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Understanding the Associations of Urogenital Microbiomes With Fertility and In Vitro Fertilization

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ABSTRACT

Infertility, defined as the inability to establish a clinical pregnancy after a year of regular, unprotected sexual intercourse, impacts 8%–12% of couples worldwide. Many of these couples turn to in vitro fertilization (IVF) to build their families. The success rate of IVF procedures is variable, with estimates of up to 40% of embryo transfers being unsuccessful. Herein we review the existing literature on the role of the female and male urogenital microbiomes and genital inflammation on fertility and IVF outcomes. We discuss the microbiome across the female reproductive tract (FRT) and identify associations with female infertility, female genital tract inflammation, and success of IVF procedures. We also discuss the male urogenital microbiome and the associations between microbial taxa, genital inflammation, and male fertility parameters. Finally, we consider microbial transfer within couples and the impact this may have on fertility and the success of IVF procedures.

1 | Introduction

Infertility, or the failure to establish a clinical pregnancy after a year of regular, unprotected sexual intercourse, is estimated to affect one in eight couples (between 8% and 12%) worldwide. Approximately one-third of couples receive a diagnosis of female factor infertility, one-third of male factor infertility, and the remaining one-third either have both female and male factor infertility or an unknown cause [1, 2]. Multiple factors can contribute to infertility including endocrine disorders, structural abnormalities, genetic defects, urogenital tract infections, and lifestyle [2]. Treatment options are typically based on the specific diagnosis of the couple and can involve lifestyle changes, surgical procedures, or the use of hormones [3]. According to a report released in 2024 by the US Department of Health and Human Services, 2.3% of all infants born in the US in 2021 were conceived through the use of ART [4].

1.1 | Female Factor Infertility

Many factors can contribute to female factor infertility, including ovulatory disorders, pelvic or tubal adhesions, endometriosis, and uterine abnormalities [2, 5]. Ovulatory disorders, including polycystic ovary syndrome or premature ovarian insufficiency, can result in anovulation (a failure of the ovary to release an egg) [2, 5]. Endometriosis, where endometrial tissue grows outside of the uterine cavity, impacts 10%–15% of reproductive-aged women

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[2, 5]. Of these women, approximately half experience infertility through increased inflammation and pelvic adhesions that can distort pelvic anatomy [2, 5]. Pelvic and tubal adhesions can also be caused by infectious processes, the most common of which is pelvic inflammatory disease (PID), with *Chlamydia trachomatis* infection carrying the greatest risk of infertility associated with PID [2, 5]. Acute and chronic inflammation can damage the structural integrity of the fallopian tube, leading to hydrosalpinxes (or blocked fallopian tubes), which can obstruct the tube and impair endometrial receptivity, thereby creating a hostile environment for implantation [2, 5]. Uterine-specific causes of infertility can include uterine lesions, fibroids, reduced endometrial receptivity, and congenital uterine abnormalities such as septum [2, 5].

1.2 | Male Factor Infertility

Male infertility can be affected by testicular deficiency, post-testicular impairment (due to ejaculatory dysfunction or obstruction to sperm delivery), and low sperm quality (determined by sperm count, motility, and mobility) [6]. The testes contribute to male fertility by producing germ cells (spermatozoa), the main sex cells that carry genetic material needed to fertilize the female ovum. Sertoli cells and Leydig cells, also found in the testes, work with accessory glands (prostate, seminal vesicles, bulbourethral glands) to secrete proteins, growth factors, metabolites, mucins, and other factors that make up the seminal plasma. Semen is made up of 2%–5% spermatozoa with the rest of the ejaculate composed of seminal plasma. Male fertility is regulated by the prostate through prostatic fluid secreted by the prostate epithelium and is influenced by aging and cellular senescence [7]. The gold standard for assessing male infertility is to analyze semen for different parameters, such as volume, concentration, spermatozoa motility, and morphology. Sperm abnormalities may be classified as oligozoospermia (with concentrations below 15 million/mL), asthenozoospermia (low motility), teratozoospermia (> 96% of sperm cells are misshapen), azoospermia (no sperm cells found in the ejaculate), or a combination of these conditions [6, 8].

1.3 | Assisted Reproductive Technologies for Infertility Treatment

There is a range of ART available that vary in cost, invasiveness, and treatment success, defined by both the establishment of pregnancy and live birth rate [4, 9]. The course of treatment can be based on both specific diagnosis and preferences of the couple [9]. Ovarian stimulation, which can be combined with intrauterine insemination, is a low-cost, less invasive option, but the success rate is relatively low at 10%–20% per cycle [9]. In vitro fertilization (IVF) involves ovarian stimulation, retrieval of mature oocytes, oocyte fertilization, and culture of blastocysts (fertilized eggs) in an embryology laboratory, prior to the transfer of a 3- or 5-day embryo into the uterus [9, 10]. The per embryo transfer success rate of IVF ranges from approximately 35%–50% [11, 12]. Although the use of IVF has provided hope to many couples facing a diagnosis of infertility, the success rate for IVF on a per-couple basis cannot be predicted and in many cases it is unknown why IVF fails, indicating a critical need to improve IVF success rates.

