Role of Micronutrients in Idiopathic Infertility and Preconception

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Abstract:

Infertility is defined as the inability to achieve a clinical pregnancy after 12 months or more of regular unprotected intercourse. It is a global health challenge that affects nearly 17.5% population worldwide. Notably, the prevalence is comparable across high-, middle-, and low-income countries, indicating the widespread nature of this issue.

Reactive oxygen species (ROS), though essential for normal cellular functions such as signalling and immune response, can cause oxidative damage when produced in excess. In idiopathic male infertility, abnormal sperm morphology is linked to elevated ROS levels and weakened antioxidant defences. This oxidative stress damages sperm DNA and germ cells, impairing spermatogenesis, semen quality, and fertilisation capacity.

Hormonal imbalance, particularly hypogonadism, is common in infertile men, who face significantly higher risks of azoospermia and reduced testicular volume—both markers of severe fertility impairment. The most common identifiable factors of female infertility are ovulatory disorders, endometriosis, tubal blockage, and uterine abnormalities.

Idiopathic infertility, in which no specific cause can be identified, makes both diagnosis and management more challenging. In such cases, micronutrient imbalances may play a critical but often overlooked role. Adequate intake of micronutrients is essential for reproductive health. Given that many essential nutrients are often deficient in reproductive-age individuals, understanding and addressing these gaps are vital for better management of infertility. Early preconception counselling, targeted supplementation, and individualised nutritional interventions may improve fertility outcomes in idiopathic cases.

This article highlights the importance of micronutrients in fertility, with supportive studies demonstrating that micronutrient supplementation significantly improved semen parameters in infertile men after 3 months of antioxidant supplementation. In women, micronutrients also play a crucial role. Nutrients such as folate support oocyte quality and maturation, zinc regulates ovulation and the menstrual cycle, and B vitamins and zinc are essential for DNA synthesis. Together, these findings highlight that targeted micronutrient therapy can enhance both male and female fertility by improving gamete quality and reproductive function.

Index Terms: idiopathic infertility, micronutrients, preconception care, folic acid, iron supplementation, omega-3 fatty acids, calcium, reproductive health

1. Introduction

1.1. *Background, prevalence of infertility, and preconception health*

Infertility is defined as the failure to achieve pregnancy despite regular, unprotected sexual intercourse for 12 months or longer [1]. Infertility can result in physical suffering, emotional humiliation, financial strain, and negatively impact an individual's mental and psychological well-being [1].

According to the most recent data published by the World Health Organization (WHO) in April 2023, the lifetime prevalence is defined as the proportion of a population that has ever experienced infertility in their lifetime, and is estimated at approximately 17.5%. This suggests that about one in every six adults worldwide faces infertility, marking a rise from the average global prevalence of 10% reported in 2016 [2]. Globally, between 1990 and 2017, the age-standardised prevalence of infertility rose annually by 0.370% in females and 0.291% in males [3]. The lifetime prevalence of infertility shows minimal variation across different income groups, with rates of 17.8% in high-income countries and 16.5% in low- and middle-income nations [2]. This data highlights that infertility is a widespread global health concern, affecting individuals across all regions [2].

Consequently, understanding the underlying causes of infertility and assessing its associated disease burden are crucial steps towards effective prevention and management [1]. Females account for 50% of all infertility cases, and are the primary contributors in approximately 70%–80% of instances [1]. Female infertility can be attributed to ovulatory dysfunction and anovulation, tubal blockage, endometriosis, diminished ovarian reserve, and abnormalities of the uterus [1, 4]. Polycystic ovary syndrome (PCOS) is the leading cause of ovulatory disorders, responsible for up to 80% of anovulation cases in women [1]. The primary clinical characteristics of PCOS, or signs of hyperandrogenism, oligo-ovulation or anovulation leading to menstrual disturbances and polycystic ovarian morphology, significantly hinder female fertility [1]. Independent of PCOS, obesity is linked to an increased risk of female infertility, particularly due to a higher likelihood of anovulatory cycles and miscarriage [1,5].

Preconception care aims at enhancing the overall health and well-being of a woman and her partner before conception, with the primary objective to identify any medical or social issues that could pose risks to either the mother or the developing foetus [6]. The interventions focus on prevention and early management, particularly targeting factors that require attention before conception or in the early stages of pregnancy to achieve the greatest benefit [7]. Although the concept of preconception care has been discussed for more than a decade, it has yet to be fully integrated into standard clinical practice [6].

