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Supplementation in Infertility: A Narrative Literature Review

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ABSTRACT

Infertility is a significant global health issue. It can have profound medical, psychological, and social consequences. As medical understanding of reproductive health advances, numerous factors contributing to reduced fertility have been identified. In recent years, nutritional supplementation has gained increasing attention as a potential adjunct to standard infertility treatments. Research now investigates its roles in various biological and reproductive processes.

To review current knowledge on the role, safety, and mechanisms of nutritional supplements in infertility treatment.

We conducted a narrative review of scientific literature from 2012 to 2025. The search included PubMed, Cochrane Library, Web of Science, and Google Scholar. We included randomized controlled trials, meta-analyses, systematic reviews, and guidelines from scientific societies. Studies of low methodological quality were excluded.

The strongest evidence supports folic acid supplementation, which acts as a methyl donor to improve oocyte quality and prevent neural tube defects. Myo-inositol demonstrated 85% effectiveness in restoring ovulation in women with polycystic ovary syndrome. Coenzyme Q10 improves oocyte quality, especially in women over 35 years old. Antioxidants and minerals support sperm health by reducing oxidative stress and enhancing seminal parameters. Omega-3 polyunsaturated fatty acids modify cell membrane fluidity to enhance sperm quality, particularly when the omega-6/omega-3 polyunsaturated fatty acids ratio is optimized. Probiotics may support treatment by promoting a healthy gut microbiota and lowering systemic oxidative stress.

Nutritional supplementation is a promising supportive approach in infertility treatment. What is more, personalized supplementation based on metabolic and genetic profiles is a future direction. Supplements are generally safe at recommended doses; however, precautions against overdose and self-medication are essential.

Keywords: infertility, reproductive health, supplementation

Content

1. Introduction

Infertility, defined as the inability to become pregnant despite regular sexual intercourse (without using fertility limitation methods) for a period longer than one year, is an increasingly serious public health problem. According to World Health Organization data, it affects 13-18% of couples in Poland and about 15%[1].

The causes of infertility are complex and multifactorial, with the most common being ovulation disorders (about 20% of cases), male factor (about 30% of cases), tubal-peritoneal factors, intrauterine factors (about 20-25% of cases), and endometriosis (about 10-15% of cases). Almost half of couples encounter a combination of factors[2].

In recent years, there has been a growing interest in nutritional supplementation as a method supporting infertility treatment. The mechanisms of action in the context of fertility are diverse - antioxidants protecting reproductive cells from damage caused by free radicals (vitamin C, E, coenzyme Q10), folic acid participating in deoxyribonucleic acid (DNA) synthesis, or minerals being cofactors in reproductive processes (selenium, zinc)[3].

This study aims to present the current state of knowledge on supplementation in infertility treatment, including recommendations, safety, and mechanisms of action.

Dietary supplements, according to Polish law, are foodstuffs intended to supplement a normal diet and constitute a concentrated source of vitamins, minerals, or other substances with nutritional or physiological effects. Unlike drugs, supplements do not require rigorous clinical trials confirming their effectiveness and safety before market introduction. Only notification to the Chief Sanitary Inspector is sufficient, without the obligation to provide quality research results.

2. Research materials and methods

A systematic review of scientific literature covering publications from 2012 to 2025 was conducted. PubMed, Cochrane Library, Web of Science, and Google Scholar databases were searched using keywords: "fertility supplements", "infertility treatment", "antioxidants reproduction", "polycstic ovary syndrome (PCOS) supplementation", "male fertility vitamins", "female fertility vitamins".

Randomized controlled trials, meta-analyses, systematic reviews, and guidelines from scientific societies were included, totaling approximately 99 studies. Studies of low methodological quality (small study groups, short observation time, lack of proper randomization) were excluded.

A key issue is the inclusion of heterogeneous patient groups in studies, which makes interpreting of results difficult. There is also insufficient data on optimal doses for different age and ethnic groups. Most studies focus on indirect parameters (semen quality, hormone levels) instead of hard endpoints (live births). This may lead to overestimation of supplement effectiveness.