2 | Mucosal Inflammation and Fertility

2.1 | Inflammation and Embryo Implantation

Embryo implantation is a physiologic inflammatory process and requires immunological tolerance to foreign antigens expressed by the embryo [13]. Embryo implantation begins with blastocyst apposition to the uterine endometrium, followed by attachment to the endometrial surface epithelium and can only occur in a receptive uterus [14]. Uterine receptivity occurs during the mid-luteal phase of the menstrual cycle and is regulated by the ovarian hormones 17-β-estradiol and progesterone [14]. Receptivity requires a variety of changes to occur including transformation of endometrial stromal cells into decidual cells, expression of inflammatory mediators and adhesion molecules and infiltration of immune cells. Most leukocytes in the uterus are uterine specific natural killer cells (uNK, 65%–70%) and antigen presenting cells (APCs, 10%–20%) including macrophages and dendritic cells (DCs) [14, 15]. In contrast to circulating NK cells, which are cytotoxic, uNK cells have lost their cytotoxic activity, which is mediated by interleukin (IL)-15 secreted by DCs and transforming growth factor beta-1 (TGF-β1) secreted by macrophages [14]. uNK cells have roles in regulating trophoblast invasion by the production of IL-8 and interferon gamma-induced protein 10 (IP-10), dampening T cell responses and producing angiogenic factors that induce vascular growth essential for the establishment of an adequate decidua [13, 14].

High levels of pro-inflammatory cytokines including IL-6, IL-8, tumor necrosis factor (TNF-α), and macrophage inflammatory protein (MIP-1β) characterize early implantation and act by recruiting and activating immune cells while also attracting the trophoblast for implantation [14–18]. APCs coordinate the immune response in the endometrium, which is critical for successful embryo implantation [18, 19]. This includes cytokine production and polarization of CD4+ T cells to T helper (Th1) and regulatory T cell (Treg) phenotypes, thereby inducing embryo tolerance. Indeed, a lack of APCs or aberrant macrophage polarization can prevent implantation from occurring in mouse models [15, 18–22]. Thus, a complex immune balance is required for successful implantation, and disruption of this balance could lead to implantation failure during IVF.

2.2 | Male Genital Inflammation

Inflammation influences seminal quality and male fertility by negatively impacting semen viability, motility, morphology, and DNA integrity [23]. An increase in inflammation leads to semen hyperviscosity (SHV), which influences sperm motility and increases sperm coagulation [24]. Urogenital inflammation could inhibit the production of nutrients necessary for the development of sperm or lead to sperm damage via increased levels of reactive oxygen species (ROS) and cytokines [25–27]. Inflammatory cytokines including IL-6, IL-1, IL-8, TNFα, and IFNγ are negatively correlated with sperm viability, motility, and DNA integrity [25, 28, 29]. Seminal fluid contains the highest concentration of molecules from the male reproductive glands, making it a logical source of metabolites potentially diagnostic of male infertility [30]. Bacterial-derived metabolites can induce inflammation and play a role in health and disease for many inflammatory

diseases, though most of these have been associated with the gut microbiome [31]. Therefore, any pro-inflammatory metabolites present in seminal fluid, whether bacterial or host-derived, maybe drivers or biomarkers of subsequent IVF outcomes.

Inflammation resulting from infections, including *E. coli* and *Chlamydia trachomatis*, has been linked to male fertility issues [32]. The enzyme granulocyte elastase, a quantitative marker of genital tract inflammation, is associated with motility, progressive motility, morphology, and low levels of intact DNA [28]. DNA fragmentation is significantly higher when bacterial infection is present [29]. Inflammatory signatures have also been linked to urogenital infections such as prostatitis, which may cause fertility issues through direct or secondary immune-mediated damage [32, 33]. Sperm DNA damage is associated with IVF outcomes, adversely impacting embryo quality and resulting in reduced implantation rates and clinical pregnancy [34, 35]. Lower sperm concentration and progressive motility are related to lower fertilization rates and fewer embryos produced [36–38]. Overall, inflammation in the male reproductive system may impact IVF success including oocyte fertilization, embryo generation, implantation, or ongoing clinical pregnancy [26, 39, 40].

3 | Microbiome and Fertility

Urogenital microbiome dysbiosis can lead to significant changes in the genital microenvironment, including increased or aberrant inflammation, which could impact fertility and the success of IVF procedures. Recent studies have investigated the impact of both the female and male urogenital microbiomes on fertility and IVF outcomes.

