IMPACT OF THE INTESTINAL MICROBIOME ON REPRODUCTIVE PATHOLOGIES OF THE UTERUS: AN ENDOMETRIOSIS PERSPECTIVE

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INTRODUTION:

Endometriosis (EM) is a chronic estrogen-dependent gynecological disease characterized by the presence of endometrial glands and endometrium-like tissue outside the uterus, accompanied by a severe inflammatory process. Sampson 's theory of retrograde menstruation is widely considered one of the most compelling hypotheses to explain the origin of EM. Recently, the human microbiome has been linked to its pathogenesis and there is some evidence that it can modulate the immune system from the gut, therefore, the generation of a dysfunctional immune response caused by intestinal dysbiosis could play an important role in the initiation and progression of the disease.

OBJETIVES:

To characterize the possible link between the intestinal microbiome and endometriosis to identify potential biomarkers related to the pathology.

PARTICIPANTS AND METHODOLOGY:

The diversity, composition and abundance of bacteria in the stool of 77 women (34 patients with MS and 43 controls)were analyzed by metagenomics of the V3-V4 regions of the 16S rRNA gene, using the *ENDOMETRIOSIS HEALTH PROFILE 5* questionnaire (EHP-5) as an indicator of the impact of pathology.

RESULTS:

18 were found Different taxa between controls and patients (p -value < 0.05): 3 families (*Bacteroidaceae , Lactobacillaceae and Desulfovibrionaceae)*, 3 genera (*Blautia , Anaerostipes and Lachnospira*) and 12 species (*Roseburia intestinalis, Bacteroides uniformis , Anaerobutyricum hallii among others*) . **Figure 1** .

The diversity of families and genera was higher in EM, while the control group presented greater species diversity. These taxa were linked with inflammation and estrogen signaling.

Anaerostipes spp . correlated positively with the item “Infertility”, while *Blautia spp* . and the *Bacteroidaceae* family They did so in the opposite direction (negative correlation) with almost the entire questionnaire, especially with “Pelvic pain” and “Difficulty walking”. **Figure 2**.

