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ORIGINAL ARTICLE

The Relationship Between Vaginal Microbiome and Infertility: A Descriptive Trend Analysis (1947-2024)

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Abstract

Background: The menstrual cycle and gestational state, as well as other physiological factors, have a substantial impact on the vaginal microbiome, which aids in preventing infections caused by pathogenic microorganisms. Dysbiosis of the vaginal microbiome can cause infertility as well as adverse outcomes in pregnancy. The aim of this study is to examine the studies examining the relationship between vaginal microbiota and infertility in Scopus and WoS databases in terms of different variables and to compare them by revealing their bibliometric profiles.

Methods: We conducted a bibliometric study to determine the scholarly papers published across all journals that addressed the relationship between the vaginal microbiome and infertility. Scopus and Web of Science (WoS) databases were accessed for all the published articles on vaginal microbiome and infertility. The number of publications by year, language, country, institute, author, journal, and impact factors (IF) are reported as bibliometric indicators.

Results: Our findings indicate that the topic is much understudied; only 161 papers met the criteria set forth in our research. But, a striking increase was observed after 2020. The United States, China and Italy drew attention as the countries that contributed the most to the literature.

Conclusion: Prospective and clinical studies on the mechanisms linking the vaginal microbiome of the female reproductive system to reproductive physiology may shed light on infertility treatment.

Key words: Bibliometric analysis; dysbiosis; infertility; vaginal microbiome

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INTRODUCTION

An essential part of human physiological processes like immunity and nutrition is handled by microbiome. In a cooperative relationship, they safeguard the human host from a variety of pathogenic microorganisms in exchange for the host's supply of food and shelter (1). Human Microbiome Project (HMP) and Integrative HMP (iHMP) are collaborative projects that have investigated the skin, gut, vaginal, and oral communities to evaluate the metagenomics, distributions, and characteristics of microorganisms from specific anatomical locations (2). The outcomes of HMP are thought to be important for determining the pathophysiology of disease and the association between changes in the microbiota and the identification of biomarkers for diagnostic purposes (3). The female genital tract also has its own microbiome, which constitutes 9% of all the bacteria in female body (4). The composition of the microbial communities in microbiome has an essential impact for the health status of an individual. The host and the native bacteria in the vaginal environment are considered to coexist in a symbiotic relationship (5). Colonization and domination of lactobacilli, typically by species like *Lactobacillus crispatus, Lactobacillus gasseri, Lactobacillus iners, and Lactobacillus jensenii,* are crucial characteristics of a healthy vaginal microbiome (6). Certain strains of lactobacilli work with the host cells and a woman's genome type to increase the production of the proper mucus and preserve the vagina's acidic environment (7). Recent research, however, has shown that there are more than 200 phylotypes in the female vagina, with the phyla Firmicutes, Bacteroidetes, Actinobacteria, and Fusobacteria being the most prevalent (8). The bacterial communities in the vaginal microflora might vary depending on factors like gestational status, contraceptive use, menstrual cycle, and sexual activity (9,10). According to how metabolic and microbial variables interact, vaginal microbiome dysbiosis can be either physiological or pathogenic. The vaginal microbiome changes significantly during pregnancy. With the dominance of one or more *Lactobacillus* species at the beginning of pregnancy, it becomes more stable and less diverse (11). Aberrant vaginal microbiome is more prevalent in women who experience idiopathic infertility (12). According to in vivo studies, the vaginal microbiome has a significant impact in embryo implantation and the pregnancy's outcome (11).

Bibliometric analyses have emerged as one of the most widely used tools to assess the reliability, scientific value, and significance of scientific research (13). Although it is not a foolproof method, bibliometrics can be a useful tool for funding organizations to use for allocating resources and for spotting possible research deficits in a subject (14). Analyzing the relationships between pertinent research institutions and evaluating the general trend of research activity can be accomplished effectively with bibliometric studies. We conducted a bibliometric study to determine the scholarly papers published across all journals that addressed the relationship between the vaginal microbiome and infertility. In order to define the direction for future investigations, we also thoroughly compared the findings of the most-cited studies. Using the bibliometric analysis method, it was aimed to examine the trends of the studies examining the relationship between "vaginal microbiota and infertility" indexed by Scopus and Web of Science (WOS), to evaluate the results of the most cited studies and to shed light on future studies.