3.1 | Microbiome in the Female Reproductive Tract (FRT)

3.1.1 | Vaginal Microbiome

The microbiome of the FRT has been well-studied, particularly that of the lower reproductive tract. The vaginal microbiome is commonly composed of species of *Lactobacillus*, including *L. crispatus, L. gasseri, L. iners*, and *L. jensenii* [41]. Although heterogeneity exists, a *Lactobacillus*-dominant (LD) vaginal profile is considered optimal because of protective characteristics associated with these communities including bacteriocins, hydrogen peroxide, and lactic acid, which lowers the vaginal pH maintaining an acidic environment unfavorable for invading pathogens [42–44]. However, *Lactobacillus* species vary considerably in their ability to produce lactic acid, antimicrobial factors, and cause inflammation [45, 46]. Vaginal dysbiosis, defined by a loss of *Lactobacillus* and an overgrowth of obligate and facultative anaerobes such as *Gardnerella*, *Prevotella*, *Atopobium*, and *Mobiluncus*, is frequently accompanied by a clinical diagnosis of bacterial vaginosis (BV) [47, 48]. BV is associated with numerous adverse reproductive health outcomes including infertility and preterm birth as well as increased risk of acquisition of sexually transmitted infections (STIs), including HIV [49–58]. Molecular classifications of the vaginal microbiome, using techniques such as 16S ribosomal RNA (rRNA) sequencing, metagenomics or metaproteomics have been able to provide more detailed classifications of microbial communities, including community state types (CST), defined by the predominant bacterium, and could have different clinical implications [48].

Many studies investigated the impact of the FRT microbiome on fertility and on IVF outcomes, with somewhat conflicting results, perhaps due to sampling site, timing of sample collection in relation to IVF procedures, and differing outcome measures defining treatment success. In studies that compared the microbiome between fertile women, typically defined as those with at least one uncomplicated pregnancy with live birth, compared to women with reproductive failure, including those with infertility, repeated implantation failure, or recurrent miscarriage, factors including vaginal pH, Nugent score and/or clinical diagnosis with BV were elevated in women with reproductive failure [59, 60]. Studies that specifically sequenced the microbiome found that species of *Ureaplasma*, *Gardnerella*, and *Atopobium* were typically increased in the vagina or cervix of infertile women, while *Lactobacillus* was typically decreased [61, 60].

The vaginal microbiome composition is associated with IVF outcomes in some studies, with definitions of success including implantation, clinical pregnancy, ongoing pregnancy, or live birth. Women with a low percentage of vaginal *Lactobacillus* species (< 20%) are less likely to have successful embryo implantation or achieve pregnancy [62, 63]. The type of *Lactobacillus* detected may be important, as women with vaginal *L. iners* or *L. gasseri* predominance have lower success rates than women with *L. crispatus* or mixed lactic acid bacteria [64]. Interestingly, the degree of dominance of *L. crispatus* was an important factor in predicting pregnancy. In one study, women who had less than 60% *L. crispatus* abundance in the vaginal microbiome had an increased pregnancy rate [65]. Other studies of the cervical microbiome found that the abundance of *L. crispatus* increased and the abundance of *L. iners* decreased successful pregnancy outcomes [66]. There are reported increases in live birth rate associated with recovery of H_2O_2-producing *Lactobacillus* from the vagina and embryo transfer catheter [67]. One study showed that microbiome alpha diversity did not differ between women who achieved pregnancy and those who did not [63], while another found having a CSTIV microbiome, which is a community state type dominated by mixed anaerobes, is associated with lower pregnancy rates [65]. Abnormal vaginal flora, defined by either a clinical diagnosis of BV or high concentrations of *G. vaginalis* and/or *A. vaginae* are associated with lower success rates [64, 67].

3.1.2 | Uterine Microbiome

In the past, the uterus was typically thought to be a sterile environment. However, recent studies using genomic detection techniques such as 16S rRNA sequencing have indicated that this is not the case [68, 69]. Major bacterial genera identified in the endometrium are similar to those detected in the vagina and include *Lactobacillus, Atopobium, Gardnerella, Streptococcus, Bifidobacterium, Sneathia*, and *Prevotella*, although the biomass is lower in the upper reproductive tract [70, 71]. In studies that compared the microbiome between the upper and lower reproductive tract, the dominant microbial community members are generally consistent, although the relative microbial proportions varied [61, 72].

The endometrial microbiome has been associated with IVF success rates, with endometrial microbial dysbiosis considered an emerging cause of implantation failure and pregnancy loss in IVF patients [72, 73]. The presence of non-*Lactobacillus* microbiota such as *Atopobium, Bifidobacterium, Gardnerella, Haemophilus, Klebsiella, Neisseria, Staphylococcus*, and *Streptocuccus* has been associated with significant decreases in implantation, pregnancy, and live birth rates, while *Lactobacillus* is associated with increased success in some studies [74, 75, 76, 77, 78]. However, other studies reported that pregnancy rates and miscarriage rates were comparable between IVF patients with eubiotic (defined as ≥ 80% *Lactobacillus* + *Bifidibacterium spp.*) compared to dysbiotic (defined as < 80% *Lactobacillus* + *Bifidobacterium spp.* with ≥ 20% other bacteria) endometrial microbiomes [71]. Indeed, some patients in this study with no *Lactobacillus* detected had ongoing pregnancies [71].

