Addressing Recurrent Implantation Failure through Nutritional Support: Focusing on the significance of Omega-3 Fatty Acids and Vitamin E – A Narrative Review

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Abstract— Recurrent Implantation Failure (RIF) is a significant challenge in assisted reproductive technology (ART), which often causes emotional and financial stress for couples. Our review explores the potential benefits of nutritional supplements like Omega-3 fatty acids (OM3FAs) and Vitamin E to improve reproductive success in women with RIF. We gathered evidence from 30 peer-reviewed studies to assess the effects of these nutrients on fertility, endometrial receptivity, and implantation success in both natural conception and ART-assisted cycles. Supplementation with Omega-3 and Vitamin E is generally safe, cost-effective, easily accessible, and has been linked to improved endometrial receptivity and higher implantation rates in women experiencing RIF.

OM3FAs may enhance fertility by reducing inflammation, improving perfusion at the implantation site, and enhancing the quality of both oocytes and sperm. Vitamin E has antioxidant properties that contribute to improved endometrial quality and receptivity. Despite promising findings, further studies are necessary to confirm their effectiveness in humans and to develop standardized supplementation protocols for use as adjuncts to support natural and ART-assisted conception. Overall, OM3FAs and Vitamin E represent promising non-invasive options to support reproductive success in women facing recurrent implantation failure.

Index Terms— Recurrent Implantation Failures, Assisted Reproductive Technology, Vitamin E, Omega -3 Fatty Acid

INTRODUCTION

Over 70 million couples of childbearing age are affected by infertility[1], and turn to Assisted Reproductive Technology (ART) which often fails due to failure of Implantation[2,3]. Recurrent Implantation Failure (RIF) is the failure to achieve a clinical pregnancy after the transfer of at least four good-quality embryos[4]. It affects nearly 10% of in-vitro fertilization embryo transfer [IVF-ET] patients globally, posing significant clinical challenges and placing an enormous emotional and financial burden on couples[5,6].

This review explores the role of supplementation with Omega-3 fatty acids and Vitamin E to increase the rate of successful implantation in the treatment of RIF.

METHODS

This narrative review evaluated the potential role of Omega-3 fatty acids (OM3FAs) and Vitamin E in the management of RIF. A comprehensive literature search was performed using PubMed, Scopus, and Google Scholar, incorporating keywords such as "Recurrent Implantation Failure," "omega-3 fatty acids," "Vitamin E," "endometrial receptivity," and "assisted reproductive technology." The search included peer-reviewed articles published between 2000 and 2024.

Studies were included if they reported clinical or mechanistic insights into the effects of OM3FAs or Vitamin E on fertility, implantation outcomes, or ART success. Both human and animal studies were considered. Articles not related to reproductive outcomes or lacking primary data were excluded.

Relevant data were curated and contextualized to provide an integrative understanding of the biological mechanisms, clinical outcomes, and nutritional considerations associated with these compounds, highlighting potential clinical applications and research gaps.

DISCUSSION

Aetiology of RIF

The current understanding of the etiological factors contributing to RIF, though limited, encompasses several broad, complex, and multifactorial clinical aspects related to maternal, paternal, and embryonic factors[6,4].

Factors like advanced age, a higher Body Mass Index (BMI), Smoking, excessive alcohol consumption, and stress are known to negatively influence successful implantation, contributing to an increase in the incidence of RIF[4].

Maternal causes of RIF stem from dysfunctions in proinflammatory responses governed by immune cell cascades, such as the CD4+ and CD25+ (Treg) cells, which trigger cytokines (Th1, Th17) that promote implantation and trophoblastic invasion[4,7]. Maternal immune tolerance is maintained by a series of cascades mediated by immune cells, and their dysfunction results in RIF, particularly

when they share identical Human Leukocyte Antigen (HLA) alleles[6]. Additionally, endometrial receptivity has been observed to decline with age and with disturbances in prostaglandin synthesis[8].

Conditions like Polycystic ovarian syndrome (PCOS), characterized by metabolic abnormalities, thrombophilias, infections, and reproductive system abnormalities like fibroids, polyps, and ductal anomalies, have been found to impact implantation negatively[6].