3. Results

Antioxidants

Oxidative stress plays a key role in the pathogenesis of both female and male infertility. ROS - reactive oxygen species, produced by mitochondrial metabolic processes; when produced in excess, they lead to reproductive cell damage and premature apoptosis4. Limited amounts of ROS are necessary for sperm maturation, but excess amounts reduce their motility and viability.
Antioxidants neutralize excess ROS. For clarity, we distinguish between enzymatic antioxidants (e.g., catalase, glutathione peroxidase) and non-enzymatic antioxidants (vitamins C, vitamin E, vitamin A, coenzyme Q10, zinc, selenium).

Coenzyme Q10 (ubiquinone) is one of the best-studied antioxidants in the context of fertility. Studies have shown that supplementation can significantly improve oocyte quality, especially in women over 35 years of age[3].

In studies, many mechanisms have been identified that contribute to the anti-ageing action of coenzyme Q10 on oocytes. Results from molecular docking and molecular dynamics simulation studies indicate that coenzyme Q10 can affect these key targets to combat oocyte ageing, also improving ovarian response to stimulation during in vitro assisted reproduction procedures[4].

N-acetylcysteine (NAC) is a precursor of glutathione, one of the most important natural intracellular antioxidants. Studies have shown the particular effectiveness of NAC in patients with PCOS. During supplementation, ovulation rates and embryo quality increased[3,5].

Vitamin C plays a multidimensional role in the body, particularly important for individuals trying to conceive[3]. Besides antioxidant properties, it participates in collagen synthesis - a key structural protein responsible for the integrity of blood vessels, mucous membranes, and extracellular matrix, which is significant for the proper functioning of reproductive organs. Additionally, vitamin C increases absorption of non-heme iron from the diet, which is important for maintaining proper iron management and preventing anaemia, which can negatively affect fertility[6].

Vitamin E is a fat-soluble antioxidant that concentrates mainly in cell membranes[3]. Its main function is protecting polyunsaturated fatty acids (PUFA) in membrane phospholipids from lipid peroxidation, i.e., oxidation leading to damage to membrane structure and function. Thanks to this, vitamin E stabilizes cell membranes, prevents loss of reproductive cell integrity, and protects against gamete function disorders. Moreover, vitamin E supports the regeneration of other antioxidants, including vitamin C, which additionally increases antioxidant protection[7,8].

The synergy between these two vitamins lies in vitamin C's ability to regenerate the oxidized form of vitamin E, restoring its ability to neutralize free radicals. Combined use of vitamins C and E leads to a significant reduction in oxidative damage to cell membranes, which is particularly important for improving oocyte and sperm quality and increasing the effectiveness of infertility treatment. Regular, appropriately balanced supplementation of both vitamins is recommended for people struggling with oxidative stress, especially in PCOS, endometriosis, or idiopathic infertility, where oxidative-reductive balance is disturbed[9,10].

Vitamins

Folic acid (vitamin B9) is essential for DNA synthesis. Supplementation of 400 microgram (mcg) per day is recommended for all women planning pregnancy and in the first trimester to prevent neural tube defects and other developmental defects[11]. Studies show that higher folic acid intake in the periconceptional period improves oocyte quality, increases the number of normal embryos, and thus improves pregnancy rates in assisted reproduction procedures[12,13].

Vitamin D maintained at an appropriate level is associated with higher pregnancy rates, live births in in vitro fertilization (IVF) procedures, and better ovarian reserve (higher anti-müllerian hormone values)[14]. Vitamin D improves uterine conditions by increasing endometrial thickness, thereby supporting implantation[15]. In men with vitamin D deficiency, supplementation improves sperm production and increases the chances of natural conception, even if it does not improve classic semen parameters[16]. Recommended doses are 1000-2000 IU (international units) per day and higher in people with deficiencies. This is particularly important in populations with a high percentage of deficiency[13].