3.1.3 | Microbiome, Inflammation, and Female Infertility

As described above, many studies have identified associations between vaginal or uterine microbiome composition and the success rates of IVF. However, few studies have investigated potential mechanisms responsible for these outcomes. As embryo implantation is a physiologic inflammatory process, microbial dysbiosis causing aberrant inflammation could influence both fertility status and success of IVF. APCs and Th1 cells, as well as the expression of pro-inflammatory cytokines TNFα, MIP-1β, IL-6, and IL-8 characterize early implantation [15, 18]. Higher levels of endometrial TNFα and lower IL-1β in IVF patients have been linked to clinical pregnancy rates [80]. In addition, a positive association has been identified between IP-10 and implantation, while there is a negative association between MCP-1 and implantation [80]. Among women with repeat implantation failure those with endometrial microbial dysbiosis, defined as < 90% microbiome from lactobacilli, had higher endometrial tissue levels of inflammatory mediators IL-6, IL-1β, HIF-1α, COX-2 [81]. Higher amounts of endometrial *Lactobacillus* were negatively related to concentrations of these inflammatory molecules and positively related to levels of IL-10/IGF-1 [81]. The presence of a non-*Lactobacillus* microbiota may trigger an inflammatory response that hinders embryo implantation [82]. Indeed, several studies have investigated the impact of vaginal microbial dysbiosis on cervicovaginal inflammation and identified associations between a non-*Lactobacillus* dominant microbiome and increased inflammation [42, 82, 83]. This includes increased APCs or altered APC transcriptional profiles exhibiting upregulation of pro-inflammatory cytokine genes including TNFα in women with non-*Lactobacillus* dominant microbiomes [42, 82, 83]. Cervicovaginal lavage from women with BV can induce maturation and activation of DCs [84]. Both a clinical diagnosis of BV as well as specific bacterial taxa in the vaginal microbiome, including *Prevotella, Sneathia, Aerococcus, Fusobacterium*, and *Gemella* have been associated with increased genital inflammation, including IL-1α, IL-8, IL-12p70, IL-6, TNFα, and MCP-1 [84, 85]. In addition to direct effects on the production of inflammatory mediators and immune cell recruitment or activation, the microbiome can also produce metabolites that could regulate host immunity [85]. Taken together, this indicates that the microbiome can modulate reproductive immunity which could impact fertility or success of IVF, although studies investigating specific mechanisms linking the microbiome to fertility are lacking.

3.2 | Microbiome in the Male Urogenital Tract

3.2.1 | Seminal Microbiome

Semen is not sterile and contains a microbiome that plays a role in male reproductive health [86, 87]. Sequencing technologies identified bacterial genera within the seminal microbiome including *Lactobacillus*, *Pseudomonas*, *Prevotella*, *Gardnerella*, and others. Some genera are similar to the female genital microbiome, and others are unique to the male microbiome, including *Stenotrophomonas* and *Brevibacillus* [89]. Although *Stenotrophomonas* has been found in the endocervical microbiome, *Brevibacillus* appears to be unique to the seminal microbiome [90]. Recent studies investigated the role of the seminal microbiome on male fertility, identifying an association with sperm quality, concentration, motility, morphology, DNA fragmentation, and semen particulate matter (PM) [86, 87, 88, 90, 91]. In general, *Lactobacillus* was associated with higher fertility, whereas other bacterial species such as *Prevotella*, *Pseudomonas, Bacteriospermia*, *Ureaplasma*, *Enterococcus*, *Mycoplasma*, and *Anaerococcus* were associated with male infertility parameters [86, 92, 93, 94].

One study associated *Gardnerella* with normal male fertility in contrast to women where *Gardnerella* can induce an inflammatory and dysbiotic microenvironment [96]. This study used next-generation sequencing to investigate associations between the seminal microbiome and fertility factors, identifying three main microbiome groups dominated by *Lactobacillus, Pseudomonas*, and *Prevotella*. The *Gardnerella* identified in this cohort was found in most (96.9%) of the samples tested, though none were *Gardnerella* dominant. Another recent study performed a comprehensive semen analysis using 16S rRNA sequencing and shotgun metabolomics to identify differences between the microbiome and bacterial functions in either healthy men or those with idiopathic infertility [97]. In this study, *Prevotella* was inversely correlated with sperm concentration, while *Pseudomonas* was positively associated with total motile sperm count and negatively associated with semen pH and varicocele [97]. This indicates that the microbiome effects on male fertility are likely multifaceted and complex, with different bacteria having additive or alternate effects on fertility factors. Structural changes in the male urogenital tract, such as vasectomies or varicoceles, were also observed to affect the seminal microbiome [97]. This pilot study also identified some bacterial functions within the S-adenosyl-L-methionine cycle that are associated with infertility which may play a role in pathogenesis of the urogenital microbiome.

