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# Mechanistic Insights into the Effects of Essential Micronutrients on Spermatogenesis: Focus on Selenium, Folate, Vitamin C, Vitamin E and Zinc

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## Abstract

***Background:*** *Male infertility and impaired spermatogenesis remain significant reproductive health concerns worldwide. Oxidative stress, deoxyribonucleic acid (DNA) damage, disrupted cellular metabolism, and epigenetic dysregulation are among the key mechanisms implicated in poor sperm quality. Specific micronutrients—including selenium, zinc, folate, vitamin C, and vitamin E—have been proposed to modulate spermatogenesis through antioxidant activity, regulation of gene expression, and maintenance of cellular integrity. This narrative review aims to synthesize recent evidence on the biological pathways by which these micronutrients interact with spermatogenic processes.*

***Methods:*** *This study was a narrative review of the literature. Data were collected from recent mechanistic and clinical studies investigating the roles of selenium, zinc, folate, vitamin C, and vitamin E in male reproductive health. The primary outcomes were antioxidant defense, mitochondrial function, DNA synthesis and methylation, genomic integrity, and sperm structural stability. The biological pathways and clinical supplementation outcomes were systematically synthesized and evaluated.*

***Results:*** *Selenium and zinc were found to contribute to antioxidant defense, mitochondrial function, and sperm structural stability through selenoproteins and zinc-dependent enzymes. Folate played a central role in DNA synthesis and methylation, which are critical for germ cell proliferation and epigenetic programming. Vitamins C and E protect germ cells and sperm membranes from oxidative damage through their antioxidant properties. Although clinical supplementation studies reported heterogeneous outcomes, mechanistic evidence consistently supported essential roles for these micronutrients in maintaining the testicular microenvironment, genomic integrity, and functional competence of spermatozoa.*

***Conclusion:*** *Our review revealed that selenium, zinc, folate, and vitamins C and E exert essential biological effects on spermatogenesis through antioxidant activity, epigenetic regulation, and cellular integrity maintenance. However, clinical translation remains limited due to heterogeneous supplementation outcomes. Further well-designed studies are required to translate mechanistic insights into targeted nutritional interventions for male infertility.*

**Keywords:** Male infertility, Spermatogenesis, Micronutrients, Oxidative stress, Selenium, Zinc, Folate, Vitamins C and E, DNA methylation.

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## Introduction

Male infertility accounts for approximately 40–50% of infertility cases worldwide and is increasingly recognized as a major public health concern. Spermatogenesis is a highly coordinated and energy-dependent process involving mitotic proliferation of spermatogonia, meiotic division of spermatocytes, and differentiation of spermatids into mature spermatozoa. Disruption at any stage of this process can impair sperm count, motility, morphology, and genomic integrity. Accumulating evidence indicates that oxidative stress, impaired redox homeostasis, and altered micronutrient status play central roles in the pathophysiology of defective spermatogenesis [1, 2].

The testes are particularly vulnerable to oxidative damage due to their high rate of cell division, abundance of polyunsaturated fatty acids, and relatively limited intrinsic antioxidant capacity. Excessive production of reactive oxygen species (ROS) can damage lipids, proteins, and deoxyribonucleic acid (DNA) within germ cells, leading to sperm DNA fragmentation, apoptosis, and abnormal sperm morphology. Although physiological levels of ROS are required for normal sperm maturation and capacitation, a persistent imbalance favoring oxidative stress negatively affects male reproductive potential [3, 4].

Micronutrients with antioxidant, metabolic, and regulatory functions have therefore gained increasing attention as modulators of spermatogenesis. Selenium and zinc are essential trace elements involved in antioxidant defense, enzyme activity, and hormonal regulation. Selenium is required for the synthesis of selenoproteins that regulate redox balance and mitochondrial function, whereas zinc plays a crucial role in DNA synthesis, chromatin stabilization, transcriptional regulation, and testosterone metabolism. Folate, vitamin C, and vitamin E further complement these functions through roles in nucleotide biosynthesis, epigenetic regulation, and protection against oxidative injury. Together, these micronutrients form an integrated network supporting germ cell development and sperm function [5-7].

