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Effect of Manganese in Teratospermia and Oligospermia

Dr. Lokesh. K[1], Dr. Borus Purushothaman[2], Dr.YashmiAgwina Xavier[3], Veerammal[4], Dr. Suman Sharma[5]
Dr. Borus Andro Lab and Research Center, Chennai, India

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ABSTRACT
Manganese (Mn) is an essential trace element involved in numerous physiological processes, including antioxidant defense and metabolism. However, emerging research suggests that abnormal levels of manganese may contribute to male infertility disorders, such as teratospermia (abnormal sperm morphology) and oligospermia (low sperm count). While manganese plays a crucial role in the function of antioxidant enzymes that protect sperm cells from oxidative damage, excessive or deficient Mn levels have been associated with compromised sperm quality. In cases of teratospermia, elevated manganese exposure has been linked to increased morphological abnormalities in sperm, potentially due to oxidative stress and disruptions in cellular signaling pathways. In oligospermia, altered manganese levels may impact spermatogenesis, leading to reduced sperm production. This review synthesizes recent findings on the relationship between manganese exposure and male infertility, emphasizing the mechanistic insights into how manganese dysregulation may exacerbate conditions like teratospermia and oligospermia. Improved understanding of manganese's role could support targeted strategies to mitigate manganese-related reproductive toxicity and improve fertility outcomes in affected individuals.

KEYWORDS: Manganese, male reproductive health, teratospermia, oxidative damage, oligospermia.

I. INTRODUCTION

Male infertility is a growing concern worldwide, with conditions such as teratospermia (abnormal sperm morphology) and oligospermia (low sperm count) affecting a significant percentage of infertile men. These conditions are influenced by various genetic, lifestyle, and environmental factors. Recent studies have highlighted the role of trace elements, including manganese (Mn), in reproductive health. Manganese, a vital micronutrient, is essential for several biological processes, such as enzyme activation, oxidative stress regulation, and cellular energy metabolism, all of which play critical roles in the production and quality of sperm.[1-5]

While manganese is necessary for cellular function, an imbalance—either deficiency or excess—can have detrimental effects on reproductive health. Specifically, abnormal levels of manganese have been associated with reduced sperm count, motility, and morphological integrity. Excessive manganese exposure has been shown to induce oxidative stress, disrupt cellular signaling, and impair testicular function, potentially leading to the formation of defective sperm cells and decreased sperm production. In cases of teratospermia, elevated manganese levels have been linked to structural sperm abnormalities, suggesting that manganese may interfere with spermatogenic pathways responsible for proper sperm development. Similarly, in oligospermia, manganese imbalance may compromise spermatogenesis, leading to lower sperm counts and increased infertility risk.[6-8]

Manganese (Mn) is a micronutrient that serves as an essential cofactor in numerous enzymatic reactions, playing roles in cellular metabolism, oxidative stress regulation, immune function, and the structural stability of cellular components. However, manganese levels in the body must be carefully regulated, as both deficiency and toxicity can lead to reproductive impairments, particularly affecting sperm morphology and count. In conditions such as teratospermia (abnormal sperm morphology) and oligospermia (low sperm count), manganese dysregulation has been associated with adverse effects on spermatogenesis and sperm quality.[9-11]