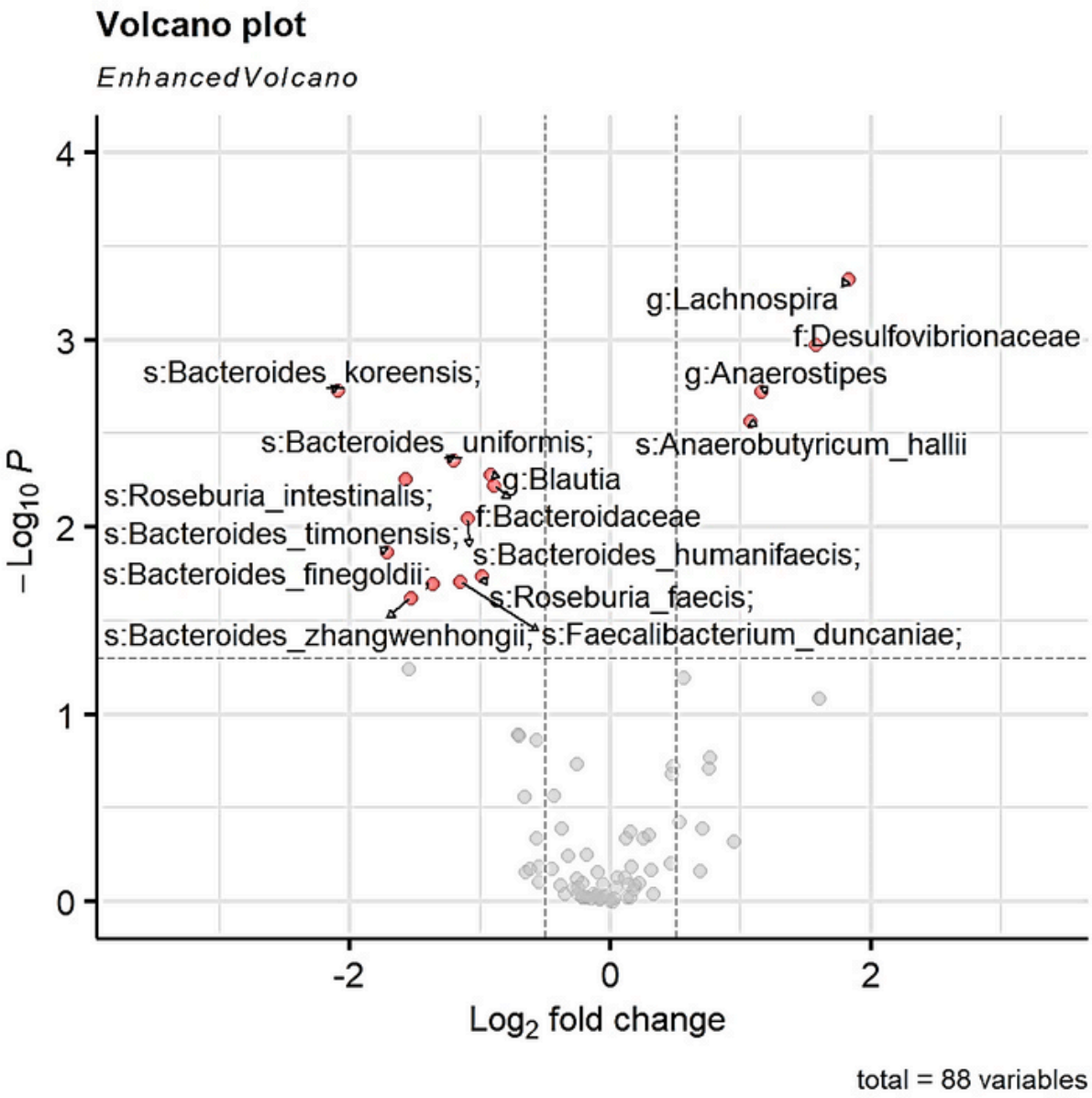

Figure 1.

VOLCANO PLOT . TAXA WHOSE ABUNDANCE SHOWED STATISTICALLY SIGNIFICANT DIFFERENCES BETWEEN THE CONTROL GROUP AND THE GROUP OF PATIENTS WITH MS. P-VALUE < 0.05

