



Review

A Narrative Review Discussing the Obstetric Repercussions Due to Alterations of Personalized Bacterial Sites Developed within the Vagina, Cervix, and Endometrium

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Abstract: Background: The reproductive tract microbiota that evolved as an integrative component has been studied intensively in the last decade. As a result, novel research, clinical opportunities, and perspectives have been derived following the close investigation of this microecological environment. This has paved the way for an update to and improvement of the management strategies and therapeutic approaches. However, obscurities, contradictions, and controversies arise regarding the ascension route from the vagina to the endometrium via the cervix, with finality in adverse obstetric outcomes. Methods: Starting from these considerations, we aimed to gather all existing data and information from four major academic databases (PubMed, ISI Web of Knowledge, Scopus, and ScienceDirect) published in the last 13 years (2010–2023) using a controlled vocabulary and dedicated terminology to enhance the coverage, identification, and sorting of potentially eligible studies. Results: Despite the high number of returned entries ($n = 804$), only a slight percentage (2.73%) of all manuscripts were deemed eligible following two rounds of evaluation. Cumulatively, a low level of *Lactobacillus* spp. and of other core microbiota members is mandatory, with a possible eubiosis-to-dysbiosis transition leading to an impairment of metabolic and endocrine network homeostasis. This transposes into a change in the pro-inflammatory landscape and activation of signaling pathways due to activity exerted by the bacterial lipopolysaccharides (LPSs)/endotoxins that further reflect a high risk of miscarriage in various stages. While the presence of some pathogenic entities may be suggestive of an adverse obstetric predisposition, there are still pros and cons of the role of specific strains, as only the vagina and cervix have been targeted as opposed to the endometrium, which recently started to be viewed as the key player in the vagina–cervix–endometrium route. Consequently, based on an individual’s profile, diet, and regime, antibiotics and probiotics might be practical or not. Conclusions: Resident bacteria have a dual facet and are beneficial for women’s health, but, at the same time, relaying on the abundance, richness, and evenness that are definitory indexes standing as intermediaries of a miscarriage.

Keywords: microbiota; vagina; cervix; endometrium; early miscarriage; late miscarriage



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1. Introduction

The intimate and highly specialized relationship between colonizing pathogenic, commensal, and symbiotic microorganisms known to exert a profound impact upon homeostasis since birth through complex networks is a concept that dates back before the culmination of the Human Microbiome and Integrative Projects ((i)HMP) [1–3]. This topic paved the way and ensured a transition to a novel dimension by offering advanced research and

clinical perspectives into the microbiome's position in the overall development, health, interplay with the immune system, and disease [4–6].

The advancement and constant accessibility of high-throughput sequencing techniques facilitate our knowledge, thus becoming tangent with outstanding research and filling distinct niches [4,7–9]. In this context, molecular biology contributed by bringing forward the concept of “microbiocenosis” and identification of anaerobic Gram-negative and Gram-positive entities [10] regarded as etiological factors in obstetric and gynecological complications [11,12].

Even though the translation of intricate ecological metrics into clinical trials remains problematic and poses a great challenge, a classifying system would be of great importance, leading to an accurate data set [13,14], as in other studies, to create community structure type (CST) clusters [15]. Based on the system regarding the five CSTs proposed by Ravel and colleagues [16], four are dominated by *Lactobacillus* spp. as follows: CST I by *Lactobacillus crispatus*, CST II by *Lactobacillus gasseri*, CST III by *Lactobacillus iners*, and CST IV by *Lactobacillus jensenii* that is otherwise loomed with over 25% by anaerobic bacteria [17]. Conversely, others proposed that machine learning algorithms ensure a prospect in order to overcome classifying discrepancies [18] and discussed how bioinformatics analyses ease the working volume to make the microbial community groups independent and comparable [19,20].

To be precise, the role of maternal microbiota started to gain attention from researchers [21–23] owing to the nonsterile status of the womb and bacterial colonization of the uterine cavity, presumably derived following the ascension route of bacteria from the vagina through the cervical canal [24–26]. Nevertheless, current working protocols and sampling methods (double-sheathed embryo transfer—ET, catheter, or transcervical device) aiming to minimize contamination provided a comprehensive overview of the communities within the endometrium [27–29] in contrast with culture- and microscopy-based procedures [30–32].

As a first-line protection against foreign entities and responsible for a dynamic balance between interdependence and mutual restriction, the vagina is a unique habitat for a broad spectrum of microorganisms and is vital [33–35] for conception and pregnancy, as well as a passage for sperm, menstrual blood, and childbirth [36–40]. However, over the course of a lifespan, the composition may vary based on a series of exogenous factors such as age, ethnicity, and geographical location [41].

Vaginal flora composition is similar to the endometrium, being dominated by *Lactobacillus* spp. involved in lactate, bacteriocins, and hydrogen peroxide production, and by other genera [16,28,29,42]. This link is partly assured by elevated estrogen levels that facilitate glycogen deposition in the vaginal epithelium cells [16,43–46] and by microbiota that intertwines with the existing microenvironment [47].

In contrast, whereas the overall diversity and richness decrease throughout gestation and stability increases due to the elevated abundance of *Lactobacillus* to prevent pathogen adherence and reducing pH in contrast with nonpregnant women, there are numerous endo- (menarche, menses, menopause, sexual activity, pregnancies, antimicrobial agents) and exogenous (stress, diet, exercise, hygienic routine, use of contraceptives, and rectal colonization) factors shaping composition [40].

Therefore, a possible alteration and depletion of lactobacilli no longer maintain the optimal conditions for carrying a baby and the host's eubiosis and might be a pillar of dysbiosis and a forerunner of poor pregnancy outcomes [48]. A number of studies have been published throughout the years that greatly expanded the sphere of information with emphasis on infections (herpes simplex virus 2 (HSV-2), human immunodeficiency virus (HIV), human papillomavirus (HPV), aerobic vaginitis (AV), and bacterial vaginosis (BV)) [49], as well as more complex conditions that include gestational diabetes, intrauterine adhesions (IUA), polycystic ovary syndrome (PCOS), recurrent implantation failure, preterm birth (PTB), preterm pre-labor rupture of fetal membranes (PPROMs), early miscarriage, infertility, and cancer [25,50,51].

Despite the recent advances, some etiologies and pathogenesis that might occur are yet to be explored to their complete potential in relation to microbiota. Cumulatively, the present manuscript follows to discuss in an objective and possible critical manner all existing studies with regard to the lower female genital tract (FGT), particularly the vagina and cervix, and the endometrium within the upper FGT with the most challenging issues in reproductive medicine.

2. Methodology

The structure and design of this manuscript adhere to the standard procedures, instructions, and indications established previously by Green et al. [52] on writing a narrative review.

2.1. Academic Databases Accessed and Search Strategy

We conducted a comprehensive search of the scientific literature aiming to identify, gather, and sort available studies within the field, utilizing four well-known academic databases: PubMed, ISI Web of Knowledge, Scopus, and ScienceDirect. Using a controlled vocabulary and scientific language, we ensured the discovery of relevant articles that align with our objective.