Male infertility has been linked to oxidative stress and abnormal protamine ratios. Protamines 1 and 2 (P1 and P2) shield sperm from oxidative damage and, more effectively, wrap compacted chromatin, playing a valuable role in fertilization and early embryogenesis[4,11].

The quality of the embryo accounts for one-third of RIFs[5]. Chromosomal abnormalities such as translocations, deletions, and mosaicism arise from the oocyte's ability to effectively cleave and fertilize or from variables related to paternal sperm[6,10]. These issues may negatively impact the embryo-endometrial communication that is necessary for a successful implantation[4].

Diagnosis of RIF:

RIF is multifactorial and requires a comprehensive and tailored diagnostic approach to elucidate its underlying aetiology.
Maternal diagnostic methods frequently include assessment of serum Anti-Mullerian Hormone (AMH) to assess ovarian reserve, predict response to stimulation, and gauge embryo quality and pregnancy potential[1]. Imaging techniques like transvaginal ultrasound and hysteroscopy aid in assessing the endometrial quality, uterine abnormalities, and intracavity lesions[10].

Reproductive genetic testing of sperm cells in men assists in identifying DNA fragmentation and abnormal chromatin packaging. Genetic karyotyping of both partners is used to identify structural chromosomal abnormalities, and preimplantation genetic testing A and M (PGT-a and PGT-M) in IVF-ET to isolate embryos with normal chromosomal content or free from specific genetic conditions before implantation[10].

Treatment Approaches

Lifestyle changes that target BMI, stress, and alcohol are advised, alongside specific interventions tailored to the underlying cause of RIF. Techniques such as ovarian stimulation, assisted hatching, and refined embryo transfer are employed to enhance IVF-ET success. Drug therapy employs antibiotics, anticoagulants, and hormones to support luteal function and improve endometrial quality[4,8]. Immunomodulators (glucocorticoids, Tacrolimus) to improve immune tolerance, intrauterine infusions (HCG, Peripheral Blood Mononuclear Cells, Platelet Rich Protein), and endometrial scratching are explored, but their efficacy is limited. Hysteroscopic surgery is carried out to address structural issues like fibroids, with inherent surgical risks[11].

Existing treatment options for implantation failure often have limited efficacy and come with significant challenges and risks. Current methods of improving endometrial receptivity are relatively invasive, difficult to perform, or expensive[2]. Their side effects are ubiquitous and inevitable as they lack a well-established safety profile. Therapy tailored to individual genetic, immunological, and physiological characteristics is still in its infancy. The role of mental health services in treating RIF, a condition that causes significant emotional and financial stress, is often overlooked. Due to the high rate of infertility and low success rates of its treatment, it is crucial to discover modifiable risk factors that affect both natural fecundity and the results of ART[1].

Some researchers have suggested giving a specific dosage of vitamin E and omega-3 fatty acids (OM3FAs) to women of reproductive age as a simple and low-cost method that may address the underlying inflammatory or immune-related issues, forming the focus of this article[2]. Figure 1. Summarizes the causative factors of RIF and current treatment options to tackle it.