Numerous studies have shown that targeted interventions can effectively raise awareness about the importance of supplementation before pregnancy [6]. Based on data collected over a decade ago, only one study showed that women from low-income backgrounds who received information about preconception health during routine family planning visits were more likely to report their pregnancies as planned [6]. Research from the United Kingdom examining healthcare professionals' knowledge and attitudes regarding preconception care indicates a strong consensus on its significance among primary care teams [6]. Therefore, preconception care represents a crucial opportunity for preventive investment [7].

Preconception health broadly encompasses the health status of both women and men throughout their lives, before any potential pregnancy [8]. There are some key reasons to consider preconception care.

First, the preconception health practices of both parents can directly influence the health of their future children through epigenetic processes [8]. Second, even in planned pregnancies, recognition of pregnancy can be delayed, leading individuals to be unaware of their pregnancy during critical early stages [8]. Third, some behaviours, such as smoking and obesity, are challenging to change quickly, and these changes are essential before conception to minimise potential harm to the foetus [8].

1.2. Definition and scope of idiopathic infertility

Male factor infertility (MFI) is responsible for approximately 20% of infertility cases, whereas a combination of both male and female factors contributes to an additional 30% [9]. In total, male-related causes are involved in up to 50% of all infertility cases, highlighting the importance of establishing a thorough and accurate diagnostic approach for men, along with the implementation of individualised and effective treatment strategies [10]. Although multiple causes have been linked to MFI, approximately 30% of affected men present with poor sperm quality without any identifiable underlying cause, a condition classified as idiopathic male infertility (IMI) [9]. Semen analysis remains a fundamental tool in the assessment of MFI [9]. However, individual semen parameters alone do not reliably predict a man’s fertility potential. An estimated 15%–40% of men may experience infertility despite having normal semen profiles, an unremarkable medical history, and no abnormalities on physical examination [9]. This condition is currently categorised as unexplained male infertility (UMI) [9]. UMI is distinct from IMI, where men exhibit abnormal semen characteristics without a clear underlying cause [9].

1.3. Challenges associated with preconception care

The key challenges in delivering effective interventions can be categorised into areas of awareness, provider compliance, and client compliance [7]. A lack of awareness, significant knowledge gaps, and a lack of confidence in service delivery hinder the importance of timely intervention [7]. At the healthcare professional level, challenges such as time constraints can limit the quality and consistency of care [7].

From the couple’s perspective, adherence is influenced by whether they view the interventions as important [7]. If there is reluctance to seek or act on medical advice, follow-through may be poor [7]. Trust and the quality of the relationship with the healthcare professional, along with strong influence from family members, also play a key role in determining whether the couple engages with and completes the recommended care [7].

1.4 Importance of micronutrients in reproductive health

Micronutrients (essential vitamins and minerals) are required in small amounts through the diet. Although they do not serve as sources of energy, they play a crucial role in various metabolic processes—both catabolic and anabolic—and must be obtained from external sources [11]. Studies have shown that micronutrient deficiencies during pregnancy can lead to pre-eclampsia, premature birth, neural tube defects (NTDs) such as spina bifida, congenital anomalies related to the cardiovascular or urinary systems, and low birthweight or small-for-gestational-age infants [11]. Furthermore, insufficient micronutrient intake during pregnancy may have long-term health implications for the child, including a higher risk of developing non-communicable diseases later in life [11].

Vitamins C, E, and A, known for their antioxidant functions, along with nutrients such as folate and zinc, help neutralise reactive oxygen species (ROS). Additionally, minerals such as copper, manganese, and zinc support the activity of superoxide dismutase—enzymes that mitigate oxidative damage. These antioxidants are vital for safeguarding DNA and other essential cellular components from oxidative injury that could otherwise trigger apoptosis [11].

Among the various micronutrients under investigation for their potential impact on fertility, folate (folic acid) and vitamin B12 have shown particularly promising associations [12]. The link between folate deficiency, altered folate and homocysteine metabolism, and NTDs is well-documented [12].

