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Pathophysiological link between varicocele and male infertility: mechanisms, clinical correlates and evidence-based insights

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Abstract: Varicocele is recognized as one of the most prevalent correctable causes of male infertility and is characterized by abnormal dilatation of the pampiniform plexus veins within the spermatic cord. Although frequently asymptomatic, its association with impaired spermatogenesis has been consistently documented in clinical and experimental studies. The present article aims to synthesize current scientific knowledge regarding the pathophysiological mechanisms that connect varicocele with male infertility, emphasizing hemodynamic disturbances, oxidative stress, endocrine dysregulation, and testicular microenvironmental alterations. Epidemiological data indicate that varicocele occurs in approximately 15% of the general male population, 35–40% of men with primary infertility, and up to 80% of those with secondary infertility. Experimental findings suggest that increased scrotal temperature, hypoxia, reflux of adrenal and renal metabolites, and excessive production of reactive oxygen species contribute to sperm DNA fragmentation, mitochondrial dysfunction, and apoptosis of germ cells. Clinical studies further demonstrate that varicocele repair may improve semen parameters and, in selected cases, enhance spontaneous pregnancy rates. However, variability in therapeutic outcomes underscores the complexity of underlying biological mechanisms. By integrating statistical data, mechanistic models, and evidence from peer-reviewed studies, this article provides a comprehensive theoretical analysis of the multifactorial processes linking varicocele to impaired male reproductive function and highlights directions for future research.

Keywords: *varicocele, male infertility, spermatogenesis, oxidative stress, hypoxia, hyperthermia, sperm DNA fragmentation, endocrine dysfunction.*

Аннотация: Варикоцеле признано одной из наиболее распространённых корректируемых причин мужского бесплодия и характеризуется патологическим расширением вен лозовидного (пампиниформного) сплетения в составе семенного канатика. Хотя заболевание часто протекает бессимптомно, его связь с нарушением сперматогенеза последовательно подтверждена в клинических и экспериментальных исследованиях. Цель настоящей статьи — обобщить современные научные данные о патофизиологических механизмах, связывающих варикоцеле с мужским бесплодием, с акцентом на гемодинамические нарушения, оксидативный стресс, эндокринную дисрегуляцию и изменения микроокружения яичка. Эпидемиологические данные свидетельствуют, что варикоцеле встречается примерно у 15% общей мужской популяции, у 35–40% мужчин с первичным





бесплодием и до 80% мужчин с вторичным бесплодием. Экспериментальные исследования показывают, что повышение температуры мошонки, гипоксия, рефлюкс метаболитов надпочечников и почек, а также избыточная продукция активных форм кислорода способствуют фрагментации ДНК сперматозоидов, митохондриальной дисфункции и апоптозу зародышевых клеток. Клинические исследования также демонстрируют, что хирургическая коррекция варикоцеле может улучшать показатели спермограммы и в отдельных случаях повышать частоту наступления спонтанной беременности. Однако вариабельность терапевтических результатов подчёркивает сложность лежащих в основе биологических механизмов. Интегрируя статистические данные, механистические модели и результаты рецензируемых исследований, статья представляет комплексный теоретический анализ многофакторных процессов, связывающих варикоцеле с нарушением мужской репродуктивной функции, а также обозначает перспективные направления дальнейших исследований.

Ключевые слова: варикоцеле, мужское бесплодие, сперматогенез, оксидативный стресс, гипоксия, гипертермия, фрагментация ДНК сперматозоидов, эндокринная дисфункция.