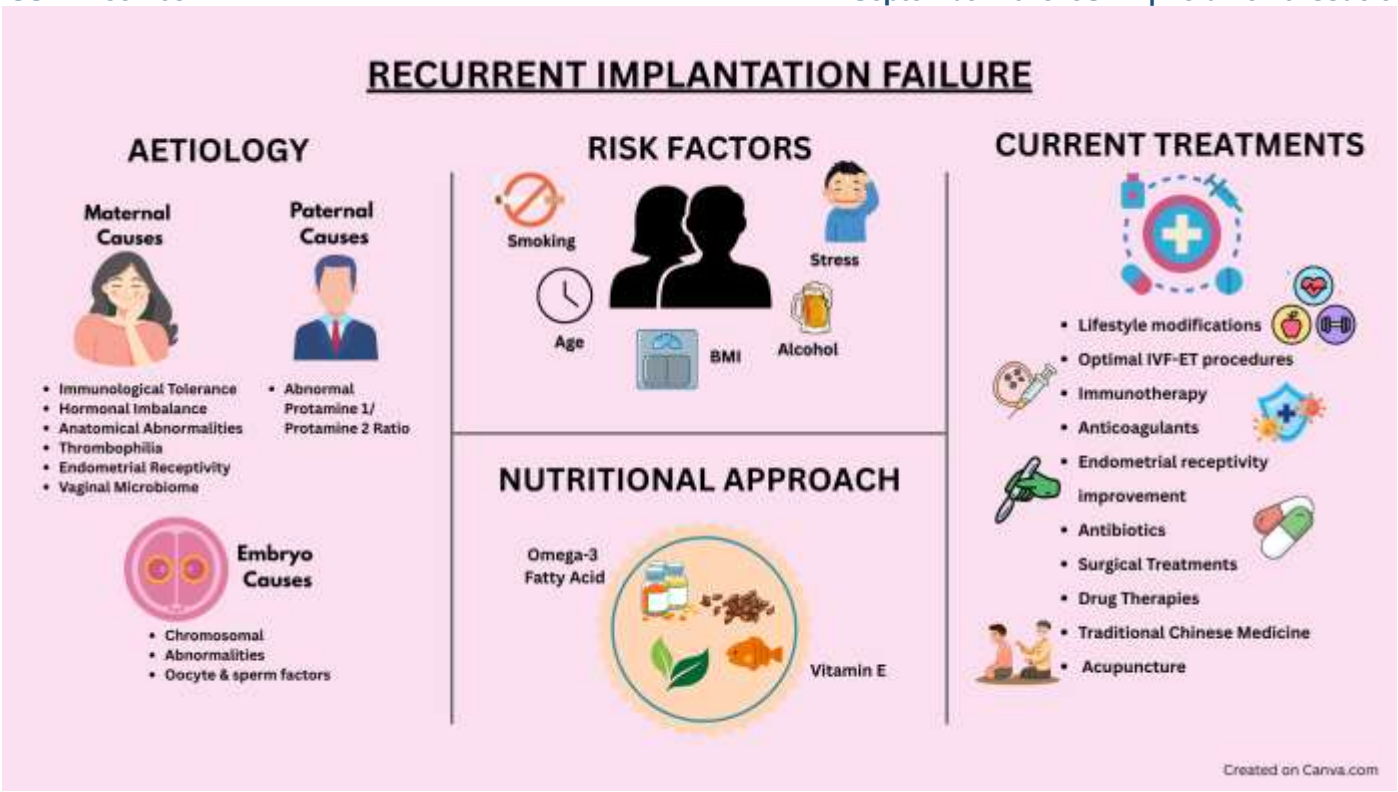

Figure 1. Overview of Risk Factors, Aetiology, Current Treatments, and Nutritional Approaches for Recurrent Implantation Failure (RIF)

Role of Omega-3

Alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are the main components of essential fatty acids, i.e., OM3FAs[13]. The chemical structures of the components of OM3FAs are depicted in Fig.2. Because the human body cannot produce OM3FAs independently, they must be obtained from the diet. ALA can be obtained from plant-based sources, but the body's conversion of ALA to EPA and DHA is inefficient[14]. OM3FA sources include walnuts, chia seeds, soybean and canola oils from plants, and flaxseed. Higher concentrations of EPA and DHA are found in fish such as salmon, mackerel, tuna, herring, and sardines. Certain foods like milk and eggs may be fortified with DHA and other omega-3 fatty acids[15]. A daily dose of 0.25 g of DHA + EPA and 1 g of ALA is considered ideal[13]. Table 1. Lists the various dietary sources of OM3FAs.