MATERIALS AND METHODS

In December 2024, the Scopus library, ISI Web of Science Core Collection (WoS) and InCites Journal Citation Reports (JCR) were accessed for all the published articles on vaginal microbiome and infertility, also for the citations of these studies. Scopus and WoS were used as the databases because of their broader coverage of journals compared with the other databases. In the research, the bibliometric profile of academic studies on the vaginal microbiome-infertility relationship in WoS and Scopus, which are the two most preferred large databases for researching academic studies, was determined and compared. Thus, the trends, changes and innovations of the studies in both databases were revealed. The aim of the study was to create and compare the bibliometric profiles of academic studies on the vaginal microbiome-infertility relationship in Web of Science (WoS) and Scopus, which are the two most preferred databases for researching academic studies. No time limitation was set for the search, original articles and reviews were included. To ensure a comprehensive coverage of all the available literature, studies pertaining to fields other than medicine, studies on nonhuman subjects, and those without abstracts were also included. We used "vaginal microbiome", "vaginal microbiota" and "vaginal flora"

for topical retrieval and the following search queries in titles, abstracts, and keywords: (vaginal microbiome AND infertility), (vaginal microbiota AND infertility), (vaginal flora AND infertility), (vaginal microbiom AND infertile), (vaginal microbiota AND infertile) and (vaginal flora AND infertile). The search protocol used here was undertaken was restricted to the articles published in English. The number of publications by year, publishing language, country, institute, author, journal, and impact factors (IF) are reported as bibliometric indicators.

Additionally, 15 countries, and 10 scientific publications that received the most citations in the literature are all discussed. The average number of citations per article, the overall number of citations, and the IF of the journals that published the articles are considered when evaluating the quality of publications. The document possessed the article's titles, publication year, document's type, abstract, authors and journals names, author's institution, journal impact factor, author's country, citations, database and language used were exported to VOSviewer software. VOSviewer, a freely available software tool for analysis, was used to make visualization maps in this study. The software primarily performs the following analyses for our study: keyword co-occurrence analysis, author and co-cited author analysis, journal and co-cited journal analysis, and country and institution analysis. A node on the VOSviewer-generated map stands for an item, such as a nation, organization, journal, or author. The number and classification of these objects are indicated by the node's size and color, accordingly. The degree of cooperation or co-citation of the items is shown by the line thickness between nodes. Statistical analysis: Frequency, percentage and arithmetic mean values were calculated in the analysis of the collected data. For statistical calculations, Microsoft Excel (Ver. 2013) was used. The data used in this study are publicly available and contain no protected health information. Therefore, institutional review board approval was not sought. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cross-sectional studies.

RESULTS

In this study, based on the search strategy presented in the methods, 161 and 163 articles were found in the Scopus and Web of Science databases between 1947 and 2024, respectively. The first article on vaginal microbiome and infertility was published in 2005, and it did not exceed ten articles per year until the end of the 2010s. In the analysis made according to the year the studies were published, an insignificant increase in the number of articles was observed until 2019, while a striking increase was observed after 2020 (Figure 1). Accordingly, there was a linear increase in the number of citations per article over time. When the studies were evaluated in terms of research subject; the majority of the publications were found in the field of "Obstetrics and Gynecology" (27.9%). This is followed by "Reproductive Biology" (21.7%), "Microbiology" (21.1%), "Immunology" (13.0%), "Medicine General Internal" (8%), "Biochemistry Molecular Biology" (6.2%) and other topics. The international literature currently includes articles from 49 different countries in terms of countries of the published literature on vaginal microbiome and infertility. The United States (US) accounts for 25.4% of all publications, ahead of China, Italy and Spain in terms of the number of publications. Figure 2 shows the top 10 countries by number of publications. Nanchang University in China and Sapienza University in Italy contributed three publications each, providing the most scientific data on vaginal microbiome and infertility. The top ten journals preferred for publication of articles on vaginal microbiome and infertility are listed in Table 1. The IF values of the journals in the list are between 3.1 and 7.0. A total of 45 articles on vaginal microbiome and infertility were published in the top ten journals listed in Table 1. In addition, 20% (n=9) of the retrieved articles were published in the journal "Frontiers in Cellular and Infection Microbiology" (IF = 4.6). The top 10 most cited articles are presented in Table 2. The most cited study was the article "The microbiota continuum along the female reproductive tract and its relation to uterine-related diseases" published in the journal "Nature Communications" (15). When the distribution of the number of citations of the articles by year is evaluated, it is seen that it has increased since 2020 and reached the highest number in 2024 (Figure 1). The network map of the publications on the vaginal microbiome-infertility relationship was displayed using the VOSviewer program. The documents shown on the map were calculated by selecting the minimum citation number as "2". It was seen that there was a complex and intense relationship between these documents on the map (Figure 3). More than one cluster was formed in