The analyses were carried out using “microbiome” as a primary dimension alongside “vagina”, “cervix”, and “endometrium”; as a second output, “early/late miscarriage”, “early pregnancy loss”, “spontaneous abortion”, “missed abortion”, “recurrent miscarriage”, and “recurrent pregnancy loss” were used.

We have concentrated solely on studies conducted on human individuals.

The adopted PubMed string was: microbiome [Title/Abstract] AND vagina [Title/Abstract] AND cervix [Title/Abstract] AND endometrium [Title/Abstract] AND early miscarriage [Title/Abstract] AND late miscarriage [Title/Abstract] AND early pregnancy loss [Title/Abstract] AND spontaneous abortion [Title/Abstract] AND missed abortion [Title/Abstract] AND recurrent miscarriage [Title/Abstract] AND recurrent pregnancy loss [Title/Abstract].

The adopted ISI Web of Knowledge, Scopus, and ScienceDirect strings were: microbiome [Title/Abstract] AND vagina [Title/Abstract] AND cervix [Title/Abstract] AND endometrium [Title/Abstract] AND early AND miscarriage [Title/Abstract] AND late AND miscarriage [Title/Abstract] AND early AND pregnancy AND loss [Title/Abstract] AND spontaneous AND abortion [Title/Abstract] AND missed AND abortion [Title/Abstract] AND recurrent AND miscarriage [Title/Abstract] AND recurrent AND pregnancy AND loss [Title/Abstract].

2.2. Inclusion and Exclusion Criteria

To complete the initial evaluation step, studies had to meet specific criteria. They had to be original experiments written in English and published between 2010 and May 2023. Only those that exclusively enrolled female patients were considered. Any literature synthesis, unavailable content, inclusion of male patients, or studies conducted on experimental models have been eliminated.

2.3. Study Selection

The papers that potentially met the criteria were assessed by examining their titles and abstracts. Subsequently, the entries were thoroughly evaluated based on the content, and any discrepancies or conflicting viewpoints were resolved through the joint approval of two expert specialists, B.D. and C.I.

2.4. Number of Entries

Over the past thirteen years, we found a total of $n = 804$ results for all main keywords across different databases. The breakdown per database is as follows: $n = 122$ (15.17%) in PubMed ($n = 86$, $n = 9$, and $n = 27$), $n = 22$ (2.73%) in ISI Web of Knowledge ($n = 8$, $n = 5$,

and $n = 9$), $n = 77$ (9.57%) in Scopus ($n = 48$, $n = 9$, and $n = 20$), and $n = 583$ (72.51%) in ScienceDirect ($n = 255$, $n = 155$, and $n = 173$), as shown in Figure 1.

Depending on the trimester when the pregnancy ceases from evolution, we identified: $n = 112$ studies for “early miscarriage”, $n = 82$ for “late miscarriage”, $n = 225$ for “early pregnancy loss”, $n = 161$ for “spontaneous abortion”, $n = 13$ for “missed abortion”, $n = 104$ for “recurrent miscarriage”, and $n = 107$ for “recurrent pregnancy loss”, as presented in Figure 2.

In a retrospective manner per year of published study, $n = 0$ in 2010, $n = 3$ in 2011, $n = 7$ in 2012, $n = 13$ in 2013, $n = 2$ in 2014, $n = 28$ in 2015, $n = 23$ in 2016, $n = 95$ in 2017, $n = 48$ in 2018, $n = 68$ in 2019, $n = 76$ in 2020, $n = 165$ in 2021, $n = 198$ in 2022, and $n = 78$ in 2023 until May, as Figure 3 suggests.

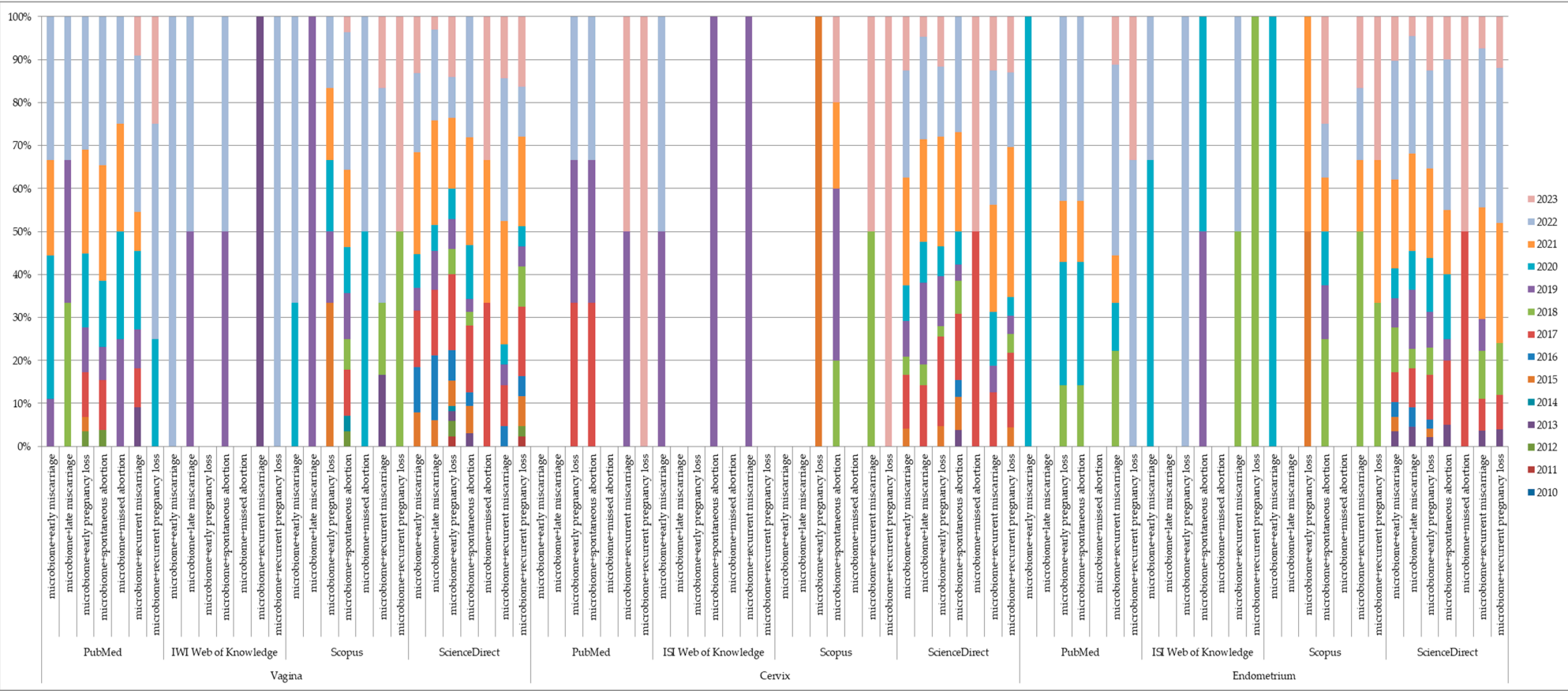


Figure 1. Cluster presenting the studies published from 2010 until 2023 on PubMed, ISI Web of Knowledge, Scopus, and ScienceDirect, based on the combination of keywords and in relation to each segment of interest along the female reproductive tract.