OM3FAs have immune-modulatory, endocrine-modulatory, and anti-inflammatory properties that are known to have cardiovascular benefits and aid in the treatment of various diseases, including rheumatoid arthritis, diabetes, and cancer, as well as promote wound healing[13,16]. In addition to a pro-resolving mechanism, OM3FAs are essential for activation of the free fatty acid (FFA)-4 receptor and inflammasome inhibition[17]. DHA and EPA exert anti-inflammatory effects on the endometrium through various mechanisms involving the eicosanoid metabolites, thromboxane, prostaglandins, leukotriene, and prostacyclin, as well as by inhibiting genes that start the inflammatory process[17,18].

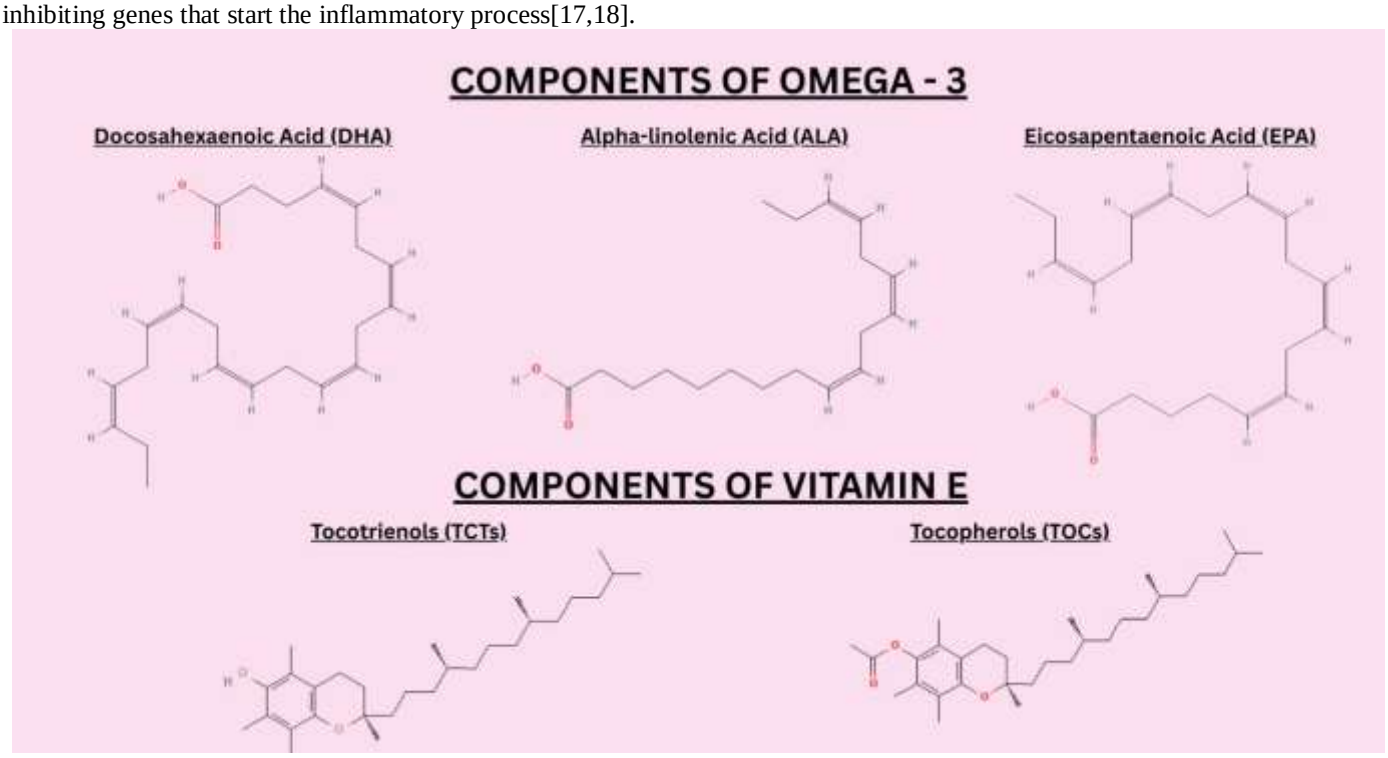

Figure 2. Chemical Structures of EPA, DHA, ALA, Tocopherol, and Tocotrienols

Omega-3 Polyunsaturated Fatty Acids (PUFAs) stimulate the production of 3-series prostaglandins (like PGE3 and PGF3α), which are typically classified as anti-inflammatory(Fig. 3). It is believed that the composition of prostaglandins in the uterus is essential for successful implantation; nevertheless, there are contradictory data on which prostaglandins promote implantation, and which are harmful. Prostaglandins and prostacyclin play a key role in decidualization, extracellular matrix remodeling, embryo transport, blastocyst growth and development, trophoblast invasion, and increased vascular permeability and angiogenesis at the implantation site, impacting the implantation of an embryo[19].

