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The Endometrial Microbiota in Assisted Reproduction Outcomes: A Narrative Review

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ABSTRACT

Studies of the correlation between women's endometrial microbiota and human reproduction are still very recent. Nevertheless, this study aimed to analyze the most recent of such studies. The keywords 'endometrial microbiota' and 'assisted reproduction' were used to search for articles published in PubMed between 2017 and 2024. After applying both the inclusion and the exclusion criteria, 13 articles were selected for this narrative review. Most articles related the Lactobacillus bacteria positively to high pregnancy rates and negatively to higher miscarriage rates or recurrent implantation failures. In conclusion, the association of endometrial microbiota with Lactobacillus favors higher pregnancy rates, while several other microorganisms of various genera and species contribute to dysbiosis and thus may lead to recurrent implantation failures and miscarriages.

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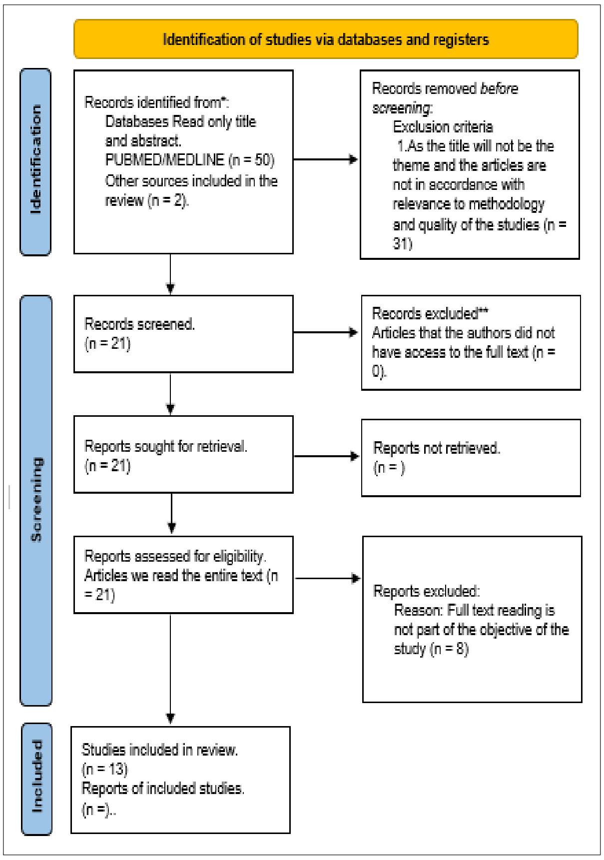
Introduction

Cases of Infertility and the desire to postpone motherhood increase every year, highlighting the need to improve assisted reproduction techniques, such as in vitro fertilization (IVF). These techniques pose challenges, among which are recurrent implantation failures (RIFs) and miscarriages. Their relationship with the endometrial microbiota has increasingly been researched as a result, several technologies have been developed, such as endometrial receptivity tests and endometrial microbiota tests, to be used as diagnostic or therapeutic tools to aid implantation. Several studies have correlated infertility with the microbiota in the female genital tract. The female genital tract can be divided into the lower tract, which covers the vaginal microbiota and the cervix, and the upper tract, which covers the uterus, the fallopian tubes, and the ovaries . In a pilot study, analyzed the microbiota in the vagina, cervix, and endometrium of fertile and infertile women. They found that, in infertile women, the Ureaplasma and Gardnerella species were more abundant in the vagina and cervix. Moreno & Simon 2018 demonstrated there was a low abundance of the Lactobacillus spp. in the endometrial microbiota in the miscarriages and low implantation and pregnancy rates of IVF. However, they warned that it was highly possible the endometrial microbiota could be contaminated by exogenous material during some IVF procedures, in which case a careful and appropriate investigation of the procedures was required [1-9].

In the last 10 years, research into the microbiota of the female upper reproductive tract has grown, providing an overview of the importance of these microorganisms in different scenarios. This narrative review aimed to address the endometrial microbiota and the most important points for constructing the profile of the microbiota in infertility outcomes.

