RESEARCH TOPIC CLI25

Decoding male reproductive dysfunction in inflammatory bowel disease (IBD): a prospective, case-control study

Research area
Medical Area

Clinical Unit name
Endocrinology and Diabetology Uni, Humanitas Gavazzeni, Bergamo

Supervisor
Dr. Walter Vena walter.vena@humanitas.it

Co- Supervisor
Dr. Alessandro Pizzocaro alessandro.pizzocaro@humanitas.it

Abstract
Inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, are chronic inflammatory conditions that primarily affect young individuals during their reproductive years. While female reproductive outcomes have been extensively investigated, data on male fertility in IBD remain limited. Available evidence suggests that reproductive dysfunction in these patients may result from both disease-related and treatment-related factors. Chronic intestinal inflammation, systemic cytokine release, oxidative stress, and nutritional deficiencies may negatively affect spermatogenesis and hormonal balance. In addition, certain medications—particularly sulfasalazine—have been associated with reversible impairments in semen quality, whereas the effects of immunomodulators and biologic therapies remain incompletely understood, potentially influencing spermatogenesis through mechanisms such as increased reactive oxygen species production.
Emerging evidence highlights the role of the gut microbiota (GM), a key regulator of host immune and metabolic homeostasis, in male reproductive health. Alterations in GM composition, a hallmark of IBD, may affect reproductive function through the gut–testis axis. Studies in non-IBD populations have linked gut dysbiosis to hypogonadism, reduced testosterone levels, and impaired spermatogenesis, suggesting a mechanistic connection that warrants investigation in IBD patients.
The central hypothesis of this study is that gut microbiota composition and function influence spermatogenesis, with a balanced microbiota supporting reproductive health. The primary aim is to evaluate reproductive function in male IBD patients by assessing the hypothalamic–pituitary–gonadal (HPG) axis and semen quality using both conventional and advanced parameters across different stages of disease activity. Secondary aims include determining the prevalence of sex steroid hormonal alterations, assessing the relationship between disease activity and semen parameters, exploring correlations between systemic inflammation and hormonal profiles, characterizing gut microbiota composition, and identifying microbial signatures associated with impaired fertility.

This prospective study will enroll adult male patients with newly diagnosed Crohn's disease or ulcerative colitis, with follow-up evaluations every six months over a 2-year period. Clinical, biochemical, and microbiological data will be collected, including hormonal profiles, semen analysis according to WHO 2021 criteria, and gut microbiota assessment. Multivariable statistical models will be used to explore associations between reproductive outcomes, inflammatory markers, disease activity, and microbiota diversity.
The primary endpoint is the prevalence of abnormal semen parameters according to WHO criteria. Secondary endpoints include the prevalence of biochemical hypogonadism, correlations between testosterone levels and inflammatory markers, associations between disease activity and semen quality, and identification of microbiota signatures linked to impaired fertility. Additionally, as an exploratory outcome, in patients with hypogonadism, the effects of androgen replacement therapy on both intestinal disease activity and reproductive parameters will be evaluated, to investigate the potential dual role of testosterone in modulating gonadal function and intestinal inflammation.
This study will provide a comprehensive and integrated evaluation of male fertility in IBD, offering novel insights into the gut–immune–testis axis and identifying potential targets for personalized therapeutic strategies and improved patient counseling.

Scientific references

1. Torres J, Chaparro M, Julsgaard M, Katsanos K, Zelinkova Z, Agrawal M, et al. European Crohn's and Colitis Guidelines on Sexuality, Fertility, Pregnancy, and Lactation. J Crohns Colitis. 2023;17(1):1-27

2. Finelli R, Leisegang K, Finocchi F, De Masi S, Agarwal A, Damiani G. The impact of autoimmune systemic inflammation and associated medications on male reproductive health in patients with chronic rheumatological, dermatological, and gastroenterological diseases: A systematic review. Am J Reprod Immunol. 2021 May;85(5):e13389. doi: 10.1111/aji.13389. Epub 2021 Jan 27. PMID: 33420722

3. Carini F, Margherita Mazzola, Gagliardo C, Scaglione M, Giammanco M, Tomasello G. Inflammatory bowel disease and infertility: analysis of literature and future perspectives. Acta Biomed. 2021 Nov 3;92(5):e2021264. doi: 10.23750/abm.v92i5.11100. PMID: 34738579; PMCID: PMC8689300

4. Park YE, Kim TO. Sexual Dysfunction and Fertility Problems in Men with Inflammatory Bowel Disease. World J Mens Health. 2020 Jul;38(3):285-297. doi: 10.5534/wjmh.190007. Epub 2019 Mar 22. PMID: 30929327; PMCID: PMC7308231

5. Chen W, Zou H, Xu H, Cao R, Zhang H, Zhang Y and Zhao J (2024) The potential influence and intervention measures of gut microbiota on sperm: it is time to focus on testis-gut microbiota axis. Front. Microbiol. 15:1478082. doi: 10.3389/fmicb.2024.1478082

6. Zikopoulos A, Christopoulos P, Kalampokas T, Gerede A, Moustakli E, Arkoulis I, Topis S, Potiris A, Christodoulaki C, Tsakiridis I, Dagklis T, Stavros S. Oxidative Stress and Inflammatory Biomarkers in Male Infertility: A Narrative Review of Diagnostic Value and Clinical Integration. Diagnostics (Basel). 2026 Feb 10;16(4):527

7. Ding X., Zhu T., Gu R., et al. (2025). Gut-microbiota-testis axis: The mechanism of gut microbiota regulating host male reproduction. The Innovation Life 3:100158

8. Bezzio C, Vena W et al. (2025) Sexual Dysfunction in Male IBD Patients on Advanced Treatments: Insights into a Neglected Dimension of Quality of Life – manuscript under revision

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Humanitas University – Via Rita Levi Montalcini, 4 – 20072 Pieve Emanuele (MI) Italy
CF 97692990159 – Tel. 02.8224.3777 – info@hunimed.eu – hunimed.eu