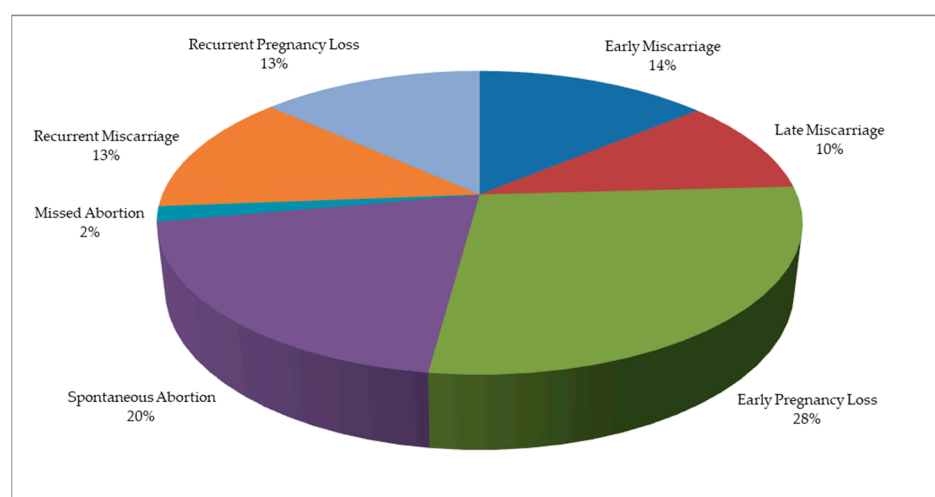


Figure 2. Percentages of studies allocated to targeted adverse obstetric outcomes.

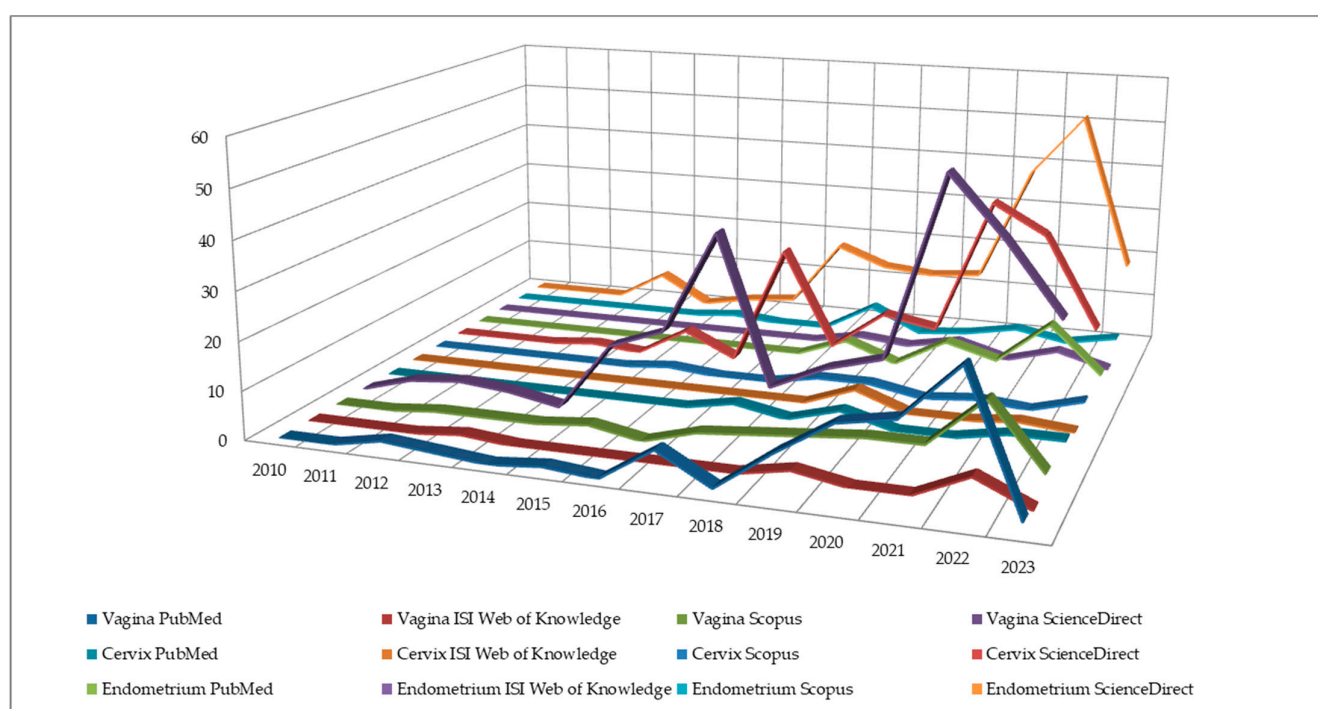


Figure 3. Trendline of the studies published between 2010 and 2023 based on the female reproductive tract per each database.

2.5. Number of Results

After eliminating the duplicates, $n = 84$ manuscripts met the eligibility criteria and were considered for further evaluation following the first phase fulfillment. However, we pulled $n = 16$, from which $n = 6$ were reviews, $n = 2$ were study protocols, $n = 2$ included animal models ($n = 1$ on cows and $n = 1$ on mice), $n = 2$ were out of the scope, $n = 1$ could not be adequately evaluated, $n = 1$ was a case report, $n = 1$ was an article written in Chinese, and $n = 1$ was an editorial. After the second stage, only $n = 22$ out of the $n = 68$ studies were considered appropriate for inclusion in the main body of this manuscript.

An overview of all studies can be observed in Table 1.

Table 1. Brief presentation of the studies considered eligible arranged based on the total number of patients and the subsequent allocation, hypervariable region, primers, and sequencing platform.

Total Number of Patients	Allocation of Patients	Hypervariable Region	Primers	Sequencing Platform	Reference
n = 1 patients	n = 1 RRF	V2–4–8 V3–6, 7–9	NS	Ion S5 XL	[53]
n = 25 patients	n = 25 RM	V4	NS	MiSeq	[54]
n = 36 patients	n = 20 Control n = 16 RM	V3–V4	341F [55] 5'-barcode-CCTACGGGNGGCWGCAG-3' 805R [55] 5'-barcode-GACTACHVGGGTATCTAATCC-3'	MiSeq	[56]
n = 50 patients	n = 25 Control n = 25 RSA	V3–V4	338F 5'-ACTCCTACGGGAGGCAGCA-3' 806R 5'-GGACTACHVGGGTWTCTAAT-3'	NovaSeq	[57]
n = 50 patients	n = 10 Control n = 20 RM n = 20 RIF	V3–V4	341F 5'-CCTACGGGNGGCWGCAG-3' 805R 5'-GACTACHVGGGTATCTAATCC-3'	MiSeq	[58]
n = 50 patients	n = 25 Control n = 25 RM	NS	NS	NS	[59]
n = 50	n = 25 Control n = 25 Embryonic miscarriage	V4	515F GTGCCAGCMGCCGCGGTAA 806R GGACTACHVGGGTWTCTAAT	PGM Ion Torrent HiSeq3000/4000	[60]
n = 50	n = 15 Control n = 13 Empty-sac miscarriage n = 22 Missed miscarriage	V4	520F 5'-AYTGGGYDTAAAGNG-3' 802R 5'-TACNVGGGTATCTAATCC-3'	MiSeq	[61]

Table 1. Cont.