Vitamin B12 (cobalamin) works together with folic acid. Its deficiency is associated with reduced semen quality (decreased sperm motility and concentration), ejaculation disorders, increased risk of miscarriages, and developmental defects. Vitamin B12 supplementation is safe and recommended in risk groups for deficiency (people on vegan diets, with absorption disorders, after bariatric surgeries) and during pregnancy planning[17,18].

Minerals

Zinc is a cofactor for numerous enzymes, including those involved in hormone synthesis and DNA replication. In men, it is important in the spermatogenesis process, which also affects semen volume, proper morphology, sperm motility, and testosterone level regulation[19].

Selenium protects gametes from lipid peroxidation. In men, it improves sperm motility. As a mineral that is simultaneously an antioxidant, it is described as a neutralizer of reactive oxygen species and, therefore, as a factor increasing fertility with regular supplementation[20–23].

Iron supplemented in non-heme form reduces the risk of ovulatory infertility by up to 40%. Iron supplementation at high doses correlates with decreased antral follicle count and increased follicle-stimulating hormone, a phenomenon known as the "iron overload" effect[24]. Meta-analyses show that iron deficiency occurs more frequently in women with unexplained infertility[25].

Other Organic Compounds

L-carnitine is a compound that transports long-chain fatty acids to sperm mitochondria. Studies show that supplementation increases progressive motility and reduces DNA fragmentation[20,26].

Myo-inositol is a secondary insulin messenger; disruptions in its level are observed especially in patients with PCOS. Meta-analysis showed that supplementation in their case reduces the homeostatic model assessment of insulin resistance index, increases sex hormone-binding globulin, and restores ovulation in up to 70%[27]. In patients undergoing IVF, the fertilisation rate increased during supplementation[28]. The combination of myo-inositol with D-chiro-inositol in a 40:1 ratio shows greater effectiveness than myo-inositol monotherapy[29,30].

Melatonin is a lipophilic antioxidant, modulating circadian rhythms in the hypothalamic–pituitary–ovarian axis. Its supplementation increases the chances of successful assisted fertilisation, increases the number of metaphase II-oocytes, and clinical pregnancies[31]. It inhibits excessive ferroptosis (reduced iron accumulation, lipid peroxidation resulting in reduced oocyte quality) and cuproptosis (copper ion accumulation binding Krebs cycle proteins). Women of advanced reproductive age have higher levels of free metal ions and increased oxidative stress in the follicular microenvironment. Melatonin, by blocking both metal-independent cell death pathways and strengthening mitochondria, can double the chances of live birth after IVF in this age group (over 38 years of age)[32,33].

Omega Acids

Eicosapentaenoic acid (EPA) has strong anti-inflammatory properties, affecting the inhibition of pro-inflammatory prostaglandins and leukotrienes. It is also an important building component of sperm cell membranes, affecting their structural and functional integrity[34]. Conducted studies show a relationship between EPA level in the body and sperm function - too low concentration may lead to increased oxidative stress, too high concentration negatively affects sperm viability[35]. Studies also showed significant improvement in total sperm count and density in the ejaculate[34].

Docosahexaenoic acid (DHA) is the main fatty acid in sperm cell membranes and plays a significant role in proper reproductive system function[36]. DHA is also a precursor of specialized pro-inflammatory mediators that regulate inflammatory and immunological processes[37]. It has been shown that decreased DHA concentration may coexist with idiopathic infertility[35].

α-linolenic acid (ALA) is primarily a precursor of EPA and DHA; however, studies do not show significant correlations between ALA concentrations in serum and chances of pregnancy or ovarian reserve parameters[38]. The effect of ALA on in vitro fertilisation looks different - higher concentrations may correlate with a decreased chance of achieving pregnancy this way. This phenomenon is not related to the overall omega-3 polyunsaturated fatty acids level, and further research is needed. No clear benefits from ALA supplementation for semen quality have been shown[39,40]. However, it has an indirect effect on the EPA and DHA increase [35].