Annotatsiya: Varikotsele erkaklar bepushtligining eng keng tarqalgan va tuzatilishi mumkin bo'lgan sabablaridan biri sifatida e'tirof etiladi hamda urug' yo'li tarkibidagi pampiniform venoz chigal tomirlarining patologik kengayishi bilan tavsiflanadi. U ko'pincha simptomsiz kechsa-da, uning spermatogenez buzilishi bilan bog'liqligi klinik va eksperimental tadqiqotlarda izchil tasdiqlangan. Ushbu maqolaning maqsadi varikotsele bilan erkaklar bepushtligi o'rtasidagi bog'liqlikni ta'minlovchi patofiziologik mexanizmlar bo'yicha zamonaviy ilmiy ma'lumotlarni umumlashtirishdan iborat bo'lib, bunda gemodinamik buzilishlar, oksidativ stress, endokrin disbalans va moyak mikro-muhitidagi o'zgarishlarga alohida e'tibor qaratiladi. Epidemiologik ma'lumotlarga ko'ra, varikotsele umumiy erkaklar populyatsiyasining taxminan 15% ida, birlamchi bepushtlik bilan og'rikan erkaklarning 35–40% ida va ikkilamchi bepushtlik holatlarining 80% gacha qismida uchraydi. Eksperimental tadqiqotlar shuni ko'rsatadiki, skrotal haroratning oshishi, gipoksiya, buyrak va buyrak usti bezlari metabolitlarining reflyuksi, shuningdek reaktiv kislorod shakllarining ortiqcha ishlab chiqilishi spermatozoid DNKsining fragmentatsiyasi, mitoxondrial disfunktsiya va jinsiy (germinal) hujayralar apoptoziga olib keladi. Klinik tadqiqotlar esa varikotsele jarrohlik yo'li bilan bartaraf etilgandan so'ng spermogramma ko'rsatkichlari yaxshilanishi va ayrim hollarda spontan homiladorlik ko'rsatkichlari oshishi mumkinligini ko'rsatadi. Biroq davolash natijalaridagi farqlilik asosiy biologik mexanizmlarning murakkabligini anglatadi. Statistik ma'lumotlar, mexanistik modellar va taqrizdan o'tgan ilmiy manbalarni integratsiya qilgan holda, mazkur maqola varikotsele bilan erkaklar reproduktiv funksiyasi buzilishi o'rtasidagi ko'p omilli jarayonlarning keng qamrovli nazariy tahlilini taqdim etadi hamda kelgusidagi ilmiy izlanishlar yo'nalishlarini belgilab beradi.





Kalit soʻzlar: varikotsele, erkaklar bepushtligi, spermatogenez, oksidativ stress, gipoksiya, gipertermiya, spermatozoid DNK fragmentatsiyasi, endokrin disfunktsiya.

Introduction: Male infertility represents a significant global health concern, contributing to nearly 40–50% of infertility cases among couples worldwide. According to epidemiological estimates, approximately 15% of couples of reproductive age experience infertility, and male factors are identified either as a primary or contributory cause in a substantial proportion of cases. Among the various etiological determinants, varicocele has emerged as one of the most extensively studied and potentially reversible conditions associated with impaired male fertility.

Varicocele is defined as abnormal dilatation and tortuosity of the pampiniform venous plexus within the spermatic cord. The condition is predominantly left-sided due to anatomical and hemodynamic factors, including the perpendicular insertion of the left testicular vein into the left renal vein and the absence of effective venous valves. Population-based studies estimate that varicocele affects approximately 15% of adult males, 20% of adolescents, and up to 40% of men presenting with primary infertility. The prevalence increases dramatically among men with secondary infertility, reaching 70–80%, suggesting a progressive pathophysiological influence over time.

The link between varicocele and male infertility has been recognized for over a century; however, the exact biological mechanisms remain incompletely understood. Early hypotheses focused primarily on scrotal hyperthermia, as the pampiniform plexus plays a crucial role in countercurrent heat exchange to maintain optimal testicular temperature for spermatogenesis. Varicocele disrupts this mechanism, leading to elevated intratesticular temperature, which can adversely affect germ cell development and Sertoli cell function. Since spermatogenesis is highly temperature-sensitive, even a mild increase of 1–2°C above physiological levels may impair sperm production.

Beyond hyperthermia, contemporary research emphasizes multifactorial mechanisms. Hemodynamic disturbances resulting from venous stasis may induce testicular hypoxia, thereby altering the microenvironment essential for germ cell survival. Reduced oxygen tension has been shown to impair mitochondrial function and ATP production, essential components of sperm motility and viability. Furthermore, venous reflux from the adrenal and renal veins may expose the testes to elevated concentrations of catecholamines, cortisol metabolites, and other potentially toxic substances.

One of the most extensively investigated mechanisms involves oxidative stress. Elevated levels of reactive oxygen species (ROS) have been detected in the semen of men with varicocele. While physiological levels of ROS are necessary for sperm capacitation and acrosome reaction, excessive production leads to lipid peroxidation of sperm membranes, protein denaturation, and DNA damage. Increased sperm DNA fragmentation index (DFI) has been consistently reported in varicocele patients, correlating with reduced fertilization potential and increased miscarriage risk.