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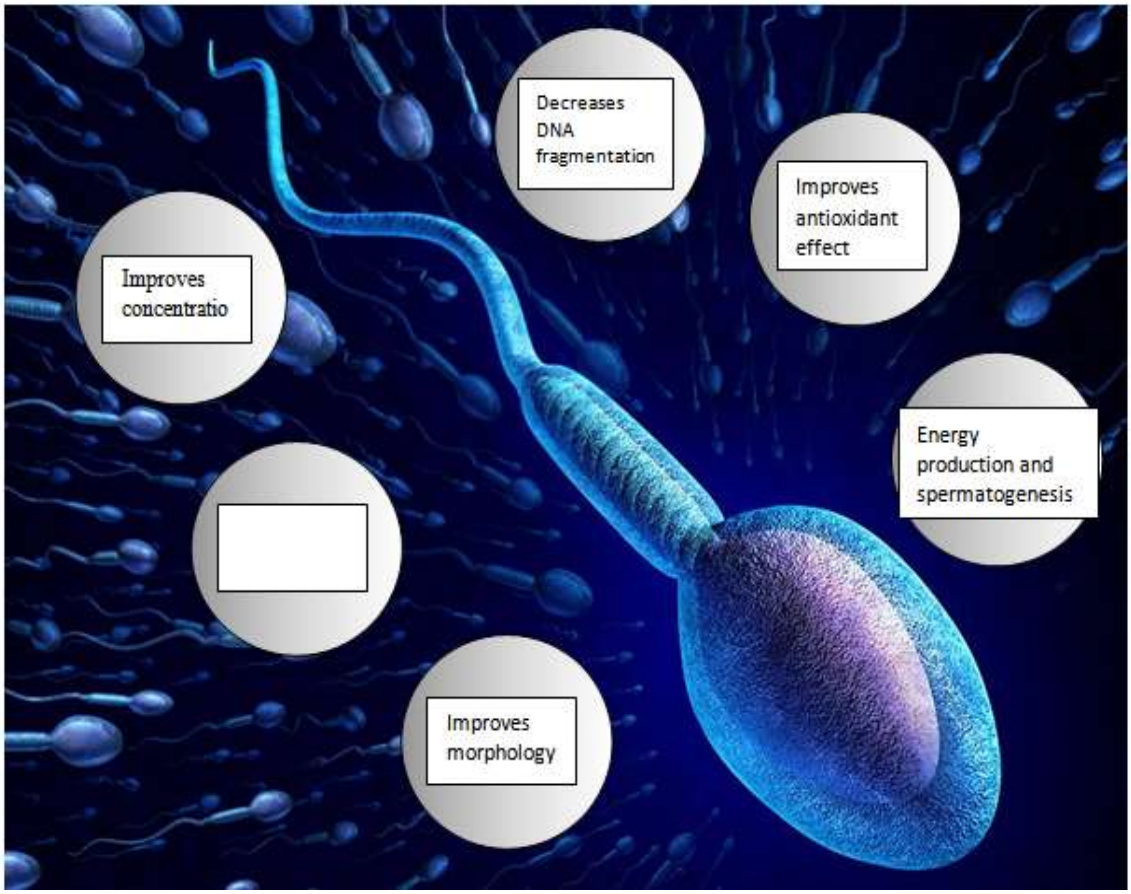

Fig 1. The effect of Manganese on Sperm

MANGANESE AND TERATOSPERMIA (ABNORMAL SPERM MORPHOLOGY)

Teratospermia, a condition characterized by abnormally shaped sperm, is one of the key factors contributing to male infertility. Manganese, a trace element essential for various biochemical processes, plays a critical role in male reproductive health. It supports antioxidant defense, energy metabolism, cellular signaling, and sperm maturation. However, imbalanced manganese levels—either excessive or deficient—have been implicated in the development of teratospermia by negatively affecting sperm morphology through multiple mechanisms. Here is a detailed look at how manganese affects sperm morphology in teratospermia.

1. Oxidative Stress and Sperm Morphology

Oxidative stress is one of the primary mechanisms linking manganese dysregulation to teratospermia. Manganese acts as a cofactor for manganese superoxide dismutase (Mn-SOD), a vital antioxidant enzyme that neutralizes superoxide radicals within the mitochondria and helps protect cells from oxidative stress. However, excessive manganese can disturb this oxidative balance, leading to excessive production of reactive oxygen species (ROS), which can damage sperm cells and cause morphological defects.

- **Membrane Damage**: ROS primarily attack the lipid bilayer of cell membranes. Sperm membranes are particularly susceptible to oxidative damage due to their high polyunsaturated fatty acid content. This damage results in membrane instability, altering the sperm's structural integrity and leading to abnormal shapes, including head deformities (e.g., double heads or elongated heads).
- **DNA Fragmentation**: Excessive ROS can also break DNA strands, resulting in fragmented or mutated DNA. This leads to abnormal nuclear morphology, manifesting in conditions like head deformation and improper chromatin condensation.

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- **Protein and Lipid Damage**: ROS can also oxidize proteins and lipids, disrupting sperm cell functionality and morphology, including midpiece abnormalities and defective tail structure.