Total Number of Patients	Allocation of Patients	Hypervariable Region	Primers	Sequencing Platform	Reference
n = 58 patients	n = 14 Control n = 21 RA n = 23 INF	V3–V4	S-D-Bact-0341-b-S-17 CCTACGGGNGGCWGCAG S-D-Bact-1290785-a-A-21 GACTACHVGGGTATCTAATCC	MiSeq	[62]
n = 58 patients	n = 27 Normal Induced Abortion n = 31 Unexplained RSA	V3–V4	338F 5'-ACTCCTACGGGAGGCAGCA-3' 806R 5'-GGACTACHVGGGTWTCTAAT-3'	MiSeq	[63]
n = 63 patients	n = 44 Became pregnant n = 19 Did not become pregnant	V4	515F [64] 5'-TCGTCGGCAGCGTCAGATGTGTATAA GAGACAGGTGYCAGCMGCCGCGGTAA-3' 806rB [64] 5'-GTCTCGTGGGCTCGGAGATGTGTATAA GAGACAGGGACTACNVGGGTWTCTAAT-3'	MiSeq	[65]
n = 85 patients	n = 39 Control n = 46 RPL	V3–V4	341F [66] 5'-CCTACGGGNGGCWGCAG-3' ITS1F [66] 5'-GGTCATTTAGAGGAAGTAA-3' 785R [66] 5'-GACTACHVGGGTATCTAATCC-3' ITS2 [66] 5'-GCTGCGTTCTTCATCGATGC-3'	MiSeq	[67]
n = 87 patients	n = 24 Elective Abortion n = 63 Missed Miscarriage	V4	515F 5'-GTGCCAGCMGCCGCGGTAA-3' 806R 5'-GGACTACHVGGGTWTCTAAT-3'	Mini Seq	[68]
n = 104 patients	n = 50 Control n = 54 Missed abortion	V1–V9	F44 RGTTYGATYMTGGCTCAG R1543 GGNTACCTTKTTACGACTT	Bacterial chip	[69]

Table 1. Cont.

Total Number of Patients	Allocation of Patients	Hypervariable Region	Primers	Sequencing Platform	Reference
n = 105 patients	n = 17 Control n = 88 Unexplained RPL	V3–V4	S-D-Bact-0341-b-S-17 5'-CCTACGGGNGGCWGCAG-3' S-D-Bact-0785-a-A-21 5'-GACTACHVGGGTATCTAATCC-3'	MiSeq	[70]
n = 109 patients	n = 20 Control n = 89 SA	NS	NS	NS	[71]
n = 126 patients	n = 18 Control n = 108 RSA	V3–V4	338F 5'-ACTCCTACGGGAGGCAGCAG-3' 806R 5'-GGACTACHVGGGTWTCTAAT-3'	MiSeq	[72]
n = 147 patients	n = 23 SA n = 36 Nonabortion n = 88 Induced Abortion	V1–V3	NS	Roche/454 GS Junior	[73]
n = 161 pregnancies	n = 83 Control n = 64 1st Trimester Miscarriage n = 14 2nd Trimester Miscarriage	V1–V2	Illumina i5 adapter 5'-AATGATACGGCGACCACCGAGATCTACAC-3' 8-bp bar code 5'-TATGGTAATT-3' 28F 5'-GAGTTTGATCCTGGCTCAG-3' Illumina i7 adapter 5'-CAAGCAGAAGACGGCATACGAGAT-3' 8-bp bar code 5'-AGTCAGTCAG-3' 388R 5'-TGCTGCCTCCCGTAGGAGT-3'	MiSeq	[18]
n = 164 patients	n = 48 SA n = 116 NP	V3–V4	343F 5'TACGGRAGGCAGCAG-3 798R 5-AGGGTATCTAATCCT3'	MiSeq	[74]

Table 1. Cont.

Total Number of Patients	Allocation of Patients	Hypervariable Region	Primers	Sequencing Platform	Reference
n = 167 patients	n = 74 Control n = 39 Aneuploid miscarriage n = 54 Euploid miscarriage	V1–V2	28F-YM GAGTTTGATYMTGGCTCAG 28F-Borrellia GAGTTTGATCCTGGCTTAG 28F-Chloroflex GAATTTGATCTTGGTTCAG 28F-Bifdo GGGTTCGATTCTGGCTCAG 388R TGCTGCCTCCCGTAGGAGT	MiSeq	[75]
n = 243 patients	n = 243 RM	NS	NS	NS	[76]

NS—not specified. RRF—repeated reproductive failure. RM—recurrent miscarriage. RSA—recurrent spontaneous abortion. RIF—recurrent implantation failure. RA—repetitive abortion. INF—infertility of unknown origin. RPL—recurrent pregnancy loss. bp—base pair. NP—normal pregnancy.

3. Results and Discussion

It has been observed that microbial ratios of the endometrium can fluctuate in both healthy individuals [27] and those experiencing menorrhagia [77]. This characterizes an increase in *Lactobacillus* during distinct phases of the menstrual cycle and a low α -diversity [78]. Vomstein et al. [58] examined the longitudinal intra-cycle changes in the follicular, ovulatory, and luteal phases, and found a decrease in the richness and evenness of species in healthy women during ovulation, with the lowest load in the luteal phase after the calculation of the Shannon index. However, this finding did not apply to RM or RIF groups, instead noting a higher similarity marked by an increase in *Firmicutes* and a decrease in *Proteobacteria* in the reference group compared to RIF and *Firmicutes* in the RM [58]. Even though this study did not emphasize significant changes in the uterine microbiota at days 2 and 7 of the menstrual cycle attributable to the ovulatory and luteal phase, Vomstein et al. [58] still noted subtle translocations that support the hypothesis of a stabilizing flora related to the evolution of the menstrual cycle. With a decrease only in the control group, the endometrium seems to provide proper conditions for proliferation, and its thickness might be used as a predictor of reproductive success [79,80].

