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The Role of Probiotic and Prebiotic Supplementation on Semen Parameters in Idiopathic Male Infertility: A Narrative Review

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Abstract: Male factors are the most prevalent cause for infertility in the world. The "gut-testis axis" theory posits that oxidative stress, systemic inflammation, and dysbiosis of the gut and seminal microbiomes are the primary etiological factors. This review focused on clarifying the efficacy of probiotic and prebiotic supplements on the semen of men who experience idiopathic infertility. We searched through PubMed (n=82), Scopus (n=71), and the Cochrane Library (n=33) between January 2020 and 2025. The search focused on randomized controlled trials (RCTs) and mechanistic research on Lactobacillus, Bifidobacterium, fructooligosaccharides (FOS), and synbiotics in human subjects or animal models. Total of 22 included studies involved human subjects, while 9 were based on animal models. Synbiotic therapy, such as Lactobacillus strains combined with FOS significantly enhance sperm concentration, progressive motility, and normal morphology compared to a placebo. These medications reduced the levels of CRP and TNF-α, which are signs of systemic inflammation. These therapies also reduce the levels of seminal lipid peroxidation and sperm DNA fragmentation (SDF). Recent findings show that using both synbiotics and antioxidants together is significantly better than using only antioxidants. Probiotic and prebiotic supplementation represents a promising, low-risk adjunctive therapy for idiopathic male infertility by restoring the gut-testis axis, ameliorating oxidative stress, and improving sperm functional integrity.

Keywords: Idiopathic male infertility, Gut-testis axis, Probiotics, Prebiotics, Semen parameters, Sperm DNA fragmentation

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Introduction

Infertility remains a significant global health issue, affecting approximately 15% of couples worldwide, with male factors contributing to nearly 50% of all cases (Agarwal et al., 2021; WHO, 2023). Despite advances in diagnostic andrology, including hormonal profiling, genetic testing, and imaging, a substantial proportion of men—estimated between 30% and 50%—are still classified as having idiopathic oligoasthenoteratozoospermia (iOAT). These patients present with abnormalities in sperm concentration, motility, and morphology without an identifiable etiology. Among the proposed mechanisms, oxidative stress (OS) and chronic low-grade inflammation are

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considered central contributors to impaired spermatogenesis (Majzoub et al., 2018; Dutta et al., 2023).

Current management strategies for iOAT have largely relied on empirical antioxidant therapy, such as L-carnitine, coenzyme Q10, and vitamins C and E, aimed at reducing reactive oxygen species (ROS). However, emerging evidence suggests that antioxidant-based approaches alone may yield inconsistent improvements in reproductive outcomes, including pregnancy and live birth rates, indicating that oxidative stress may represent a downstream manifestation rather than the primary underlying cause (Smits et al., 2021). This limitation highlights the need to explore upstream systemic mechanisms contributing to male infertility.

In this context, the concept of the "gut–testis axis" has emerged as a novel framework linking intestinal microbiota with male reproductive function. This bidirectional axis integrates metabolic, endocrine, and immunological pathways, through which gut microbiota can influence spermatogenesis and hormonal regulation (Lundy et al., 2021; Ding et al., 2020). Dysbiosis—defined as an imbalance in microbial composition—is increasingly associated with systemic inflammation, metabolic dysfunction, and impaired reproductive health. Although the exact prevalence of infertility directly attributable to dysbiosis remains unclear, conditions strongly linked to altered gut microbiota, such as obesity, metabolic syndrome, and chronic inflammation, are highly prevalent among men with idiopathic infertility (Salas-Huetos et al., 2017; Zhao et al., 2024).

Mechanistically, dysbiosis may increase intestinal permeability, allowing translocation of bacterial lipopolysaccharides (LPS) into systemic circulation, a condition known as metabolic endotoxemia. This process can activate inflammatory pathways and disrupt the integrity of the blood–testis barrier, ultimately impairing spermatogenesis and sperm function (Santacroce et al., 2022; Zeng et al., 2025). These findings suggest that targeting the gut microbiota may represent a promising upstream therapeutic strategy rather than solely addressing oxidative stress as a downstream consequence.

Accordingly, modulation of the gut microbiota through probiotic, prebiotic, and synbiotic supplementation has gained attention as a potential adjunctive approach in the management of idiopathic male infertility. This narrative review aims to synthesize contemporary evidence published between 2020 and 2025 to explore the potential role of these interventions in improving semen parameters and functional sperm outcomes, including sperm DNA fragmentation (SDF), while also highlighting current limitations and future research directions.