In sperm with oxidative damage, deformities like coiled or bent tails and irregular midpieces reduce motility, making fertilization unlikely and contributing to teratospermia.[12-19]

2. Impact on Calcium Signaling and Morphogenesis

Calcium ions (Ca^{2+}) are crucial for sperm function, including motility, capacitation, and acrosome reaction. Manganese, similar to calcium, can enter cells through calcium channels and influence calcium-dependent signaling pathways. However, excess manganese disrupts intracellular calcium levels, which has a profound effect on sperm structure and morphology.

- **Sperm Maturation**: Proper calcium signaling is essential for the development of a mature and functional sperm cell. High manganese levels may disrupt calcium-dependent processes required for sperm head formation and tail development. This disruption can result in misshapen heads and malformed tails, which are characteristic of teratospermia.
- **Acrosome Integrity**: Calcium signaling plays a role in acrosome reaction—the release of enzymes that help sperm penetrate the egg. Altered calcium balance due to excessive manganese can impair acrosome formation, leading to structural abnormalities such as misshapen acrosomes or defective head shapes.
- **Tail Morphology and Motility**: Calcium regulates flagellar movement, enabling sperm to swim effectively toward the egg. High manganese levels can alter calcium signaling, affecting the tail structure and leading to curled or bent tails. This reduces forward motility and hinders the sperm's ability to fertilize the egg.[20-23]

3. Mitochondrial Dysfunction and Morphology

Sperm motility depends heavily on mitochondrial function, which generates ATP in the midpiece of the sperm cell, providing the energy needed for flagellar movement. Manganese plays a dual role here: while normal levels support mitochondrial health, excessive manganese disrupts mitochondrial function, leading to oxidative stress within the mitochondria.

- **ATP Production**: High manganese levels disrupt the electron transport chain, reducing ATP synthesis. This energy deficit impairs the structure and function of the sperm tail, leading to malformed tails and reduced motility.
- **Mitochondrial Structural Integrity**: Excessive manganese accumulation in mitochondria increases ROS production and mitochondrial membrane permeability, leading to mitochondrial dysfunction. This results in midpiece deformities and affects energy supply, contributing to abnormal sperm morphology.[24-29]

4. Epigenetic and Genetic Damage

Manganese-induced oxidative stress can also affect sperm DNA, causing genetic and epigenetic changes that impact sperm structure and integrity.

- **DNA Damage and Fragmentation**: High manganese levels increase oxidative damage to sperm DNA, resulting in DNA fragmentation and mutations. Damaged DNA in the sperm nucleus may lead to structural abnormalities in the head, such as improper chromatin condensation and nuclear malformations.
- **Epigenetic Modifications**: Manganese toxicity can cause epigenetic changes in sperm, affecting genes responsible for sperm development and morphology. Altered gene expression can lead to abnormal head and tail structures, characteristic of teratospermia, affecting fertility.[30-35]

5. Cellular Toxicity and Apoptosis

At high concentrations, manganese exerts toxic effects on cells in the testes, specifically the Sertoli and Leydig cells, which are essential for nourishing and supporting developing sperm cells. This cellular toxicity can result in impaired spermatogenesis, leading to higher rates of teratospermia.

- **Sertoli Cell Dysfunction**: Sertoli cells support and nourish developing sperm cells. Manganese-induced toxicity in Sertoli cells can disrupt nutrient and signaling support, impairing sperm development and resulting in structural abnormalities in mature sperm.
- **Leydig Cell Dysfunction**: Leydig cells produce testosterone, a hormone critical for spermatogenesis and sperm morphology. High manganese levels can disrupt Leydig cell function, reducing testosterone levels, which indirectly affects the structure of sperm cells and can contribute to teratospermia.

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6. Hormonal Disruptions via the HPG Axis

The hypothalamic-pituitary-gonadal (HPG) axis regulates reproductive hormones like testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), which are crucial for sperm development and morphology. Manganese has neurotoxic effects that can disrupt the HPG axis.