different colors between these documents. In addition, the co-citation analysis network map on the vaginal microbiome-infertility relationship was visualized in the VOSviewer program (Figure 4). When the minimum citation number was selected as 20, 45 of the 5569 cited authors met the threshold value. The author with the highest number of co-citations was Moreno I. with 172 citations (16). When the co-citation analyzes of the vaginal microbiota-infertility studies were evaluated, it was seen that the literature was divided into three groups: Moreno I. (endometrial (effect of the microbiome on implantation), Ravel J. (effects of the vaginal microbiome on female physiology) and Haahr T. (effect of bacterial vaginosis in IVF patients) (16-18).

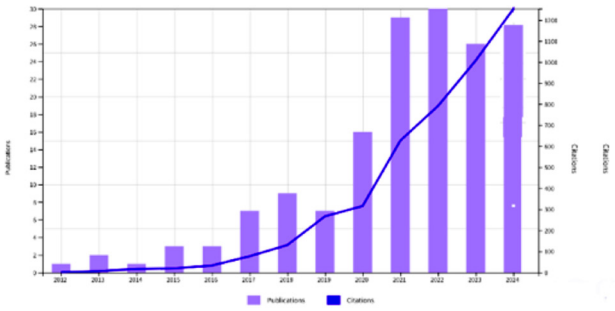

Figure 1: Publication year-specific and citation trends in the quantity of publications research on vaginal microbiome and infertility

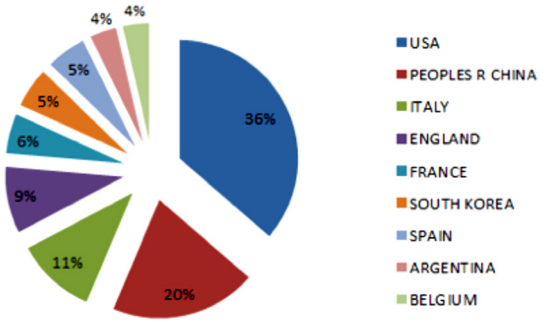

Figure 2: The top ten countries regarding the quantity of publications on vaginal microbiome and infertility

Table 1. The top 10 Journals in terms of publication quantity.

Journal	Number of Publications	Total Citations	Average citation per year	Impact Factor (2023)
Frontiers in Cellular and Infection Microbiology	9	158	19.75	4.6
Journal of Assisted Reproduction and Genetics	6	237	16.93	3.2
American Journal of Reproductive Immunology	4	79	19.88	3.1
Diagnostics	4	33	11	3.5
Frontiers in Endocrinology	4	26	8.67	5.2
International Journal of Molecular Sciences	4	57	14.25	6.2
Journal of Clinical Medicine	4	32	6.4	4.2
Microorganisms	4	58	11.6	4.1
Archives of Gynecology and Obstetrics	3	32	6.4	2.5
Fertility and Sterility	3	422	32.4	7.0