Arachidonic acid (AA) is an important long-chain polyunsaturated fatty acid from the omega-6 group present in cell membranes. In seminal fluid, AA is a substrate for prostaglandin formation, which affects sperm motility and function. Prostaglandin concentration is significantly lower in men with fertility problems, which may suggest that AA pathway disorders may worsen semen parameters and reduce fertility[41]. Studies show that a higher omega-6/omega-3 polyunsaturated fatty acids ratio and increased AA in semen are characteristics of infertile men because they correlate with lower sperm motility[42]. In this case, the situation is quite different. While prostaglandin pathways arising from AA are crucial for ovulation, implantation, and proper pregnancy course, excessive or disturbed AA metabolite production is associated with PCOS pathogenesis, endometriosis, and pregnancy complications

such as preeclampsia[42,43]. AA negatively affects the percentage of pregnancies achieved in assisted reproduction procedures – intracytoplasmic sperm injection or IVF [44,45].

Omega-3 to omega-6 ratio

Contemporary Western diet is characterized by significant predominance of omega-6 polyunsaturated fatty acids (LA, AA) over omega-3 polyunsaturated fatty acids (ALA, EPA, DHA); typical omega-6/omega-3 polyunsaturated fatty acids ratio is 15:1 to over 25:1, while physiological optimum is estimated at 1:1-4:1. Analyzing benefits and losses, AA supplementation is not recommended in infertility treatment - most publications emphasize the importance of maintaining balance between omega-6 polyunsaturated fatty acids and omega-3 polyunsaturated fatty acids and avoiding excess AA in diet. Too much omega-6 polyunsaturated fatty acids leads to an inflammatory state, which negatively affects gonadal function, spermatogenesis, and embryo implantation[34]. Studies show that supplementation of omega-3 acids alone without maintaining a proper omega-6/omega-3 polyunsaturated fatty acids ratio does not bring full metabolic and reproductive benefits, particularly regarding high consumption of plant oils rich in ALA[46–48]. Higher omega-6/omega-3 polyunsaturated fatty acids ratio in semen strongly correlates with increased sperm DNA fragmentation, higher lipid peroxidation level, and lower sperm motility[34,49]. In women's case, studies show that a higher omega-6/omega-3 polyunsaturated fatty acids ratio was significantly associated with increased risk of primary infertility in women aged 20-34 years[50].

Probiotics

Role of probiotics in male infertility

Semen quality disorders are one of the most common causes of male infertility. Increasingly, research indicates that a factor exacerbating these problems may be chronic oxidative stress and intestinal microbiota disorders. Probiotics, mainly strains from the *Lactobacillus* and *Bifidobacterium* genera, represent a promising, non-invasive option supporting the treatment of idiopathic male infertility[51]. Clinical studies show that probiotic supplementation may contribute to the improvement of semen parameters such as ejaculate volume, sperm count and motility, as well as reduction of sperm genetic material fragmentation and levels of oxidative stress and inflammatory markers. This is mainly caused by the antioxidant and anti-inflammatory action of probiotics as well as improvement in the absorption of microelements necessary for spermatogenesis, i.e., zinc and selenium[52,53]. These effects may also occur through modulation of

the "gut-testis" axis. Healthy intestinal flora reduces endotoxemia and affects systemic immunological processes, which may have beneficial effects on testicular function and semen parameters. Importantly, benefits from probiotic therapy are most often observed after a minimum of 8-12 weeks of use, and the safety of this type of intervention is very high[53].

Role of probiotics in female infertility

Proper microbiome of the reproductive system, especially *Lactobacillus* dominance in the vagina, plays a key role in providing conditions for embryo implantation, pregnancy maintenance, and protection against inflammatory conditions and infections. Vaginal and uterine flora disorders increase the risk of implantation failures, miscarriages, and chronic inflammation; therefore, there is growing interest in the role of probiotics in therapy supporting female infertility treatment[54–56]. Probiotic supplementation, especially during antibiotic therapy, has shown potential in increasing biochemical pregnancy rates and reducing premature miscarriages in patients with chronic endometrial inflammation[57]. In studies, we can observe that administration of specific strains such as *Ligilactobacillus salivarius*, for 3 to 6 months in women with recurrent pregnancy losses or unexplained infertility, increased pregnancy rates[54]. In studies on women with PCOS, oral probiotic and symbiotic supplementation improved metabolic parameters (insulin resistance, lipid profile, reduced hyperandrogenism) and could beneficially affect ovulation, although evidence for direct fertility improvement is limited[56].

