on the effectiveness of supplemental diets in aging patients with ovarian dysfunction need to be accumulated in the future.

AUTHOR CONTRIBUTIONS

The authors contributed to the conception of the work, making a figure, and drafting and revising this manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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