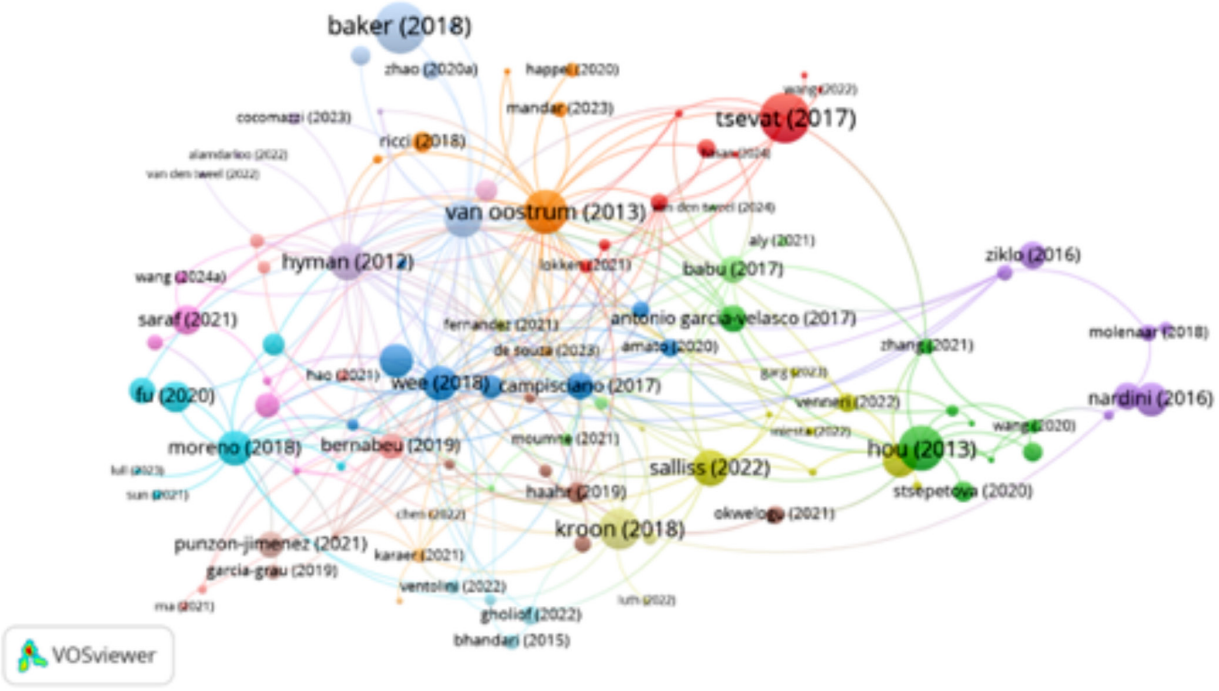

Figure 3: The network map of the publications on the vaginal microbiome-infertility relationship (VOSviewer)

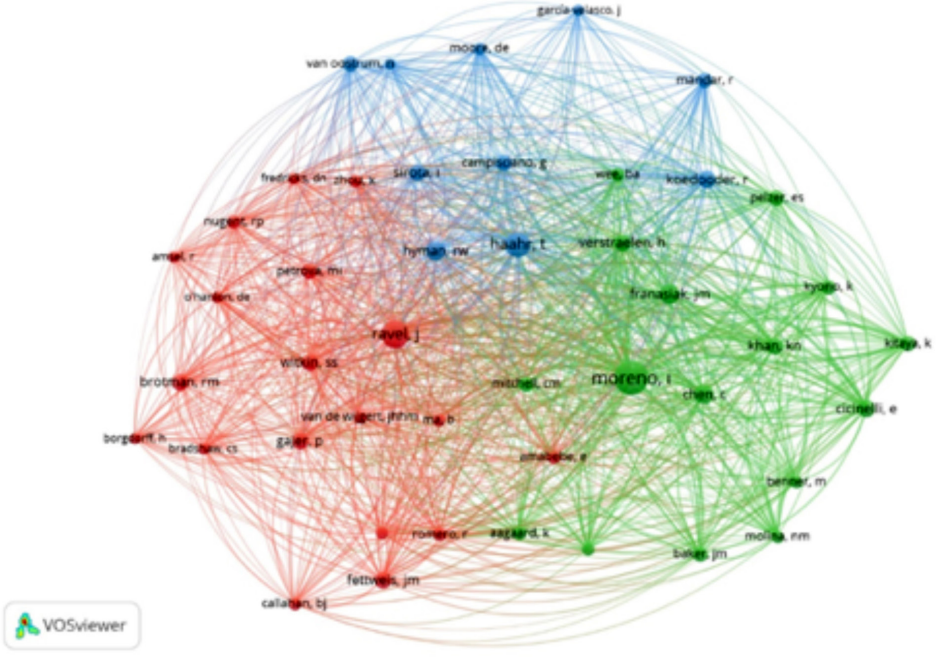

Figure 4: The co-citation analysis network map on the vaginal microbiome-infertility relationship (VOSviewer)