Female microbial-induced inflammation contributes to poor reproductive health outcomes, and a similar effect may occur in the male reproductive tract [96, 97]. Indeed, some studies on HIV-infected men found evidence to support a relationship between pro-inflammatory cytokines and seminal microbes, with infertility associated with an increase in IL-10 and decreased IL-1β [98, 99]. Chronic inflammatory conditions such as inflammatory prostatitis show a decrease in seminal Lactobacillus and an

increase in *Proteobacteria*. Chronic inflammation of the male genitals can be caused by a genitourinary infection resulting in epididymitis, epididymo-orchitis, or bacterial prostatitis and can lead to infertility if untreated [100, 101, 102]. These infections can disrupt spermatogenesis and damage structures leading to irreversible oligospermia or azoospermia. Overall, male genital inflammation is estimated to contribute to 13%–15% of male infertility cases [32, 103]. These infections are often present with leukocytospermia, an abundance of peroxidase-positive leukocytes in seminal fluid frequently seen in the male partner of couples experiencing infertility [104, 105]. Bacteria such as *G. vaginalis*, *Leptotrichia*, and *Sneathia* species have been implicated in male genitourinary infections [106, 107, 108].

3.2.2 | Penile Microbiome

The penile microbiome, located on the outer area of the penis such as the foreskin or coronal sulcus, has been found to be up to 20-fold higher in total bacterial abundance than in the urethra [111]. Recent studies on the penile microbiome identified the presence of numerous bacterial species which can vary depending on the individual and are associated with factors such as sexual practices, infection, and even the urogenital microbiome of their partner [112]. Much like the vaginal microbiome, the penile microbiome has been separated into community types (CTs) based on the most dominant bacterial genera, including *Corynebacterium*, *Streptococcus*, *Sneathia, Prevotella, Finegoldia*, and *L. iners* [112]. In adolescents from South Africa and Uganda, foreskin microbiome profiles included *Corynebacterium, Peptoniphilus, Anaerococcus*, and *Finegoldia* [113].

Penile microbiome CTs are associated with circumcision status. In one study, Mehta et al. showed that only 4%–8% of circumcised men had *Finegoldia*- or *Prevotella*-dominated microbiomes, while 60%–86% of circumcised men had other microbiome profiles [112]. The penile microbiome has been observed to change in children undergoing elective circumcision, with alpha diversity decreasing post-circumcision, including a decrease in *Prevotella and Sulfurimonas* taxa and a decrease in thiosulfate reductase and polysulfate reductase bacterial metabolic pathways [114]. This study also looked at the mycobiome, identifying a decrease in *Saccharomycetales* and *Pleosporales* after circumcision [114]. As puberty occurs, changes to the penile and perineal microbiome may occur, as indicated in a recently published pilot study [115]. Though circumcision is associated with a change in the microbiome, the size of the foreskin was not observed to be associated with either increased penile anaerobes or pro-inflammatory cytokines in a study investigating mechanisms for reduced HIV acquisition risk with circumcision [116]. Though there are studies that show male circumcision provides beneficial effects for female sex partners by lowering the risk of HPV/cervical cancer or STI acquisition, studies investigating the penile microbiome contributions to male or female infertility and IVF outcomes are lacking [117].

3.2.3 | Microbiome, Inflammation, and Male Infertility

Inflammation of the male genital tract is largely induced by either structural damage or microbe-host pathogenic interactions. Structurally induced inflammation can lead to infertility and includes ejaculatory duct obstructions, inflammation of the epididymis, testicular torsion, and varicocoele [118]. In addition, inflammation can indirectly affect semen quality by impairing the functions of accessory glands and causing dysregulation of spermatogenesis [119]. Inflammation in response to pathogens can also induce tissue damage and sperm dysfunction, though tissue repair usually follows clearance of the pathogen [118, 119]. In the event of a failure to eliminate an infection, chronic inflammation, and recruitment of activated macrophages, lymphocytes, and cytokine expression are associated with infertility [116, 120, 121].

Potential regulation of the immunological and inflammatory responses by the seminal microbiome is thought to also be a factor in fertility, as similar bacterial species in the gut have been demonstrated to influence the immune system [124]. Pathogenic bacterial species in the male genital tract (such as *Staphylococcus* and *Chlamydia*) are linked to chronic prostatitis, urethritis, and inflammation, however less than 10% of men who suffer from chronic prostatitis have confirmed bacterial infections [32, 123, 124]. A reduction of *Lactobacillus* species in semen has been shown in patients with prostatitis, indicating microbiome dysbiosis (such as an overgrowth of *E. coli* and *U. urealyticum*) is a contributing factor in chronic inflammation in the male genital tract [125]. Inflammatory pathways that link male microbial factors with infertility include the dysregulation of key pro-inflammatory cytokines (TNFα, IL1α, IL1β) that are harmful to sperm production [118].