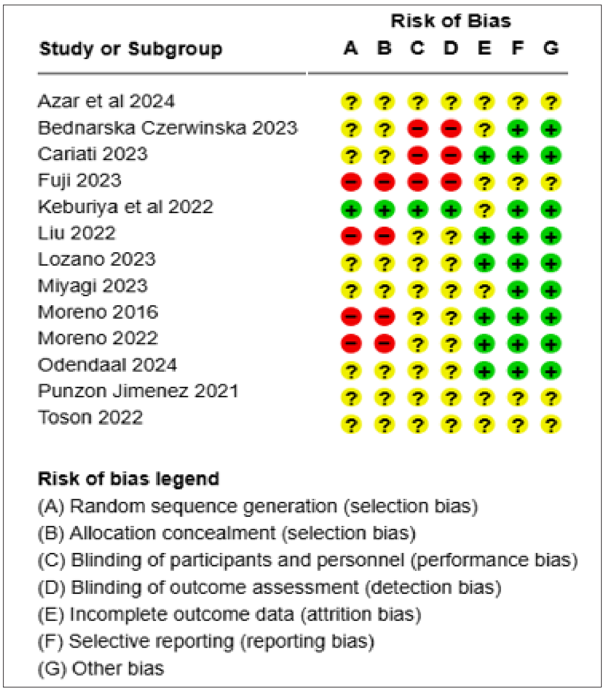
Material and Methods

Case-control, cross-sectional, prospective, and retrospective cohort studies published between February 2017 and February 2024 were considered eligible for this narrative review. The authors adopted a method similar to the one employed by, in which the keywords 'endometrial microbiota' and 'assisted reproductive' were used in the search. A total of 50 articles were identified in the PubMed database and 2 articles in other databases (MEDLINE, EMBASE). Reviews, editorials, letters, case reports, lectures, summaries, books, opinions, in vitro studies, studies of diagnostic methodologies, and studies in animal models were excluded, and a search for unpublished studies was not performed. Other factors taken into consideration for exclusion were the relevance of the topic as well as the methods used and the quality of the articles. When the inclusion and exclusion criteria were applied, 31 articles with titles not relevant to the topic were excluded. The 21 remaining articles were fully read. Of these, 8 articles did not meet the objectives of this narrative review and were also excluded, leaving a total of 13 articles. As these met all the eligibility criteria, they entered the narrative review (Figure 1, 2). Finally, data extraction targeted the bacteria of interest and their respective assisted reproduction-related functions in the endometrium [10].



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.



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Results

Of the 13 articles included in the narrative review, the least recent is from 2017, and is a study conducted in partnership by researchers from Spain and the United States. In 2021, two studies, one from Spain and the other from Japan, and a Spanish review were published. In 2022, three studies came to light, one each from the United States, Spain, and China. In 2023, five articles were published, one from Poland, two from Spain, and two from Japan. In 2024, the most recent article in our selection, one from Great Britain, was published. See table 1 for the main findings of these articles.

Table 1: Main Findings of the Studies Selected for this Narrative Review

Author and Year	Study Design	Type of Sample	Testing Procedures	Number of Women	Available Demographic Data	Main Findings
Odendaal 2024	Mini review	Human endometrium	application of sensitive molecular-based approaches, including high-throughput next-generation sequencing (NGS) of bacterial 16S rRNA genes	-	-	There is a growing body of evidence demonstrating an association between endometrial microbiota composition and early pregnancy loss, including miscarriage.
Bednarska Czerwinska 2023	Clinical research	Microbiome changes in the endometrium and uterine cervix	next-generation sequencing (NGS)	177 women	Caucasian, aged 18-45 years, BMI (mean) 24.2±4.8	Lactobacillus spp. were the main bacteria identified in the cervix and endometrium, and present before, during, and after successful embryo transfer. E. coli and G. vaginalis reduced the protective effect of Lactobacilli before, during, and after embryo transfer
Cariati 2023	Prospective cohort study	Endometrial microbiota profile	microbiological, molecular, and culture screenings, as well as routine blood chemistry, and genetic and ormonal tests, were prescribed to all patients in the study	93 infertile women	BMI 25.18 ± 1.06,	A eubiotic endometrial microbiota could be considered a permissive microbial community for ongoing pregnancy, regardless of the presence of minimal pathogenic bacteria.
Fuji 2023	Prospective cohort study	Endometrial microbiota	an endometrial biopsy	185 eligible patients	Age (years-mean) 36.9 ± 4.7, BMI (mean) 21.8 ± 3.0	The findings suggest that the quantity (rather than proportion) of Lactobacillus in the endometrium is important in the development of endometrial receptivity.
Lozano 2023	Prospective cohort study	Characterization of the endometrial microbiome	next-generation sequencing (NGS)	45 patients	Age (years-mean) 39.44 ± 3.89,	The results demonstrate the existence of an endometrial microbiota characteristic of RIF patients and show that there might be a relationship between population of the endometrial microbiome and embryo implantation failure.
Miyagi 2023	Prospective cohort study	Endometrial and vaginal microbiomes	next-generation sequencing (NGS)	34 women	Age (years-mean) 36, BMI (mean) 22.7 ± 0.8	We hypothesize that the balance between the abundance of Lactobacillus and pathological bacteria influences pregnancy.