- **Testosterone Reduction**: High manganese exposure can reduce testosterone levels by inhibiting the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus. Insufficient testosterone disrupts spermatogenesis and results in abnormal sperm morphology.
- **LH and FSH Imbalance**: Imbalanced LH and FSH levels, caused by manganese disruption in the HPG axis, lead to impaired testicular function and abnormal spermatogenesis, increasing the incidence of sperm with defective heads, tails, or midpieces.[36-40]

MANGANESE AND OLIGOSPERMIA (LOW SPERM COUNT)

Oligospermia, defined as a low sperm count, is a common cause of male infertility, reducing the likelihood of successful fertilization. Manganese (Mn), an essential trace element, plays a critical role in various physiological processes, including enzyme activation, oxidative stress management, mitochondrial function, and hormone regulation. While moderate levels of manganese are beneficial, an imbalance—either excessive or deficient manganese levels—has been associated with oligospermia. Here is an in-depth analysis of how manganese influences sperm production, count, and the onset of oligospermia.

1. Manganese's Role in Spermatogenesis

Spermatogenesis, the process by which sperm are produced in the testes, is highly sensitive to manganese levels. Manganese is a cofactor for several enzymes critical to cell division, energy production, and oxidative stress regulation, all essential processes in spermatogenesis. Both manganese deficiency and toxicity can impair spermatogenesis, leading to oligospermia by reducing sperm production.

- **DNA Synthesis and Cell Division**: Manganese is necessary for enzymes involved in DNA synthesis and cellular division. Sufficient manganese levels ensure the rapid cell division and differentiation that occur during spermatogenesis. However, insufficient manganese levels can disrupt these enzymes, slowing or halting cell division in the seminiferous tubules, thereby decreasing sperm output and leading to oligospermia.
- **Seminiferous Tubule Dysfunction**: Excessive manganese can have toxic effects on the cells within the seminiferous tubules (Sertoli cells and germ cells), resulting in fewer sperm cells being produced. This toxicity disrupts the delicate balance of cell proliferation and differentiation, leading to oligospermia by decreasing the population of viable sperm cells.[41-44]

2. Oxidative Stress and Its Impact on Sperm Count

Manganese plays a role in antioxidant defense as a cofactor for manganese superoxide dismutase (Mn-SOD), an enzyme that neutralizes reactive oxygen species (ROS) within the mitochondria. Oxidative stress is a significant factor contributing to oligospermia, and manganese dysregulation can disrupt the oxidative balance within sperm cells.

- **Antioxidant Function of Mn-SOD**: Mn-SOD mitigates oxidative stress by reducing ROS levels. Moderate manganese levels support this function, protecting sperm cells from oxidative damage. However, when manganese levels are excessively high, it paradoxically increases ROS production and overwhelms Mn-SOD capacity, leading to oxidative stress in the testes.
- **Oxidative Damage to Spermatogenic Cells**: Excess ROS can damage spermatogenic cells (the cells involved in sperm production) by attacking their cellular membranes, DNA, and proteins. This damage impairs the viability of developing sperm cells, reducing their numbers and contributing to oligospermia. ROS-induced DNA damage may also lead to apoptosis (cell death), further lowering sperm counts.

3. Mitochondrial Dysfunction and Energy Deficiency in Sperm Production

Mitochondrial health is crucial in sperm cells because mitochondria generate ATP, the energy currency required for sperm motility and maturation. Manganese plays an essential role in mitochondrial function, but excessive manganese disrupts the mitochondrial electron transport chain, which can negatively impact sperm production.

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- **Disruption of ATP Production**: High manganese concentrations can impair mitochondrial function, reducing ATP synthesis and energy availability for sperm production. An energy-deficient environment within the testes hinders the process of spermatogenesis, leading to lower sperm counts and contributing to oligospermia.
- **Mitochondrial ROS and Cellular Damage**: Excessive manganese levels in the mitochondria increase ROS production, which damages mitochondrial DNA, proteins, and membranes. This damage not only impairs ATP production but also induces oxidative stress within the testes, further reducing the viability of sperm cells.[45-49]

4. Hormonal Disruption via the Hypothalamic-Pituitary-Gonadal (HPG) Axis

Manganese can cross the blood-brain barrier and accumulate in the hypothalamus, a region of the brain that regulates the hypothalamic-pituitary-gonadal (HPG) axis, which controls reproductive hormones essential for spermatogenesis. Dysregulation of the HPG axis due to manganese exposure can disrupt hormone levels and contribute to oligospermia.