In a randomised controlled trial (RCT), women who received a multivitamin supplement containing 800 µg of folic acid before conception showed a higher conception rate (71.3%) compared to those given a trace element placebo (67.9%) over a 14-month follow-up. Another RCT involving sub-fertile women found that those taking a multivitamin with 400 µg of folic acid for 3 months achieved a pregnancy rate of 26%, in contrast to only 10% in the placebo group [12]. Folic acid supplementation is also reported to improve markers of female reproductive health, ranging from reduced incidence of anovulation to enhanced success rates in assisted reproductive technologies (ART), suggesting that folate's benefits extend beyond its established role in preventing NTDs [12].

2. Pathophysiology of Idiopathic Infertility

2.1. Oxidative stress and reproductive function

ROS, along with reactive nitrogen and chlorine species, are generated under both normal and pathological conditions in humans [13]. Although free radicals are essential for physiological processes such as signal transduction, gene transcription, platelet aggregation, immune modulation, leukocyte adhesion, and angiogenesis, excessive ROS can oxidise DNA, lipids, and proteins, leading to cellular damage and death [13].

Oxidative stress (OS) has been recognised as a factor in the development of IMI. Evidence suggests that sperm cells with abnormal morphology are prone to excessive production of ROS and often have diminished antioxidant defenses [9]. This imbalance is particularly prominent in men with idiopathic infertility [9]. The detrimental effects of OS on male reproductive health are multifaceted due to toxic by-products that damage germ cells and sperm DNA and impair key aspects of male fertility, including spermatogenesis, semen quality, fertilisation potential, and may have long-term health implications for the offspring [9].

2.2. Role of hormonal dysregulation

Male hypogonadism is commonly observed among infertile men and can present in different underlying pathophysiological features [10]. These individuals may exhibit either primary or secondary hypogonadism, which can be differentiated based on serum levels of total testosterone (tT), follicle-stimulating hormone (FSH), and luteinising hormone (LH) [10]. Compared to men with normal hormone levels, they are at a substantially increased risk, up to 24 times more likely, to experience azoospermia and are 13 times more likely to present with reduced testicular volume, highlighting a severe impairment in fertility potential.[9]. Furthermore, sex hormone-binding globulin (SHBG) modulates the bioavailability of testosterone, demonstrating an age-related increase while showing an inverse relationship with body mass index (BMI) [9]. These dynamics necessitate the incorporation of a thorough hormonal evaluation—including tT, FSH, and LH—during the assessment of MFI.

2.3. Impact of lifestyle and environmental factors

Today's fast-paced, demanding lifestyles are often associated with elevated stress levels, which have been implicated in male subfertility [9]. Beyond stress, dietary habits are also closely associated with testicular function, reproductive capacity, and sperm health [9]. For example, obesity is linked with increased oxidative stress, a key contributor to poor semen parameters and sperm DNA fragmentation [9]. Additionally, smoking and excessive alcohol consumption adversely affect spermatogenesis [9].

3. Overview of Key Micronutrients in Fertility

3.1. Role of folate in female fertility

Folate plays a key role in oocyte quality, maturation, fertilisation, and implantation. The reduced risk of ovulatory infertility seen with multiple micronutrient (MMN) use is largely attributed to B vitamins, particularly folate. Studies involving either single or combined micronutrient supplementation have shown fertility benefits in both healthy women and those with subfertility [11]. Supplementing with folic acid during in vitro fertilisation (IVF) has been linked to improved follicular fluid homocysteine profiles, enhanced embryo quality, and higher pregnancy rates. A 2-fold rise in follicular fluid folate was associated with a 3.3-fold increase in pregnancy likelihood [11].

3.2. Role of vitamin D in female fertility

Vitamin D receptors are present across reproductive tissues, highlighting their relevance to fertility regulation. Women with suboptimal vitamin D intake or deficient serum 25(OH)D levels may have reduced chances of conception [11]. Deficiency is also linked to fertility-reducing conditions such as PCOS and may negatively affect outcomes of assisted reproductive techniques such as IVF [11]. In patients with PCOS and vitamin D deficiency, supplementation has shown potential in improving menstrual regularity and alleviating metabolic disturbances [11].

3.3. Vitamin B12

Low levels of vitamin B12 are frequently observed among women facing fertility challenges. Over 50% of infertile women have been reported to have suboptimal B12 levels, and other studies have similarly linked B12 deficiency to reduced fertility potential in women [11].