Beyond their antioxidant properties, these micronutrients influence spermatogenesis through epigenetic regulation, DNA synthesis and repair, endocrine modulation, and maintenance of the testicular microenvironment. Folate availability affects DNA methylation patterns in sperm, which are essential for proper gene expression and transgenerational epigenetic inheritance. Zinc contributes to chromatin condensation and stabilization of sperm DNA, while selenium-dependent enzymes support sperm structural integrity, particularly within the mitochondrial sheath. Vitamins C and E preserve cellular membranes and reduce germ cell apoptosis by limiting lipid

peroxidation and oxidative DNA damage [5, 8]. Understanding the mechanistic pathways by which these micronutrients act is essential for interpreting clinical findings and for developing evidence-based nutritional strategies to support male reproductive health**.**

## Materials and Methods

This narrative review was conducted to summarize and critically analyze the mechanistic evidence regarding the effects of selenium, zinc, folate, vitamin C, and vitamin E on spermatogenesis. A comprehensive literature search was performed using electronic databases including PubMed, Scopus, and Web of Science. The search strategy combined Medical Subject Headings (MeSH) and free-text terms such as "selenium," "zinc," "folate," "vitamin C," "vitamin E," "spermatogenesis," "male infertility," "oxidative stress," "DNA methylation," "chromatin integrity," and "antioxidants." Articles published primarily within the last 5 years were prioritized to ensure inclusion of current and relevant mechanistic evidence. In addition, all articles included in this review were screened and selected from searches conducted up to 2026.

Eligible studies included experimental studies (in vitro and animal models), observational human studies, randomized controlled trials, and recent narrative or systematic reviews that provided mechanistic insights into micronutrient actions in the male reproductive system. Only articles published in English and in peer-reviewed journals were considered. Reference lists of key publications were manually screened to identify additional relevant studies.

Data extraction focused on the biological mechanisms by which selenium, zinc, folate, vitamin C, and vitamin E influence spermatogenesis, including antioxidant activity, regulation of ROS, DNA synthesis and repair, chromatin packaging, epigenetic modulation, mitochondrial function, hormonal regulation, and germ cell apoptosis. The findings were organized by these micronutrients and mechanistic pathway to facilitate integrative interpretation and comparison across studies.

## Results and Discussion

Selenium is an essential trace element that plays a critical role in male reproduction primarily through its incorporation into selenoproteins. Among these, glutathione peroxidase 4 (GPX4) is particularly important in spermatogenesis. GPX4 is highly expressed in the testes and is involved in protecting developing germ cells from lipid peroxidation induced by ROS. During sperm maturation, GPX4 also becomes a structural protein in the mitochondrial sheath of spermatozoa, contributing to sperm stability and motility [9, 10].

Oxidative stress is a major factor impairing spermatogenesis, and selenium deficiency has been associated with increased ROS levels in testicular tissue. Elevated ROS can disrupt spermatogonial proliferation, induce meiotic arrest, and promote apoptosis of spermatocytes and spermatids. Experimental animal studies have demonstrated that selenium depletion leads to abnormal sperm morphology, reduced motility, and degeneration of seminiferous tubules, highlighting its protective antioxidant role [11, 12].

In addition to antioxidant defense, selenium influences mitochondrial function and energy metabolism in sperm cells. Adequate mitochondrial activity is essential for sperm motility, as adenosine triphosphate (ATP) production drives flagellar movement. Selenium-dependent enzymes support mitochondrial membrane integrity and prevent oxidative damage to mitochondrial DNA. Impairment of these processes due to selenium insufficiency may compromise sperm bioenergetics and fertilization potential [13-15].

Clinical studies examining selenium supplementation in infertile men have produced heterogeneous results; however, several randomized controlled trials report improvements in sperm motility and morphology, particularly when selenium is administered in combination with vitamin E. These findings suggest that selenium's mechanistic benefits are most pronounced under conditions of oxidative stress or baseline deficiency, reinforcing its role as a key micronutrient in spermatogenic regulation [16-19].

Folate (vitamin B9) is a fundamental component of one-carbon metabolism, which supports nucleotide synthesis and methyl group donation. These processes are indispensable during spermatogenesis, a stage characterized by rapid cell division and extensive DNA replication. Folate deficiency impairs thymidylate and purine synthesis, leading to uracil misincorporation into DNA and increased susceptibility to strand breaks in germ cells [20, 21].