- **Gonadotropin-Releasing Hormone (GnRH) Suppression**: Excess manganese can impair the hypothalamus' ability to release GnRH, a hormone responsible for stimulating the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. Reduced GnRH release leads to decreased levels of LH and FSH, hormones essential for testosterone production and sperm production.
- **Testosterone Production**: Testosterone, produced by Leydig cells in the testes, is critical for spermatogenesis. High manganese exposure disrupts Leydig cell function, lowering testosterone levels. Insufficient testosterone weakens the stimulation needed for sperm production, leading to lower sperm counts and contributing to oligospermia.
- **Imbalance of LH and FSH**: LH stimulates Leydig cells to produce testosterone, while FSH supports Sertoli cell function, which is essential for nurturing developing sperm cells. Alterations in LH and FSH levels due to manganese interference can impair spermatogenesis, reducing sperm count and leading to oligospermia.

5. Toxic Effects on Sertoli and Leydig Cells in the Testes

Sertoli and Leydig cells are essential for supporting sperm development and maturation within the testes. Manganese toxicity can directly affect these cells, disrupting spermatogenesis and reducing sperm count.

- **Sertoli Cell Toxicity**: Sertoli cells play a crucial role in supporting, nourishing, and protecting developing sperm cells. Excessive manganese disrupts Sertoli cell function, impairing their ability to provide necessary support for sperm maturation. This disruption reduces the overall efficiency of sperm production, contributing to oligospermia.
- **Leydig Cell Toxicity**: Leydig cells are responsible for producing testosterone, the hormone essential for spermatogenesis. Manganese toxicity can damage Leydig cells, leading to decreased testosterone production and impaired spermatogenesis, resulting in lower sperm counts and contributing to oligospermia.[50-53]

6. Immune and Inflammatory Response in the Testes

Excessive manganese exposure has been linked to inflammatory and immune responses within the testes, further impairing spermatogenesis and reducing sperm count.

- **Pro-inflammatory Cytokine Production**: High levels of manganese have been associated with increased production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), within the testes. These cytokines can induce inflammation in testicular tissue, causing cellular damage in the seminiferous tubules where sperm production occurs.
- **Fibrosis and Tissue Damage**: Chronic inflammation in the testes can lead to fibrosis, scarring, and tissue damage. This condition reduces the availability of healthy cells needed for spermatogenesis and compromises the structural integrity of testicular tissue, leading to reduced sperm count and oligospermia.[54]

DOSE-DEPENDENT EFFECTS OF MANGANESE ON SPERM QUALITY

Manganese (Mn) is a trace element that is essential for various biological processes, including antioxidant defense, energy metabolism, and hormone regulation. The effects of manganese on sperm quality follow a dose-dependent pattern,

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where low to moderate manganese levels support reproductive health, but excessive manganese exposure can have toxic effects. Understanding this dose-dependent relationship is crucial for maintaining optimal sperm quality and preventing fertility issues.

1. Low to Moderate Manganese Levels: Support for Sperm Quality

- **Antioxidant Defense**: Manganese acts as a cofactor for manganese superoxide dismutase (Mn-SOD), an important antioxidant enzyme in the mitochondria that neutralizes reactive oxygen species (ROS). At low to moderate levels, manganese helps protect sperm from oxidative damage, preserving cell integrity, morphology, and motility.
- **Energy Production**: Manganese plays a role in energy metabolism by supporting enzymes involved in ATP production. Adequate energy supply is essential for sperm motility and overall quality. By supporting mitochondrial function, manganese at optimal levels aids in producing the energy required for the tail movement and acrosome reaction necessary for successful fertilization.
- **Spermatogenesis and Hormone Regulation**: Manganese helps in the production and regulation of reproductive hormones, including testosterone, which is critical for spermatogenesis. Healthy hormone levels support normal sperm production, leading to high-quality sperm with typical morphology and motility.

In these low to moderate doses, manganese generally enhances sperm quality, supporting optimal morphology, motility, and viability. Studies suggest that these levels are beneficial and are typically obtained through a balanced diet without the need for supplementation.[8-16]

2. High Levels of Manganese: Adverse Effects on Sperm Quality

When manganese levels become excessive, often due to environmental or occupational exposure, the benefits are reversed, and toxic effects can impair sperm quality.