The most well-understood functional inflammatory pathway affecting male infertility is a response to oxidative stress. Oxidative stress has been indicated as one of the most important causes of male infertility because if left unchecked it can contribute to poor sperm motility, sperm DNA damage, and low sperm counts through damage to reproductive cells and intracellular components [120, 125, 126]. Pathogenic bacteria, as well as bacteria associated with a dysbiotic male genital microbiome, have been shown to induce oxidative stress in the male genital tract [90, 121].

Thus, there are several ways in which the male genital microbiome can influence male fertility. However, associations between the male genital microbiome, inflammation, and IVF outcomes have not been investigated.

4 | Inter-Couple Factors in Fertility

4.1 | Urogenital Microbiome Associations With Fertility Within Couples

Fertility is often evaluated in male and female partners considering IVF, creating a natural clinical context to evaluate microbiome effects on fertility status and IVF outcomes. At this couple level, individual female and male microbiome factors will interact across partners and contribute to couple fertility. The composition of urogenital microbiomes within couples generally have common taxa represented regardless of fertility status and IVF outcomes, with one report showing male and female partners contained similar levels of *G. vaginalis, L. crispatus*, and *Mycoplasma* species [129]. Another study found 56% of couples

shared predominant genera and 41% of shared species within the reproductive tract, including *G. vaginalis*, *L. iners*, *L. japonicus*, *L. jensenii*, and *L. agilis* [130]. *G. vaginalis* and *L. iners* are associated with BV in females and have been found within the male microbiome which may impact fertility status and IVF outcomes [131].

Although abundance of *Lactobacillus* spp. in the vaginal microbiome is linked with successful reproduction there is conflicting evidence as to whether male reproductive microbiomes are associated with IVF outcomes [129, 130, 131]. A study of couples with unexplained infertility undergoing intrauterine insemination (IUI) found a link between vaginal *L. crispatus* abundance, but not the seminal microbiome with IUI success rate [134]. Another study found that high *L. gasseri* in females and colonization of *L. jensenii* in the male partner were associated with successful IVF outcomes [130]. Conversely, one report found that *Lactobacillus* abundance in semen is associated with failed embryo implantation [129]. Although *Lactobacillus* in females is reliably correlated with successful IVF, its impact on male partner contribution to IVF success is less clear.

Collectively, studies of couples receiving IVF treatment have found that (1) there are similar microbiomes between partners, (2) abundance of *Lactobacillus* spp. within the female microbiome associates with greater likelihood of IVF success, and (3) the relationship of *Lactobacillus* spp. or other microbiome species in the male microbiome with IVF success and fertility remains unclear.

4.2 | Cross-Partner Microbiome Transmission Can Affect Genital Inflammation and Fertility

Evidence to support interactions, disruptions, and subsistence of microbiome populations between partners is reflected in reports from couple studies. Commensal strains in the male and female reproductive microbiomes along with sexual practices may also play a role in influencing the state and function of urogenital microbiomes and impact fertility via modification of one or both partner's microbiomes. *G. vaginalis* overgrowth in the vaginal microbiome is associated with leukocytospermia and genital inflammation within the partnered male. In seminal fluid, the association of *G. vaginalis* with sperm quality is debated, with some reports indicating suboptimal sperm parameters, others report no relationship, and some report *G. vaginalis* abundance is associated with healthy semen parameters [88, 132, 133, 134, 135].

Two organisms associated with seminal fluid quality and infertility that may be transmitted between couples are *Ureaplasma parvum* and *Ureaplasma urealyticum* [93, 136]. *Ureaplasma* in females are frequently isolated from the genital tract and thought to be commensal organisms, however they have recently been associated with increased presence of *G. vaginalis* and inflammatory mediators [137, 138]. In couples in which the male partner has inflammatory prostatitis it has been observed that their female partners have higher levels of *U. parvum* and increased vaginal microbiome diversity after intercourse [142]. However, there is more consensus on the detrimental association of *Ureaplasma* spp. with fertility in males compared to females. In males, both *U. urealyticum* and *U. parvum* are associated with suboptimal sperm quality [134, 136, 140, 141]. In females, the link to infertility of *Ureaplasma* spp. is less defined, with the role of *U. parvum* disputed and *U. urealyticum* associated with infertility if a coinfection is present [142, 143, 144].

