Journal Of Research Technology & Engineering
www.jrte.org

Microbial and Immunological Influences on Reproductive Health: Unraveling the Effects of Microbial Exposures and Immune Interactions on Gametogenesis and Embryo Development (A Comprehensive Literature review)

*A.M.M.T.B Aththanayaka, B.S.W.M.T.B. Dayananda, H.D.U.N Hathurusinghe, S.P Amarasena

Department of Biomedical Sciences, Faculty of Health Sciences, CINEC campus, Malabe, Sri Lanka, CO 10115
*Corresponding Author Email: melanaththanayaka.official@gmail.com

Received:05 Apr 2024; Revised: 12 June 2024; Accepted: 22 June 2024; Available online: 10 July 2024

Abstract— This literature review examines the intricate balance between microbial exposures and immunological interactions in reproductive health, focusing on gametogenesis and embryo development. It discusses how different microbes affect reproductive tissues, their pathways of entry, and their specific impacts on spermatogenesis and oogenesis. The review also explores how microbes interfere with gamete development and early embryogenesis, emphasizing the role of the immune system, including cytokines and immune cells, in responding to microbial presence. It integrates case studies and clinical evidence to highlight the complex interactions between microbial exposures and immune responses, discussing their implications for fertility and pregnancy outcomes. Current interventions for managing microbial infections and immunomodulatory treatments are reviewed, identifying gaps in knowledge and future research opportunities. This comprehensive analysis aims to improve reproductive health by understanding and managing the interplay between microbial and immune factors.

Index Terms— Embryo Development, Gametogenesis, Immune Interactions, Microbial Exposures, Reproductive Health.

1 Introduction

The reproductive tract microbiome plays a crucial role in maintaining reproductive health and influencing gametogenesis and embryo development. Microbial communities in the male and female reproductive tracts are integral to fertility and fitness [1, 2, 3]. In particular, a healthy vaginal microbiota is associated with increased expression of defense and other immune factors that contribute to reproductive tract homeostasis. These microbial communities help maintain an environment conducive to reproductive success [3,4]. Microbial communities in the reproductive tracts of both males and females are essential for reproductive health. In females, the vaginal microbiota, predominantly composed of *Lactobacillus* species, creates an acidic environment that protects against pathogenic bacteria and infections [5]. This microbiota is linked to increased expression of defense and other immune factors, which are crucial for maintaining the homeostasis of the reproductive tract [3, 4, 6]. In males, the seminal microbiota has been shown to play a role in sperm health and motility, thereby contributing to overall fertility [7].

Dysbiosis, or an imbalance in the reproductive microbiome, can lead to significant reproductive health issues. In females, dysbiosis is associated with a range of clinical disorders, including bacterial vaginosis, pelvic inflammatory disease, and adverse pregnancy outcomes such as preterm birth [8, 9]. These conditions often involve the maternal immune system, which reacts to the abnormal microbiota composition, leading to inflammation and other pathological responses [3]. In males, dysbiosis in the seminal microbiota can affect sperm quality and function, thereby affecting fertility and the likelihood of successful conception [7, 10, 11]. The relationship between the reproductive tract microbiome and the host immune system is a key regulator of reproductive health. A healthy microbiota supports the expression of immune factors that protect the reproductive tract from infections and maintain a balanced immune response [12]. Dysbiosis, on the other hand, can trigger immune system dysregulation, leading to inflammation and increased susceptibility to infections. This delicate balance between the microbiome and the immune system is crucial for reproductive success, as it influences the environment in which gametogenesis and embryo development occur [3, 12, 13, 14].

Microbial exposures and immune interactions influence gametogenesis and embryo development through several mechanisms. For instance, the seminal microbiota can impact offspring epigenetics, potentially affecting gene expression patterns and immune system modulation [4, 15]. Furthermore, microbial metabolites produced in the reproductive tract microenvironment play significant roles in shaping local immunity and influencing reproductive outcomes. These metabolites can modulate the immune response, ensuring a conducive environment for embryo implantation and development [16, 17].

Understanding the complex interactions between microorganisms, metabolites, and the immune system in the reproductive tract is crucial for developing targeted therapies to improve reproductive health. Insights into how the microbiome and immune system interact can lead to new strategies for preventing and treating reproductive health issues caused by dysbiosis [16]. This knowledge is particularly important for addressing infertility, adverse pregnancy outcomes, and other reproductive disorders that have significant implications for individuals and public health [2, 16]. The reproductive tract microbiome and its interaction with the immune system are emerging as important drivers of reproductive success. These interactions have significant implications for gametogenesis, embryo development, and overall reproductive health [15, 16]. By unraveling these complex relationships, researchers can develop targeted therapies aimed at improving reproductive outcomes, thereby advancing reproductive medicine [2, 16] . Fig. 1 shows the interaction between microbial activities and immune influences on reproductive health. These interactions affect crucial stages, such as gametogenesis and embryo development, ultimately guiding the development of targeted therapies for reproductive health issues. Understanding these interactions is essential for addressing the challenges associated with reproductive health and improving the quality of life for those affected by reproductive disorders [2, 13, 16].

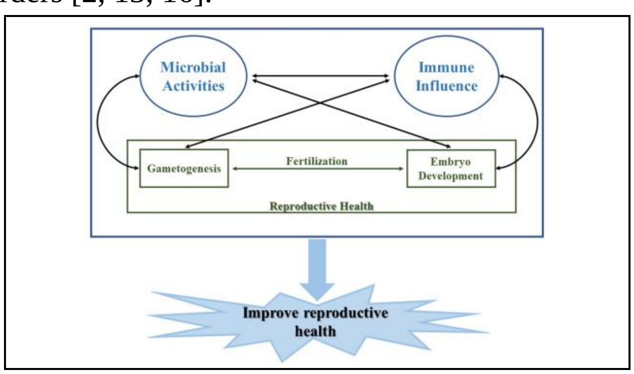

Fig. 1. Diagram illustrating the interplay between microbial activities and immune influences on reproductive health. The interactions between microbial activities and immune influences affect key stages of reproductive health, including gametogenesis and embryo development. These interactions ultimately guide the development of targeted therapies to address reproductive health issues.
Source; Author Made

2 MATERIAL AND METHODOLOGY

This literature review aimed to investigate the microbial and immunological influences on reproductive health, focusing on gametogenesis and embryo development. A systematic and comprehensive search was conducted in electronic databases, including PubMed, Google Scholar, Scopus, Web of Science, and EMBASE, covering publications up to June 2024. The following keywords and MeSH terms were utilized: "reproductive health," "microbial exposures," "immune interactions," "gametogenesis," "spermatogenesis," "oogenesis," "embryo development," and "cytokines." Boolean operators (AND, OR) were employed to refine the search and ensure the capture of relevant articles addressing the interplay between microbial exposures, immune responses, and reproductive processes. The inclusion criteria for the studies were peer-reviewed articles published in English, original research studies focusing on the effects of microbial exposures on reproductive tissues, gametogenesis, or embryo development, and studies examining immunological responses within reproductive tissues in the context of microbial presence. Both human and animal studies were included to provide a comprehensive understanding of the topic. Exclusion criteria included studies not directly related to reproductive health or microbial and immunological interactions, non-original research articles such as reviews, editorials, and commentaries, and studies lacking sufficient methodological details or relevant results. The selected studies were critically appraised to ensure the quality and relevance of the gathered literature. Data extraction focused on the types of microbes affecting reproductive health, pathways of microbial entry and colonization, immune responses to microbial presence, and the impact of these factors on gametogenesis and embryo development. Additionally, case studies and clinical evidence were analyzed to provide practical insights into the real-world implications of these interactions. This rigorous methodological approach ensured a comprehensive understanding of the current state of knowledge and identified areas requiring further research, contributing to the advancement of reproductive health through better management of microbial and immunological influences.

3 MICROBIAL INFLUENCES ON REPRODUCTIVE TISSUES

The reproductive tract microbiome, consisting of diverse microbial communities including bacteria, viruses, fungi, and protozoa, plays a pivotal role in maintaining reproductive health and influencing fertility. Commensal microbes, particularly *Lactobacillus species*, are vital in promoting a healthy reproductive environment by producing antimicrobial compounds, competing with pathogens, and modulating the immune response [13, 18]. These beneficial microbial communities in the male and female reproductive tracts contribute significantly to sperm health, embryo implantation, and overall reproductive success [13, 2]. At the cellular level, microbes can interact with reproductive tissues, affecting processes such as gametogenesis (spermatogenesis and oogenesis) and embryo development and implantation. Additionally, microbial metabolites produced in the reproductive tract microenvironment are crucial in shaping local immunity and influencing reproductive outcomes [13, 19, 20]. These metabolites can modulate the immune response, ensuring an environment conducive to successful reproduction [16].

The interaction between resident microbes in the reproductive tract and the host immune system is essential in maintaining a balanced immune environment that supports reproductive success. Dysbiosis, or an imbalance in the microbiome, can lead to immune system dysregulation, resulting in inflammation and increased susceptibility to infections [21, 22]. This imbalance can disrupt the delicate equilibrium necessary for optimal reproductive function. Microbial metabolites interact with immune cells in reproductive tissues, emphasizing the need for a healthy microbiome to sustain reproductive health [19, 20]. Moreover, Microbial communities in the reproductive tract also play a role in hormone regulation, which is critical for reproductive functions. Changes in the composition of the microbiome have been linked to alterations in levels of hormones such as estrogen and progesterone [23, 24]. These hormones are essential for processes like gametogenesis, embryo development, and the maintenance of a successful pregnancy [24, 25]. An imbalanced microbiome can thus have profound effects on reproductive hormone levels, potentially leading to reproductive health issues.

3.1 Types of Microbes Affecting Reproductive Health.

The reproductive health landscape is significantly influenced by various types of microbes, such as Beneficial microbes, Pathogenic microbes, and Opportunistic pathogens. Beneficial microbes, such as *Lactobacillus* species, are the predominant commensal bacteria in the female reproductive tract, where they contribute to a healthy vaginal environment by producing antimicrobial compounds, maintaining an acidic pH, and modulating the immune response, thereby protecting against pathogenic microorganisms [26, 27].

In the male reproductive system, commensal bacteria are equally crucial in maintaining a balanced microbiome and promoting sperm health [28, 29]. Conversely, pathogenic microbes can cause infections leading to adverse reproductive outcomes. Bacterial pathogens like *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are known to cause pelvic inflammatory disease, infertility, and ectopic pregnancy [30]. Viral pathogens, such as Human Papillomavirus (HPV) and Herpes Simplex Virus (HSV), have been linked to cervical cancer and genital lesions, respectively [31, 32]. Additionally, fungal pathogens like *Candida* species can cause vaginal candidiasis, and protozoan pathogens such as *Trichomonas vaginalis* are responsible for trichomoniasis [33, 34]. Opportunistic pathogens, such as those associated with bacterial vaginosis, can become pathogenic under certain conditions. Bacterial vaginosis, characterized by an overgrowth of anaerobic bacteria including *Gardnerella vaginalis*, *Atopobium vaginae*, and *Prevotella* species, leads to an imbalance in the vaginal microbiome and has been linked to an increased risk of preterm birth, pelvic inflammatory disease, and HIV acquisition [35, 36, 37, 38]. As discussed above, the microbial composition of the female and male reproductive systems is crucial for human health, with different microbial compositions potentially leading to a variety of complications. Fig. 2 illustrates the microbial composition of both the female (Fig. 2a) and male (Fig. 2b) reproductive systems. Finally, microbial dysbiosis refers to a disruption in the normal microbial balance, which can significantly impact reproductive health. Factors such as antibiotic use, hormonal changes, and lifestyle factors can cause dysbiosis, leading to increased susceptibility to infections, infertility, and adverse pregnancy outcomes, including preterm birth and stillbirth [23, 39, 40, 41].