It is possible that an imbalance in RM and RIF patients who have low levels of *Lactobacillus* spp. and have experienced a pregnancy [81] or undergone a controlled ovarian stimulation (COS) protocol could be a contributive factor for endometrial and vaginal dissimilarity in favor of *Prevotella* and *Atopobium* [82]. Although RIF and RM are common in nulliparous women, research concentrated on endometrial microbiota is limited [54,83] and has produced mixed results, completed by others that failed to demonstrate the correlation with reproductive success [64,83–85]. *Proteobacteria* and *Dialister* may have a direct impact on reproductive function in women with RIF, further associating with endometriosis (EMS) and chronic EMS [86]. This may represent a potential marker for dysbiosis in this category of patients [87]. Antibiotics are currently the only option to improve the live birth rate (LBR) in chronic EMS as a countermeasure to probiotics' low efficiency [88–91]. Multiple routes for microorganism ascension have been proposed over the years. The two options point to endometrial colonization that portrays hematogenous colonization of the oral and placental flora [92], whereas the most accepted remains that through the cervix. Uterine microbiota via the cervix regulates the traffic between the sites, and the mucus plug serve as an indicator of infection [93], shaped by the lactic acid bacteria strains' pH transitions [27,94]. Gonadal hormones influence the composition and function of the vaginal microbiota [95] with *Lactobacillus* spp. being prevalent in women with chronic EMS or endometrial polyps [96]. Additional data ascertain the presence of a positive and uneven distribution of the endometrial microbiota in RM and endometrial polyp chronic EMS patients [96,97].

The use of combined oral contraceptives (COCs) and levonorgestrel intrauterine system (LNG-IUS) can support the growth of *Lactobacillus* spp. during the follicular and luteal grades, as it correlates with the menses [98]. Some studies investigate the effectiveness of balloon placement versus intrauterine device (IUD) for patients who aborted or had intrauterine adhesions (IUAs), as there is no significant difference in ongoing pregnancy rates between the two groups. However, the patients who underwent balloon placement had a lower miscarriage risk, but with no differences in terms of IUA recurrence, American Fertility Society (AFS) score reduction, or chronic endometritis rates, and an increase in bacterial load compared to those who used the balloon stent [99]. Though the mycobiome remains underexplored, there is no significant difference between the groups, except for an increase in *Dialister*, *Filobasidium*, and *Exophiala*, and a decrease in *Bifidobacterium* in IUA patients [100].

From current knowledge, it is clear that *Lactobacillus* spp. fulfill a vital role in safeguarding the vagina in the early stages of pregnancy. Among them, *Lactobacillus crispatus* is particularly important. To understand the importance of *Lactobacillus* species, it is essential to note that glycogen is broken down into small polymers and then metabolized to produce D-lactic acid, bacteriocins, and hydrogen peroxide. These synthesized compounds confer

protection against the growth, establishment, and proliferation of pathogens that cause infections [95,101,102]. *Cutibacterium* and *Anaeroba* have been identified as predictors of miscarriage in patients with recurrent pregnancy loss (RPL). Despite *Cutibacterium*'s dominance in the skin, it has also been found in the uterine endometrium [103] and in follicular fluid [104], where it can exert detrimental effects when present with *Bifidobacterium*, *Gardnerella vaginalis*, *Atopobium*, and *Lactobacillus* (though not *Prevotella*) based on the geographic location [105]. While oral probiotics were found to be ineffective in altering the vaginal microbiota [106], a reevaluation of the cervicovaginal microbiome showed an increase in the interleukin 6 (IL-6) in patients predisposed to RPL [107]. This discovery could prove to be useful in determining which patients are suitable for progesterone (P4) therapy [108].

When certain bacteria are depleted, it cause an increase in *Streptococcus*, *Peptoniphilus*, *Ureaplasma*, *Dialister*, *Prevotella*, *Bacteroidetes*, and *Firmicutes* [109]. These stand as triggers of inflammation, which in turn enhances the up-regulation of metalloproteinases [110,111] and pro-inflammatory cytokines [112], disturbing iron processing and decreasing the red blood cells (RBCs). In severe cases of inflammation or bleeding [113,114], tissue inhibitors of metalloproteinases (TIMPs) [115] are inhibited, thus exacerbating the severity. Miscarriage can be linked to hormonal signaling dysregulation between estradiol (E2) and P4 levels with substrate availability [116,117], which causes a drop in *Lactobacillus* spp. levels. Estrogen promotes glycogen accumulation in the vaginal cells, for which *Lactobacillus* spp. are exploiting it as a carbon source [16]. The ratio of *Firmicutes* and *Bacteroidetes* increases in women who miscarry [118], indicating a holistic dysbiosis of the rectal microbiome. This relationship is primarily influenced by host factors such as age and gestational weeks, rather than the action of a specific pathogen [119].

Women with *Lactobacillus* spp.-dominant flora have higher rates of successful implantation, pregnancies, and LBR after in vitro fertilization (IVF)-ET compared with those with non-*Lactobacillus*-dominant flora, such as [29] as *Klebsiella*, *Neisseria*, *Bifidobacterium*, and *Gardnerella* [120]. Interestingly, the microbiota of the uterine endometrium does not seem to have any impact on the IVF-ET outcomes of infertile women [85] or pregnancy/miscarriage rates [84,121]. To ensure the utmost accuracy of sample collection, it is recommended to use an ET catheter [53,54] during clinical practice to prevent contamination with harmful bacteria from the cervical canal that may affect the embryo [122,123].

Although *Lactobacillus crispatus* is regarded as a part of a healthy microenvironment [124], it is less abundant in women with EMS [87] and RPL [67] in comparison to *Lactobacillus iners* in the endometrium of RPL women and *Gardnerella vaginalis*. Peuranpää et al. [67] highlighted a varying ratio of *Lactobacillus crispatus* and *Gardnerella vaginalis* in RPL and healthy women. Despite the limited evidence demonstrating a relationship between the microbiome and RPL [55,65,67], a correlation between the PTBs and the cervicovaginal microbiota is known [125,126]. *Lactobacillus crispatus* in the vagina correlates with autophagy from the epithelial cells, and low levels of mediators, epithelial p62 with *Gardnerella*, and stress-related 70 kilodalton heat shock proteins (hsp70) lead to *Lactobacillus iners*, *Streptococcus* and *Bifidobacterium* dominance [127,128]. Standard laboratory protocols targeting vitamin D deficiency, mid-luteal P4, and chronic endometritis [129], molecular techniques directed in sequencing the 16S rRNA gene, and IVF/IVF-intracytoplasmic sperm injection (ICSI) can help predict microbiome composition alterations. In this context, a forecast of a clinical pregnancy can be made [130], as well as with RIF patients, as the endometrium is colonized by *Streptococcus*, *Staphylococcus*, *Neisseria*, *Klebsiella*, *Phyllobacterium*, and *Sphingomonas* [131–133]. The latter two are involved in carbohydrate and fat metabolism by regulating the immune cells' Th17 and ratio of Th1 and Th17, based on the synthesized LPSs [118,133]. This further explains the chronic endometritis [134] due to the pro-inflammatory landscape and the relative abundance of *Prevotella_1*, *Prevotellaceae_UCG_003*, and *Selenomonas_1*, as well as the correlations of imidazolepropionic and 1,4-methylimidazoleacetic acids with recurrent miscarriages [118].

A study by Garcia-Grau et al. [53] reported the case of a woman who underwent several ET cycles that resulted in RRF. Investigations and medication that included antibiotics

and probiotic vaginal tampons indicate virulence genes implicated in biofilm and antibiotic resistance of *Gardnerella vaginalis*, documented to cause dysbiosis [135]. Complementary to these observations stand much more severe complications, such as subfertility [136], in early [29,53,137], late [138], and spontaneous miscarriage [81]. It is noteworthy that genital flora is dynamic and can be manipulated by external factors, such as the body mass index (BMI) adjusted to the RPL group [67] and further translocations that occur with aging. It is relatively stable in the 20–40 interval, and alterations arise after 50 years [139]. Despite the best efforts, the mechanisms behind a more diverse microbiota are still not fully deciphered [140–142] and connected to cytokine level disturbances [57]. In vitro experiments showed that *Lactobacillus crispatus* prevents the attachment of pathogens by binding to the decidualized endometrial cells [143].