Methods

Search Strategy and Study Selection

A structured literature search was conducted using three major electronic databases: MEDLINE (PubMed), Scopus, and the Cochrane Library. The search was limited to articles published between January 1, 2020, and February 2025 to ensure inclusion of the most recent evidence.

The search strategy incorporated combinations of the following keywords: "male infertility," "idiopathic infertility," "sperm quality," "sperm DNA fragmentation," "gut-testis axis," "probiotics," "prebiotics," and "synbiotics."

A total of 186 records were initially identified (PubMed: n=82; Scopus: n=71; Cochrane Library: n=33). After removal of duplicate records (n=32), 154 articles underwent title and abstract screening. Of these, 71 full-text articles were assessed for eligibility, and 39 studies were ultimately included in the final synthesis.

Study Characteristics

The included studies consisted of:

1. 14 randomized controlled trials (RCTs) involving human participants
2. 8 observational or prospective cohort studies
3. 9 mechanistic animal studies
4. 8 systematic reviews used to support contextual understanding

Among these, 22 studies involved human subjects, while 9 studies were based on animal models. The duration of interventions in human studies ranged from 6 weeks to 6 months, with most studies covering at least one full spermatogenic cycle (~74 days).

Inclusion and Exclusion Criteria

Inclusion Criteria

Studies were included if they met the following criteria:

1. Randomized controlled trials (RCTs), prospective cohort studies, or high-quality mechanistic animal studies
2. Participants diagnosed with idiopathic infertility or iOAT, or animal models of metabolic infertility
3. Interventions involving oral supplementation with probiotics (e.g., Lactobacillus, Bifidobacterium), prebiotics (e.g., FOS, inulin), or synbiotics
4. English-language, peer-reviewed, full-text articles

Exclusion Criteria

Studies were excluded if they:

1. Focused on obstructive azoospermia or known genetic infertility (e.g., Klinefelter syndrome)
2. Investigated female infertility exclusively
3. Were conference abstracts, editorials, or non-peer-reviewed preprints

Reflexivity and Bias Consideration

The authors acknowledge that restricting the search to English-language and open-access publications may introduce selection bias, potentially excluding relevant studies from subscription-based journals or non-English sources. Additionally, as a narrative review, this study inherently allows for interpretative synthesis of heterogeneous evidence. To enhance methodological rigor and transparency, this review adhered to the SANRA (Scale for the Assessment of Narrative Review Articles) guidelines (Baethge et al., 2019).

The search process was considered saturated when additional searches did not yield new randomized controlled trials or mechanistic studies relevant to microbiome-based interventions in idiopathic male infertility within the defined timeframe.

Data Extraction and Analysis

Data were extracted systematically from each included study, including study design, sample size, population characteristics, type of intervention (probiotic strains or prebiotic compounds), duration of treatment, and primary outcomes such as sperm concentration, motility, morphology, and sperm DNA fragmentation (SDF).

Given the heterogeneity of study designs, interventions, and outcome measures, a qualitative synthesis approach was employed. The analysis focused on identifying consistent trends across studies, particularly regarding improvements in semen parameters, modulation of oxidative stress, and reduction of inflammatory markers, while also considering variability in study protocols.

Discussion

Recent evidence from randomized controlled trials and mechanistic studies consistently suggests that modulation of the gut microbiota through probiotic, prebiotic, and synbiotic supplementation is associated with improvements in both conventional semen parameters and functional sperm integrity (Helli et al., 2022; Abbasi et al., 2021; Asadi et al., 2023). Rather than representing isolated findings, the available literature demonstrates a reproducible pattern of benefit across heterogeneous study designs, populations, and intervention protocols.

Across multiple RCTs conducted between 2020 and 2025, supplementation with probiotics or synbiotics has been associated with significant improvements in sperm concentration, progressive motility, and morphology (Helli et al., 2022; Abbasi et al., 2021). Although individual studies vary in terms of probiotic strains, dosage, and duration of treatment, the direction of effect remains largely consistent. Importantly, these improvements are frequently accompanied by reductions in systemic inflammatory markers such as C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α), as well as increases in total antioxidant capacity (TAC), suggesting a systemic anti-inflammatory and antioxidant effect (Helli et al., 2022; Santacroce et al., 2022).

Improvements in sperm DNA fragmentation (SDF) represent one of the most clinically relevant findings across studies. Several trials have demonstrated significant reductions in SDF following synbiotic supplementation, alongside decreased lipid peroxidation (Abbasi et al., 2021; Zarehoroki et al., 2025). Given that elevated SDF is strongly associated with fertilization failure and adverse reproductive outcomes, these findings suggest that microbiome modulation may contribute to improved sperm functional integrity (Agarwal et al., 2022).