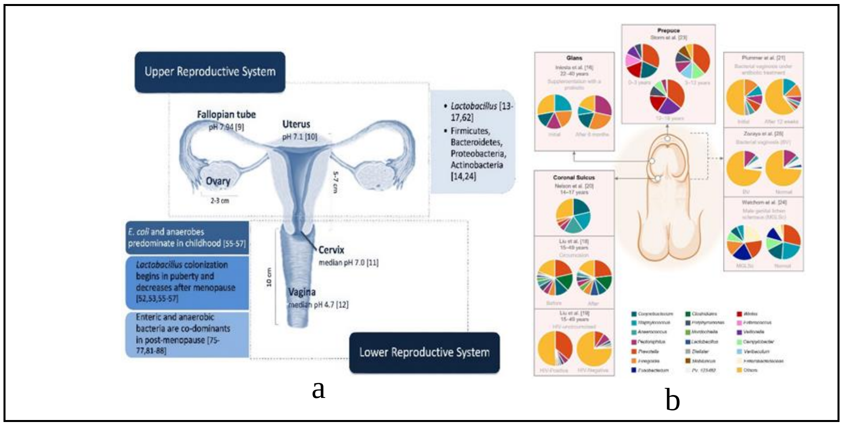

Fig. 2. Microbial composition of the human female and male reproductive tract. a: depicts the key microbes influencing female reproductive health. *Lactobacillus* reigns supreme, keeping the environment acidic and unfriendly to harmful invaders. *Enterobacteria* and *Actinobacteria* represent some troublemakers, while a balanced mix of bacteria thrives in the uterus. Watch out for *E. coli* and certain anaerobes - their overgrowth can lead to problems [42], b: The figure shows the diverse microbial communities present in different parts of the male genital tract, including the glans, prepuce, and coronal sulcus, under various conditions and age groups. It highlights how these microbial compositions change with age, probiotic supplementation, circumcision, HIV status, antibiotic treatment for bacterial vaginosis, and in conditions like male genital lichen sclerosus. Each pie chart represents the relative abundance of different bacterial genera, providing insights into how these factors influence the genital microbiota [43].
Sources; [42,43]

3.2 Pathways of Microbial Entry and Colonization in Reproductive Tissues

Microbes can infiltrate and colonize reproductive tissues through several pathways, each with significant implications for reproductive health. Ascending infections are a primary route, where microbes from the lower genital tract ascend through the cervical canal into the uterus and fallopian tubes [24, 44]. This pathway is particularly common for sexually transmitted infections like chlamydia and gonorrhea, which can cause pelvic inflammatory disease and infertility [30]. Another pathway is hematogenous spread, where microbes enter reproductive tissues through the bloodstream. Systemic infections, such as those caused by *Listeria monocytogenes* or *Treponema pallidum* (syphilis), can disseminate and impact reproductive organs [45,46]. Sexual transmission also plays a critical role, with unprotected intercourse facilitating the direct transfer of pathogens to reproductive tissues [31, 32]. Risk factors include multiple sexual partners and lack of barrier contraception, which heighten the chance of acquiring sexually transmitted infections. Additionally, maternal-fetal transmission can occur during pregnancy, where microbes like group B *Streptococcus* or Zika virus are passed from mother to fetus, potentially affecting fetal development and pregnancy outcomes [47, 48]. Lastly, medical procedures, such as hysteroscopy or intrauterine device (IUD) placement, can inadvertently introduce microbes into the reproductive tract. Ensuring proper sterilization and infection control measures during such interventions is crucial to prevent iatrogenic infections [49,50].

As Fig. 3, Factors such as lifestyle choices, geographic and social conditions, racial and genetic predispositions, and reproductive age all play critical roles in shaping the microbial environment of the female reproductive system. Additionally, the microbiota of a partner's semen also contributes to this complex interplay. These factors collectively influence the pathways of microbial entry and colonization in reproductive tissues, ultimately affecting female health, reproductive health, couples' health, and even offspring's health [42].

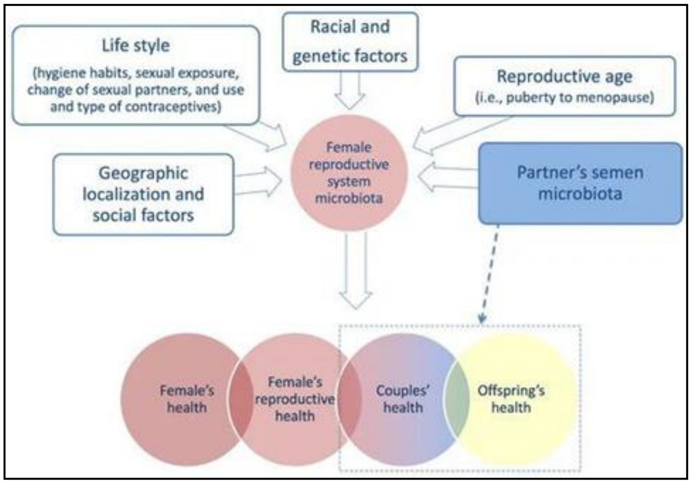

Fig. 3. The various factors influencing the female reproductive system microbiota and their subsequent impact on health outcomes, including female health, reproductive health, couples' health, and offspring's health.
Source; [42]

This visual representation underscores the importance of understanding these diverse influences to improve reproductive health outcomes.

4 MICROBIAL EFFECTS ON GAMETOGENESIS

Microbes, including bacteria, viruses, and fungi, can have significant impacts on various biological processes in the human body. Understanding the influence of microbes on gametogenesis is crucial for addressing issues related to human fertility and reproductive health. Gametogenesis is a fundamental, highly regulated developmental process of gametes, eggs (oocytes) and sperms (spermatozoa) [51,52,53]. Pathogenic microbes have been extensively studied for their ability to disrupt spermatogenesis and oogenesis, leading to impaired gamete development and function. According to previous research findings it has been found out that microbiota have effects on male and female reproductive systems. These effects may be beneficial or harmful and also the effect may occur directly or indirectly [54].

4.1. Influence on Spermatogenesis

Micro-organisms related to male reproductive organs can be mutualistic or harmful, influencing sperm quality and production. Mutualistic microbes, such as *Lactobacillus*, contribute to the formation of healthy sperm during spermatogenesis. Conversely, harmful microbes, including *Pseudomonas, Prevotella*, and *Haemophilus*, can directly impact sperm production or cause indirect damage through inflammation and infections like Male Accessory Gland Infections (MAGI). [54, 55, 56,]. MAGI, which includes conditions such as prostatitis and epididymitis, can severely impair spermatogenesis and sperm function by releasing inflammatory mediators and reactive oxygen species (ROS) [56, 57, 58, 59].

In addition, microbiota consist within the sperm fluid greatly affect on male infertility. It is caused by the low sperm production and also the presence of *Pseudomonas* and *Prevotella* show pathological effects on producing a low quality of sperms. Moreover, it has been found out that there is a strong correlation between high concentration of *Anaerocccus* and the sperm quality [54]. Notably, bacteria such as *Chlamydia trachomatis, Neisseria gonorrhoeae, and Escherichia coli* can directly impair various stages of spermatogenesis by inducing DNA fragmentation and cell membrane damage. Moreover, gut microbiota, including *Lactobacillus spp. and Bifidobacterium spp*., influence male reproductive health by affecting hormone synthesis and metabolism. Chronic microbial infections can lead to long-term infertility or subfertility and may result in epigenetic changes in sperm, potentially impacting future generations.

Understanding these microbial effects is crucial for developing strategies to mitigate their negative impacts on male fertility [60, 61, 62].

4.2. Impact on Oogenesis.

The female reproductive tract microbiome plays a crucial role in supporting oogenesis. However, microbial dysbiosis in the reproductive tract microbiome, can significantly negatively impact this critical process [63, 64, 65]. Studies have shown that certain pathogenic microbes can directly interfere with oocyte development and quality. For example, research has found that lower pH conditions simulating microbial imbalances can reduce oocyte size and fecundity in marine organisms like the coral *Primnoa pacifica*. This suggests that disruptions to the delicate vaginal and uterine microbiome can have detrimental effects on oocyte maturation and competence. Indirectly, microbial infections can also impact oogenesis by disrupting the hormonal regulation of this process. Infections can trigger an immune response that impairs ovarian function and hormone production, leading to impaired oocyte development [64, 65]. Chronic microbial infections in the female reproductive tract have been linked to infertility or subfertility and may even result in epigenetic changes in oocytes that can be passed on to offspring. Understanding the mechanisms by which microbes can interfere with oogenesis is crucial for addressing issues related to female fertility and reproductive health. Maintaining a healthy reproductive tract microbiome is essential for supporting normal oocyte development and ensuring the best possible outcomes for assisted reproductive technologies and natural conception [63, 64, 65, 66].

4.3 Mechanism of microbial interference with gamete development.

The mechanisms by which microbes interfere with gamete development are complex and multifaceted, impacting gametogenesis through molecular, cellular, and immune response pathways [1, 67, 68]. At the molecular level, certain microbes release toxins or metabolites that disrupt essential cellular processes, such as bacterial infections with Chlamydia trachomatis, Neisseria gonorrhoeae, and Escherichia coli, which induce DNA fragmentation and cell membrane damage in sperm [1, 67]. Microbes can also alter the cellular environment of gametes, causing oxidative stress that leads to DNA damage and reduced developmental competence in both sperm and oocytes [1, 67, 68]. Additionally, the body's immune response to microbial infections can mediate inflammation, impairing sperm production and oocyte maturation, and chronic infections can disrupt hormonal balance and cause long-term reproductive organ damage. Environmental factors and lifestyle choices, such as diet and hygiene, further influence microbial effects on gametogenesis. Understanding these mechanisms is crucial for developing targeted interventions to prevent and treat microbial-induced infertility, improving reproductive outcomes for affected individuals [1, 67, 68, 69].

5 Microbial Impacts on Embryo Development

The development of embryos is a complex process influenced by various factors, including microbial exposure. Microbes can interact with the reproductive system at multiple stages, potentially affecting embryo quality and development. Understanding these interactions is crucial for improving reproductive health outcomes and mitigating risks associated with microbial infections.

5.1 Microbial Effects on Early Embryogenesis

Microbial exposure during early embryogenesis can significantly influence the developmental trajectory of embryos. Pathogenic bacteria, viruses, and protozoa infections have been associated with pregnancy complications such as miscarriage and preterm birth. These microbial pathogens can directly infect the placenta or amniotic fluid, leading to inflammatory responses that may compromise the embryo's development and viability. For instance, bacterial vaginosis has been linked to increased risks of preterm birth due to ascending infections that reach the uterus and amniotic cavity [70].

Maternal gut microbiota can impact the intrauterine environment, affecting embryonic development through immune modulation and metabolic changes. The maternal microbiome can produce metabolites that cross the placental barrier, influencing fetal growth and immune system development. Furthermore, the gut microbiota's role in maintaining maternal immune homeostasis is critical for preventing adverse pregnancy outcomes. Disruptions in maternal gut microbiota, such as dysbiosis, can lead to an imbalance in immune responses, which may result in conditions like preeclampsia and gestational diabetes, further affecting embryonic development [70, 71].

While these pathways are previously identified to influence microbes during post-embryonic stages, recent evidence reveals a significant role of the external microbiome in communicating with the developing embryo. Studies have shown that the microbiome of the reproductive tract, including the vaginal and uterine microbiota, can directly interact with the embryo and modulate its developmental processes. This interaction can occur through the release of microbial metabolites and immune signaling molecules that influence gene expression and cell differentiation in the embryo. Understanding these complex interactions between the maternal microbiome and the developing embryo opens new avenues for therapeutic interventions aimed at improving pregnancy outcomes and embryonic health. Table 1 provides a clear and organized view of the different microbial influences on early embryogenesis, along with their key effects.