Moreno 2022	Prospective observational study	Endometrial microbiota composition	next-generation sequencing (NGS)	342 infertile patients	-	The findings indicate that the endometrial microbiota composition before embryo transfer is a useful biomarker to predict reproductive outcome.
Liu 2022	Prospective cohort study	Microbiota in the lower and upper female tracts	next-generation sequencing (NGS)	50 women	Age (mean) 32.56 ± 3.50, BMI (mean) 22.19 ± 3.49	Our data suggested altered microbial biodiversity in the vagina, cervix, and uterine lavage fluid in the abortion group.
Toson 2022	Review	Endometrial microbiome	next-generation sequencing (NGS)	-	-	Despite growing evidence of the impact of microbiota on gynecological and obstetrical conditions, there is still no consensus on the endometrial bacterial core.
Punzon Jimenez 2021	Review	Microbiome of the female genital tract	next-generation sequencing (NGS)	-	-	Detection of bacterial species related to poor reproductive outcomes, infertility, or gynecological diseases could shape new tools for their diagnosis and treatment.
Moreno 2016	Review	Endometrial microbiota	-	-	-	The approach to manipulation of the endometrial microbiome in an effort to improve reproductive outcomes will evolve and improve.
Azar et al 2024	Review	Endometrial microbiome	next-generation sequencing (NGS)	-	-	The optimal endometrial microenvironment for maintaining health is characterized by a dynamic ecosystem in which Lactobacillus bacteria predominate.
Keburiya et al 2022	Clinical trial	uterine microbiota	Performance of microbiological examination of the embryo transfer catheter	130 women	-	The microflora of the uterine cavity and cervical canal differed in qualitative composition in 87.9% of the patients.

Calculations for the risk of bias of the 13 articles yielded the following results: 13.18% had a risk of bias, 53.84% had an unclear risk of bias, and 30.76% had a low risk of bias. Therefore, in conclusion, the articles do not reach a good level of quality.

Discussion

Several studies in this narrative review indicate that a female endometrial microbiota dominated by Lactobacillus spp. determines positive reproductive results. The article by, aimed to review the literature on endometrial microbiome and highlight the importance of this subject as a reproductive factor when treating infertile women. Their article discusses the human microbiome project launched in 2007, which has changed the understanding of women's uterine microbiome. For example, the physiological conditions of the uterine microbiome have gained prominence instead of just being relegated to pathologies. The authors conclude that it is necessary to investigate in-depth the vaginal and uterine microbiomes to improve the physiological conditions for reproduction [11].

State that an abnormal endometrial microbiota is associated with recurrent implantation failure, and they demonstrate that there is a low abundance of Lactobacillus spp. in patients with RIF and, on the other hand, the presence of genera such as, point out that the previous literature suggests a domination of non-Lactobacillus communities in implantation failure; however, there are studies that diverge, as the one by, by suggesting that the uterine microbiota in patients with RIF does not alter the pregnancy rate and concluding that the focus on the characterization of the microbiome of the female reproductive tract in the existing literature should be expanded in future research to encompass the distinctions between a healthy and a, in a meta-analysis, characterized the endometrial microbiome as two types: a microbiota with dominant Lactobacillus spp. (90% of abundance), and a microbiota with nondominant Lactobacillus spp. (<90% of abundance). They found that the dominance of Lactobacillus spp. appears to be favorable to maximizing endometrial receptivity and the chances of pregnancy, while a dysbiotic nondominance of Lactobacillus spp. increases the chances of pathogens and unfavorable results in reproduction (15) [12-15].

Aimed to analyze the vaginal and endometrial microbiota to determine a biomarker of RIF in women. The authors were able to construct a profile of the microbiota, in which 5 genera of bacteria were increased in the patients with RIF, and concluded that rates of vaginal but not endometrial Lactobacillus spp. are markers for patients with RIF., had a similar objective, and concluded that the genus of bacteria populating the endometrium of women with RIF characterized their microbiota profile as distinct from that of women without RIF. Punzon-, in a literature review, found that low variability of Lactobacillus spp. in the female genital tract is associated with better reproductive results [16-18].