BV is dysbiosis of the vaginal microbiome, with risk factors including unprotected sex and new or multiple sex partners, and is linked to inflammation of the female genital tract [148]. The male genital region can host many BV-associated microbes [94, 128, 146]. In infertile couples, seminal fluid may contain microbes implicated in BV [135]. There are also more incidents of BV with semen exposure in unprotected sex, which suggests that the interaction of the genital secretions or genital surfaces can facilitate the transmission of these bacteria. Though there are mixed reports on the efficacy of condom use in preventing BV [147, 148, 149], there is clear evidence that microbes can be transmitted and that microbiome composition is correlated across partners [150, 151, 152, 153, 154, 155]. In one report, female partner BV status could be predicted based on their male partner's microbiome composition [131]. Moreover, males with a female partner with BV exhibited a microbiome more similar to their partnered female than to a non-partnered female with BV [158].

Sexual practices also impact the transmission of microbes between partners with implications for fertility. Unprotected sex alters male and female urogenital microbiome regardless of being a first-lifetime or recurring sexual experience, with more sexual experience being correlated with greater microbiome diversity in both females and males [128, 156, 157, 158]. One report found non-monogamous males were more likely to have a BV-associated CST, though other reports dispute this [158, 159]. Non-monogamous females have a higher vaginal microbiome diversity index, with higher *Gardnerella* and *Prevotella* populations [163].

Finally, an anatomical factor that impacts microbe transmission across partners is male circumcision, with female partners of circumcised men experiencing fewer genital disruptions such as genital ulceration and trichomonas [161, 162]. Moreover, females with circumcised partners experience fewer cases of BV and their respective partners contain less BV-associated bacteria in the penile environment when compared to uncircumcised males [162]. In summary, microbial exchange occurs bidirectionally between partners, with multiple sex partners facilitating new interactions with unique environments, and fluctuations of the microbiome between partners can impact inflammation and fertility if microbiomes are unable to recover to their previous undisturbed state.

4.3 | Other Sexual Practices and Fertility

Urogenital microbiomes and microenvironments can be impacted by other sexual practices including oral-to-genitalia sex, anal sex, same-sex intercourse, and non-monogamy. Oral microbes may be transmitted between partners and may be associated with disruption of the vaginal flora and BV risk [162, 163]. Other types of transmission events have been reported; these include transfer of *Lactobacillus* spp. from the vaginal microbiome to male oral cavity and the development of recurrent gingivitis in a female partner after oral sex with a male partner with a history of chronic urethral infections [167]. These case