Table 1. Summary of Microbial Effects on Early Embryogenesis

Aspect	Description	Key Effects on Embryogenesis	Sources
Maternal Gut Microbiota	Microbiota in the maternal gut that produce metabolites and modulate immune responses.	Influences fetal growth, Immune system development, Maintains maternal immune homeostasis	[73]
Reproductive Tract Microbiota	Microbiota in the vaginal and uterine environments that interact directly with the embryo	Releases microbial metabolites, Modulates gene expression, Affects cell differentiation	[63,74]
Pathogenic Infections	Infections by bacteria, viruses, and protozoa that can affect the placenta and amniotic fluid.	Induces inflammatory responses, Increases risk of miscarriage and preterm birth	[73,75]
Microbial Metabolites	Compounds produced by microbiota that can cross the placental barrier and affect the	Alters metabolic pathways, Influences immune responses	[73]

	embryo.		
Immune Modulation	Microbiota-mediated regulation of the maternal immune system.	Prevents adverse pregnancy outcomes, Affects immune development of the embryo	[73]
Inflammatory Responses	Body's reaction to pathogenic infections that can impact embryonic development.	Compromises embryo development and viability	[73,75]
Direct Microbial Interaction	Interaction between reproductive tract microbiota and the embryo through signaling molecules.	Modulates developmental processes	[63,73]
Metabolic Changes	Changes in maternal metabolism due to microbiota that affect the intrauterine environment.	Impacts embryonic growth and health	[73]

5.2 Long-term Consequences of Microbial Exposure on Embryo Quality

Microbial exposure during early human development can have long-term consequences on embryo quality and offspring health. Several studies have found evidence of live bacteria, including *Staphylococcus* and *Lactobacillus* species, in fetal organs as early as the second trimester of pregnancy. This microbial exposure appears to prime the fetal immune system, activating memory T cells in fetal lymph nodes [76]. microbial exposure impacts embryo quality and long-term health outcomes through various mechanisms. The maternal gut and skin microbiome, along with the placental microbiome, influence the developing embryo by modulating nutrient transfer and the immune environment through microbial metabolites, cytokines, and non-coding RNAs. These interactions impact neurodevelopment, metabolic pathways, and immune function, potentially leading to conditions such as neurodevelopmental delays, metabolic disorders, and immune dysregulation. The fig 4 highlights the critical role of the gut-brain axis in mediating these effects, emphasizing the importance of maternal microbial health for the offspring's long-term well-being [71,73,79].

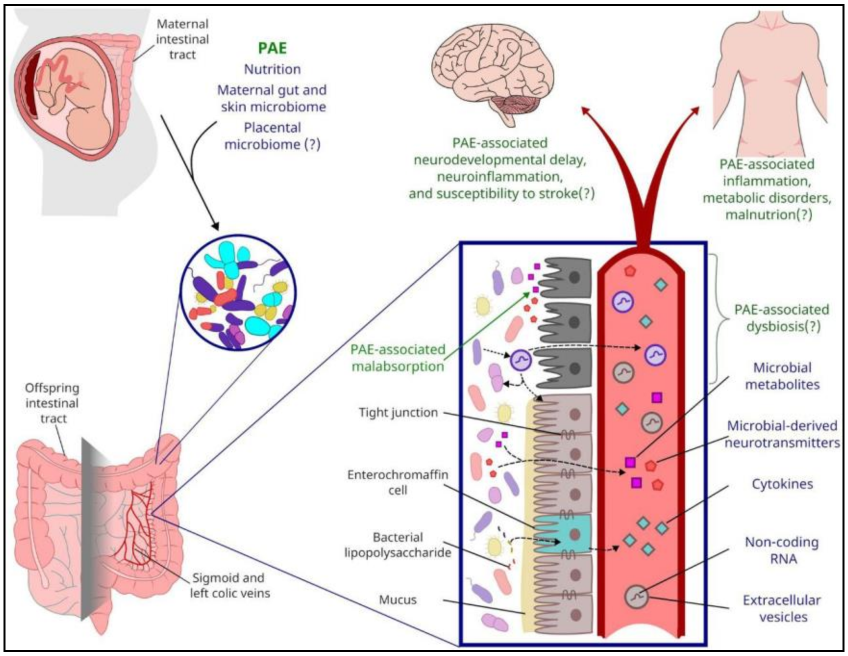

Fig. 4. Long-term Consequences of Microbial Exposure on Embryo Quality; This figure depicts how maternal microbial exposure affects embryo quality and long-term health outcomes. The maternal gut and skin microbiome, along with the placental microbiome, influence the developing embryo by modulating nutrient transfer and immune environment through microbial metabolites, cytokines, and non-coding RNAs. These interactions impact neurodevelopment, metabolic pathways, and immune function, potentially leading to conditions such as neurodevelopmental delays, metabolic disorders, and immune dysregulation. The figure highlights the critical role of the gut-brain axis in mediating these effects, emphasizing the importance of maternal microbial health for the offspring's long-term well-being.
Source; [79]

Chronic infections and microbial dysbiosis can lead to sustained inflammation, oxidative stress, and epigenetic changes that impair embryo development [71,77]. Prenatal exposure to pathogens like Zika virus and cytomegalovirus has been linked to severe developmental defects and neurological issues in offspring [71]. However, the specific long-term effects of microbial contamination on embryo quality are not fully understood. One study found that contamination of embryos by *Staphylococcus pasteuri* during IVF did not significantly impact short-term laboratory or pregnancy outcomes [78]. More research is needed to elucidate the mechanisms by which microbial exposures during early development can influence embryo quality and offspring health in the long run.

6. Immunological Interactions in Reproductive Tissues

Reproductive tissues harbor a unique immunological environment essential for balancing protection against pathogens and tolerance towards allogeneic antigens, such as sperm and the fetus. The immune system in these tissues involves a complex interplay of various immune cells and cytokines that are critical for processes like gametogenesis, implantation, and pregnancy maintenance. Understanding the immune responses in reproductive tissues helps elucidate their roles in both supporting normal reproductive functions and defending against microbial threats, ensuring successful fertilization, embryo development, and pregnancy outcomes.

6.1 Overview of Immune System in Reproductive Health

The immune system plays a crucial role in maintaining reproductive health by balancing protection against pathogens and tolerance towards allogeneic antigens, such as sperm and the fetus [80,81]. In reproductive tissues, the immune system comprises various cells, including macrophages, dendritic cells, natural killer cells, and T cells, which work together to create a unique immunological environment. This environment is essential for processes such as implantation, placentation, and the maintenance of pregnancy [82]. The immune system's role extends to gametogenesis, where it helps in the removal of defective gametes and supports the proper development of sperm and oocytes [81].

The adaptive and innate immune systems work together to provide protection throughout the female reproductive tract [80,81]. Innate immunity uses non-specific mechanisms to rapidly respond to pathogens, while adaptive immunity provides gradual, specific responses through antibodies and T cells [80]. Immune cells in the reproductive tract, such as lymphocytes and natural killer cells, interact with reproductive cells to promote tolerance or activation. Dysregulation of this delicate balance can lead to autoimmune disorders affecting fertility, such as endometriosis and pelvic inflammatory disease [80,82]. The immune system in the reproductive tract is also influenced by sex hormones, which prepare the tract for successful fertilization, implantation, and pregnancy [80,81]. Changes in the immune system during lactation and infections can further impact reproductive health [80].

6.2 Immune Responses to Microbial Presence in Reproductive Tissues

The presence of microbes in reproductive tissues can trigger a range of immune responses aimed at protecting against infections. These responses include the activation of pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) on immune and epithelial cells, leading to the production of antimicrobial peptides, cytokines, and chemokines. Table 2 shows overall key Immune Responses to Microbial Presence in Reproductive Tissues.

Table 2. Key Immune Responses to Microbial Presence in Reproductive Tissues

Immune Response	Trigger	Mechanism	Outcome	Sources
Activation of PRRs	Microbial patterns	Recognition by TLRs on immune/epithelial cells	Initiates downstream signaling	[83,84]
Production of Antimicrobial Peptides	PRR activation	Synthesis by epithelial cells	Direct pathogen killing	[83,85]
Cytokine and Chemokine Release	PRR activation	Secretion by immune and epithelial cells	Recruitment of immune cells	[83,84,85]
Inflammation	Cytokine signaling	Immune cell activation	Pathogen clearance	[84,85]
Tissue Damage	Chronic immune response	Persistent inflammation	Impaired reproductive functions	[86]
Immune Cell	Chemokine	Migration of	Pathogen	[83,84]

Recruitment	signaling	immune cells to infection site	elimination	

The table summarizes the key immune responses triggered by the presence of microbes in reproductive tissues. It outlines the specific immune responses, their triggers, mechanisms, and outcomes, highlighting the balance between microbial defense and maintaining reproductive tissue integrity.

So, These molecules help to recruit immune cells to the site of infection and initiate inflammation to clear the pathogens. However, an excessive or chronic immune response can lead to tissue damage, affecting reproductive functions such as fertilization, implantation, and embryonic development. The delicate balance between effective microbial defense and maintaining tissue integrity is critical for reproductive success.

6.3 Role of Cytokines and Immune Cells in Gametogenesis and Embryo Development

Cytokines and immune cells play a crucial role in regulating gametogenesis and embryo development. Cytokines such as interleukins (ILs), interferons (IFNs), and tumor necrosis factors (TNFs) help maintain the delicate immune environment within the reproductive system [87,88,89]. During gametogenesis, cytokines influence the maturation of gametes and the elimination of defective ones. For example, IL-1α, TGF-β3, and TNF-α regulate the tight junctions between Sertoli cells and germ cells in the seminiferous epithelium, which is crucial for spermatogenesis[73]. Immune cells like macrophages and natural killer (NK) cells also contribute to the regulation of gametogenesis by providing necessary growth factors and cytokines[87,89]. The immune system ensures a conducive environment for implantation and embryo development. Macrophages, NK cells, and regulatory T cells (Tregs) help modulate the immune response to avoid rejection of the semi-allogeneic embryo while promoting tissue remodeling and placental development[89,90]. The interplay between immune cells and cytokines is vital for successful reproduction and healthy embryo development. For example, IL-6 and leukemia inhibitory factor (LIF) are secreted by both the embryo and uterine endometrium, forming part of an ongoing and reciprocating dialogue that is essential for embryo attachment and implantation. Mast cells and macrophages populate the uterine endometrium during embryo development and are involved in achieving the correct balance between inflammatory and anti-inflammatory reactions at the uterus [89]. In summary, cytokines and immune cells are integral to gametogenesis and embryo development, ensuring the maturation of gametes, a conducive environment for implantation, and healthy embryo development. The delicate balance between immune cells and cytokines is crucial for successful reproduction.

7. COMBINED EFFECTS OF MICROBIAL EXPOSURES AND IMMUNE RESPONSES.

The interplay between microbial exposures and the host immune system is vital for sustaining a healthy reproductive environment. Microbes can directly interact with immune cells and signaling pathways, while their metabolic products also influence the immune system [21, 22]. Microbial ligands, such as lipopolysaccharides (LPS) or peptidoglycans bind to host receptors like Toll-like receptors (TLRs) on immune cells. This binding triggers the production of inflammatory factors, including cytokines and chemokines, which recruit and activate additional immune cells to the site of infection [91,92]. Microbes can also stimulate the release of antimicrobial peptides and proteins by immune cells, aiding in pathogen elimination [93,94]. Additionally, microbial metabolites such as short-chain fatty acids (SCFAs) and indole derivatives play a significant role in modulating immunity in the reproductive tract. These metabolites influence the differentiation and function of immune cells, such as regulatory T cells (Tregs) and innate lymphoid cells (ILCs), and can alter the expression of genes involved in immune responses and inflammation [95,96].