Omega-3 has been found to positively impact fertility, affecting oocyte, embryo implantation, and menstrual cycle function in animal and human studies[20]. A significant correlation exists between semen quality and men's dietary omega-3, fish consumption, and use of fish oil supplements. It has been demonstrated that eating nuts improves the quality of men's semen in the general population[21].

Studies on humans and animals have demonstrated that a diet high in omega-3 PUFAs increases female fecundity. Omega-3 has been demonstrated to modulate steroidogenesis and prostaglandin production, which enhances uterine function. In women, a high omega-3 fatty acid intake was associated with greater blood levels of oestradiol and better-quality embryos. Studies on cows that were given omega-3 supplements have shown additional supportive evidence, including larger follicles and higher fertility. Although these results are not directly applicable to humans, they are unquestionably encouraging[14]. Scientists discovered that feeding omega-3 PUFAS to heifers increased their reproductive efficiency and increased the expression of important genes during the implantation window[3].

The vasoactive involvement of Prostaglandins (PGs) in ovulation, fertilization, and the late stages of pregnancy leading up to delivery has long been established. There is strong evidence that PUFAs can alter biochemical pathways linked to PG synthesis and steroid biosynthesis, which regulate reproductive function in several ways. The process of fertilization also depends on the PUFA component of the sperm and egg membranes. By changing the expression of several pertinent enzymes and their quantities, as well as acting as substrates and competitive inhibitors of epoxidation, PUFAs influence the synthesis of PGs. Embryo implantation has also been shown to be affected by PGs[3].