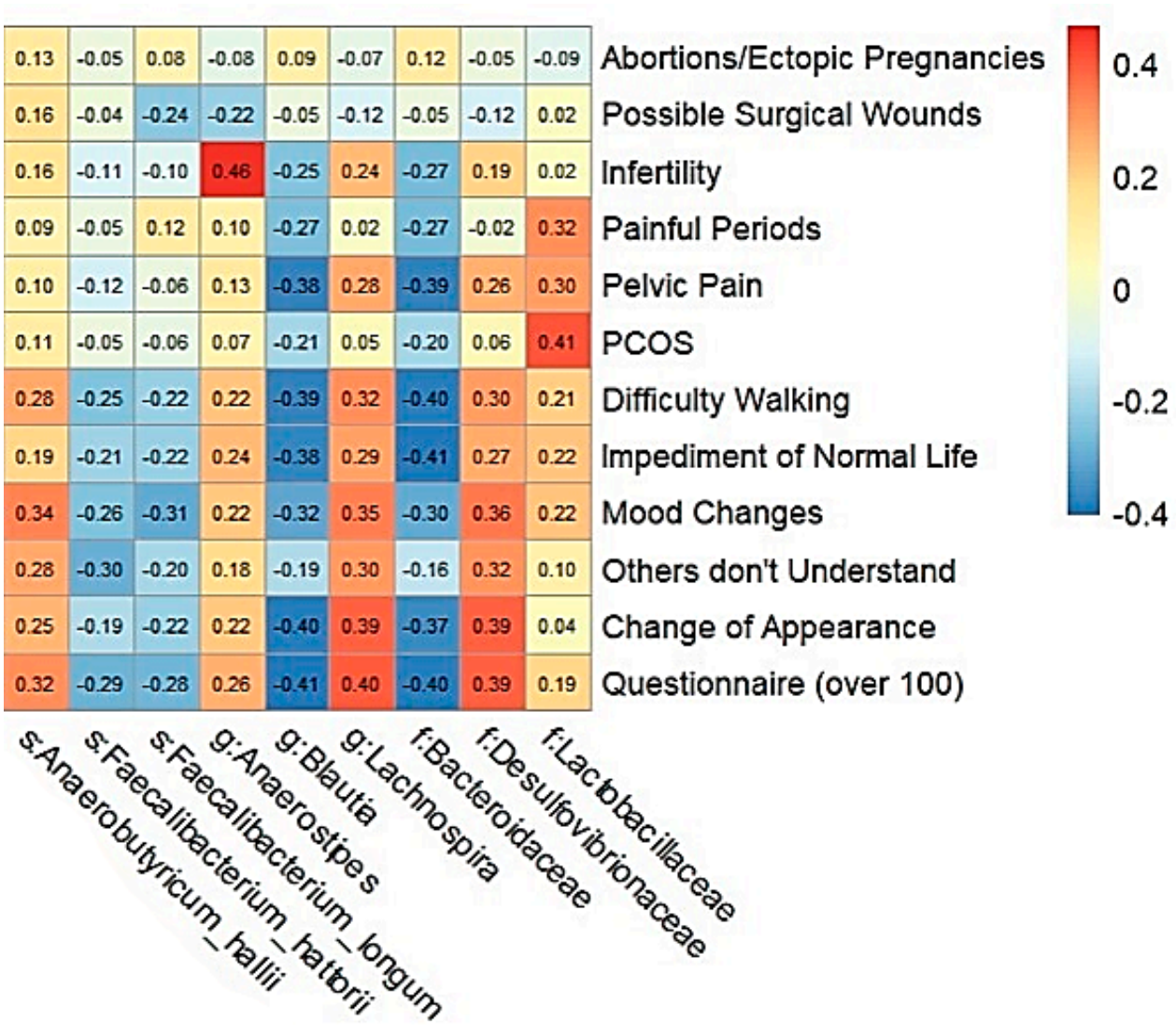

Figure 2.

FIGURE 2. CORRELATION GRAPH SHOWING MICROORGANISMS FROM THE STUDY PARTICIPANT GROUPS AND EHP-5 SCORES FOR SOME OF THE DISEASE-RELATED VARIABLES ANALYZED .

CONCLUSIONS:

The etiopathogenesis of MS could be related to intestinal dysbiosis. Furthermore, the identified taxa and their metabolites, components of the estrobolome , could play a key role in the onset of the disease, being proposed as potential prognostic, diagnostic and therapeutic targets for the future. Our work shows for the first time how imbalances in the intestinal microbiome are associated with the main symptoms of MS, with a clear focus on pain modulation.

REFERENCES:

1. MW Laschke and MD Menger , "The gut microbiota: a puppet master in the pathogenesis of endometriosis ?, " Am J Obstet Gynecol , vol. 215, no. 1, pp. 68.e1-68.e4, Jul. 2016, doi : 10.1016/J.AJOG.2016.02.036.
2. J. Lamceva , R. Uljanovs , and I. Strumfa , "The Main Theories on the Pathogenesis of Endometriosis," Mar. 01, 2023, Multidisciplinary Digital Publishing Institute (MDPI) . doi :10.3390/ijms24054254.
3. G. Bonavina and HS Taylor, "Endometriosis-associated infertility: From pathophysiology to tailored treatment," Oct. 26, 2022, Frontiers Media SA doi :10.3389/fendo.2022.1020827.
4. L. Philip et al. , "Endometriosis associated infertility: A critical review and analysis on etiopathogenesis and therapeutic approaches," Sep. 01, 2020, MDPI AG . doi : 10.3390/medicine56090460.
5. AW Horne and SA Missmer , "Pathophysiology, diagnosis, and management of endometriosis," 2022, BMJ Publishing Group . doi :10.1136/bmj-2022-070750.
6. J. Załęcka , K. Pankiewicz , T. Issat , and P. Laudański , "Molecular Mechanisms Underlying the Association between Endometriosis and Ectopic Pregnancy," Apr. 01, 2022, MDPI . doi :10.3390/ijms23073490.
7. C. Zhong et al. , "Analysis of IVF/ICSI Outcomes in Endometriosis Patients With Recurrent Implantation Failure: Influence on Cumulative Live Birth Rate," Front Endocrinol (Lausanne) , vol. 12, Jul. 2021, doi : 10.3389/fendo.2021.640288.
8. W. Fan, Z. Yuan, M. Li, Y. Zhang, and F. Nan, "Decreased oocyte quality in patients with endometriosis is closely related to abnormal granulosa cells," 2023, Frontiers Media SA . doi :10.3389/fendo.2023.1226687.
9. AM Sanchez et al. , "Is the oocyte quality affected by endometriosis? A review of the literature," Jul. 12, 2017, BioMed Central Ltd. doi :10.1186/s13048-017-0341-4.
10. Mr. Simopoulou et al. , "Getting to know endometriosis-related infertility better: A review on how endometriosis affects oocyte quality and embryo development," Mar. 01, 2021, MDPI AG . doi :10.3390/biomedicines9030273.
11. E. Pascoal et al. , "Strengths and limitations of diagnostic tools for endometriosis and relevance in diagnostic test accuracy research," Sep. 01, 2022, John Wiley and Sons Ltd . doi :10.1002/uog.24892.
12. G. Jones, S. Kennedy, A. Barnard, J. Wong, and C. Jenkinson , "Development of an endometriosis quality-of-life instrument: The Endometriosis Health Profile-30," Obstetrics and gynecology , vol. 98, no. 2, pp. 258–264, 2001, doi : 10.1016/S0029-7844(01)01433-8.
13. G. Jones, C. Jenkinson , and S. Kennedy, "Development of the Short Form Endometriosis Health Profile Questionnaire: the EHP-5," Qual Life Res , vol. 13, no. 3, pp. 695–704, Apr. 2004, doi : 10.1023/B:QURE.0000021321.48041.0E.
14. SH Ahn , V. Singh, and C. Tayade , "Biomarkers in endometriosis: challenges and opportunities," Mar. 01, 2017, Elsevier Inc. doi : 10.1016/j.fertnstert.2017.01.009.
15. M. Králíčková , AS Laganà , F. Ghezzi , and V. Vetvicka , "Endometriosis and risk of ovarian cancer: what do we know ?, " Jan. 01, 2020, Springer . doi :10.1007/s00404-019-05358-8.
16. ME Salliss , LV Farland , ND Mahnert , and MM Herbst-Kralovetz , "The role of gut and genital microbiota and the estrobolome in endometriosis, infertility and chronic pelvic pain," Hum Reprod Update , vol. 28, no. 1, pp. 92–131, 2021, doi : 10.1093/HUMUPD/DMAB035.
17. H. Elkafas , M. Wall, A. Al-Hendy, and N. Ismail, "Gut and genital tract microbiomes : Dysbiosis and link to gynecological disorders," 2022. doi : 10.3389/fcimb.2022.1059825.
18. F. Hearn- Yeates , AW Horne, SM O'Mahony , and PTK Saunders, "The impact of the microbiota–gut–brain axis on endometriosis-associated symptoms: mechanisms and opportunities for personalized management strategies," Apr. 01, 2024, BioScientifica Ltd. doi : 10.1530/RAF-23-0085.
19. 19. R. Qin, G. Tian , J. Liu, and L. Cao, "The gut microbiota and endometriosis: From pathogenesis to diagnosis and treatment," Nov. 24, 2022, Frontiers Media SA doi :10.3389/fcimb.2022.1069557.
20. 20. A. Svensson , L. Brunkwall , B. Roth, M. Orho-Melander , and B. Ohlsson , "Associations Between Endometriosis and Gut Microbiota," 2021, doi : 10.1007/s43032-021-00506-5/Published.
21. C. Uzuner , J. Mak , F. El- Assaad , and G. Condous , "The bidirectional relationship between endometriosis and microbiome ," 2023, Frontiers Media SA doi : 10.3389/fendo.2023.1110824.
22. C. Talwar , V. Singh, and R. Kommagani , "The gut microbiota: a double-edged sword in endometriosis," Oct. 01, 2022,