An imbalance in the reproductive microbiome can trigger immune system dysregulation. Such as inflammations and infections. Dysbiosis can be caused by factors such as antibiotic use, hormonal changes, and lifestyle factors. When the normal microbial balance is disrupted, it can lead to an overgrowth of pathogenic microbes and a shift in the immune response. The consequences of dysbiosis-induced immune dysregulation include chronic inflammation, tissue damage, and an increased risk of reproductive tract infections. Thus, the delicate balance between the microbiome and the immune system is crucial for maintaining a healthy reproductive environment and supporting successful reproduction [21, 23, 40].

7.1 Synergistic and Antagonistic Interactions.

Synergistic and antagonistic interactions between microbes and the immune system play pivotal roles in reproductive health. Positive, or synergistic, interactions are evident in the relationship between commensal microbes like Lactobacillus species and the immune system. These beneficial microbes enhance the immune response by producing antimicrobial compounds, competing with pathogens, and modulating immune activity to maintain a healthy reproductive environment [27]. Studies indicate that a stable and diverse reproductive tract microbiome, particularly one dominated by Lactobacillus, is linked to improved fertility, successful embryo implantation, and reduced risks of adverse pregnancy outcomes. For instance, women with a Lactobacillus-dominated vaginal microbiome have shown higher success rates in in vitro fertilization (IVF) compared to those with a more diverse microbiome. It underscores the importance of these synergistic interactions [13].

Conversely, antagonistic interactions between pathogenic microbes and the immune system can lead to dysbiosis, characterized by an imbalance in the reproductive microbiome. Dysbiosis triggers immune system dysregulation, causing inflammation and increasing susceptibility to infections [22, 24]. This disruption can result in serious reproductive complications. Such as, bacterial vaginosis, chlamydia, and candidiasis. These complications can ascend to the upper reproductive tract, leading to pelvic inflammatory disease, infertility, and adverse pregnancy outcomes. For example, women with bacterial vaginosis have been found to have a higher risk of preterm birth compared to those with a healthy vaginal microbiome, highlighting the detrimental impact of antagonistic interactions [18, 97].

7.2 Mechanisms of Immune Modulation by Microbes

Microbes in the reproductive system modulate immune responses through various mechanisms, significantly affecting reproductive health. Microbial metabolites such as short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, play a crucial role in immune modulation [19, 20, 95]. These SCFAs interact with host immune cells by binding to G-protein coupled receptors (GPCRs). It regulate inflammatory responses and promote the differentiation of regulatory T cells (Tregs). Additionally, vitamins produced by microbes, such as vitamin B9 (folate) and vitamin K, are essential for immune function and homeostasis. These metabolites influence both local and systemic immunity, thereby affecting overall reproductive health and function [95,98,99].

Direct interactions between microbes and immune cells in the reproductive tract also play a significant role.

Microbes engage with immune cells like dendritic cells and macrophages through pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) [16, 100]. These interactions activate signaling cascades that lead to the production of inflammatory mediators, chemokines, and antimicrobial peptides. The balance between pro-inflammatory and anti-inflammatory outcomes from these interactions is vital for maintaining reproductive homeostasis [16, 18].

Regulation of inflammatory responses by microbes and their metabolites is another critical aspect of immune modulation in the reproductive tract. Dysbiosis can lead to chronic inflammation, endometriosis, polycystic ovary syndrome, and recurrent pregnancy loss. Thus, maintaining a balance between pro-inflammatory and anti-inflammatory responses is essential for preserving reproductive health and function [101,102].

Moreover, microbes in the reproductive tract can influence hormone levels and signaling pathways crucial for reproductive processes like ovulation, embryo implantation, and pregnancy maintenance. Alterations in the reproductive microbiome composition can affect estrogen, progesterone, and other reproductive hormones, leading to disruptions in ovarian function, menstrual cycle irregularities, and impaired fertility. These multifaceted interactions underscore the complex and significant role of microbes in modulating immune responses and maintaining reproductive health [95,101,102].

8. Therapeutic and Preventative Approaches

In addressing microbial infections within reproductive tissues, current interventions primarily focus on antimicrobial therapies tailored to specific pathogens encountered in these environments. Effective management often requires a targeted approach, considering the delicate balance needed to preserve fertility and mitigate potential adverse outcomes on embryonic development. These interventions encompass a spectrum from antibiotics to antiviral agents, aiming to eradicate pathogens while minimizing collateral damage to host tissues. Additionally, supportive therapies such as probiotics and local antimicrobial applications show promise in restoring microbial balance and bolstering local immune responses.

8.1 Current Interventions for Managing Microbial Infections in Reproductive Tissues

Current interventions for managing microbial infections in reproductive tissues involve a combination of antibiotic therapy, Antifungal therapies, Antifungal, Vaccines, Immunomodulators, Photodynamic therapy, Nanotechnology based approaches, herbal compounds, Bio film disruption, surgical interventions, supportive care, and addressing complications. Preoperative patient assessment, antimicrobial prophylaxis, and aseptic techniques are crucial for preventing postoperative infections. Intraoperative measures include infection control and instrument sterilization, while postoperative care involves wound management and early infection detection [103].

Probiotics have shown regulatory effects on the female reproductive tract, contributing to homeostasis and influencing the health of offspring. Probiotic treatments have been proposed as a novel strategy to improve reproductive performance and alleviate associated reproductive diseases in both males and females, as well as to improve the health of offspring. Probiotics may exert beneficial effects on reproduction through the modulation of microbiota composition, regulation of metabolism, promotion of the epithelial barrier, and improvement of immune function [1]. Table 3 interpret the overview of Advanced Interventions for Managing Microbial Infections in Reproductive Tissues.

Table 3. Overview of Advanced Interventions for Managing Microbial Infections in Reproductive Tissues

Intervention	Mechanism of Action	Applications	Benefits	Limitations	Recent Advancements
Antibiotics	Inhibition of bacterial cell wall synthesis, protein synthesis, nucleic acid synthesis, or metabolic pathways	Treatment of bacterial infections in reproductive tissues	Broad-spectrum activity, well-studied efficacy, quick action	Antibiotic resistance, disruption of normal microbiota, side effects	Development of new antibiotics targeting resistant strains, nanoparticle-based delivery systems, combination therapies
Antifungal Agents	Disruption of fungal cell membrane integrity or inhibition of ergosterol synthesis	Management of fungal infections like candidiasis in reproductive tissues	Effective against a wide range of fungi, relatively safe	Limited efficacy against resistant strains, potential toxicity with prolonged use	Introduction of novel antifungal compounds, improved formulations for better tissue penetration, antifungal peptides
Probiotics	Competitive exclusion, production of antimicrobial substances, modulation of immune responses	Prevention and treatment of bacterial vaginosis, yeast infections	Restoration of normal microbiota, enhancement of local immunity, minimal side effects	Variable efficacy, strain-specific effects, regulatory challenges	Engineered probiotics for enhanced antimicrobial activity, use of synbiotics (probiotics prebiotics), targeted delivery systems
Antiviral Agents	Inhibition of viral replication, entry, or assembly	Treatment of viral infections like herpes simplex virus (HSV)	High specificity, potential for prophylactic use	Development of resistance, limited spectrum, potential for systemic side effects	Development of broad-spectrum antivirals, CRISPR-based antiviral strategies, topical antiviral formulations
Vaccines	Induction of specific	Prevention of sexually	Long-term protection,	Vaccine hesitancy,	Development of next-generation

	immune responses against pathogens	transmitted infections (STIs)	reduction in infection rates, herd immunity benefits	need for booster doses, cold chain requirements	vaccines (e.g., mRNA vaccines), thermostable vaccines, single-dose formulations
Immunomodulators	Modulation of immune system to enhance pathogen clearance or reduce inflammation	Adjunctive therapy for chronic infections, enhancement of vaccine efficacy	Targeted immune responses, potential to reduce antibiotic use	Risk of autoimmune reactions, variable responses in different individuals	Novel immunomodulatory agents, use of cytokine therapies, personalized immunotherapy approaches
Photodynamic Therapy (PDT)	Activation of photosensitizers by light to produce reactive oxygen species that kill pathogens	Treatment of localized infections in reproductive tissues	Minimally invasive, selective targeting of infected tissues, reduced resistance development	Limited penetration depth of light, need for specific equipment	Development of new photosensitizers with better tissue penetration, combination with other therapies for enhanced efficacy
Nanotechnology-Based Approaches	Use of nanoparticles to deliver antimicrobial agents or directly kill pathogens	Targeted delivery of antibiotics, antivirals, antifungals	Enhanced drug delivery, reduced systemic toxicity, potential to overcome resistance mechanisms	Complexity in formulation, regulatory hurdles, potential for unknown long-term effects	Development of multifunctional nanoparticles, stimuli-responsive drug release systems, nanoparticles with inherent antimicrobial properties
Herbal and Natural Compounds	Antimicrobial properties of plant-derived compounds	Alternative or adjunctive treatment for microbial infections	Wide range of active compounds, potential for fewer side	Variable potency, potential for allergic reactions, limited clinical trials	Isolation of bioactive compounds, standardization of herbal formulations, combination with

			effects, use in traditional medicine		conventional therapies
Biofilm Disruptors	Disruption of biofilm structure to enhance antimicrobial efficacy	Treatment of biofilm-associated infections in reproductive tissues	Increased susceptibility of pathogens to antibiotics, potential to prevent chronic infections	Variable efficacy, potential for toxicity to host tissues	Development of specific biofilm disruptors, combination with antibiotics for synergistic effects, use of enzymes and peptides for biofilm degradation

Table 3 provides a comprehensive overview of advanced interventions currently utilized for managing microbial infections in reproductive tissues. Each intervention is detailed with its mechanism of action, applications in clinical settings, associated benefits such as efficacy and safety profiles, limitations such as resistance development or side effects, and recent advancements in the field. This structured presentation aims to inform healthcare professionals and researchers about the diverse strategies available, from traditional antibiotics and antifungal agents to cutting-edge nanotechnology-based approaches and immunomodulators. The table underscores the ongoing evolution and innovation in treatment modalities aimed at combating microbial infections in sensitive reproductive tissues, highlighting the multifaceted approaches to optimize patient outcomes and reduce the burden of infectious diseases in this critical area of healthcare.

Diagnostic tools, including blood tests, imaging, and microbiological cultures, aid in timely identification of infections. Management strategies encompass antibiotic therapy, Antifungal therapies, surgical interventions, supportive care, and addressing complications. The review underscores the necessity of personalized approaches, multidisciplinary collaboration, and innovative technologies in future infection management [103,104].

8.2 Future Directions in Preventive Strategies

Future directions in preventive strategies encompass a dynamic landscape poised to revolutionize healthcare. Personalized medicine is advancing with genomics and tailored interventions based on individual genetic profiles and lifestyle data [127]. Digital health technologies, including wearable devices and telehealth platforms, offer real-time monitoring and personalized interventions [127]. The microbiome's role in health is expanding, with probiotics and fecal microbiota transplantation (FMT) showing promise in modulating immunity[3]. New vaccines and immunotherapies are under development for infectious diseases and chronic conditions like cancer. AI and predictive analytics are transforming disease risk assessment and early intervention planning through data integration. Behavioral interventions, coupled with policy changes addressing socio-environmental factors, aim to promote health equity and reduce disparities [127]. These innovations herald a future where preventive strategies are increasingly personalized, proactive, and impactful on global health outcomes.