Table 2. The top 10 Studies in terms of citation quantity

Authors	ArticleTitle	Source Title	Year	Country	Journal IF	Times Cited
Chen et al. (15)	The microbiota continuum along the female reproductive tract and its relation to uterine-related diseases	*Nature Communications*	2017	China	14.7	534
Baker et al. (25)	Uterine Microbiota: Residents, Tourists, or invaders?	*Frontiers in İmmunology*	2018	USA	0.95	231
Tsevat et al. (19)	Sexually transmitted diseases and infertility	*American Journal of Obstetrics and Gynecology*	2017	USA	3.4	219
Hou et al. (26)	Microbiota of the seminal fluid from healthy and infertile men	*Fertility and sterility*	2013	USA	2.25	171
vanOostrum et al. (21)	Risks associated with bacterial vaginosis in infertility patients: a systematic review and meta-analysis	*Human reproduction*	2013	Belgium	2.19	163
Kroon et al. (6)	Cervicovaginal microbiota, women's health, and reproductive outcomes	*Fertility and Sterility*	2018	Australia	2,18	144
Sirota et al. (24)	Potential influence of the microbiome on infertility and assisted reproductive technology	*Seminars in Reproductive Medicine*	2014	USA	1,3	121
Hyman et al. (22)	The dynamics of the vaginal microbiome during infertility therapy with in vitro fertilization-embryo transfer	*Journal of assited reproduction and genetics*	2012	USA	0.94	116
Saliss et al. (27)	The role of gut and genital microbiota and the estrobolome in endometriosis, infertility and chronic pelvic pain	*Human reproduction update*	2022	USA	3.62	110
Moreno et al. (16)	Evidence that the endometrial microbiota has an effect on implantation success or failure	*American Journal of Obstetrics and Gynecology*	2016	Spain	2.25	107

DISCUSSION

Chen et al. (15) conducted urogenital system microbiome analyzes of 10 women in a study published in the journal "Nature Communications" with IF 3.13 in 2017 and found that cervical sampling would be sufficient without the need for more invasive sampling due to the similarity between uterine microbiome and cervical microbiome. Furthermore, it has been revealed that bacterial vaginosis is associated with preterm birth and sexually transmitted diseases (STDs), with a high *Lactobacillus* content acting as a protective factor. Moreno et al. (16) examined the effect of vaginal microbiome on implantation in a study published in the "American Journal of Obstetrics and Gynecology" in 2015 with an IF of 3.22. Low *Lactobacillus* content have been shown to be associated with failed implantation (p=0.02) (16). Smith et al. (17) mentioned the effects of vaginal microbiome on female reproductive physiology in the study published in the "Journal of Physiology" with an IF of

6.22 in 2017. Tsevat et al. (19) in the study published in the "American Journal of Obstetrics and Gynecology" with an IF of 3.22 in 2017, it was noted that *Chlamydia trachomatis and Neisseria gonorrhoeae* are absolutely associated with tubal factor infertility and that the microbiome of women of reproductive age is associated with infertility.