From a mechanistic perspective, the gut–testis axis provides a unifying explanation for these clinical observations. Dysbiosis is associated with increased intestinal permeability and metabolic endotoxemia, allowing lipopolysaccharides (LPS) to enter systemic circulation and trigger inflammatory cascades (Santacroce et al., 2022). This process may disrupt the integrity of the blood–testis barrier and impair spermatogenesis through oxidative stress and immune-mediated pathways (Zeng et al., 2025; Wang et al., 2025). Conversely, restoration of microbial balance through probiotic and prebiotic supplementation has been shown to enhance antioxidant defenses via Nrf2-mediated pathways and reduce systemic inflammation (Signorini et al., 2024).

The role of synbiotics appears particularly important, as combining probiotics with prebiotic substrates enhances bacterial survival and metabolic activity, leading to more consistent clinical outcomes (Abbasi et al., 2021). Furthermore, emerging evidence suggests a synergistic effect between microbiome-targeted therapy and conventional antioxidants. Studies combining synbiotics with antioxidant formulations have demonstrated greater improvements in sperm motility and more pronounced reductions in DNA fragmentation compared with antioxidants alone

(Zarehoroki et al., 2025; De Leo et al., 2022). This supports the hypothesis that gut microbiota may influence not only endogenous oxidative balance but also the bioavailability and efficacy of oral antioxidant therapy.

Although human data on isolated prebiotic supplementation remain limited, mechanistic and animal studies provide supportive evidence. Prebiotics such as inulin and fructooligosaccharides promote the production of short-chain fatty acids (SCFAs), particularly butyrate, which enhances gut barrier integrity and reduces endotoxemia (Rahimiyan-Heravan et al., 2020). Experimental models have demonstrated that these effects may translate into improved Leydig cell function and restoration of testicular architecture, particularly in metabolic-associated infertility (Rahimiyan-Heravan et al., 2020).

Despite these promising and consistent trends, heterogeneity remains a key limitation. Variability in probiotic strains, colony-forming units, duration of supplementation, and study populations limits direct comparability across studies. Nevertheless, the convergence of findings across different study designs strengthens the overall inference that microbiome modulation may represent a meaningful adjunctive approach in the management of idiopathic male infertility.

Limitations and Future Directions

Although the overall findings across studies demonstrate a relatively consistent trend toward improvement in semen parameters and sperm functional integrity following microbiome-targeted interventions, these results should be interpreted with caution. Across multiple randomized and observational studies, probiotic and synbiotic supplementation generally show directional agreement in improving sperm concentration, motility, morphology, and reducing sperm DNA fragmentation, despite variations in study populations, intervention duration, and formulation (Helli et al., 2022; Abbasi et al., 2021; Asadi et al., 2023). This consistency suggests a sigpotentially meaningful biological effect mediated through modulation of oxidative stress and systemic inflammation.

However, important methodological limitations must be considered. Significant heterogeneity exists across studies in terms of probiotic strains, dosages (colony-forming units), combinations with prebiotics or antioxidants, and duration of therapy, which limits direct comparability and prevents standardization of clinical protocols (McFarland et al., 2023). Furthermore, most studies rely on surrogate endpoints such as semen parameters and biochemical markers rather than clinically relevant outcomes, including pregnancy and live birth rates. While improvements in these surrogate markers are encouraging, their translation into definitive reproductive success remains uncertain.

Therefore, although microbiome modulation appears to offer promising adjunctive benefits in idiopathic male infertility, the current evidence base remains insufficient to draw definitive clinical conclusions. Future research should prioritize well-designed, large-scale multicenter randomized controlled trials with standardized interventions and longer follow-up periods. In addition, integration of advanced approaches such as metagenomic sequencing may help identify specific microbial signatures associated with fertility, enabling more targeted and personalized therapeutic strategies (Osadchiy et al., 2024).

Conclusions

Combining probiotics and prebiotics may be a novel way in treatment of idiopathic male infertility. These therapies act on the gut-testis axis, which is the fundamental cause of oxidative stress and inflammation through the body, rather than just the symptoms. Due to published evidence from 2020 to 2025, we conclude that synbiotic supplementation may improves sperm concentration, motility, and morphology in men with iOAT. The benefit originates from reduced systemic inflammation, less oxidative stress in semen, and low fragmentation of sperm DNA. Probiotics are a safe and helpful, especially when used alongside antioxidants or surgical procedures like varicocelectomy.

Shared decision-making is still very important. As part of a whole-person approach to care, health care providers ought to discuss about these supplements. They should also be aware that while the evidence for sperm parameters is strong, the investigation on live birth outcomes is still evolving.

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