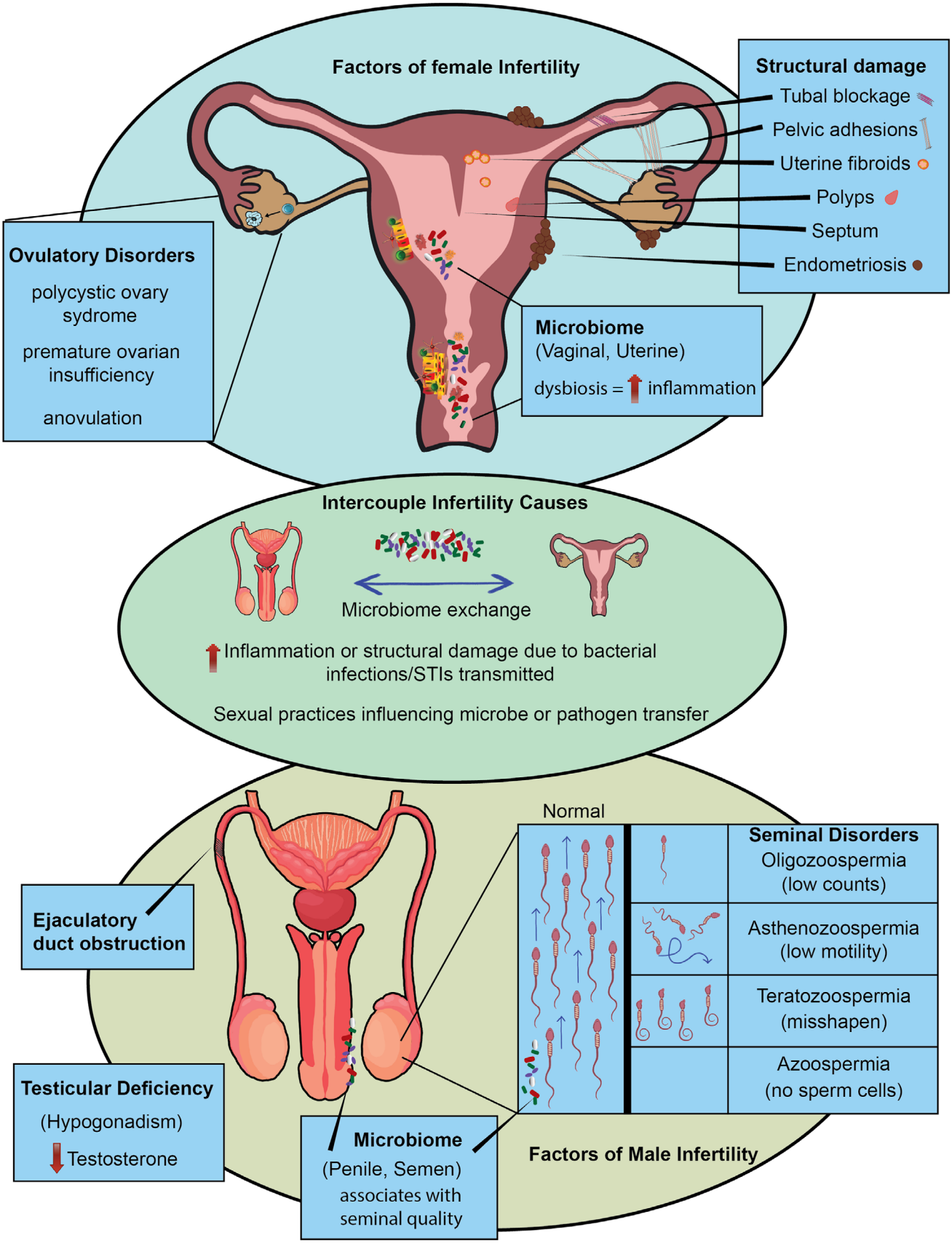

FIGURE 1 | Overview of female and male partner factors affecting fertility with overlapping areas between partners shown. Female fertility can be affected by structural damage to the female genital tract, ovulatory disorders, microbiome, and inflammatory dysregulation. Male partners are affected by numerous seminal disorders, obstructions, testicular deficiency, or the microbiome. Inter-couple factors include the exchange of microbial species or STIs that can lead to increased inflammation.

studies show that microbial transmission between reproductive microenvironments is possible and oral-to-genital microbe transmission needs to be further explored for implication in fertility.

Anal intercourse is another route by which microbe transmission may impact fertility by modifying the risk of BV [162, 165]. In one study, receptive oral-anal intercourse was only marginally associated with BV risk [169]. Conversely, there are reports that suggest the rectal microbiome may supportively maintain vaginal microbe populations [170]. Such examples demonstrate that oral and anal microbiomes can be transmitted between environments, but a gap remains in understanding how this transmission specifically impacts vaginal and seminal microbiomes and their role in fertility fitness.

The sexual practices of same-sex couples may impact their reproductive microbiomes and thus potential fertility and likelihood of success if considering IVF. As is the case with heterosexual couples, some reports indicate that women who have sex with women (WSW) that engage in oral sex have an association with risk of BV, though other reports do not find this risk [168, 169, 170]. In WSW there is a heightened risk of BV when the other partner has BV, but, unlike heterosexual intercourse, the increased BV risk in WSW may not be associated with the number of female sex partners in one's lifetime [168, 171, 172, 173, 174]. In one study, BV Nugent scores tended to be similar between WSW in stable long-term and shorter-term relationships [174]. The evidence is inconsistent as to whether WSW who engage in anal intercourse have an increased risk of BV [171, 174, 175]. Since BV is a risk factor for reduced fertility, understanding how sexual practices in WSW impact risk of BV is important for comprehending their effect on fertility.

In men who have sex with men (MSM), the microbiome literature tends to focus on STIs and not the impact on fertility. MSM that are undergoing ART procedures typically require the use of a donor ovum and a surrogate, likely making it difficult to understand microbial impacts on IVF outcomes, although direct impacts on semen parameters could still be studied. Ultimately, sexual practices in MSM and WSW populations may impact fertility via the increased risk of contracting infections associated with impaired fertility parameters, indicating that further study of the reproductive tract microbiomes in same-sex couples may be important for understanding how sexual practices impact fertility and likelihood of success of IVF.

5 | Summary and Future Directions

Numerous factors affect fertility in both men and women, including structural issues, inflammation, and the genital microbiome (Figure 1). Studies of the urogenital microbiome have identified associations between microbial composition, fertility, and success of IVF procedures. In both the vaginal and seminal microbiomes *Lactobacillus* has been associated with normal fertility, and vaginal *Lactobacillus* with increased IVF success rates. Data on the uterine microbiome and IVF success rates shows conflicting results, which could be related to the timing of sample collection. In addition, contamination of uterine specimens during sample collection remains a concern. Although there is evidence of the transfer of microbial species between partners, the impact of this on fertility and/or IVF success has not been studied. In addition, few studies have investigated potential mechanisms linking the genital microbiome to inflammation and the impact this has on fertility and IVF outcomes. Well-controlled studies on the impact of the urogenital microbiome on fertility and IVF success could identify new testing or treatment avenues for couples undergoing IVF procedures. Indeed, testing or treatment for microbial dysbiosis during infertility testing is limited to those presenting with clinical symptoms. As evidence from the vaginal microbiome demonstrates that even asymptomatic microbial dysbiosis can modulate inflammatory profiles, this could represent an important area of investigation to improve the success of IVF procedures.

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Ethics Statement

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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