Yarbrough et al. (20) in the study published in the journal "Human Reproduction Update" with an IF 3.2 in 2015, it was noted that antimicrobial peptides (AMP) produced by vaginal microbiome components in the female reproductive system are a protective barrier against exogenous pathogens. vanOostrum et al. (21) in a meta-analysis study, published in the journal "Human Reproduction" with an IF of 2.22, in 2013, it was found that bacterial vaginosis was associated with infertility and In vitro fertilization (IVF) failure. Additionally, it was discovered that it only had an impact on preclinical pregnancy loss and not on the incidence of pregnancy. Hyman et al. (22) in a study published in the "Journal of Assisted Reproduction and Genetics" with an IF 0.92 in 2012, the clinical correlation of vaginal microbiome with IVF treatment was investigated. Vaginal sampling of 30 women during IVF and if pregnant, 4th-6th week of pregnancy taken during the week. It has been discovered that the vaginal microbiome influences pregnancy success on the day of embryo transfer and that the bacterial diversity of the vaginal microbiome changes during several hormone cycles.

When the most cited articles were examined, very few studies were found showing the clinical correlation of vaginal microbiota with reproductive physiology and infertility. The role of microbiome in examining the physiology of the reproductive system is undeniable and more screening and sampling is needed in the clinical setting. In the majority of studies, attention is drawn to the importance of *Lactobacillus*, and it emerges as a factor that should be evaluated in the prevention of infections and, accordingly, reproductive failure. Prospective studies evaluating demographic and behavioral factors, the effects of co-infections, and the impact of the vaginal microbiome will provide guidance to unravel the relationship between these pathogens and impaired fertility and adverse pregnancy outcomes.

In human reproduction, the reproductive tract microbiota at the embryo-maternal interface is gaining more interest since it may affect the mother's and the child's health both before and after delivery, in addition to the likelihood of becoming pregnant (4). In a study assessing vaginal and endometrial samples of healthy volunteers, non-infertile patients, and patients receiving in vitro fertilization (IVF) treatment, results showed that the healthy volunteers presented low diversity microbiota (≥90% *Lactobacillus* species), with 25% of the women presenting different taxonomic profiles in endometrial and vaginal samples (23). Researchers links unfavorable pregnancy outcomes following both natural and in vitro fertilization (IVF) conceptions to opportunistic infections in the lower female reproductive tract (18). Thus, it is worth considering whether in vitro fertilization (IVF) outcomes could be influenced by the microbial taxa present in the reproductive tract during infertility treatment (4). In fact, bacterial vaginosis and other variations from the low-diversity vaginal microbiome have been strongly linked to lower post-IVF pregnancy rates (18). As a limitation of our study, we would like to point out that only the studies included in the WoS and Scopus databases were included in our study, and therefore it is insufficient to cover the entire literature.

In this study, 161 original studies, from 1947 to 2024, on the relationship of the vaginal microbiome with infertility were retrieved from the WoS and Scopus databases and analyzed using VOSviewer to generate knowledge maps. This bibliometric analysis reveals a surge in microbiome research over the past three years, with the goal of understanding the role of vaginal microbiome in successful reproduction and proving its value. We also listed the distribution of journals, authors and countries on the subject and highlighted the key features of the vaginal microbiome by examining the most cited articles in databases. The United States, China and Italy drew attention as the countries that contributed the most to the literature. Prospective and clinical studies on the mechanisms linking the vaginal microbiome of the female reproductive system to reproductive physiology may shed light on infertility treatment.

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Abbreviations list

WoS: Web of Science
IF: Impact factor
HMP: Human Microbiome Project
iHMP: Integrative HMP
JCR: Journal Citation Reports
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
STDS: Sexually transmitted diseases
AMP: Antimicrobial peptides
IVF: In vitro fertilization

Ethics approval and consent to participate

The data used in this study are publicly available; contain no protected health information or patient information from the authors' institutions. Neither human nor animal subject data are used in our investigation. Therefore, institutional review board approval was not sought.

Consent for publication

Not applicable since this study contains no protected health information or patient information.

Availability of data and materials

The data used in this study are publicly available. Also, the data that support the findings of this study are available on request from the corresponding author.

Competing interests

None to declare.

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Authors' contributions

Idea/Concept: ME, İK. Desıgn: İK. Control/Supervısıon ME, İK. Data Collectıon And/Or Processıng: ME, İK. Analysıs And/Or Interpretatıon: ME, İK. Lıterature Revıew: ME, İK. Wrıtıng The Artıcle: ME. Crıtıcal Revıew: ME, İK. References And Fundıngs: İK. Materıals: İK.

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