9. Future Directions and Research Opportunities

9.1 Gaps in Current Knowledge and Research Needs

The current research on microbial and immune influences on reproductive health has identified several key gaps that require further exploration. Firstly, microbial diversity and dynamics necessitate more research to understand how variations in microbial communities, including those in the vagina, gut, and systemic sites, impact fertility and pregnancy outcomes [3,128]. Investigating the composition and effects of the microbiome in specific locations within the female reproductive tract, such as the ovaries, endometrium, and placenta, is particularly crucial, given current limitations primarily observed in women with preexisting conditions [128]. Secondly, immune modulation is essential. Understanding the immune mechanisms that regulate tolerance towards paternal antigens during pregnancy and their implications for fertility treatments is crucial [3,128]. Distinguishing between healthy and pathological microbiota-immunome interactions will be critical for developing targeted therapies [128]. Thirdly, deeper insights are required into microbiota-host interactions and their influence on gametogenesis, embryo implantation, and fetal development [3,128]. Acquiring knowledge on how antibodies, particularly IgA and IgM, identify and respond to bacteria is pivotal for understanding microbiota-immunome interactions in reproductive health. Addressing these gaps will require implementing strictly controlled studies, shifting from microbiome to microbiota studies, and leveraging innovative technologies such as mFLOW-Seq and PhIP-Seq to assess live microbes and their dynamics [128]. Standardized methods are essential to comprehend the roles of microbiota and the immune system in clinical disorders, laying the groundwork for large-scale personalized medicine and diagnostic trials [3,128].

9.2 Potential for Novel Therapeutics and Interventions

Emerging research in reproductive immunology and fertility presents promising avenues for therapeutic interventions. Probiotics and Microbial Supplementation are garnering interest for their potential to modulate vaginal and gut microbiota composition, aiming to enhance fertility outcomes. Studies highlight the restoration of a healthy vaginal microbiome, predominated by Lactobacillus species, which can effectively treat conditions like bacterial vaginosis and optimize chances of successful conception and pregnancy [129]. Immunomodulatory Strategies are also advancing, with targeted therapies such as lymphocyte immunotherapy (LIT) showing promise in regulating immune responses critical to fertility and pregnancy success. These therapies modulate the balance of pro-inflammatory and anti-inflammatory cytokines, alongside regulating the frequencies of Th17 and regulatory T cells, particularly beneficial for patients experiencing recurrent pregnancy loss [129,130]. Precision Medicine Approaches further enhance treatment efficacy by integrating personalized microbiome and immune profile data. Advanced genomic technologies enable clinicians to identify specific immunological factors influencing conception and pregnancy maintenance, facilitating customized treatment protocols tailored to individual needs [129,131,132]. Together with the integration of digital health technologies in fertility management, these emerging therapeutic strategies hold significant promise in transforming reproductive immunology, ultimately improving outcomes for individuals navigating fertility challenges.

9.3 Long-term Goals for Improving Reproductive Health through Microbial and Immune Management

Long-term goals for improving reproductive health through microbial and immune management encompass several critical objectives. Firstly, enhancing fertility treatments involves integrating strategies to optimize the reproductive tract microbiome and modulate the immune system within assisted reproductive technologies (ART), aimed at enhancing success rates [133,134]. These efforts seek to create a more conducive environment for embryo implantation and fetal development. Secondly, preventative care initiatives aim to establish guidelines for maintaining microbial and immune health to mitigate reproductive complications [3]. Recommendations may include dietary adjustments, lifestyle modifications, and targeted interventions designed to sustain a healthy microbiome and balanced immune function, thereby reducing risks associated with infertility, recurrent pregnancy loss, and conditions like endometriosis. Thirdly, holistic approaches advocate for interdisciplinary collaborations to comprehensively address reproductive health through advancements in microbiome and immunology [3,133,135]. By integrating expertise from microbiology, immunology, reproductive medicine, and systems biology, researchers can gain a deeper understanding of the intricate interactions between microbiota, the immune system, and reproductive health. This knowledge serves as a foundation for developing innovative diagnostic tools and tailored therapeutic interventions.

These future directions highlight the transformative potential of leveraging microbial and immune insights to optimize reproductive health outcomes [3,133,134,135]. Through enhanced fertility treatments, preventative care guidelines, and holistic research approaches, the aim is to significantly improve the quality of life for individuals and couples facing challenges related to reproductive health.

10. Conclusion

This comprehensive review elucidates the critical roles that microbial exposures and immunological interactions play in reproductive health, particularly in gametogenesis and embryo development. It is evident that the intricate balance between beneficial and pathogenic microbes, along with the immune system's responses, significantly influences reproductive outcomes. The review highlights the profound impact of microbial presence on spermatogenesis and oogenesis, emphasizing the mechanisms through which these microbes interfere with gamete development. Moreover, the exploration of microbial effects on early embryogenesis and long-term embryo quality underscores the necessity of understanding these interactions to improve fertility outcomes. Immune responses in reproductive tissues, mediated by cytokines and various immune cells, further complicate the reproductive landscape. The synergistic and antagonistic interactions between microbial exposures and immune responses reveal a complex web of influences that can either support or hinder reproductive processes. The implications of these interactions for fertility and pregnancy outcomes are profound, necessitating targeted therapeutic and preventative strategies. Current interventions, including the management of microbial infections and immunomodulatory treatments, show promise but also highlight the need for further research to develop more effective and comprehensive approaches. The identified gaps in knowledge and research needs present significant opportunities for future investigations. Advancing our understanding of the interplay between microbial and immune factors in reproductive health will pave the way for novel therapeutics and interventions, ultimately improving reproductive outcomes. In conclusion, this review underscores the importance of a holistic approach to reproductive health that considers both microbial and immunological influences. By addressing the intricate interactions between these factors, we can enhance fertility and pregnancy outcomes, offering hope for individuals facing reproductive challenges and contributing to the broader field of reproductive medicine.

11 REFERENCES

[1] Feng, T., & Liu, Y. (2022). Microorganisms in the reproductive system and probiotic's regulatory effects on reproductive health. *Computational and structural biotechnology journal*, *20,* 1541–1553. https://doi.org/10.1016/j.csbj.2022.03.017

[2] Gao, H., Liu, Q., Wang, X., Li, T., Li, H., Li, G., Tan, L., & Chen, Y. (2024). Deciphering the role of female reproductive tract microbiome in reproductive health: A review. *Frontiers in Cellular and Infection Microbiology*, *14*, 1351540. https://doi.org/10.3389/fcimb.2024.1351540

[3] Al-Nasiry, S., Ambrosino, E., Schlaepfer, M., Morré, S. A., Wieten, L., Voncken, J. W., Spinelli, M., Mueller, M., & Kramer, B. W. (2020). The Interplay Between Reproductive Tract Microbiota and Immunological System in Human Reproduction. *Frontiers in immunology*, *11*, 378. https://doi.org/10.3389/fimmu.2020.00378

[4] Lehtoranta, L., Ala-Jaakkola, R., Laitila, A., & Maukonen, J. (2022). Healthy vaginal microbiota and influence of probiotics across the female life span. Frontiers in microbiology, 13, 819958. https://doi.org/10.3389/fmicb.2022.819958

[5] Kumar, L., Dwivedi, M., Jain, N., Shete, P., Solanki, S., Gupta, R., & Jain, A. (2023). The female reproductive tract microbiota: Friends and foe. *Life*, *13*(1313). https://doi.org/10.3390/life13061313

[6] Günther, V., Allahqoli, L., Watrowski, R., Maass, N., Ackermann, J., von Otte, S., & Alkatout, I. (2022). Vaginal Microbiome in Reproductive Medicine. *Diagnostics (Basel, Switzerland)*, *12*(8), 1948. https://doi.org/10.3390/diagnostics12081948

[7] Garcia-Segura, S., del Rey, J., Closa, L., Garcia-Martínez, I., Hobeich, C., Castel, A. B., Vidal, F., Benet, J., Ribas-Maynou, J., & Oliver-Bonet, M. (2022). Seminal microbiota of idiopathic infertile patients and its relationship with sperm DNA integrity. *Frontiers in Cell and Developmental Biology*, *10*, 937157. https://doi.org/10.3389/fcell.2022.937157

[8] Mao, X., Chen, H., Peng, X., Zhao, X., Yu, Z., & Xu, D. (2023). Dysbiosis of vaginal and cervical microbiome is associated with uterine fibroids. *Frontiers in Cellular and Infection Microbiology*, *13*, 1196823. https://doi.org/10.3389/fcimb.2023.1196823

[9] van de Wijgert, J. H., & Jespers, V. (2017). The global health impact of vaginal dysbiosis. *Research in microbiology*, *168*(9-10), 859-864.

[10] Pay, A., Turienzo, A., García, E. M., Ortiz, J. A., Lledó, B., Hortal, M., ... & Bernabeu, R. (2024). Vaginal microbiome dysbiosis influences partner's sperm motility. *Reproductive BioMedicine Online*, *48*, 104044.

[11] Neto, F. T. L., Viana, M. C., Cariati, F., Conforti, A., Alviggi, C., & Esteves, S. C. (2024). Effect of environmental factors on seminal microbiome and impact on sperm quality. *Frontiers in Endocrinology*, *15*, 1348186. https://doi.org/10.3389/fendo.2024.1348186

[12] Morawiec, E., Czerwiński, M., Czerwińska, A. B., & Wiczkowski, A. (2022). Semen dysbiosis-just a male problem?. *Frontiers in cellular and infection microbiology*, *12*, 815786. https://doi.org/10.3389/fcimb.2022.815786

[13] O'Mahony, S. M., & Comizzoli, P. (2023). Special series on the role of the microbiome in reproduction and fertility. *Reproduction and Fertility*, *4*(4). https://doi.org/10.1530/RAF-23-0080

[14] Ault-Seay, T. B., Moorey, S. E., Mathew, D. J., Schrick, F. N., Pohler, K. G., McLean, K. J., & Myer, P. R. (2023). Importance of the female reproductive tract microbiome and its relationship with the uterine environment for health and productivity in cattle: A review. *Frontiers in Animal Science*, *4*, 1111636. https://doi.org/10.3389/fanim.2023.1111636

[15] Comizzoli, P., Power, M. L., Bornbusch, S. L., & Muletz-Wolz, C. R. (2021). Interactions between reproductive biology and microbiomes in wild animal species. *Animal microbiome*, *3*(1), 87. https://doi.org/10.1186/s42523-021-00156-7

[16] Li, H., Zang, Y., Wang, C., Li, H., Fan, A., Han, C., & Xue, F. (2020). The interaction between microorganisms, metabolites, and immune system in the female genital tract microenvironment. *Frontiers in Cellular and Infection Microbiology*, *10*, 609488. https://doi.org/10.3389/fcimb.2020.609488

[17] Yoo, J. Y., Groer, M., Dutra, S. V. O., Sarkar, A., & McSkimming, D. I. (2020). Gut microbiota and immune system interactions. *Microorganisms, 8*(1587). https://doi.org/10.3390/microorganisms8101587

[18] Bhattacharya, K., Dutta, S., Sengupta, P., & Bagchi, S. (2023). Reproductive tract microbiome and therapeutics of infertility. *Middle East Fertility Society Journal*, *28*(1), 11. https://doi.org/10.1186/s43043-023-00136-8

[19] Pelzer, E., Gomez-Arango, L. F., Barrett, H. L., & Nitert, M. D. (2017). Maternal health and the placental microbiome. *Placenta*, *54*, 30-37. https://doi.org/10.1016/j.placenta.2016.12.003

[20] Moreno, I., & Franasiak, J. M. (2017). Endometrial microbiota—new player in town. *Fertility and sterility*, *108*(1), 32-39. https://doi.org/10.1016/j.fertnstert.2017.05.034