Hypothesized that the endometrial microbiota was related to human reproductive outcomes such as live birth rates, clinical pregnancies, and miscarriages. The researchers observed that several species of bacteria were related to unfavorable reproductive outcomes, whereas dominance of Lactobacillus spp. was related to an increase in live births., decided to investigate whether the altered microbiota influenced recurrent miscarriages. They found that there is an altered biodiversity in the microbiota in fluids from the vagina, cervix, and uterine cavity of women with higher rates of miscarriages. In a recent review of the endometrial microbiota and its impact on conception, stated that the studies still had many limitations. For example, there are few studies on the subject and there is much variability in sample size and study designs hindering standardization [19-21].

studied how the balance of Lactobacillus affected the rates of pregnancy and reproductive pathologies and found that a high proportion of Lactobacillus spp. was present in women with higher pregnancy rates and that a negative imbalance of Lactobacillus spp. was associated with low pregnancy rates in women. Investigated the impact of women's age by relating endometrial receptivity to the microbiota, finding that the female microbiota pattern changes as women age as follows: there is a decrease in lactobacilli concomitant with a lessening of receptivity and a tendency for a reduced endometrium. researched the profiles of microbiota cultures and correlated them with pregnancy rates and found that women in the groups with a high rate of lactobacilli correlated with high pregnancy rates. In contrast, the groups of women with higher incidences of subspecies of Staphylococcus and Enterobacteriaceae related positively to higher rates of implantation failures. In another study, conducted a comparative study of the dynamics of microbiota changes between the endometrium and the uterine cervix during embryonic implantation. They concluded that Lactobacillus spp. has a favorable connection with the success of embryo transfer, while the species Escherichia coli and Gardnerella vaginalis have a reduced protective effect on embryo transfer [22-25].

In this recent review, aimed to analyze the microbiota in light of pregnancy loss. The authors argue that the dominance of Lactobacillus spp. is also associated with miscarriages, but that the exact mechanisms of positive or negative reproductive results are still not clear, raising the hypothesis that cross-contamination has not been controlled by the studies carried out so far. The researchers conclude there is a large body of evidence demonstrating an association between the composition of the endometrial microbiota and early pregnancy loss, including miscarriages. Nevertheless, the causality for this association remains without robust evidence and further studies are needed to determine the factors that predispose microbiota responses. Also necessary are clearer ways to identify and stratify interventionist strategies with greater beneficial reproductive results [26].

The literature comparing in vitro fertilization and the chance of death in infertile women has found that the chance of death is associated with the woman's gestational age, that is, the older the woman becomes pregnant, the greater the chance of death. Women also have a greater chance of death from diseases related to metabolic syndrome, so women with overweight and obese body mass index are more likely to have a fatal outcome when infertile. When considering ethnicity, infertile white women have a higher chance of mortality risk compared to fertile white women and so do black women. However, in Asian and Hispanic women, there was no difference in mortality risks between infertile and fertile patients. Strengths and limitations of the study [27,28].

The main strength of this review is the topicality of the issue addressed here: endometrial microbiota in assisted reproduction. Studies on this topic began only a few years ago and promising advances in reproductive treatment have been demonstrated. The limitations are those of a recent subject in the scientific literature, namely few studies with a low and varied number of patients and many methodological variations and study designs, making standardization of the subject difficult. Narrative review work has a study design that is not based on experimental work and, therefore, does not present novel results. Instead, it gives an overview of the relevant studies of a topic in the literature. Although aware of the limitation of this type of study design, we know that a narrative review has the benefit of bringing forward the latest news on a topic in the literature.

Conclusion

We conclude that the association of endometrial microbiota with Lactobacillus spp. has favorable results for higher pregnancy rates. Conversely, an overpopulation of several other microorganisms from various genera and species, such as E. coli, G. vaginalis, and Staphylococcus spp., and species of the Enterobacteriaceae family, among other species present in the endometrial microbiota, may result in dysbiosis, which potentially leads to recurrent implantation failures and miscarriages. Additionally, the quality of the articles falls short of an adequate level. Further research is still needed to better understand the biodiversity of the female endometrial microbiota.

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