3.4. Zinc

Zinc plays a critical role in female reproduction, particularly in ovulation and menstrual cycle regulation. It is also essential for DNA synthesis, in oocyte development, alongside certain B vitamins [11]. Folate and zinc together influence apoptosis, which is necessary for normal processes such as follicle atresia, corpus luteum regression, and endometrial shedding [11].

3.5. Selenium

Zinc was the most frequently included ingredient in dietary supplements, followed by selenium, arginine, coenzyme Q10, folic acid, and carnitine, together accounting for components in over 60% of formulations [14].

3.6. Iron

Women with low ferritin levels ($\leq$30 µg/L) are associated with lower conception rates and higher miscarriage risks. Patients seeking help for infertility should be screened early for a possible association with iron deficiency.[15].

3.7. Omega-3 fatty acids

Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are the most biologically active forms of omega-3 fatty acids. DHA is a critical component of foetal brain and retinal cell membranes, influencing visual and neural function. Maternal omega-3 intake directly affects foetal DHA levels, as the body is inefficient at converting precursors such as α-linolenic acid (ALA) into DHA [16].

3.8. Antioxidants (coenzyme Q10)

CoQ10 is a lipid-soluble coenzyme involved in mitochondrial energy production and antioxidant defence helps reduce oxidative stress, which is linked to poor ovarian response and age-related fertility decline. Reduced CoQ10 levels are linked to hypogonadism and disturbances in steroid hormone levels. CoQ10-treated women have high-quality embryos, fewer cycle cancellations due to poor embryo development, and higher clinical pregnancy rate and live birth rate [17].

4. Evidence Linking Micronutrients to Male Infertility

4.1. Sperm quality and oxidative stress

Oxidative stress has also been implicated as a cause of male infertility [10]. A careful balance between ROS and antioxidants is necessary for optimal sperm function, and excess seminal ROS results in oxidative stress, leading to sperm DNA fragmentation (SDF) and damage to the sperm plasma membrane. Moreover, oxidative stress has been associated with impaired sperm motility, sperm count, and abnormal sperm morphology [10].

The effectiveness of a combined antioxidant therapy in improving male infertility focuses on semen parameters and the sperm DNA fragmentation index (DFI). Men with infertility, when administered oral micronutrient capsules daily for 3 months, reported significantly improved sperm concentration, sperm count, and sperm vitality. These findings suggest that antioxidant-based micronutrient supplementation can enhance sperm quality and reduce DNA fragmentation in men with infertility [18].

4.2. Role of micronutrient supplementation in male factor idiopathic infertility

A prospective observational study evaluated the impact of micronutrient supplementation on semen parameters (oligozoospermia and asthenozoospermia) in infertile men aged 25–50 years with abnormal semen profiles. 70 men received one antioxidant tablet twice daily for 3 months, with semen analyses conducted before and after the intervention. The primary outcomes assessed were changes in sperm count and motility. Following treatment, mean sperm count significantly increased from 12.34 ± 1.84 million/mL to 15.50 ± 4.69 million/mL ($p < 0.05$), whereas rapid progressive motility improved from 28.84% ± 20.77% to 47.44% ± 25.02% ($p < 0.05$). Non-progressive sperm decreased from 40.34 % ± 21.12% to 28.32 % ± 15.47% ($p < 0.05$). Overall, 72.86% showed improvement in semen parameters. The study concluded that micronutrient therapy significantly enhances sperm count and motility in infertile men, particularly those with oligozoospermia and asthenozoospermia [19].

5. Evidence Linking Micronutrients to Female Infertility

5.1. Oocyte quality and ovulatory function

In female reproduction, ROS are involved in crucial events such as folliculogenesis, oocyte maturation, ovulation, corpus luteum formation, luteolysis, endometrial cycling, implantation, embryogenesis, and pregnancy [13]. However, an imbalance in ROS contributes to oocyte dysfunction, impaired meiotic progression, reduced gonadotropin activity, steroidogenesis inhibition, DNA damage, and diminished ATP production [13]. Oxidative stress and apoptosis play key roles in follicular atresia and luteal regression [13]. Antioxidants may offer reproductive benefits by neutralising harmful ROS effects. Additionally, nutrients such as folate are critical for oocyte quality and maturation, zinc influences ovulation and the menstrual cycle, and enzymes necessary for DNA synthesis depend on zinc and B vitamins [13]. Data from the Nurses' Health Study II suggest that iron supplementation and non-haeme dietary iron may reduce the risk of ovulatory infertility [13].