[21] Łaniewski, P., Barnes, D., Goulder, A., Cui, H., Roe, D. J., Chase, D. M., & Herbst-Kralovetz, M. M. (2018). Linking cervicovaginal immune signatures, HPV and microbiota composition in cervical carcinogenesis in non-Hispanic and Hispanic women. *Scientific reports*, *8*(1), 7593. https://doi.org/10.1038/s41598-018-25879-7

[22] Ruff, W. E., Greiling, T. M., & Kriegel, M. A. (2020). Host–microbiota interactions in immune-mediated diseases. *Nature Reviews Microbiology*, *18*(9), 521-538. https://doi.org/10.1038/s41579-020-0367-2

[23] Romero, R., Hassan, S. S., Gajer, P., Tarca, A. L., Fadrosh, D. W., Nikita, L., ... & Ravel, J. (2014). The composition and stability of the vaginal microbiota of normal pregnant women is different from that of non-pregnant women. *Microbiome*, *2*, 1-19. https://doi.org/10.1186/2049-2618-2-4

[24] Moreno, I., & Simon, C. (2019). Deciphering the effect of reproductive tract microbiota on human reproduction. *Reproductive medicine and biology*, *18*(1), 40-50. https://doi.org/10.1002/rmb2.12249

[25] Gajer, P., Brotman, R. M., Bai, G., Sakamoto, J., Schütte, U. M., Zhong, X., Koenig, S. S., Fu, L., Ma, Z. S., Zhou, X., Abdo, Z., Forney, L. J., & Ravel, J. (2012). Temporal dynamics of the human vaginal microbiota. *Science translational medicine*, *4*(132), 132ra52. https://doi.org/10.1126/scitranslmed.3003605

[26] Ravel, J., Gajer, P., Abdo, Z., Schneider, G. M., Koenig, S. S., McCulle, S. L., ... & Forney, L. J. (2011). Vaginal microbiome of reproductive-age women. *Proceedings of the National Academy of Sciences*, *108*(supplement_1), 4680-4687. https://doi.org/10.1073/pnas.1002611107

[27] Witkin, S. S., Linhares, I. M., & Giraldo, P. (2007). Bacterial flora of the female genital tract: function and immune regulation. *Best Practice & Research Clinical Obstetrics & Gynaecology*, *21*(3), 347-354. https://doi.org/10.1016/j.bpobgyn.2006.12.004

[28] Weng, S. L., Chiu, C. M., Lin, F. M., Huang, W. C., Liang, C., Yang, T., ... & Huang, H. D. (2014). Bacterial communities in semen from men of infertile couples: metagenomic sequencing reveals relationships of seminal microbiota to semen quality. *PloS one*, *9*(10), e110152. https://doi.org/10.1371/journal.pone.0110152

[29] Hou, D., Zhou, X., Zhong, X., Settles, M. L., Herring, J., Wang, L., ... & Xu, C. (2013). Microbiota of the seminal fluid from healthy and infertile men. *Fertility and sterility*, *100*(5), 1261-1269. https://doi.org/10.1016/j.fertnstert.2013.07.1991

[30] Haggerty, C. L., Gottlieb, S. L., Taylor, B. D., Low, N., Xu, F., & Ness, R. B. (2010). Risk of sequelae after Chlamydia trachomatis genital infection in women. *The Journal of infectious diseases, 201*(Supplement_2), S134-S155. https://doi.org/10.1086/652395

[31] Bosch, F. X., Broker, T. R., Forman, D., Moscicki, A. B., Gillison, M. L., Doorbar, J., ... & de Sanjose, S. (2013). Comprehensive control of human papillomavirus infections and related diseases. *Vaccine, 31*, H1-H31. https://doi.org/10.1016/j.vaccine.2013.10.003

[32] Looker, K. J., Magaret, A. S., Turner, K. M., Vickerman, P., Gottlieb, S. L., & Newman, L. M. (2015). Global estimates of prevalent and incident herpes simplex virus type 2 infections in 2012. *PloS one, 10*(1), e114989. https://doi.org/10.1371/journal.pone.0114989

[33] Sobel, J. D. (2007). Vulvovaginal candidosis. *The Lancet, 369*(9577), 1961-1971. https://doi.org/10.1016/S0140-6736(07)60917-9

[34] Kissinger, P. (2015). Trichomonas vaginalis: a review of epidemiologic, clinical and treatment issues. *BMC infectious diseases, 15*, 1-8. https://doi.org/10.1186/s12879-015-1055-0

[35] Fredricks, D. N., Fiedler, T. L., & Marrazzo, J. M. (2005). Molecular identification of bacteria associated with bacterial vaginosis. *New England Journal of Medicine, 353*(18), 1899-1911. https://doi.org/10.3390/nu16040546

[36] Verstraelen, H., Verhelst, R., Claeys, G., De Backer, E., Temmerman, M., & Vaneechoutte, M. (2009). Longitudinal analysis of the vaginal microflora in pregnancy suggests that L. crispatus promotes the stability of the normal vaginal microflora and that L. gasseri and/or L. iners are more conducive to the occurrence of abnormal vaginal microflora. *BMC microbiology, 9*, 1-10. https://doi.org/10.1186/1471-2180-9-116

[37] 3Allsworth, J. E., & Peipert, J. F. (2007). Prevalence of bacterial vaginosis: 2001–2004 national health and nutrition examination survey data. *Obstetrics & Gynecology, 109*(1), 114-120.

[38] Atashili, J., Poole, C., Ndumbe, P. M., Adimora, A. A., & Smith, J. S. (2008). Bacterial vaginosis and HIV acquisition: a meta-analysis of published studies. *AIDS (London, England), 22*(12), 1493–1501. https://doi.org/10.1097/QAD.0b013e3283021a37

[39] Petrova, M. I., Reid, G., Vaneechoutte, M., & Lebeer, S. (2017). Lactobacillus iners: friend or foe?. *Trends in microbiology, 25*(3), 182-191. https://doi.org/10.1016/j.tim.2016.11.007

[40] Donders, G. G., Van Calsteren, K., Bellen, G., Reybrouck, R., Van den Bosch, T., Riphagen, I., & Van Lierde, S. (2009). Predictive value for preterm birth of abnormal vaginal flora, bacterial vaginosis and aerobic vaginitis during the first trimester of pregnancy. *BJOG: An International Journal of Obstetrics & Gynaecology, 116*(10), 1315-1324. https://doi.org/10.1111/j.1471-0528.2009.02237.x

[41] Stout, M. J., Zhou, Y., Wylie, K. M., Tarr, P. I., Macones, G. A., & Tuuli, M. G. (2017). Early pregnancy vaginal microbiome trends and preterm birth. *American journal of obstetrics and gynecology, 217*(3), 356-e1. https://doi.org/10.1016/j.ajog.2017.05.030

[42] Tomaiuolo R, Veneruso I, Cariati F, D'Argenio V. Microbiota and Human Reproduction: The Case of Female Infertility. *High-Throughput. 2020; 9*(2):12. https://doi.org/10.3390/ht9020012

[43] Gonçalves MFM, Fernandes ÂR, Rodrigues AG, Lisboa C. Microbiome in Male Genital Mucosa (Prepuce, Glans, and Coronal Sulcus): A Systematic Review. *Microorganisms. 2022; 10(12)*:2312. https://doi.org/10.3390/microorganisms10122312

[44] Salim, R., Ben-Shlomo, I., Colodner, R., Keness, Y., & Shalev, E. (2002). Bacterial colonization of the uterine cervix and success rate in assisted reproduction: results of a prospective survey. *Human Reproduction, 17*(2), 337-340. https://doi.org/10.1093/humrep/17.2.337

[45] Janakiraman V. (2008). Listeriosis in pregnancy: diagnosis, treatment, and prevention. *Reviews in obstetrics & gynecology, 1*(4), 179–185.

[46] Radolf, J. D., Tramont, E. C., & Salazar, J. C. (2015). Syphilis (treponema pallidum). *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, 2684-2709.

[47] Perez-Muñoz, M. E., Arrieta, M. C., Ramer-Tait, A. E., & Walter, J. (2017). A critical assessment of the "sterile womb" and "in utero colonization" hypotheses: implications for research on the pioneer infant microbiome. *microbiome, 5,* 1-19. https://doi.org/10.1186/s40168-017-0268-4

[48] Besnard, M., Lastere, S., Teissier, A., Cao-Lormeau, V. M., & Musso, D. (2014). Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014. *Eurosurveillance, 19*(13). https://doi.org/10.2807/1560-7917.ES2014.19.13.20751

[49] Eschenbach, D. A., Rosene, K., Tompkins, L. S., Watkins, H., & Gravett, M. G. (1986). Endometrial cultures obtained by a triple-lumen method from afebrile and febrile postpartum women. *Journal of Infectious Diseases, 153*(6), 1038-1045. https://doi.org/10.1093/infdis/153.6.1038

[50] Hemsell, D. L., Obregon, V. L., Heard, M. C., & Nobles, B. J. (1989). Endometrial bacteria in asymptomatic, nonpregnant women. *The Journal of reproductive medicine, 34*(11), 872-874.

[51] Larose, H., Shami, A. N., Abbott, H., Manske, G., Lei, L., & Hammoud, S. S. (2019). Gametogenesis: A journey from inception to conception. *Current Topics in Developmental Biology, 132,* 257-310. https://doi.org/10.1016/bs.ctdb.2018.12.006

[52] Sing, T. L., Brar, G. A., & Ünal. E. (2022). Gametogenesis: Exploring an Endogenous Rejuvenation Program to Understand Cellular Aging and Quality Control. *Annual Review, 56,* 89-112. https://doi.org/10.1146/annurev-genet-080320-025104

[53] Saitou, M., & Miyauchi, H. (2016). Gametogenesis from pluripotent stem cells. *Cell Press, 18,* 721-735. http://dx.doi.org/10.1016/j.stem.2016.05.001

[54] Colella, M., Topi, S., Palmirotta, R., D'Agostino, D., Charitos, I. A., Lovero, R., & Santacroce, L. (2023). An Overview of the Microbiota of the Human Urinary Tract in Health and Disease: Current Issues and Perspectives. *Multidisciplinary Digital Publishing Institute, 13*(1486), 2-21. https://doi.org/10.3390/life13071486

[55] Keck, C., Gerber-Schafer, C., Clad, A., Wilhelm, C., & Breckwoldt, M. (1998). Seminal tract infections: Impact on male fertility and treatment options. *Human Reproduction Update, 4*(6), 891-903. https://doi.org/10.1093/humupd/4.6.891

[56] Vignera, S. L., Condorelli, R. A., Vicari, E., Tumino, D., Morgia, G., Favilla, V., Cimino, S., & Calogero, A. E. (2013). Markers of semen inflammation: supplementary semen analysis. *Journal of Reproductive Immunology, 100*(1), 2-10. https://doi.org/10.1016/j.jri.2013.05.001

[57] La Vignera, S., Vicari, E., Condorelli, R. A., D'Agata, R., & Calogero, A.E. (2011). Male accessory gland infection and sperm parameters (review). *International Journal of Andrology, 34,* e330-e347. https://doi.org/10.1111/j.1365-2605.2011.01200.x

[58] Ochsendorf, F. R. (1999). Infection in the male genital tract and reactive oxygen species. *Human Reproduction Update, 5*(5), 399-420. https://doi.org/10.1093/humupd/5.5.399

*[59]*Ochsendorf, F. R. (2009). Infection and reactive oxygen species. *Andrologia*. *https://doi.org/10.1111/j.1439-0272.1998.tb02830.x*

[60] Redgrove, K. A., & McLaughlin, E. A. (2014). The role of the immune response in Chlamydia trachomatis infection of the male genital tract: a double-edged sword. Frontiers in immunology, 5, 534. https://doi.org/10.3389/fimmu.2014.00534