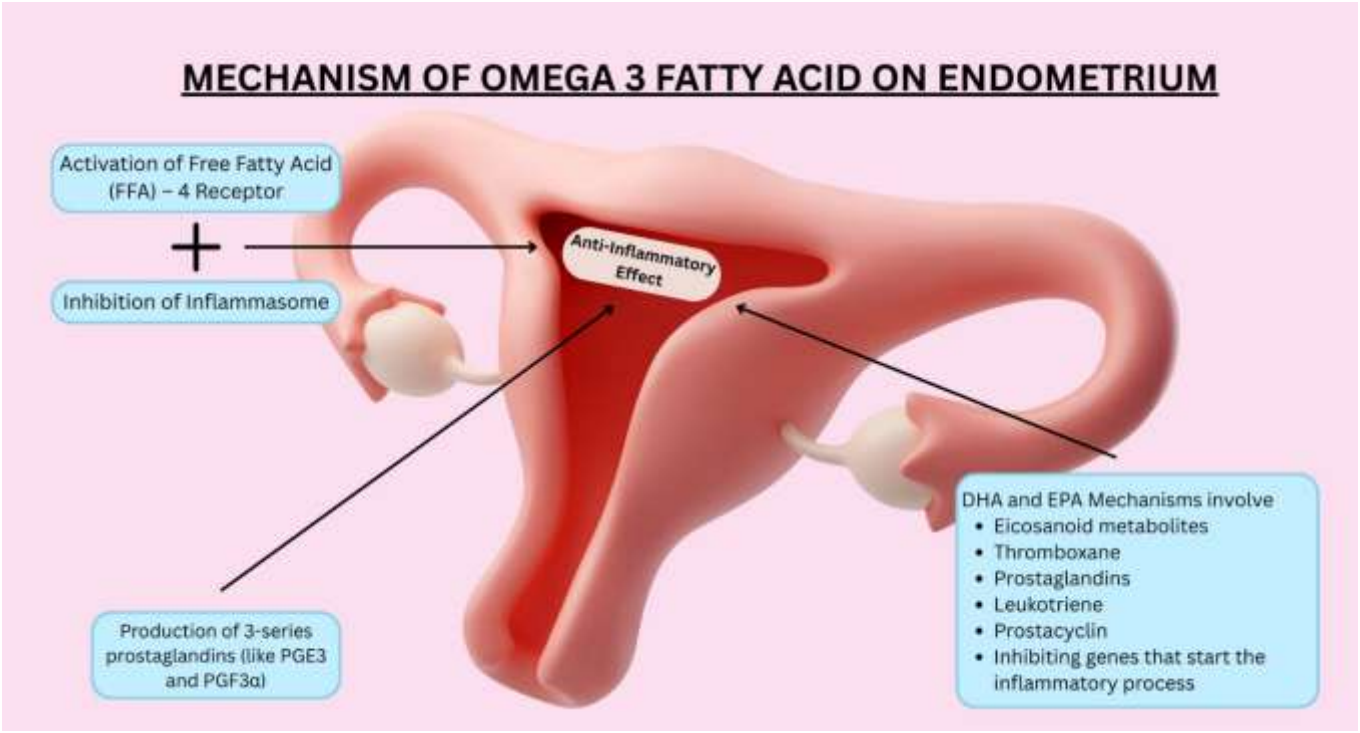

Figure 3. Anti-Inflammatory Mechanisms of OM3FAs in Reproductive Health.

Several animal studies have established the crucial involvement of PGs in implantation. A delay in implantation leading to reduced foetal growth and pregnancy failure was observed in female mice that were deficient in Cyclooxygenase-2 (COX-2) or cytoplasmic phospholipase A2 (cPLA2); administration of exogenous PGs at the appropriate time restored embryo implantability. A study on pigs highlights the role of prostaglandin E2(PGE2) in maintaining luteal function during early implantation and embryo development, and its role in the expression of chemokines, which enables trophectoderm to stick to the decidua in preparation for implantation. Large-scale synthesis of PGE2 10–12 days post-oestrus activates PG receptors in the endometrium, increasing uterine receptivity for implantation. Along with embryo-mediated signalling, PGs have a protective action on the corpus luteum, shielding it from lysis[3]. Emerging evidence suggests that COX-2 and its associated signalling pathways play a critical role in the pathophysiology of recurrent spontaneous abortion. In baboon models, embryonic IL-1β (Interleukin 1β) stimulates COX-2 expression in stromal fibroblasts at the implantation site, leading to increased prostaglandin production, which is essential for implantation. Notably, studies in mice have shown that COX-2 wild-type embryos can implant in COX-2-deficient uteri, although implantation is followed by delayed decidualization, indicating that maternal COX-2 facilitates, but is not strictly required for, early implantation[3].

By encouraging the expression of genes and proteins involved in implantation, OM3FAs improve endometrial receptivity. The immune modulatory action of OM3FAs supports a balanced Th1/Th2 cytokine response, decreasing the risk of immune-mediated rejection of the embryo. They also aid in lowering oxidative stress and shield the developing embryo and endometrium from harm. Omega-3 PUFAs improve placental development and function, ensuring that the foetus receives the right amount of oxygen and nutrients and lowers the chance of miscarriage-causing pregnancy problems[16].

Table 1: Dietary Sources, Biological Functions, and Metabolic Conversion of Omega-3 Fatty Acids and their Constituents.