Endometrial dysbacteriosis weakens the tight junctions, which leads to the adherence of pathogens to endometrial stroma [140]. The Toll-like receptors (TLRs) current on the surface of endometrial cells are activated, resulting in localized immune reactions [142]. This mixed effect can cause remodeling of spiral arteries [144] and disruptions of the placenta due to the inadequate development of the natural killer (NK) cells that are vital in trophoblast invasion [145]. Subsidiary studies have shown a unique flora reuniting thirteen taxa in the endometrial tissue, eight in the fluid, and twenty-two different in abundance. The four genera frequently encountered are *Flavobacterium*, *Achromobacter*, *Exiguobacterium*, *Brevundimonas*, and phyla *Verrucomicrobiaceae*, according to Liu et al. [54]. Multivariable logistic regression analyses have emphasized that *Ureaplasma* spp. and prior miscarriages are independent risk factors for euploid karyotype, but related to preterm delivery in prospective gestations, according to Shi et al. [65].

Through the 16S rRNA sequencing of specific hypervariable regions, over four hundred patients were categorized into groups, leading to significant discoveries [18,59,68,70]. *Lactobacillus* spp. was the predominant species in both the cervix and vagina, but its prevalence decreased in cases of first-trimester miscarriage [18], and RM [59], according to Al-Memar, Caliskan, and their collaborators. The gestational age and RBCs count are responsible for the fluctuations in the α -diversity, as indicated by Guang et al. [68], as it extrapolates in richness and hierarchical clustering analysis [18,68]. Mori et al. [70] strengthen the abovementioned pointing toward the prevalence of *Lactobacillus* spp., especially *Lactobacillus iners*, and several pathogens. *Gardnerella vaginalis*, *Atopobium vaginae*, and *Bifidobacterium breve* are believed pivotal for the host's eubiosis. Patients with either RPL or a history of chorioamnionitis or miscarriage exhibit a separate microbial pattern compared to controls. Specifically, in terms of *Delftia* in the RPL and chorioamnionitis and *Streptococcus*, *Chloroplast*, *Microbacterium*, *Delftia*, *Anaerobacillus*, and *Cutibacterium* in the chorioamnionitis, with miscarriage groups containing the last two genera [70].

Recent research has firmly established a causality link between a prior growth of certain pathogens, especially *Atopobium*, and first-trimester spontaneous abortion (SA). This correlation is reflected in the β -diversity of the analyzed sites. *Proteobacteria* and *Pseudomonas* may be responsible for the cases of RSA compared to women who suffered a natural pregnancy-induced abortion, as suggested by Seo, Liu, Fan, et al. [57,63,73]. Demographic data [73] and published papers indicate that the highest percentage of cases occurs in women aged 45–54 years old, with poor education, an unmarried status, and a history of pelvic inflammatory disease (PID) [146]. There is a current debate about the possible connection between SA and human papillomavirus (HPV) [147]. High-risk (HR)-HPV oncogenic basis has previously been addressed [73]. The proposed passages for this relation include alternative proof that HPV is accountable for the apoptosis process of infected trophoblasts, which negatively impacts implantation and placental physiology [148–151].

A regulated intake of *Ligilactobacillus salivarius* CECT5713 significantly enhances the reproductive prospects, according to Fernández et al. [62]. Otherwise, it can culminate in an increase in *Atopobium vaginae*, *Sneathia sanguinegens*, and *Leptotrichia amnionii* [73]. Analyses carried out targeting *Ligilactobacillus salivarius* CECT5713 underlined its antimicrobial action against *Gardnerella vaginalis*, *Streptococcus agalactiae*, *Candida albicans*, *Candida glabrata*, *Candida*

parapsilosis, and *Ureaplasma urealyticum*. This capability is facilitated by its ability to build L-lactic acid and acetic acid molecules [152] responsible for the transition of the host's dysbiosis-to-eubiosis state [153–155]. One key benefit of *Ligilactobacillus salivarius* CECT5713 is the activity of inactivating pathogens found at the reproductive tract level [156–162]. Its viability depends on the low pH to hamper the growth in the local vaginal biofilm [163,164]. Another strong point is the vaginal cells' adhesion rate and co-aggregation with vaginal pathogen *Streptococcus agalactiae* [156] or *Candida* spp., interconnected to the binding sites [165,166] that are strain-specific characteristics [156,167–169]. Approximately $9 \log_{10}$ CFU/day for half a year increases the chances of a successful pregnancy up to 56% [62]. However, there is some controversy surrounding former observations that suggest a persistent bacterial richness of *Lactobacillus* among the groups enrolled [57] and later contradicted in another manuscript [73].

Irrespective of the *Cutibacterium* and *Staphylococcus* spp. as part of the core microbiota [57,103], under typical homeostasis circumstances, alteration facilitates an interchangeable phenomenon of bacterial load complementary to the causative facet in repetitive abortions. This shift in microbial abundance triggers an in-chain reaction that disturbs the cytokine landscape. It activates the IL-6 and gamma interferon (IFN γ) [57] and further confirms the hypothesis of an increase in chemokine (C-C motif) ligand (CCL) 2/3/4/5/8 cytokines in villus tissues [63] knowing that *Bacillus pumilus* could direct the messenger RNA (mRNA) up-regulation of IL-1 α , IL-6, IL-8, and of C-X-C motif chemokine ligand 1-3 (CXCL1-3) in inflammation [170,171]. Women who have experienced RSA reunite *Corynebacterium_1*, *Burkholderia-Caballeronia-Paraburkholderia*, *Sphingomonas*, *Rhodococcus*, *Megasphaera*, *Sneathia sanguinegens*, and *Pseudomonas*, as in [63], and can be re-drafted following aspirin and metformin administration to restore *Lactobacillus* spp. balance, based on a study from Zhao et al. [72]. Recent publications suggest personalization among the constitutive niches. Therefore, studies accentuate the tendency of microorganisms to migrate and illustrate the acidic pH and Nugent score. These are completed by the abnormalities of the immune transforming growth factor beta 1 and 2 (TGF- β 1/2), and vascular endothelial growth factor (VEGF) levels [62]. This notwithstanding, a low pH and Nugent score correlate with the high concentration and dominance of lactobacilli [16,172,173], which occasions that exemplified the consequences of uncontrolled antibiotics administration across various stages of life. It is counterproductive for the lactobacilli population [174] and provoke fertility impairment or embryo implantation failure [62]. *Lactobacillus crispatus/gasseri/iners/jensenii* are predominant in the vagina [62], with the mention that is less common or absent in other habitats [16,175,176]. Assuming that a co-dominance of multiple species in the community is not typical [176], *Lactobacillus crispatus* has been positively associated with the reproductive outcomes after treatment compared to *Lactobacillus iners/gasseri*, unless *Lactobacillus salivarius* ascended as the dominant species. Fluctuations between these strains are not uncommon [177], and their respective roles have been extensively studied [176–180]. On the other hand, others maintain the role of *Lactobacillus crispatus* on reproductive health [181–183], contrary to *Lactobacillus iners* that presumably accomplish dual functions for vaginal health [184,185] or to induce translocations [124,135,178,180,186].