- **Oxidative Stress and DNA Damage**: Excess manganese disrupts the balance of ROS and antioxidant defenses, overwhelming Mn-SOD and increasing oxidative stress. Elevated ROS levels damage sperm membranes, proteins, and DNA. This oxidative damage can lead to sperm DNA fragmentation, abnormal morphology (such as head or tail deformities), and reduced sperm viability.
- **Mitochondrial Dysfunction and Reduced ATP Production**: High manganese levels disrupt mitochondrial function by impairing the electron transport chain, reducing ATP synthesis. This energy deficit affects sperm motility, as ATP is required for flagellar movement. Reduced motility limits the sperm's ability to reach and fertilize the egg, negatively impacting overall sperm quality.
- **Hormonal Imbalance**: Excess manganese can interfere with the hypothalamic-pituitary-gonadal (HPG) axis, which regulates testosterone and other reproductive hormones. Disrupted hormone levels affect spermatogenesis, reducing sperm production and leading to lower sperm counts and compromised quality.
- **Toxicity in Testicular Cells**: High manganese concentrations have been shown to damage Sertoli and Leydig cells in the testes. Sertoli cells support developing sperm, while Leydig cells produce testosterone. Toxic effects on these cells impair spermatogenesis and reduce the health and viability of sperm, contributing to reduced sperm quality and potentially leading to oligospermia or teratospermia.[33-36]

3. Dose Thresholds and Sperm Quality Impact

Studies on manganese exposure indicate that moderate dietary manganese intake (2-5 mg/day) is generally beneficial, while exposure exceeding this level, especially in occupational or environmental settings, is associated with sperm abnormalities. For instance, manganese exposure beyond the normal physiological range (above 10 mg/day) has been linked to increased rates of oligospermia (low sperm count) and teratospermia (abnormal sperm morphology). However, individual tolerance to manganese can vary based on genetic and health factors, so personal thresholds may differ.

4. Practical Implications and Recommendations

- **Optimal Dietary Intake**: Maintaining manganese intake within the recommended dietary allowance (RDA) range—2.3 mg/day for adult men—is essential for supporting sperm quality without risking toxicity.
- **Monitoring High-Risk Exposure**: Individuals in high-risk occupations (e.g., welding,

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mining) should monitor manganese levels, as excessive exposure can lead to reproductive toxicity and impaired sperm quality.

- **Further Research and Personalized Recommendations**: Since manganese tolerance varies among individuals, further research could help identify precise dose thresholds for optimizing sperm quality across different populations.[12,13]

II. CONCLUSION

Manganese, a trace element essential for various biological processes, plays a complex role in male reproductive health, influencing sperm morphology and count. While moderate manganese levels are beneficial, supporting antioxidant defenses, energy metabolism, and hormonal balance, both deficiency and excess of this element can negatively impact sperm quality. In cases of teratospermia, manganese dysregulation has been associated with increased oxidative stress, mitochondrial dysfunction, and cellular damage, leading to abnormal sperm shapes and reduced fertility. Similarly, in oligospermia, high manganese exposure can disrupt spermatogenesis and impair hormone regulation through oxidative damage, cellular toxicity, and interference with the hypothalamic-pituitary-gonadal (HPG) axis, resulting in lower sperm count. During these years a few clinical preliminaries have been created to research the impacts of cell reinforcement supplementation **(**as Vitamin-A(as beta carotene), Vitamin-C(as ascorbic acid), Vitamin-D3(as cholecalciferol), Vitamin-E, Vitamin-B1, Vitamin-B6(as pyridoxal-5-phosphate), folic acid, Vitamin-B12, Biotin(as d-biotin), Selenium (as selenomethionine), Copper(as anhydrous copper sulfate), Zinc(as zinc citrate), Molybdenium(ammonium molybdate), L-Carnitine, L-Tartate, L-Arginine, Lycopene(10%), Grape seed extract, N-Acetyl L-Cysteine, Coenzyme- Q10, Astaxanthin, Ginseng extract**)**. Antioxidants had promising effects on sperm concentration, motility, morphology, and DNA fragmentation, according to many of them and so it is considered to be the first line treatment.

Overall, manganese helps in improving the sperm concentration, motility, morphology, antioxidant effect by decreasing the oxidative stress and providing energy for the process of spermatogenesis. While balanced levels support reproductive health, excessive exposure—often from environmental or occupational sources—poses risks for both sperm morphology and quantity. This dose-dependent impact underscores the importance of maintaining manganese within optimal physiological ranges for promoting fertility and preventing reproductive issues like teratospermia and oligospermia.

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