Omega-3 Fatty Acids	Sources	Properties/Functions	Conversion in the Body
ALA (Alpha-Linolenic Acid)	Flaxseeds- Chia seeds- Walnuts- Hempseed oil- Soybean oil- Canola oil	Essential for growth and development- Limited conversion to EPA and DHA	Must be obtained through diet- Poor conversion to EPA/DHA
EPA (Eicosapentaenoic Acid)	Fish (Salmon, Mackerel, Tuna, Herring, Sardines)- Fortified foods (yogurt, eggs, milk, juices)	Immune-modulatory- Endocrine-modulatory- Anti-inflammatory	Directly absorbed through diet (fish, seafood)
DHA (Docosahexaenoic Acid)	Fish (Salmon, Mackerel, Tuna, Herring, Sardines)- Microalgae- Algae oil- Fortified foods (eggs, milk, juices, soy drinks)	Supports brain and eye health- Anti-inflammatory	Directly absorbed through diet (fish, algae)
Sources (Fish and Marine)	Salmon- Mackerel- Tuna- Herring- Sardines	Rich in EPA and DHA- Potential for contaminants in fish oil	Provide EPA and DHA directly
Plant-Based Sources (ALA)	Walnuts- Chia seeds- Flaxseed- Hempseed oil- Soybean and Canola oil	Provide ALA, which can be converted to EPA and DHA (inefficiently)	Limited conversion to EPA and DHA in the body
Fortified Foods	Yogurt- Eggs- Milk- Soy drinks- Juices	Fortified with DHA and other omega-3 fatty acids	Sources of DHA in diet
Supplements	DHA-rich supplements (phospholipids, free fatty acids, triglycerides)	Rich in DHA- Often found in dietary supplements	Easy access to DHA and EPA directly

Role of VITAMIN E

Discovered by Evans and Bishop in 1922. Vitamin E was called "anti-sterility factor X," essential for reproduction. Tocopherols and tocotrienols, the constituents of Vitamin E, are present in various foods and plants, ranging from edible oils to nuts. Sources include wheat, rice bran, barley, oat, coconut, palm and annatto, rye, amaranth, walnut, hazelnut, poppy, safflower, maize, and the seeds of grape and pumpkins[22].

Antioxidants control the excessive generation of Reactive Oxygen Species (ROS) and are classified as: enzymatic and non-enzymatic. Natural antioxidants or endogenous antioxidants are other names for enzymatic antioxidants, which include glutathione (GSH) reductase, catalase, superoxide dismutase (SOD), and glutathione (GSH) peroxidase. Endogenous antioxidants significantly aid the defence of both the placenta and trophoblast cells against Oxidative Stress (OS). According to reports, SOD primarily contributes to cellular defence by converting two superoxide (O^{2-}) molecules into hydrogen peroxide (H_2O_2) and molecular oxygen (O_2) [22]. The dual role of ROS and superoxide dismutase (SOD) as second messengers to control endometrial function has drawn attention recently[9]. H_2O_2 is converted to O_2 and water (H_2O) by catalase in peroxisomes. Glutathione peroxides are oxidized by GSH reductase and GSH peroxidase, which eliminate lipid hydroperoxides and H_2O_2. Vitamin E complements this system and protects lipid membranes from peroxidative damage and supports reproductive success by mitigating OS[22].

Vitamin E is a lipid-soluble, exogenous substance processed by the liver and kidney and functions as a peroxyl radical scavenger in vivo capable of disposing, scavenging, or suppressing the formation of ROS[9,23].

Data from a meta-analysis demonstrates that oral vitamin E supplementation promotes endometrial growth in women of reproductive age, particularly those with a thin endometrium; the continued pregnancy rate did not significantly differ between the Vit E and control groups. Vitamin E may increase endometrial secretory activity and improve endometrial thickness by preventing oxidation and enhancing endometrial health by increasing capillary blood flow in several different organs, although its efficacy is debatable[23].

An investigation by Salas-Huetos et al.[21] found an inverse relation between EPA+DHA intake and risk of pregnancy loss, and that men's consumption of total OM3FAs was favourably correlated with sperm count, concentration, and motility, and influenced semen quality. However, no significant correlation was found between the total omega-3 intake and implantation, clinical pregnancy, and live birth probabilities. The investigation concluded that women with dietary patterns high in OM3FAs and omega-3-rich foods may have an enhanced likelihood of conception[21]. Their findings are supported by another study that found an increased fecundity by over 47% and a 22% higher frequency of sexual intercourse in couples with a higher intake of seafood[24].