As we explore this topic further, conflicting reports [55,56] arise regarding the microbial profile similarities of the α -diversity and β -diversity. There has been noted a decline in *Bifidobacterium* spp. to the detriment of an increase in *Gardnerella* spp. in the reference group and *Atopobium* spp., as formerly shown in the RSA group [73], as these microbes are documented in advancing uterine and peripheral NK cell counts [55,63,76]. Sialidases are enzymes documented to catalyze the subtraction of sialic acid from eclectic glycoconjugates found in both *Prokaryota* and *Eukaryota* domains that are essential for the pathogenesis and nutritional requirements of pathogens. Vaginal sialidase activity is persistent in all samples as in the cases of BV [187], thus implying the leukocyte esterase (LE) inflammatory indicator for urogenital tract and periprosthetic joint infections [188,189], which was statistically higher in the RSA group [72]. Kuon et al. [76] suggest combining conventional

and molecular protocols without 16S rRNA sequencing and show a prevalence of vaginal infections-related entities in the RM group. They found a high colonization of *gram-negative anaerobes* (20.5%), *Gardnerella vaginalis* (19.0%) through the elevated peripheral natural killer (pNK) cells, *Enterobacteriaceae* (14.8%), group B *Streptococcus* (11.0%), and *Candida* species (7.9%), coupled with the absence of *Lactobacillus* spp. (14.5%), but *Chlamydia trachomatis* was detectable in only 0.53% [76].

Recent data has unequivocally demonstrated that *Lactobacillus* sp. partakes in maintaining women's health by the amount of lactic acid and hydrogen peroxide to suppress the proliferation of pathogens such as *Mobiluncus* sp. *Bacteroides*, *Prevotella*, and *Gardnerella vaginalis* [190,191], which is responsible for BV. Conversely, a sub-optimal abundance of *Lactobacillus inners/crispatus* and *johnsonni* ratios and an interchange with *Atopobium vaginae*, *Aerococcus christensenii*, *Leptotrichia amnionii*, *Prevotella amnii*, *Lactobacillus fornicalis*, *Ureaplasma parvum*, *Mycoplasma hominis*, and *Sneathia sanguinegens* can result in severe pregnancy-related complications. These vary from BV to preterm delivery, abortion, and chorioamnionitis [192–194], and even a decline in the secretion of leukocyte protease inhibitor (SLPI) in the vagina [195]. Metronidazole is a first-line drug prescribed for treating BV, but includes its limitations. While it is effective in the short term, a relapse occurs in 20% of patients with BV within one month [196] and up to 58% within one year [197]. Additionally, resistance to the drug can develop, with a range detection of 75–100% in women with recurrent BV after a therapeutic administration [198], which can be attributed to variable susceptibility or intrinsic feature [199]. Probiotics [200] and synthetic compounds like amoxicillin/clavulanic acid or clindamycin have been reviewed as alternatives, but there are concerns regarding dose and duration [201].

In standard clinical settings, when anaerobic microorganisms replace *Lactobacillus* spp. [202], diagnosis methods involve Nugent's scoring system [203] or Amsel's criteria [204]. To manage the risk of second-trimester loss and PTB [138,205,206], international guidelines recommended screening programs [207–209], even for women with a low risk of miscarriage due to the absence of *Lactobacillus* spp. [210]. Certain socio-demographic characteristics, age, clinical history, and *Gardnerella vaginalis* among populations can cause abnormal vaginal flora in women with RPL, BV, or recurrence of BV, increasing the risk of experiencing adverse pregnancy outcomes from 20 weeks to less than 37 weeks [211–213]. Prior to BV manifestations, a conversion occurs, leading to a dominance of *Lactobacillus iners* during remission and transitory episodes, but ultimately benefiting other microorganisms in the pre-conversion phase [214]. Although personalized treatment guidance based on probiotics and antibiotics may reflect the IVF and reproductive developments in succeeding ET cycles [131,132], it cannot prevent BV in pregnant women [106].

Bifidobacterium, similar to certain *Lactobacillus* spp. has a marked impact on the microenvironment [57]. Studies of microecologies in the vagina and cervix have led to the conclusion of dominant *Firmicutes* and *Actinobacteria*, with slight differences in the vaginal *Lactobacillus*, and minor ones in the relative abundance of *Bifidobacterium* and *Gardnerella* spp. in the vagina. In a group that underwent RSAs, high levels of several bacteria were found, including *Bacteroidetes*, *Crenarchaeota*, *Cutibacterium*, *Atopobium*, and *Staphylococcus* spp., with a tendency of increase in the last three genera [57]. A recent publication demonstrated a relative abundance of *Bacteroides*, *Tenericutes*, *Fusobacteria*, *Proteobacteria*, and *Firmicutes*, analogous to those from cervical intraepithelial neoplasia (CIN) samples [215] and higher operational taxonomic units (OTUs) in the non-abortion group in comparison to induced abortions or SAs [73]. Possible contributing factors for cervical microbiota dysbiosis in the non-abortion group as compared to SA include individual hygiene practices, genetic factors, glycogen level, or the method used for sample collection and sequencing [16,216,217].

Research to explore the association between a disrupted microbial flora and missed abortion reveals on the computational bioinformatic cladograms an altered α -diversity based on the Simpson index and high Shannon index in the patient's group, according to Sun, Liu, Oliveira et al. [61,69,71]. The relative abundance of *Firmicutes*, *Lactobacillus crispatus*, *jensenii*, and *gasseri* and, intriguingly, in *Mycoplasma genitalium* and *Ureaplasma*

parvum appeared to be reduced but is counterbalanced by high richness and diversity of *Bacteroides*, *Miscellaneous-Crenarchaeota*, *Escherichia/Shigella*, *Acetobacter*, *Staphylococcus*, *Bacillus*, and *Halomonas*. They concluded that these modifications were associated with the metabolic function in the case group, having different CSTs and ranging from a dozen to hundreds or thousands of OTUs with a space under the receiver-operating curve (ROC) of 86.76% and 93.33%. Subsidiary observations referring to this gynecological condition attribute multiple arguments toward a disbalance between *Lactobacillus* and *Gardnerella* as frequently observed events. Moreover, the high prevalence of euploid miscarriages than aneuploid due to dissimilarities in genera *Fam_Finegoldia*, *Lac_Coprococcus_3*, and *Lac_Roseburia* is linked to 80% of embryonic miscarriages, according to Jiao, Grewal, Xu and their collaborators [56,61,75]. These translocations follow a linear reactivity in the up-regulation of pro-inflammatory cytokine levels IL-1 β /2/6/8/10/12p70 and an influx of polymorphonuclear cells in placental tissue [56,61,75].