*[61]*Gonzales, G. F., Munoz, G., Sanchez, R., Henkel, R., Gallegos-Avila, G., Diaz-Gutierrez, O., Vigil, P., Vasquez, F., Kortebani, G., Mazzolli, A., & Bustos-Obregon, E. (2004). Update on the impact of Chlamydia trachomatis infection on male fertility. *Andrologia*. *https://doi.org/10.1046/j.0303-4569.2003.00594.x*

[62] Wei, M., Liu, H., Wang, Y., Sun, M., & Shang, P. (2024). Mechanisms of Male Reproductive Sterility Triggered by Dysbiosis of Intestinal Microorganisms. *Multidisciplinary Digital Publishing Institute, 14*(694), 1-18. https://doi.org/10.3390/life14060694

[63] Rizzo, A. E., Gordon, J. C., Berard, A. R., Burgener, A. D., & Avril, S. (2021). The Female Reproductive Tract Microbiome-Implications for Gynecologic Cancers and Personalized Medicine. *Journal of personalized medicine, 11*(6), 546. https://doi.org/10.3390/jpm11060546

[64] Lafioniatis, A., Samara, A. A., Makaritsis, P. K., Dafopoulos, S., Sotiriou, S., & Dafopoulos, K. (2024). Understanding the Role of Female Genital Tract Microbiome in Recurrent Implantation Failure. *Journal of Clinical Medicine, 13*(11), 3173. https://doi.org/10.3390/jcm13113173

[65] Gholiof, M., Adamson-De Luca, E., & Wessels, J. M. (2022). The female reproductive tract microbiotas, inflammation, and gynecological conditions. *Frontiers in reproductive health, 4*, 963752. https://doi.org/10.3389/frph.2022.963752

[66] Chen, C., Song, X., Wei, W., Zhong, H., Dai, J., Lan, Z., ... & Jia, H. (2017). The microbiota continuum along the female reproductive tract and its relation to uterine-related diseases. *Nature communications, 8*(1), 875. https://doi.org/10.1038/s41467-017-00901-0

[67] Wang, S., Zhang, K., Yao, Y., Li, J., & Deng, S. (2021). Bacterial Infections Affect Male Fertility: A Focus on the Oxidative Stress-Autophagy Axis. *Frontiers in cell and developmental biology*, *9*, 727812. https://doi.org/10.3389/fcell.2021.727812

[68] Wang, H., Xu, A., Gong, L., Chen, Z., Zhang, B., & Li, X. (2022). The microbiome, an important factor that is easily overlooked in male infertility. *Frontiers in microbiology*, *13*, 831272. https://doi.org/10.3389/fmicb.2022.831272

[69] Kaltsas, A., Zachariou, A., Markou, E., Dimitriadis, F., Sofikitis, N., & Pournaras, S. (2023). Microbial Dysbiosis and Male Infertility: Understanding the Impact and Exploring Therapeutic Interventions. *Journal of personalized medicine, 13*(10), 1491. https://doi.org/10.3390/jpm13101491

[70] Mesa, M. D., Loureiro, B., Iglesia, I., Fernandez Gonzalez, S., Llurba Olivé, E., García Algar, O., Solana, M. J., Cabero Perez, M. J., Sainz, T., Martinez, L., Escuder-Vieco, D., Parra-Llorca, A., Sánchez-Campillo, M., Rodriguez Martinez, G., Gómez Roig, D., Perez Gruz, M., Andreu-Fernández, V., Clotet, J., Sailer, S., Iglesias-Platas, I., … Cabañas, F. (2020). The Evolving Microbiome from Pregnancy to Early Infancy: A Comprehensive Review. *Nutrients*, *12*(1), 133. https://doi.org/10.3390/nu12010133

[71] Bolte, E.E., Moorshead, D. & Aagaard, K.M. Maternal and early life exposures and their potential to influence development of the microbiome. *Genome Med 14*, 4 (2022). https://doi.org/10.1186/s13073-021-01005-7

[72] Green, E., Harishchandra, A., Ranasinghe, P., Di Giulio, R., & Jayasundara, N. (2024). The external microbiome communicates with the developing zebrafish (Danio rerio) embryo through the protective chorion and influences developmental trajectory. *bioRxiv*. https://doi.org/10.1101/2024.05.28.596134

[73] Sajdel-Sulkowska, E.M. The Impact of Maternal Gut Microbiota during Pregnancy on Fetal Gut–Brain Axis Development and Life-Long Health Outcomes. *Microorganisms 2023*, 11, 2199. https://doi.org/10.3390/microorganisms11092199

[74] Zhu, B., Tao, Z., Edupuganti, L., Serrano, M. G., & Buck, G. A. (2022). Roles of the Microbiota of the Female Reproductive Tract in Gynecological and Reproductive Health. *Microbiology and molecular biology reviews : MMBR*, *86*(4), e0018121. https://doi.org/10.1128/mmbr.00181-21

[75] Kumar, M., Saadaoui, M., & Al Khodor, S. (2022). Infections and Pregnancy: Effects on Maternal and Child Health. *Frontiers in cellular and infection microbiology*, *12*, 873253. https://doi.org/10.3389/fcimb.2022.873253

[76] Mishra, A., Lai, G. C., Yao, L. J., Aung, T. T., Shental, N., Rotter-Maskowitz, A., Shepherdson, E., Singh, G. N., Pai, R., Shanti, A., Wong, R. M. M., Lee, A., Khyriem, C., Dutertre, C. A., Chakarov, S., Srinivasan, K. G., Shadan, N. B., Zhang, X.-M., Khalilnezhad, S., Cottier, F., Tan, A. S. M., Low, G., Chen, P., Fan, Y., Hor, P. X., Lee, A. K. M., Choolani, M., Vermijlen, D., Sharma, A., Fuks, G., Straussman, R., Pavelka, N., Malleret, B., McGovern, N., Albani, S., Chan, J. K. Y., & Ginhoux, F. (2021). Microbial exposure during early human development primes fetal immune cells. *Cell*, *184*(13), 3394-3409.e20. https://doi.org/10.1016/j.cell.2021.04.039

[77] Nuriel-Ohayon, M., Neuman, H., & Koren, O. (2016). Microbial Changes during Pregnancy, Birth, and Infancy. *Frontiers in microbiology*, *7*, 1031. https://doi.org/10.3389/fmicb.2016.01031

[78] Zheng, T., Li, Q., Chen, N. et al. Analysis of the clinical outcomes of microbial contamination caused by environmental contamination of the embryology laboratory during IVF-ET treatment cycles. *BMC Pregnancy Childbirth 23, 190 (2023)*. https://doi.org/10.1186/s12884-023-05516-6

[79] Upreti, D., Rouzer, S. K., Bowring, A., Labbe, E., Kumar, R., Miranda, R. C., & Mahnke, A. H. (2023). Microbiota and nutrition as risk and resiliency factors following prenatal alcohol exposure. *Frontiers in Neuroscience, 17*. https://doi.org/10.3389/fnins.2023.1182635

[80] Wira, C. R., & Fahey, J. V. (2004). The innate immune system: gatekeeper to the female reproductive tract. *Immunology*, *111*(1), 13–15. https://doi.org/10.1111/j.1365-2567.2004.01796.x

[81] Nguyen, P. V., Kafka, J. K., Ferreira, V. H., Roth, K., & Kaushic, C. (2014). Innate and adaptive immune responses in male and female reproductive tracts in homeostasis and following HIV infection. *Cellular & molecular immunology*, *11*(5), 410–427. https://doi.org/10.1038/cmi.2014.41

[82] Lee, S. K., Kim, C. J., Kim, D. J., & Kang, J. H. (2015). Immune cells in the female reproductive tract. *Immune network*, *15*(1), 16–26. https://doi.org/10.4110/in.2015.15.1.16

[83] Monin, L., Whettlock, E. M., & Male, V. (2020). Immune responses in the human female reproductive tract. *Immunology*, *160*(2), 106–115. https://doi.org/10.1111/imm.13136

[84] Yüzen, D., Arck, P.C. & Thiele, K. Tissue-resident immunity in the female and male reproductive tract. *Semin Immunopathol 44*, 785–799 (2022). https://doi.org/10.1007/s00281-022-00934-8

[85] Gudisa, R., Goyal, K., Gupta, P., & Singh, M. P. (2021). Localized and systemic immune response in human reproductive tract. *Frontiers in Cellular and Infection Microbiology*, 11. https://www.frontiersin.org/articles/10.3389/fcimb.2021.649893

[86] https://doi.org/10.3389/fcimb.2021.649893

[87] Amarante-Mendes, G. P., Adjemian, S., Branco, L. M., Zanetti, L. C., Weinlich, R., & Bortoluci, K. R. (2018). Pattern recognition receptors and the host cell death molecular machinery. *Frontiers in Immunology*, 9. https://www.frontiersin.org/articles/10.3389/fimmu.2018.02379. https://doi.org/10.3389/fimmu.2018.02379.

[88] Loveland, K. L., Klein, B., Pueschl, D., Indumathy, S., Bergmann, M., Loveland, B. E., Hedger, M. P., & Schuppe, H. C. (2017). Cytokines in Male Fertility and Reproductive Pathologies: *Immunoregulation and Beyond. Frontiers in endocrinology, 8*, 307. https://doi.org/10.3389/fendo.2017.00307

[89] Francomano, D., Sanguigni, V., Capogrosso, P., Deho, F., & Antonini, G. (2021). New Insight into Molecular and Hormonal Connection in Andrology. *International journal of molecular sciences, 22*(21), 11908. https://doi.org/10.3390/ijms222111908

[90] Campanile, G., Baruselli, P. S., Limone, A., & D'Occhio, M. J. (2021). Local action of cytokines and immune cells in communication between the conceptus and uterus during the critical period of early embryo development, attachment and implantation – Implications for embryo survival in cattle: A review. *Theriogenology, 167*, 1-12. https://doi.org/10.1016/j.theriogenology.2021.02.020

[91] Yockey, L. J., & Iwasaki, A. (2018). Interferons and Proinflammatory Cytokines in Pregnancy and Fetal Development. *Immunity*, *49*(3), 397–412. https://doi.org/10.1016/j.immuni.2018.07.017

[92] Anahtar, M. N., Byrne, E. H., Doherty, K. E., Bowman, B. A., Yamamoto, H. S., Soumillon, M., Padavattan, N., ... & Kwon, D. S. (2015). Cervicovaginal bacteria are a major modulator of host inflammatory responses in the female genital tract. *Immunity*, *42*(5), 965-976. https://doi.org/10.1016/j.immuni.2015.04.019

[93] Zarember, K. A., & Godowski, P. J. (2002). Tissue expression of human Toll-like receptors and differential regulation of Toll-like receptor mRNAs in leukocytes in response to microbes, their products, and cytokines. *The journal of immunology, 168*(2), 554-561. https://doi.org/10.4049/jimmunol.168.2.554

[94] Wira, C. R., Ghosh, M., Smith, J. M., Shen, L., Connor, R. I., Sundstrom, P., ... & Fahey, J. V. (2011). Epithelial cell secretions from the human female reproductive tract inhibit sexually transmitted pathogens and Candida albicans but not Lactobacillus. *Mucosal immunology, 4*(3), 335-342. https://doi.org/10.1038/mi.2010.72

[95] Sonnenberg, G. F., & Artis, D. (2012). Innate lymphoid cell interactions with microbiota: implications for intestinal health and disease. *Immunity, 37*(4), 601-610. https://doi.org/10.1016/j.immuni.2012.10.003

[96] Mirzaei, R., Kavyani, B., Nabizadeh, E., Kadkhoda, H., Asghari Ozma, M., & Abdi, M. (2023). Microbiota metabolites in the female reproductive system: Focused on the short-chain fatty acids. *Heliyon, 9*(3), e14562. https://doi.org/10.1016/j.heliyon.2023.e14562