Oxford University Press . doi : 10.1093/ biolre /ioac147.
23. F. Tang et al. , "Unraveling the microbial puzzle: exploring the intricate role of gut microbiota in endometriosis pathogenesis," 2024, Frontiers Media SA . doi :10.3389/fcimb.2024.1328419.
24. J. Shan et al. , "Gut microbiota imbalance and its correlations with hormone and inflammatory factors in patients with stage 3/4 endometriosis," Arch Gynecol Obstet , vol. 304, no. 5, pp. 1363–1373, Nov. 2021, doi : 10.1007/s00404-021-06057-z.
25. R. Kapoor , CA Stratopoulou , and MM Dolmans, "Pathogenesis of endometriosis: New insights into prospective therapies," Nov. 01, 2021, MDPI . doi :10.3390/ijms222111700.
26. M. Liu et al. , "Effects of the gut microbiota and its metabolite short-chain fatty acids on endometriosis," 2024, Frontiers Media SA . doi :10.3389/fcimb.2024.1373004.
27. H. Kobayashi, "Gut and reproductive tract microbiota: Insights into the pathogenesis of endometriosis (Review)," Jul. 01, 2023, Spandidos Publications . doi : 10.3892/br.2023.1626.
28. S. Hu, Q. Ding, W. Zhang, M. Kang, J. Ma, and L. Zhao, "Gut microbial beta -glucuronidase : a vital regulator in female estrogen metabolism," 2023, Taylor and Francis Ltd. doi :10.1080/19490976.2023.2236749.
29. RM Marquardt, TH Kim, JH Shin, and JW Jeong , "Progesterone and estrogen signaling in the endometrium: What goes wrong in endometriosis ?, " 2019. doi : 10.3390/ijms20153822.
30. F. Chiaffarino et al. , "Endometriosis and irritable bowel syndrome: a systematic review and meta-analysis," Jan. 01, 2021, Springer Science and Business Media Deutschland GmbH . doi :10.1007/s00404-020-05797-8.
31. A. Pantelis , N. Machairiotis , and DP Lapatsanis , "The Formidable yet Unresolved Interplay between Endometriosis and Obesity," 2021, Hindawi Limited . doi :10.1155/2021/6653677.
32. N. Jimenez et al. , "Vaginal and rectal microbiome contribute to genital inflammation in chronic pelvic pain," BMC Med , vol. 22, no. 1, Dec. 2024, doi : 10.1186/s12916-024-03500-1.
33. I. Jiang, PJ Yong, C. Allaire , and MA Bedaiwy , "Intricate Connections between the Microbiota and Endometriosis," Int J Mol Sci , vol. 22, no. 11, Jun. 2021, doi : 10.3390/IJMS22115644.
34. C. Guo and C. Zhang, "Role of the gut microbiota in the pathogenesis of endometriosis: a review," 2024, Frontiers Media SA . doi :10.3389/fmicb.2024.1363455.
35. Y. Wei et al. , "Gut dysbiosis -derived β - glucuronidase promotes the development of endometriosis," Fertil Steril , May 2023, doi : 10.1016/J.FERTNSTERT.2023.03.032.
36. I. Iavarone et al. , "Correlations between Gut Microbial Composition, Pathophysiological and Surgical Aspects in Endometriosis: A Review of the Literature," Medicine (Kaunas) , vol. 59, no. 2, Feb. 2023, doi : 10.3390/MEDICINA59020347.
37. L. Huang et al. , "Gut Microbiota Exceeds Cervical Microbiota for Early Diagnosis of Endometriosis," Front Cell Infect Microbiol , vol. 11, p. 788836, Dec. 2021, doi : 10.3389/FCIMB.2021.788836/BIBTEX.