Table 1 summarizes analyzed substances.

Table 1. Analyzed substances in the context of supporting infertility treatment.

GROUP	SUBSTANCE
ANTIOXIDANTS	Coenzyme Q10, N-acetylcysteine, Vitamin C, Vitamin E
VITAMINS	Folic acid, Vitamin D, Vitamin B12
MINERALS	Zinc, Selenium, Iron
OTHER ORGANIC COMPOUNDS	L-carnitine, Myo-inositol, Melatonin
GROUP	**SUBSTANCE**
OMEGA ACIDS	-
PROBIOTICS	-

Safety and Example Drug Interactions

The safety of dietary supplement use is a key aspect of therapy, as these substances, compared to drugs, should always be treated as merely supportive solutions to the problem. It should be remembered that, unlike drugs, their registration does not require such restrictive testing, and they can be purchased without a doctor or pharmacist recommendation. This is particularly important for patients simultaneously taking medications for conditions accompanying infertility. Attention should be paid to whether supplement inclusion does not increase the risk of worsening baseline therapy effectiveness. The following chapter contains an analysis of the safety profile and examples of potential interactions and adverse effects with the most commonly used medications for the selected supplements discussed above.

Coenzyme Q10

According to the literature, this substance shows great safety. The most common adverse symptom is mild dyspepsia. Possible weakening of warfarin action effect – regular international normalized ratio (INR) monitoring recommended[58].

N-acetylcysteine

NAC may intensify the hypotensive effect of nitroglycerin by increasing nitric oxide availability[59] and also increasing bleeding risk[60].

Vitamin C

Meta-analysis of 16 randomized controlled trials (RCTs) showed increased hyperoxaluria, but without a significant increase in kidney stone risk[61]. Large oral doses may cause diarrhea and bloating in patients[62].

Vitamin E

Supplementation ≥400 IU per day was associated with increased intracerebral bleeding in meta meta-analysis of 27 RCTs[63]. Concurrent administration with vitamin K antagonists (warfarin, acenocoumarol) may increase INR[64].

Vitamin D

A systematic review of 48 RCTs showed a 54% increase in hypercalcemia, but no increase in kidney stones[65]. Hypercalcemia risk is potentiated by the concurrent use of thiazides and calcium preparations[66].

Vitamin B12

Metformin treatment for longer than 1 year may lower vitamin B12 concentrations[67]. Proton pump inhibitors reduce B12 absorption by up to 50% - sublingual route worth considering[68,69].

Zinc

Dose above 40 milligram (mg) per day for 8 weeks may induce copper deficiency and anaemia[70].

Selenium

Supplementation may be associated with **alanine aminotransferase** increase; this suggests attention to liver enzyme levels and functional efficiency[71]. Preparation metabolism is conducted by cytochrome P450 1A2 - potential interaction with clozapine may occur, increasing its level by 18%[72].

Iron

Oral preparations at a 60 mg dose reduce levothyroxine bioavailability by 40%; the minimum supplementation interval indicated is 4 hours[73]. Supplementation increases dyspepsia risk, especially in pregnant women[74].

L-carnitine

Dose 2 g/d is well tolerated, with single cases of mild diarrhea noted[75]. Potentially may intensify acenocoumarol action - INR monitoring is recommended[76].

Melatonin

Fluvoxamine increases melatonin urea under the curve AUC 12-fold, so there is a risk of a strong increase in sleepy effect[77].

Omega-3 fatty acids (EPA, DHA, ALA)

Doses of 4 grams per day may cause INR increase - caution should be exercised when using oral anticoagulants[78].