Endocrine dysfunction represents another important dimension of varicocele-associated infertility. Leydig cell impairment may reduce testosterone synthesis, while





alterations in the hypothalamic–pituitary–gonadal axis may disrupt hormonal regulation of spermatogenesis. Some clinical investigations have demonstrated lower serum testosterone levels in men with clinically significant varicocele, particularly in advanced grades.

Histopathological studies further reveal degeneration of seminiferous tubules, thickening of the basement membrane, and apoptosis of germ cells in affected testes. These structural changes suggest that varicocele exerts chronic progressive damage, potentially explaining the higher prevalence in men with secondary infertility compared to those with primary infertility

Despite the established association, not all men with varicocele develop infertility, and not all infertile men with varicocele benefit from surgical correction. This variability indicates the presence of individual susceptibility factors, including genetic predisposition, antioxidant capacity, and environmental influences.

The purpose of this article is to provide a comprehensive theoretical and evidence-based analysis of the pathophysiological mechanisms underlying the relationship between varicocele and male infertility. By integrating epidemiological statistics, experimental data, and clinical observations, the study seeks to clarify current scientific understanding and highlight areas requiring further investigation. Materials and Methods (700 words)

The present article was developed as a structured narrative review grounded exclusively in peer-reviewed scientific literature obtained from recognized international academic databases. A comprehensive literature search was conducted using PubMed, Scopus, Web of Science, Embase, and Google Scholar. Only publications indexed in reputable scientific repositories and published in English were considered eligible for inclusion.

The search strategy incorporated combinations of the following keywords: “varicocele,” “male infertility,” “pathophysiology,” “oxidative stress,” “sperm DNA fragmentation,” “testicular hypoxia,” “scrotal hyperthermia,” and “endocrine dysfunction.” Boolean operators were used to refine the search and ensure retrieval of highly relevant articles. The search period primarily focused on studies published between 2000 and 2025 to ensure contemporary scientific relevance, although foundational earlier works were also considered when necessary for theoretical context.

Inclusion criteria comprised original research articles, systematic reviews, meta-analyses, randomized controlled trials, prospective cohort studies, and doctoral dissertations addressing the pathophysiological relationship between varicocele and impaired spermatogenesis.

Studies were required to include statistical analyses, clearly defined methodology, and measurable outcomes such as semen parameters, hormonal levels, oxidative stress markers, or DNA fragmentation indices.

Exclusion criteria included case reports, opinion articles without empirical data, non-peer-reviewed publications, duplicate studies, and articles lacking methodological transparency. Animal studies were included selectively when they provided mechanistic insight relevant to human pathophysiology.





Data extraction involved systematic evaluation of study design, sample size, population characteristics, diagnostic criteria for varicocele, laboratory methods for semen analysis, oxidative stress assessment techniques, and reported statistical outcomes. Particular attention was paid to prevalence data, mean differences in semen parameters, hormonal changes, and correlations between varicocele grade and infertility severity.

Quality assessment of selected studies was performed based on methodological rigor, clarity of statistical reporting, reproducibility of findings, and sample representativeness. Studies with high risk of bias or insufficient statistical power were excluded from final synthesis.

The synthesized evidence was categorized into thematic domains: epidemiology and prevalence, scrotal hyperthermia, oxidative stress and DNA damage, hypoxia and microcirculatory disturbances, endocrine alterations, histopathological changes, and outcomes following varicocele repair. This thematic organization allowed for structured integration of mechanistic and clinical findings.

The present review does not involve direct human or animal experimentation. All information was derived from previously published scientific literature. The objective was to provide a comprehensive theoretical synthesis rather than to conduct new empirical analysis.

Results: Analysis of the selected literature demonstrates a consistent association between varicocele and impaired semen quality. Epidemiological data indicate that varicocele is present in approximately 35–40% of men with primary infertility and up to 80% of men with secondary infertility. Meta-analytical findings reveal significantly reduced sperm concentration, motility, and morphology in varicocele patients compared to fertile controls.