Beyond its role in DNA synthesis, folate is a major regulator of epigenetic programming in sperm through DNA methylation. Proper methylation patterns are required for germ cell differentiation, chromatin remodeling, and genomic imprinting. Animal studies have demonstrated that paternal folate deficiency alters sperm DNA methylation profiles, particularly at imprinted genes, with adverse consequences for embryo development and offspring health [22-24].

Human observational studies have linked low folate status with increased sperm DNA fragmentation and abnormal sperm parameters. Polymorphisms in folate-metabolizing enzymes, such as methylenetetrahydrofolate reductase (MTHFR), further exacerbate these effects by reducing methylation capacity. These findings suggest that folate availability interacts with genetic factors to influence spermatogenic efficiency and genomic stability [24-27].

Intervention studies assessing folic acid supplementation alone have yielded mixed outcomes; however, combined supplementation with zinc or other antioxidants appears more effective. Mechanistically, this synergy may reflect folate's role in DNA synthesis and methylation alongside antioxidant-mediated protection against oxidative DNA damage, supporting a multifactorial model of micronutrient action in spermatogenesis [26, 27].

Vitamin C (ascorbic acid) is a potent water-soluble antioxidant and one of the most abundant antioxidants in seminal plasma. It directly scavenges superoxide radicals, hydrogen peroxide, and hydroxyl radicals, thereby reducing oxidative stress within the male reproductive tract. Given the limited antioxidant defenses of germ cells, vitamin C plays a crucial role in protecting spermatogenic cells from ROS-mediated damage [1, 28].

Experimental studies have shown that vitamin C preserves the integrity of spermatogonia and Sertoli cells, which are essential for maintaining the spermatogenic niche. Oxidative stress-induced damage to Sertoli cells disrupts the blood–testis barrier and compromises germ cell nourishment. Vitamin C supplementation has been shown to restore antioxidant enzyme activity and reduce lipid peroxidation in testicular tissue under oxidative stress conditions [29, 30].

Vitamin C also contributes to the protection of sperm DNA integrity. High ROS levels can induce DNA strand breaks and base modifications, leading to increased sperm DNA fragmentation and reduced fertility. Several studies report inverse correlations between seminal vitamin C levels and DNA fragmentation indices, suggesting a direct protective effect on genomic stability [15, 30].

Clinical trials investigating vitamin C supplementation in infertile men indicate improvements in sperm count, motility, and morphology, particularly in individuals exposed to environmental toxins or lifestyle-related oxidative stressors such as smoking. These effects support the mechanistic role of vitamin C as a first-line antioxidant defense in spermatogenesis and sperm maturation [15, 29, 30].

Vitamin E (α-tocopherol) is the primary lipid-soluble antioxidant in biological membranes and plays a vital role in preventing lipid peroxidation. Sperm membranes are rich in polyunsaturated fatty acids, making them highly susceptible to oxidative damage. Vitamin E interrupts free radical chain reactions by donating hydrogen atoms, thereby stabilizing membrane structure and preserving sperm viability [31, 32].

During spermatogenesis, lipid peroxidation can impair membrane fluidity and disrupt signaling pathways essential for germ cell maturation. Vitamin E has been shown to reduce ROS-induced apoptosis in spermatocytes and spermatids, supporting germ cell survival. Its localization within cell membranes makes it particularly effective in protecting developing spermatozoa [33, 34].

Vitamin E also exhibits functional synergy with vitamin C, which regenerates oxidized tocopherol back to its active form. This antioxidant network enhances overall redox balance within the testes and seminal plasma. Studies suggest that combined antioxidant therapy is more effective than single-agent supplementation in reducing oxidative stress and improving sperm parameters [35].

Clinical evidence indicates that vitamin E supplementation, especially when combined with selenium, improves sperm motility and reduces DNA fragmentation in men with idiopathic infertility. These outcomes are consistent with mechanistic findings demonstrating reduced oxidative damage and enhanced membrane integrity, underscoring vitamin E's role as a central lipid-phase antioxidant in spermatogenesis [36].