Arachidonic acid

No RCT data available for this preparation. Observational data suggest a potential increase in platelet aggregation - this fact should be considered in antiplatelet therapy with aspirin[79].

Probiotics

Bacteremia risk of 0.02% shown, mainly in immunosuppressed patients[80]. Concurrent use with beta-lactam antibiotics reduces their drug concentration in the intestine by 25%, which may modify the microbiome[81].

Table 2 and Table 3 summarize potential interactions and adverse effects of the presented substances.

Table 2 and 3. Example interactions and/or adverse effects of selected supplements used in infertility. Table 3 continues the list presented in Table 2.

Supplement	Example interactions and/or adverse effects
Coenzyme Q10	Weakening warfarin action effect – regular INR monitoring recommended
N-acetylcysteine (NAC)	Intensification of nitroglycerin hypotensive effect by increasing NO availability; INR prolongation increases bleeding risk
Vitamin C	Large oral doses may cause diarrhoea and bloating
Vitamin E	Concurrent administration with vitamin K antagonists (warfarin, acenocoumarol) increases INR
Vitamin D	Hypercalcemia risk is potentiated by the concurrent use of thiazides and calcium preparations
Vitamin B12	Interaction with proton pump inhibitors reduces vitamin B12 absorption
Zinc	High doses may cause copper deficiency and anaemia
Selenium	Potential interaction with clozapine through CYP1A2 metabolism – an increase in clozapine level
Iron	Decreased levothyroxine bioavailability – minimum 4 h interval indicated

Supplement	Example interactions and/or adverse effects
L-carnitine	Potential intensification of acenocoumarol action – INR monitoring recommended
Myo-inositol	No significant interactions with CYP450
Melatonin	Fluvoxamine increases melatonin AUC 12-fold – risk of a strong increase in sleepy effect
Omega-3 acids (EPA, DHA, ALA)	High doses cause INR increase – caution with oral anticoagulants
Arachidonic acid	Potential increase in platelet aggregation – attention with antiplatelet therapy with aspirin
Probiotics	Concurrent use with β-lactam antibiotics reduces their concentration in the intestine

4. Discussion

Interpretation of study results and current state of knowledge

Analysis of available studies on supplementation in infertility treatment reveals a complex picture of the effectiveness and safety of individual substances. Latest meta-analyses from 2025 confirm earlier observations regarding supplement effectiveness hierarchy, while simultaneously emphasizing significant methodological limitations of most available studies[82].

Particularly valuable are results concerning myo-inositol, where the latest meta-analysis of 16 studies showed significant improvements in total sperm motility (standardized mean difference (SMD) 0.90; 95% confidence interval (CI): 0.34 to 1.46; p-value (p) =0.001) and progressive sperm motility (SMD 1.48; 95% CI: 0.37 to 2.59; p=0.008). What is particularly important, a significant reduction in sperm DNA fragmentation was also observed (SMD −1.37; 95% CI: −2.43 to −0.32; p=0.01), which may be crucial for offspring quality[29].

In the context of female infertility, a meta-analysis concerning omega-3 acids from 2024, including 1789 women undergoing infertility treatment, showed statistically significant improvements in pregnancy rates (odds ratio (OR) =1.74; $p \leq 0.01$) and fertilisation rates (OR=2.14; $p \leq 0.01$). These results are particularly promising in the context of the growing popularity of omega-3 acid supplementation[83].

Limitations of current studies and methodological challenges

Population and methodology heterogeneity of study and populations applicability:

One of the fundamental problems in supplementation studies in infertility is significant heterogeneity of studied populations. Patients differ not only in terms of infertility causes, but also in age, ethnic origin, nutritional status, and coexisting diseases. This diversity makes result generalization difficult and may explain contradictory results between studies. What is more, it makes it difficult to compare results between the studies.

Moreover, it is also worth noting that most studies were conducted on Caucasian populations, which greatly limits the usefulness of the results for other ethnic groups or geographical regions. In addition, nutritional status constitutes a significant difference due to differences in dietary practices across populations, which may affect the effectiveness of interventions[82].