Studies examining scrotal temperature confirm a mean intratesticular temperature elevation of 1.5–2.0°C in men with clinical varicocele. This increase correlates negatively with total sperm count and progressive motility. Experimental data suggest that elevated temperature disrupts Sertoli cell tight junctions and impairs meiotic division of germ cells.

Oxidative stress markers are significantly elevated in semen samples of affected individuals. Levels of malondialdehyde, a marker of lipid peroxidation, are reported to be two to three times higher in varicocele patients compared to controls. Concurrently, total antioxidant capacity is markedly reduced. Sperm DNA fragmentation index is elevated in up to 40–50% of patients with clinically significant varicocele, compared to 10–15% in fertile populations.

Microcirculatory studies reveal impaired venous drainage and reduced oxygen tension in testicular tissue. Hypoxia-inducible factors are upregulated, promoting apoptotic pathways in germ cells. Histological analyses demonstrate seminiferous tubule atrophy and increased germ cell apoptosis rates.

Endocrine investigations show that approximately 10–20% of men with high-grade varicocele exhibit decreased serum testosterone levels. Leydig cell dysfunction is particularly evident in long-standing cases.





Clinical outcome studies indicate that microsurgical varicocelectomy improves sperm concentration by an average of 9–12 million/mL and enhances motility by 10–15% in appropriately selected patients. Spontaneous pregnancy rates following surgery range from 30% to 40% within one year, though results vary based on patient selection and severity.

Collectively, the data confirm that varicocele exerts multifactorial detrimental effects on spermatogenesis through thermal, oxidative, hypoxic, endocrine, and structural mechanisms.

Discussion: The relationship between varicocele and male infertility represents a complex interplay of hemodynamic, cellular, and molecular disturbances. While early theories emphasized scrotal hyperthermia as the primary mechanism, contemporary research demonstrates that temperature elevation alone cannot fully explain the spectrum of observed reproductive dysfunction.

Hyperthermia disrupts the finely regulated environment required for spermatogenesis. Germ cells are particularly sensitive to thermal stress, and sustained temperature elevation induces protein misfolding and oxidative damage. However, temperature changes also amplify other pathogenic processes, including ROS overproduction.

Oxidative stress appears to be a central mediator. Spermatozoa possess limited cytoplasmic antioxidant defenses, rendering them vulnerable to ROS-induced lipid peroxidation and DNA damage. Elevated DNA fragmentation compromises fertilization, embryo development, and pregnancy sustainability. Importantly, oxidative stress may persist even after surgical correction in some patients, suggesting irreversible cellular injury in advanced case.

Hypoxia further compounds these effects. Venous stasis reduces oxygen delivery and promotes accumulation of metabolic byproducts. Hypoxia-inducible pathways trigger apoptosis and disrupt mitochondrial respiration, leading to reduced sperm motility.

Endocrine iterations highlight systemic consequences. Testosterone deficiency may not be universal but appears significant in long-standing or high-grade varicocele. Reduced androgen support impairs spermatogenic efficiency and may influence libido and overall reproductive health.

The variability of clinical outcomes following varicocelectomy underscores individual heterogeneity. Genetic predisposition, duration of disease, baseline sperm quality, and antioxidant capacity likely determine reversibility of damage.

From a pathophysiological perspective, varicocele should be regarded as a progressive microvascular disorder with systemic oxidative implications rather than merely a localized venous abnormality. Future research should focus on identifying biomarkers predictive of surgical success and exploring adjunct antioxidant therapies.

Conclusion. Varicocele represents a multifactorial pathophysiological condition strongly associated with male infertility. Epidemiological evidence demonstrates high prevalence among infertile men, particularly in cases of secondary infertility. Mechanistically, varicocele induces scrotal hyperthermia, oxidative stress, hypoxia, endocrine imbalance, and structural degeneration of testicular tissue. These interconnected processes impair spermatogenesis, increase sperm DNA fragmentation, and reduce overall reproductive potential. Although surgical correction





improves semen parameters and pregnancy rates in selected patients, therapeutic outcomes vary, reflecting the complexity of underlying biological mechanisms. Early detection and individualized management strategies are therefore essential. Understanding the integrated pathophysiological pathways linking varicocele and infertility provides a foundation for improved diagnostic precision and targeted therapeutic interventions. Continued research integrating molecular biomarkers, genetic profiling, and long-term clinical outcomes will further refine management approaches and enhance reproductive prognosis in affected men.

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