5.2. Nutritional factors in endometrial receptivity

Endometrial receptivity is when the endometrium is fully prepared to receive a well-developed embryo [20]. It aligns with the window of implantation (WOI), which spans approximately 3–6 days during the secretory phase of the menstrual cycle [21]. This critical window can be disrupted by inflammation or uterine structural abnormalities, potentially shifting or shortening the WOI and impairing implantation [21]. Dietary factors such as higher intake of complex carbohydrates have been associated with increased birth rates in IVF patients, potentially through enhanced endometrial thickness and receptivity [22]. Additionally, a randomised controlled trial found that a supplement containing myo-inositol, probiotics, and micronutrients notably reduced time-to-conception in overweight women, and the likelihood of conceiving was 1.47 times greater than that of overweight controls, potentially due to improved inflammation regulation as indicated by lower C-reactive protein (CRP) levels [23].

5.3. Role of micronutrients in unexplained infertility and PCOS

Reduced vitamin B12 levels in women with PCOS and insulin resistance may contribute to hyperinsulinemia, insulin resistance, and elevated homocysteine (Hcy) levels [24]. Elevated Hcy is associated with granulosa cell apoptosis, impaired villous angiogenesis, implantation failure and early pregnancy loss, as well as poor oocyte maturation, lower fertilisation rates and reduced embryo quality [24]. Therefore, vitamin B12 is essential for homocysteine remethylation to methionine [24].

Vitamin B9 or blood folate levels are often reduced in women with PCOS, and folic acid alone or in combination with B9 vitamins can improve fasting insulin levels and other outcomes. Folate and fatty acids reduce the risk of NTDs. Therefore, many countries have introduced mandatory folic acid fortification guidelines to increase folate intake in women of childbearing age [24].

Vitamin D deficiency is widespread in PCOS, affecting 67%–85% of women, and is linked to worsened symptoms such as insulin resistance, menstrual irregularities, infertility, obesity, hyperandrogenism, and increased cardiovascular risk [24]. Vitamin D has a key role in reproductive function by influencing anti-mullerian hormone (AMH) signalling, FSH sensitivity, and progesterone synthesis in granulosa cells [24]. Supplementing vitamin D in deficient PCOS patients can normalise elevated AMH levels and increase anti-inflammatory markers such as sRAGE [24]. Furthermore, combining vitamin D and calcium with metformin has shown potential benefits in improving menstrual regularity and ovulation in PCOS women [24].

Selenium (Se), with potent antioxidant properties, plays a key role in neutralising free oxygen radicals through ROS signalling pathways [25]. Its intake has been inversely associated with serum CRP levels, indicating its anti-inflammatory potential. Higher selenium consumption may help reduce the risk of oxidative stress and inflammation-driven disorders by modulating lipid metabolism [25]. Notably, lower Se levels have been reported in women with PCOS, and supplementation has shown potential benefits in improving insulin metabolism, triglyceride (TG), and very low-density lipoprotein (VLDL) levels [25].

Zinc (Zn), another critical antioxidant micronutrient, is a structural component of superoxide dismutase and a cofactor for various antioxidant enzymes. It contributes to lowering insulin resistance (IR) and inflammatory markers [25]. Women with PCOS and metabolic syndrome (MetS) were found to have significantly lower dietary intake of antioxidants, such as selenium, zinc, chromium, carotenoids, and vitamin E, compared to healthy controls ($p < 0.05$). Interestingly, patients with PCOS without MetS consumed more of these micronutrients than those with MetS, suggesting a potential protective role against metabolic complications in PCOS [25].

6. Micronutrients in Preconception Care

6.1. Recommended dietary allowances

Many countries have adopted periconceptional folic acid supplementation to prevent NTDs [26]. The WHO advises a daily intake of 400 µg of folic acid, beginning at least 2 months before conception and continuing through the first 12 weeks of pregnancy to reduce the risk of NTDs [26]. The Chinese Nutrition Society (CNS) recommends starting folic acid 3 months before conception and continuing throughout pregnancy [26].

WHO recommends a daily supplement of 30–60 mg of iron combined with 400 µg of folic acid throughout pregnancy to reduce the incidence of low birth weight (LBW), maternal anaemia, and iron deficiency [26]. WHO also recommends 1.5–2.0 g of daily calcium supplementation from 20 weeks of gestation until delivery to lower the risk of pre-eclampsia [26].