Methodological quality:

The latest systematic review from 2024 concerning male supplements showed that less than half of the antioxidant supplements available on the market have been tested in clinical trials, and available studies are generally characterized by low methodological quality, according to small sample sizes and short observation periods. Authors emphasize that only two supplements have been tested in high-quality clinical trials[84]. This prevents the generalization of results and creates a need for well-designed trails.

Endpoint problematic

Most studies focus on indirect measures, such as semen quality or hormone levels, rather than the most important outcome: live births. Relying on these surrogate markers can overestimate the effect of supplements, because improvements in these parameters do not necessarily translate into better pregnancy rates or fertility.

This is illustrated by The Males, Antioxidants, and Infertility Trial conducted by the National Institutes of Health on 171 couples, which showed no statistically significant differences in semen parameters between the group receiving antioxidants and placebo after three months. Moreover, live birth rates did not differ significantly between groups (15% vs 24%)[84,85]. This highlights the need for well-designed, future studies with clinically meaningful outcomes.

Mechanistic bases of supplement action

Oxidative stress and antioxidant systems

Latest molecular studies provide an increasingly detailed picture of mechanisms through which oxidative stress affects reproductive functions[85]. Lipid peroxidation remains one of the key damage mechanisms, especially in the context of sperm cell membranes rich in polyunsaturated fatty acids[86,87].

Studies from 2025 indicate that oxidative stress leads to three main types of damage: lipid peroxidation, DNA fragmentation, and protein oxidation. Each of these mechanisms contributes to reduced sperm quality and male infertility [85].

Gut-reproduction axis

A revolutionary discovery of recent years is the identification of the gut-reproduction axis. Studies show that the intestinal microbiome can affect reproductive functions through

modulation of sex hormone levels, insulin sensitivity, the immune system, and gonadal microbiota[88,89].

Particularly interesting are study results on the microbiome-gut-testis axis, where intestinal dysbiosis may contribute to altered immune responses, inflammatory state, and hormonal disorders, potentially playing a role in fertility problem pathogenesis. Animal studies showed that selenium supplementation may improve male fertility factors through strengthening this axis [90].

Personalized medicine and pharmacogenomics

Genetic polymorphisms and supplementation response

Pharmacogenomics development opens new possibilities for personalized supplementation. Particularly important are polymorphisms of genes encoding folate-metabolizing enzymes (MTHFR). Patients with MTHFR C677T polymorphism may require higher folic acid doses or direct 5-methyltetrahydrofolate supplementation[91,92]. Meta-analysis from 2009 showed that MTHFR C677T TT polymorphism was associated with significantly increased breast cancer risk (OR 1.62; 95% CI: 1.14-2.30), while high folate intake showed inverse correlation with this cancer risk. These results emphasize the importance of supplementation individualization based on genetic profile[93].

Nutrigenomics and nutrition personalization

Latest reviews from 2024 emphasize nutrigenomics potential in supplementation optimization. Integration of genetic, metabolomic, and microbiome data may enable precise supplement selection. However, studies show that despite almost 20 years of research and commercial offers, evidence for gene-based nutritional recommendation effectiveness is still generally lacking[94].

Artificial intelligence in nutrition personalization

The application of artificial intelligence in nutrition personalization presents promising perspectives. Machine learning algorithms can analyze complex genetic, phenotypic, and behavioural datasets to generate highly personalized nutritional recommendations. A 2025 study showed that a 6-week AI-based nutritional program significantly increased richness (Chao1 index) and diversity (Faith's phylogenetic diversity) of intestinal microbiota[95].

Therapeutic Recommendations

Based on the analysis of available studies, the following guidelines for safe supplementation with the above-mentioned preparations can be adopted:

INR determination every 2–4 weeks in patients treated with warfarin taking vitamin E >200 IU/d, omega-3 in a dose greater than or equal to 2 grams per day, or NAC.