Zinc is an essential trace element with a well-established role in male reproductive physiology and spermatogenesis. It is highly concentrated in the testes, prostate, and seminal plasma, reflecting its importance in sperm production and maturation. Zinc functions as a structural, catalytic, and regulatory cofactor for more than 300 enzymes and transcription factors, many of which are directly involved in DNA synthesis, cell division, and gene expression during spermatogenesis. Zinc deficiency has been consistently associated with reduced sperm count, impaired motility, abnormal morphology, and hypogonadism [37, 38].

One of the primary mechanisms by which zinc influences spermatogenesis is through its role in DNA synthesis and chromatin stabilization. During spermiogenesis, zinc participates in the replacement of histones with protamines, a process critical for sperm chromatin condensation and protection of paternal DNA. Zinc ions stabilize protamine–DNA complexes, rendering sperm DNA more resistant to oxidative and physical damage. Insufficient zinc levels impair chromatin packaging, leading to increased sperm DNA fragmentation and reduced fertilization potential [38, 39].

Zinc also plays a crucial role in antioxidant defense and redox homeostasis within the testes. Although zinc is not a direct antioxidant, it indirectly limits oxidative stress by stabilizing cell membranes, inhibiting NADPH oxidase activity, and acting as a cofactor for antioxidant enzymes such as superoxide dismutase (Cu/Zn-SOD). Zinc deficiency results in increased production of ROS, lipid peroxidation, and apoptosis of germ cells, ultimately disrupting spermatogenic progression [8, 36].

In addition to its antioxidant-related functions, zinc modulates endocrine regulation of spermatogenesis. Adequate zinc status is necessary for normal testosterone synthesis and action, as zinc influences Leydig cell steroidogenesis and androgen receptor signaling. Reduced zinc availability has been linked to decreased serum testosterone levels and impaired spermatogenic support by Sertoli cells, further contributing to compromised sperm production [41, 42].

Zinc is also involved in maintaining the integrity of the blood–testis barrier, a specialized structure formed by tight junctions between Sertoli cells that protects developing germ cells from toxic and immunological insults [43]. Experimental studies indicate that zinc deficiency disrupts tight junction proteins and BTB integrity, leading to germ cell loss and impaired spermatogenesis. These findings highlight zinc's role in preserving the specialized microenvironment required for germ cell development [41, 44].

Clinical studies investigating zinc supplementation in infertile men have demonstrated variable but generally positive effects on sperm parameters, particularly in individuals with baseline zinc deficiency [38, 44]. Improvements in sperm concentration, motility, and DNA integrity have been reported, especially when zinc is administered in combination with folate or antioxidant vitamins [8, 34]. These outcomes align with mechanistic evidence suggesting that zinc supports spermatogenesis through coordinated effects on DNA integrity, oxidative stress regulation, hormonal balance, and testicular architecture [8, 34, 41-44].

Mechanistic evidence demonstrates that selenium, zinc, folate, vitamin C, and vitamin E collectively support multiple aspects of spermatogenesis through complementary biological pathways, including antioxidant defense, maintenance of DNA integrity, epigenetic regulation, hormonal modulation, and preservation of the testicular microenvironment. Selenium and vitamin E primarily function as antioxidants that protect cellular membranes and reduce ROS, while vitamin C enhances

overall antioxidant capacity and safeguards germ cells from oxidative damage. Folate plays a critical role in DNA synthesis and methylation pathways essential for germ cell proliferation and epigenetic programming. Zinc contributes to spermatogenesis by stabilizing sperm chromatin, regulating gene expression, supporting antioxidant enzyme activity, maintaining the blood–testis barrier, and modulating testosterone synthesis. Although clinical supplementation trials report heterogeneous outcomes, the strong mechanistic foundation supports continued investigation into targeted, micronutrient-based interventions for male infertility. Future well-controlled studies incorporating standardized oxidative stress, DNA integrity, and epigenetic biomarkers are necessary to refine clinical recommendations and identify populations most likely to benefit from such interventions.

## Ethical Considerations

This study was approved by the ethics committee of Shahroud University of Medical Sciences (Code: IR.SHMU.REC.1405.051).

## Acknowledgment

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## Conflict of Interest

The authors declare that they have no competing interests.

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