6.2. Preconceptional supplementation guidelines

In industrialised nations, many women of reproductive age fall short of recommended intakes for essential micronutrients such as folate, vitamin B6, vitamin B12, vitamin D, calcium, iodine, iron, and selenium, potentially creating a suboptimal environment for conception. Given the role of micronutrients, particularly folate, vitamins B6 and B12, vitamin D, and antioxidants, in reproductive health, restoring their levels through diet or supplementation may enhance fertility outcomes [11].

Evidence shows that a balanced, nutrient-rich preconception diet improves fertility and increases the likelihood of conception and ongoing pregnancy. A healthy diet also correlates with higher RBC folate levels, which are linked to better fertilisation rates and mature oocyte counts in women undergoing infertility treatment. Moreover, higher serum and follicular fluid vitamin D levels have been associated with improved IVF success rates [11].

Despite food availability, various socioeconomic and cultural factors can hinder optimal dietary intake, resulting in micronutrient deficiencies even in well-resourced settings [11]. Additionally, a balanced diet alone may not be sufficient to meet all micronutrient requirements. Therefore, experts strongly recommend the use of supplements, ideally beginning 6 months before conception [27].

6.3. Clinical recommendations and best practices

Nutrition guidelines for maternal health recommend supplementation with essential micronutrients. These include Iron—recommended by American College of Obstetricians and Gynecologists (ACOG), Public Health Agency of Canada (PHAC), Royal Australian College of General Practitioners (RACGP) and Federation of Obstetric and Gynecologic Societies of India (FOGSI); Calcium—recommended by ACOG, PHAC and RACGP; Vitamin D—recommended by ACOG, PHAC and RACGP; Iodine—recommended by RACGP and Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) [28].

Guidelines also recommend healthy weight management, physical activity, and smoking/alcohol cessation before conception [28]. Advises vaccination against rubella, hepatitis B, and influenza before pregnancy [28]. Emphasises preconception screening and managing conditions such as diabetes, hypertension, and thyroid disorders [28]. Emphasises the importance of screening for depression and anxiety before pregnancy [28]. Advises reducing exposure to harmful chemicals and pollutants affecting fertility [28]. Encourages family planning discussions and contraceptive counselling for those considering pregnancy [28]. High-quality evidence supports daily folic acid intake to reduce the risk of NTDs [28].

Supplement recommendations should be tailored for individuals with specific dietary needs, such as those following vegan or vegetarian diets, or those with food intolerances [27]. The International Federation of Gynecology and Obstetrics (FIGO) recommends consultation with a nutritionist, and recommends women with special nutritional considerations, such as multiple gestation, obesity and overweight, prior history of bariatric surgery, diabetes, hypertension, gastrointestinal disorders, and other conditions [29].

They should also be adapted for individuals with PCOS, and special consideration is needed for those with a history of pregnancy complications related to nutrition, such as NTDs or pre-eclampsia [27].

7. Clinical Trials and Meta-analyses Overview

7.1. Micronutrient supplements as antioxidants in improving sperm quality and reducing DNA fragmentation

A study evaluating the impact of combined antioxidant therapy on infertile men with high sperm DFI showed significant improvements in semen parameters and DNA integrity after 3 months of supplementation. Participants received two daily oral capsules, each containing 60 mg vitamin E, 400 µg folic acid, 30 mg selenium, 125 mg L-arginine, 220 mg L-carnitine, 7.5 mg coenzyme Q10, 40 mg L-glutathione, and 20 mg zinc citrate. Post-treatment analysis revealed a reduction in the mean DFI from 45.6% ± 17.2% to 34.8% ± 20.3%, an increase in sperm concentration from 29.7×10^6/mL to 35.7×10^6/mL ($p < 0.001$), an increase in total sperm count from 72.1×10^6 to 95.5×10^6 ($p = 0.012$) and an improvement in sperm vitality from 75.5% ± 17.1% to 81.1% ± 14.4% ($p < 0.001$). These findings support the role of antioxidant and micronutrient supplementation in enhancing sperm quality and DNA integrity in men experiencing infertility [18].