Administer zinc and iron a minimum of 2 hours before or 4 hours after fluoroquinolone or tetracycline antibiotic.

Vitamin D in doses greater than 4000 IU per day - necessary assessment of calcium concentration, estimated glomerular filtration rate, and urine calcium concentration every 3 months.

Annual vitamin B12 level determinations; oral supplementation 1000 mcg per day when result <300 picomole per liter.

Avoid probiotics in people with neutropenia or heart valves.

Future Challenges and Research Directions

Need for high-quality methodological studies

There is an urgent need to conduct larger, multicenter randomized studies with appropriately long observation periods and hard endpoints. Future studies should also include stratification according to infertility causes, age, and patient genetic profile.

It is also necessary to create clear regulatory standards for supplements dedicated to infertility treatment, considering their specificity and potential long-term effects on reproductive health.

Summary

Analysis of available clinical studies allows hierarchization of supplements in terms of their effectiveness in infertility treatment. The strongest scientific evidence concerns folic acid, whose effectiveness in improving oocyte quality and preventing neural tube defects is indisputable. The European Society of Human Reproduction and Embryology (ESHRE) recommends folic acid supplementation at a 400 mcg/day dose for all women planning pregnancy, regardless of fertility status. Pharmacogenomics development opens new possibilities for supplementation. Polymorphisms of genes encoding folate-metabolising enzymes (MTHFR) may affect folic acid

requirements. Patients with MTHFR C677T polymorphism may require higher folic acid doses or direct 5-methyltetrahydrofolate supplementation[6].

Myo-inositol shows 85% effectiveness in improving ovulation and pregnancy rates in women with PCOS. Meta-analysis including 812 patients showed that myo-inositol supplementation shortens ovarian stimulation time, reduces gonadotropin requirements, and improves embryo quality. Particularly important is the impact on insulin sensitivity, as insulin resistance is one of the main pathogenetic mechanisms of PCOS[30].

The American Society for Reproductive Medicine (ASRM) recognizes antioxidant supplementation as justified in men with infertility, especially after demonstrating oxidative stress. Supplementation should be conducted for a minimum of 3 months (spermatogenesis duration). Individual therapy based on baseline semen parameters and oxidative stress markers is recommended. Excessive antioxidant doses should be avoided as they may act pro-oxidatively[96].

Supplementation in infertility treatment represents a promising therapeutic area but requires a careful and scientific approach. The strongest evidence of effectiveness concerns folic acid, myo-inositol, coenzyme Q10, and zinc. An individual approach to each patient is crucial, considering case specificity, laboratory test results, and the presence of coexisting diseases.

Most supplements used in infertility treatment are characterized by a good safety profile when used in recommended doses. Most common adverse effects are mild and mainly include gastrointestinal disorders.

The future of supplementation in infertility treatment will probably be based on personalized medicine, using genetic, metabolomic, and microbiome data for optimal supplement selection. Further high-quality methodological quality studies are necessary, including larger patient groups and longer observation times.

Patient education and interdisciplinary cooperation between gynecologists, dietitians, and pharmacologists will be key to optimizing therapeutic results. Supplementation should be treated as an element of a comprehensive approach to infertility treatment, not as an alternative to conventional therapeutic methods.

5. Conclusions

Infertility currently represents one of the most important reproductive health problems for couples, requiring a comprehensive therapeutic approach. Clinical studies have shown that selected supplemental substances, especially the active forms of folic acid (5-metylotetrahydrofolian) and coenzyme Q10, receive exceptionally positive evaluations in the context of supporting infertility treatment, resulting in a significant increase in therapy success rates. Other substances, such as antioxidants, vitamins, and supplements, may also have a positive impact on increasing fertility, especially when combined with holistic therapy, which includes lifestyle and mental health care.

In the light of growing fertility problems in contemporary society, there is an urgent need to conduct more clinical studies with improved methodology and a precisely selected study group. Only through systematic high-quality studies will it be possible to utilize the supplementation potential in comprehensive treatment fully.

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Supplementary materials

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