As previously mentioned, a lack of *Lactobacillus* spp. (*Lactobacillus jensenii*, *Lactobacillus gasseri*, but not *Lactobacillus iners*), *Firmicutes* and *Saccharibacteria* can contribute to first-trimester miscarriages. This is due to an increase in the α -diversity of certain genera including *Fam_Finegoldia*, *Lac_Coprococcus_3*, and *Lac_Roseburia*, *Proteobacteria*, *Actinobacteria*, *Chlamydiae*, and *Fusobacteria* [18,60,69], which is also noted in ectopic pregnancies [218]. It is worth noting that women who experience embryonic miscarriage exhibit low levels of IL-10 expression compared to IL-2 in the control group. Vaginal metabolites such as xanthine, benzoate, ascorbate, fumarate, and inosine are predictors. Furthermore, Th2 and regulatory T cells (Treg) are correlated to these secreted cytokines [60,219,220]. Interestingly, there was no *Mycoplasma genitalium*, *Mycoplasma hominis*, and *Ureaplasma* spp. in the patient group [69], but further investigations are necessary to confirm this.

There has been some uncertainty surrounding the role of vaginal flora in determining obstetric outcomes due to the presence of *Ureaplasma* spp., which was found to be similar in both groups analyzed. However, when the lower genital tract is infected with *Mycoplasma hominis*, *Ureaplasma urealyticum*, and *Ureaplasma parvum*, it can lead to placental tissue infection and alter the tolerogenic state, consequently triggering extrinsic apoptotic pathways [71]. It is believed that vaginal dysbiosis is linked to low levels of *Lactobacillus* spp., which can lead to chromosomally normal miscarriages [61,75,221], with premature delivery [222], infertility [223], IVF failure [224], premature rupture of membranes (PROM) [225], PID [226], and RM [56]. This dysbiosis might be correlated with *Fusobacterium*, *Finegoldia*, *Coprococcus*, *Roseburia*, *Atopobium*, and *Prevotella* [18,56,60,61]. Despite some predicting the involvement of vaginal microbiota in adverse pregnancy outcomes from PTB [227–230] to postpartum complications [231], others argue that the *Lactobacillus* vagitype may not be a factor [232,233].

Lactobacillus spp. are key strains that can help the host to prevent cerclage failure [234] and premature cervical dilatation, while *Gardnerella vaginalis* abundance is also reported to be responsible for unsuccessfully rescuing cerclage cases [235], considering that those who had an insertion of a transabdominal cerclage for large loop excision of the transformation zone (LLETZ) or a cone biopsy results in a high rate of live births [236]. Depletion of *Lactobacillus* spp. and the shifts that occur may be due to post-pregnancy IVF-ICSI treatment [130], infertility [64] of known or unknown origin, and RPL [237]. The analyses of samples collected from women who underwent a total hysterectomy with bilateral salpingo-oophorectomy present a high abundance of *Firmicutes* and *Lactobacillus* [238]. Besides the non-*Lactobacillus*-dominated niche [64], patients display distinctive profiles of the menstrual blood-NK subtype [237]. A recent method illustrates a fast and inexpensive diagnostic tool to determine culturable and non-culturable microorganisms in patients with infertility and EMS [239]. Nonetheless, others reveal no distinctions between *Lactobacillus*-dominant (>80%) and non-dominant (<80% and >20% opportunistic entities; e.g., *Atopobium*, *Gardnerella*, *Streptococcus*, *Staphylococcus*, *Corynebacterium*, and *Bifidobacterium*) endometria on pregnancy and miscarriage rates [84,240]. A recent study presents the case of a woman who experienced a spontaneous miscarriage in the eighth week and subsequently

during a successful pregnancy. As discussed above, there was a high bacterial diversity and a low *Lactobacillus* abundance, notably translocations between *Lactobacillus crispatus* and *Lactobacillus iners* in relation to PTB, prior to SA, scheduled, or before birth [81,241,242]. Conversely, another publication opposes these results and supports a sporadic presence of *Lactobacillus iners* and *Lactobacillus crispatus* in the middle endometrium, but rather being colonized by *Acinetobacter*, *Pseudomonas*, *Cloacibacterium*, and *Comamonadaceae* [243].

Several studies discussed race/ethnicity and sample location as probable causes for PTB irrespective of the usual depletion of *Lactobacillus* and the increase in putative novel bacteria. These changes in load proved not to be correlated with PTB [244], subsequent data rejecting this since a positive *Ureaplasma* in the vagina can cause preterm delivery, especially in women with threatened premature labor [245]. This is probably correlated with the vaginal level of β -defensin-2, as it reduces the risk of spontaneous PTB [233]. The bacterial DNA signatures of *Gardnerella vaginalis* (clade 4), *Lactobacillus iners*, and *Ureaplasma parvum* (serovars 3 and 6) through the algorithms (GLU test) developed may identify women with a singleton at high risk of spontaneous PTB at less than 34 to 37 weeks of gestation [246]. Even though PPRM is common among women [246], community disturbances occur before the PPRM in females at low and high risk and in only 3% of those who delivered at term [247]. Therefore, an increase in the abundance of *Prevotella*, *Peptoniphilus*, *Streptococcus*, and *Dialister* could be considered an early sign of PPRM [247], while a reduction in *Bacteroides* that is, however, detectable in the first two weeks in both vaginally-born and Caesarean (C)-section delivered infants, demonstrate the mother-to-fetal transmission [248].

4. Conclusions

It can be concluded that the reproductive tract microbiome is a complex and intertwined network whose overall integrity and functionality require a relatively low abundance of species, especially representatives of the four CSTs. Independently of the crucial roles and imperative presence of *Lactobacillus crispatus*, *gasseri*, *iners*, and *jensenii*, and of potentially pathogenic in a state of eubiosis as part of the core microbiota, an ascension route of microorganisms from the vagina through the cervix to the endometrium has been theorized. These lactic acid bacteria strains play a central part in synthesizing agents that prevent pro-inflammatory processes in cases of dysbiosis but also modulate metabolic and endocrine functions. However, there is still debate about the involvement of each *Lactobacillus* spp. strain in the reproductive success and outcomes that need to be further addressed. This is of utmost importance since several pathogens may be regarded as indicators of the risk of possible adverse obstetric events. Conclusively, the vagina and cervix are niches accessible to investigate, while the data on the endometrium is scarce due to the high chance of also collecting other bacteria from the reproductive tract. Apart from a woman's profile, desiring to naturally remain pregnant and successfully carry a gestation or, in some circumstances, through assisted reproductive technology (ART) interventions, it should be emphasized that each individual possesses their own personalized flora. There are a multitude of endo- and exogenous factors shaping the sites and reflects in the lack of antibiotics and probiotics regimes efficiency. We can decipher the mechanisms responsible and map the common species by delineating and dissolving all contradictions and diverging results offered by various teams over the years. In conclusion, the reproductive tract microbiotas have dual facets as both ally and foe. Thus, additional data are compulsory to advance and begincomprehending its complexity and full potential.

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