7.2. Micronutrient supplements enhancing ovulation and embryo quality

The rationale behind using dietary supplements (DS) in fertility is to address deficiencies or optimise levels of key nutrients—including vitamins, minerals, carbohydrates, fatty acids and proteins—that support hormonal balance, ovulation and gamete quality, ultimately enhancing the chances of conception [30]. Folic acid is the only universally recommended supplement for women planning pregnancy, primarily to prevent NTDs. Importantly, folic acid has also been linked to reductions in non-NTD anomalies such as cleft palate and genitourinary defects [30].

Myo-inositol and D-chiro-inositol, in PCOS, have been shown to improve ovulation and oocyte quality. Melatonin, concerning female fertility, has demonstrated benefits in oocyte and embryo quality as well as luteal function [30].

Vitamin D3, found in approximately 30% of supplements, has roles in follicle recruitment and endometrial function via anti-Müllerian hormone modulation and cell proliferation. Yet, clinical evidence does not link serum vitamin D levels with IVF outcomes [30].

With antioxidant and insulin-sensitising effects, N-acetyl cysteine has shown promise in enhancing ovulation and embryo quality, especially in PCOS. Coenzyme Q10 (CoQ10), crucial for mitochondrial energy and oxidative protection, supports oocyte quality and mitigates age-related gamete decline [30].

***7.3 Impact of supplementation during the preconception and pregnancy period on maternal and fetal outcomes*.**

Micronutrient intake patterns and associated outcomes were analysed in a retrospective study of 500 pregnant women aged 18–40 years with spontaneous conception. The study analysed that iron supplementation intake increased significantly from 1.2% in the 1st trimester to 94.6% in the 3rd trimester, whereas folic acid intake peaked at 93% in the 1st trimester but dropped to 6.6% by the 3rd trimester. Calcium intake increased sharply from 1.2% preconception to 96.4% in the 3rd trimester. Omega-3 fatty acid intake was negligible but reached 11.4% in the 3rd trimester. Multivitamin intake increased from 0.4% to 40.8%, whereas multiminerals were used by only 6.4% in the 3rd trimester.[31].

Table 1: Micronutrient intake across different stages

Micronutrient	Preconception (%)	1st Trimester (%)	2nd Trimester (%)	3rd Trimester (%)
Iron	3%	1.2%	90.4%	94.6%
Folic acid	20%	93%	17.6%	6.6%
Calcium	1.2%	-	94.2%	96.4%
Omega-3 fatty acids	0%	-	4.4%	11.4%
Multivitamins	0.4%	0.4%	19.8%	40.8%
Multiminerals	0%	-	-	6.4%

Pregnancy outcomes included 86.2% term deliveries, 9% preterm, and 4.8% post-dated pregnancies. The incidence of preterm delivery was significant in the subjects not taking the folic acid supplement [31]. Maternal–foetal complications included the incidence of SGA increased in the subjects not taking folic acid regularly. Incidence of intrauterine growth restriction (IUGR) was associated with low or irregular iron intake. Incidence of severe anaemia was also associated with low or irregular iron intake [31]. The study concluded that micronutrient supplementation improved foetal outcomes and reduced maternal complications, with omega-3 fatty acids linked to higher birth weight, and iron and folic acid deficiencies associated with maternal anaemia, IUGR, and SGA. Calcium supplementation was effective in reducing pre-eclampsia risk, and multivitamins and multiminerals showed positive effects on neonatal health.[31].

8. Efficacy and Safety of Supplementation Use in the Preconception Period

Folic acid reduces the risk of NTDs and supports placental growth. Iron helps prevent maternal anemia, low birth weight, and preterm delivery, while calcium lowers the risk of pre-eclampsia, particularly in populations with low dietary calcium intake. Multivitamins and multiminerals improve maternal immune function, energy metabolism, and stress response [31]. Safe dose of folic acid was 400 mcg daily; iron 30–60 mg elemental iron daily. Calcium 1.5–2 g daily in populations with low calcium intake or tailored to individual dietary intake. Iron supplementation should be monitored to avoid gastrointestinal side effects. Omega-3 fatty acids have no established preconception dosage, but supplementation during pregnancy is reported to be beneficial [31].

Conclusion

Given the crucial role of micronutrients such as folate, vitamins B6 and B12, vitamin D, and antioxidants in fertility, ensuring adequate levels of these nutrients may potentially improve outcomes in cases of idiopathic infertility.

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