In vitro research that gave mice omega-3 fatty acid supplements revealed elevated implantation markers in the stroma and endometrial epithelium, including leukaemia inhibitory factor and laminin, which would promote the endometrium to create a favourable implantation environment. Research on cows has suggested that including omega-3 and omega-6 fatty acids in their diet has been shown to affect various aspects of the reproductive process, including follicular development and the generation of progesterone and PGF2α, which control embryo survival and implantation[17].
A meta-analysis gathered that higher omega-3 PUFA, through diet or added supplements, increased the likelihood of clinical pregnancy in women of childbearing age[14].

Sugawa et al.[25] investigated the effect of omega-3 PUFA intake on ART outcomes in Japanese women but found no significant benefit compared to the control group. Limitations in sample size, study design, and participant diversity may explain the contradictory findings. Interestingly, despite these findings, it was observed that among women who had fertility therapy, those who became pregnant had higher serum omega-3 levels than those who did not. The study also noted that no long-term data studies on the effectiveness of OM3FAs in women have been conducted, with trials lasting anything from three weeks to a full year, with positive results noticed among some after two or three months[25,26].

When it comes to fertility, PUFAs are involved in several processes. It is interesting to note that while higher dietary intakes of polyunsaturated fatty acids (PUFAs) have been shown to improve female fertility, they may also have detrimental effects on key reproductive processes like oocyte quality, endometrial receptivity, and subsequent embryo implantation rates whenever their concentration rises too high. Chiu et al.[12] found that higher serum omega-3 PUFA levels were positively associated with implantation, clinical pregnancy, and live birth rates per cycle in women undergoing fertility treatment. Additionally, an elevated omega-6: omega-3 ratio was inversely correlated with peak oestradiol levels, suggesting a reduced ovarian response to stimulation[12].
Randomised control trials were conducted in women undergoing IVF by Nouri et al.[27] and Al-Alousi et al.[28] They demonstrated that multivitamin supplementation positively influences fertilization rates and embryo quality[27,28].

In a descriptive longitudinal study, Jahangirifar et al.[29] reported a positive association between ALA intake and the number of oocytes retrieved. Conversely, a higher intake of EPA and DHA was associated with a reduced number of metaphase II oocytes, highlighting the differential effects of various OM3FAs on oocyte maturation[29].

The study conducted by Trop-Steinberg et al.[20] showed that PCOS patients who were treated with clomiphene and randomly received omega-3 supplements had increased clinical pregnancy rates and reduced number of treatment cycles, lowered BMI rates, and increased endometrium thickness. This leads to increased odds of becoming pregnant[20].

Antioxidant-rich diets have demonstrated reduced OS in both human and animal studies. In rats, vitamin E supplementation lowered free radical production and urinary peroxidation markers. In women, higher intake of antioxidant-rich fruits and vegetables correlated with reduced OS. Antioxidants like SOD also appear critical during decidualization. Melatonin and α-tocopherol supplementation in an IVF study revealed significantly reduced intrafollicular OS markers, suggesting their protective role in oocyte maturation[9].

In fertile women, oral supplementation of Vitamin E increased endometrial thickness, particularly in those suffering from a thin endometrium[23].

In a study by Cicek et al.[30], women with unexplained infertility undergoing controlled ovarian stimulation and IUI received either clomiphene citrate alone or with 400 IU/day of vitamin E. While vitamin E did not significantly affect implantation or pregnancy rates, it was associated with increased endometrial thickness on the day of hCG administration. These findings suggest that vitamin E enhances endometrial quality by counteracting clomiphene's anti-estrogenic effects[30].

CONCLUSION

As RIF is multifactorial, precise diagnosis with personalized treatment is essential. Further human studies are needed to evaluate the independent and combined effects of omega-3 and vitamin E in both natural conception and ART settings. Although limited by small sample sizes and ethical constraints, current evidence suggests that dietary supplementation with omega-3 and vitamin E may boost implantation success by improving gamete quality, embryo development, endometrial receptivity, immune tolerance, and

implantation success. Although these supplements offer a cost-effective, accessible, and low-risk adjunct to fertility treatments, their dosage must be carefully considered to avoid potential adverse effects.

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