[97] Ye, X., Li, H., Anjum, K., Zhong, X., Miao, S., Zheng, G., Liu, W., & Li, L. (2022). Dual Role of Indoles Derived From Intestinal Microbiota on Human Health. *Frontiers in immunology, 13*, 903526. https://doi.org/10.3389/fimmu.2022.903526

[98] Horne, A. W., Stock, S. J., & King, A. E. (2008). Innate immunity and disorders of the female reproductive tract. *REPRODUCTION*, *135*(6), 739-749. Retrieved Jun 28, 2024, from https://doi.org/10.1530/REP-07-056

[99] Liu, X. F., Shao, J. H., Liao, Y. T., Wang, L. N., Jia, Y., Dong, P. J., Liu, Z. Z., He, D. D., Li, C., & Zhang, X. (2023). Regulation of short-chain fatty acids in the immune system. *Frontiers in immunology, 14,* 1186892. https://doi.org/10.3389/fimmu.2023.1186892

[100] Ney, L. M., Wipplinger, M., Grossmann, M., Engert, N., Wegner, V. D., & Mosig, A. S. (2023). Short chain fatty acids: key regulators of the local and systemic immune response in inflammatory diseases and infections. *Open biology*, *13*(3), 230014. https://doi.org/10.1098/rsob.230014

[101] Collins, M. K., McCutcheon, C. R., & Petroff, M. G. (2022). Impact of estrogen and progesterone on immune cells and host–pathogen interactions in the lower female reproductive tract. *The Journal of Immunology, 209*(8), 1437-1449. https://doi.org/10.4049/jimmunol.2200454

[102] Jiang, I., Yong, P. J., Allaire, C., & Bedaiwy, M. A. (2021). Intricate Connections between the Microbiota and Endometriosis. *International journal of molecular sciences*, *22*(11), 5644. https://doi.org/10.3390/ijms22115644

[103] Kobayashi, H. (2023). Gut and reproductive tract microbiota: Insights into the pathogenesis of endometriosis (Review). *Biomedical Reports*, *19*, 43. https://doi.org/10.3892/br.2023.1626

[104] Ronghe, V., Modak, A., Gomase, K., & Mahakalkar, M. G. (2023). From Prevention to Management: *Understanding Postoperative Infections in Gynaecology*. *Cureus, 15*(10), e46319. https://doi.org/10.7759/cureus.46319

[105] Nakandalage, R.; Guan, L.L.; Malmuthuge, N. Microbial Interventions to Improve Neonatal Gut Health. *Microorganisms 2023*, *11*, 1328. https://doi.org/10.3390/microorganisms11051328

[106] Kapoor, G., Saigal, S., & Elongavan, A. (2017). Action and resistance mechanisms of antibiotics: A guide for clinicians. *Journal of anaesthesiology, clinical pharmacology*, *33*(3), 300–305. https://doi.org/10.4103/joacp.JOACP_349_15

[107] Halawa, E. M., Fadel, M., Al-Rabia, M. W., Behairy, A., Nouh, N. A., Abdo, M., Olga, R., Fericean, L., Atwa, A. M., El-Nablaway, M., & Abdeen, A. (2024). Antibiotic action and resistance: updated review of mechanisms, spread, influencing factors, and alternative approaches for combating resistance. *Frontiers in pharmacology*, *14*, 1305294. https://doi.org/10.3389/fphar.2023.1305294

[108] Ghannoum, M. A., & Rice, L. B. (1999). Antifungal agents: mode of action, mechanisms of resistance, and correlation of these mechanisms with bacterial resistance. *Clinical microbiology reviews*, *12*(4), 501–517. https://doi.org/10.1128/CMR.12.4.501

[109] Bertelli, G., Sciturro, M., Ray, S. D., & Parmar, M. S. (2024). Antifungal agents. In P. Wexler (Ed.), *Encyclopedia of Toxicology* (4th ed., pp. 603-614). Academic Press. https://doi.org/10.1016/B978-0-12-824315-2.00353-5

[110] Kausar, S., Said Khan, F., Ishaq Mujeeb Ur Rehman, M., Akram, M., Riaz, M., Rasool, G., Hamid Khan, A., Saleem, I., Shamim, S., & Malik, A. (2021). A review: Mechanism of action of antiviral drugs. *International journal of immunopathology and pharmacology*, *35*, 20587384211002621. https://doi.org/10.1177/20587384211002621

[111] Ianevski, A., Ahmad, S., Anunnitipat, K. et al. Seven classes of antiviral agents. Cell. Mol. *Life Sci. 79*, 605 (2022). https://doi.org/10.1007/s00018-022-04635

[112] Latif, A., Shehzad, A., Niazi, S., Zahid, A., Ashraf, W., Iqbal, M. W., Rehman, A., Riaz, T., Aadil, R. M., Khan, I. M., Özogul, F., Rocha, J. M., Esatbeyoglu, T., & Korma, S. A. (2023). Probiotics: mechanism of action, health benefits and their application in food industries. *Frontiers in microbiology*, *14*, 1216674. https://doi.org/10.3389/fmicb.2023.1216674

[113] Bermudez-Brito, M., Plaza-Díaz, J., Muñoz-Quezada, S., Gómez-Llorente, C., & Gil, A. (2012). Probiotic mechanisms of action. *Annals of Nutrition and Metabolism*, *61*(2), 160–174. https://doi.org/10.1159/000342079

[114] Centers for Disease Control and Prevention. (2023, May 24). Explaining how vaccines work. In Provider resources for vaccine conversations with parents. Retrieved from https://www.cdc.gov/vaccines

[115] Quach, H., Ritchie, D., Stewart, A. K., Neeson, P., Harrison, S., Smyth, M. J., & Prince, H. M. (2010). Mechanism of action of immunomodulatory drugs (IMiDS) in multiple myeloma. *Leukemia*, *24*(1), 22–32. https://doi.org/10.1038/leu.2009.236

[116] Bascones-Martinez, A., Mattila, R., Gomez-Font, R., & Meurman, J. H. (2014). Immunomodulatory drugs: oral and systemic adverse effects. *Medicina oral, patologia oral y cirugia bucal*, *19*(1), e24–e31. https://doi.org/10.4317/medoral.19087

[117] Hou, Y., Yang, X., Liu, R., Zhao, D., Guo, C., Zhu, A., Wen, M., Liu, Z., Qu, G., & Meng, H. (2020). Pathological mechanism of photodynamic therapy and photothermal therapy based on nanoparticles. *International Journal of Nanomedicine, 2020*(15), 6827–6838. https://doi.org/10.2147/IJN.S269321

[118] Li, T., & Yan, L. (2018). Functional polymer nanocarriers for photodynamic therapy. *Pharmaceuticals, 11*(4), 133. https://doi.org/10.3390/ph11040133

[119] Allison, R. R., & Moghissi, K. (2013). Photodynamic Therapy (PDT): PDT Mechanisms. *Clinical endoscopy, 46*(1), 24–29. https://doi.org/10.5946/ce.2013.46.1.24

[120] Hetta, H. F., Ramadan, Y. N., Al-Harbi, A. I., A Ahmed, E., Battah, B., Abd Ellah, N. H., Zanetti, S., & Donadu, M. G. (2023). Nanotechnology as a Promising Approach to Combat Multidrug Resistant Bacteria: A Comprehensive Review and Future Perspectives. *Biomedicines, 11*(2), 413. https://doi.org/10.3390/biomedicines11020413

[121] Yılmaz GE, Göktürk I, Ovezova M, Yılmaz F, Kılıç S, Denizli A. Antimicrobial Nanomaterials: A Review. *Hygiene. 2023; 3*(3):269-290. https://doi.org/10.3390/hygiene3030020

[122] Beyth, N., Houri-Haddad, Y., Domb, A., Khan, W., & Hazan, R. (2015). Alternative antimicrobial approach: Nano-antimicrobial materials. *Evidence-Based Complementary and Alternative Medicine, 2015*(1), 246012. https://doi.org/10.1155/2015/246012

[123] Stan, D., Enciu, A. M., Mateescu, A. L., Ion, A. C., Brezeanu, A. C., Stan, D., & Tanase, C. (2021). Natural Compounds With Antimicrobial and Antiviral Effect and Nanocarriers Used for Their Transportation. *Frontiers in pharmacology, 12*, 723233. https://doi.org/10.3389/fphar.2021.723233

[124] Rybczyńska-Tkaczyk, K., Grenda, A., Jakubczyk, A., & Bik-Małodzińska, M. (2023). Natural compounds with antimicrobial properties in cosmetics. *Pathogens, 12*(2), 320. https://doi.org/10.3390/pathogens12020320

[125] Noh, S., Go, A., Kim, D. B., Park, M., Jeon, H. W., & Kim, B. (2020). Role of Antioxidant Natural Products in Management of Infertility: A Review of Their Medicinal Potential. Antioxidants (*Basel, Switzerland), 9*(10), 957. https://doi.org/10.3390/antiox9100957

[126] Machado, D., Castro, J., Palmeira-de-Oliveira, A., Martinez-de-Oliveira, J., & Cerca, N. (2016). Bacterial Vaginosis Biofilms: Challenges to Current Therapies and Emerging Solutions. *Frontiers in microbiology, 6*, 1528. https://doi.org/10.3389/fmicb.2015.01528

[127] Roy, R., Tiwari, M., Donelli, G., & Tiwari, V. (2018). Strategies for combating bacterial biofilms: A focus on anti-biofilm agents and their mechanisms of action. *Virulence, 9*(1), 522–554. https://doi.org/10.1080/21505594.2017.1313372

[128] Boyd, R. C., Castro, F. G., Finigan-Carr, N., Okamoto, S. K., Barlow, A., Kim, B. E., Lambert, S., Lloyd, J., Zhang, X., Barksdale, C. L., Crowley, D. M., Maldonado-Molina, M., Obasi, E. M., & Kenney, A. (2023). Strategic Directions in Preventive Intervention Research to Advance Health Equity. Prevention science : *the official journal of the Society for Prevention Research, 24(*4), 577–596. https://doi.org/10.1007/s11121-022-01462-5

[129] Lingasamy, P., Modhukur, V., Mändar, R., & Salumets, A. (2023). Exploring Immunome and Microbiome Interplay in Reproductive Health: Current Knowledge, Challenges, and Novel Diagnostic Tools. *Seminars in reproductive medicine, 41*(5), 172–189. https://doi.org/10.1055/s-0043-1778017

[130] Abdolmohammadi-Vahid, S., Danaii, S., Hamdi, K., Jadidi-Niaragh, F., Ahmadi, M., & Yousefi, M. (2016). Novel immunotherapeutic approaches for treatment of infertility. *Biomedicine & Pharmacotherapy, 84*, 1449-1459. https://doi.org/10.1016/j.biopha.2016.10.062

[131] Abdolmohammadi-Vahid, S., Aghebati-Maleki, L., Ahmadian-Heris, J., Danaii, S., & Yousefi, M. (2023). Recent Advances in Immunotherapeutic Approaches for Recurrent Reproductive Failure. *IntechOpen*. doi: 10.5772/intechopen.108869

[132] Norman, R. J. (2022). Immunology in reproductive medicine: Is current testing and therapy justified by science? Fertility and Sterility. Advance online publication. https://doi.org/10.1016/j.fertnstert.2022.04.018

[133] Abrahams, V. M. (2011). Reproductive immunology: the clinical view. *Expert Review of Clinical Immunology*, *7*(5), 555–556. https://doi.org/10.1586/eci.11.61

[134] .Krog, M. C., Madsen, M. E., Bliddal, S., Bashir, Z., Vexø, L. E., Hartwell, D., Hugerth, L. W., Fransson, E., Hamsten, M., Boulund, F., Wannerberger, K., Engstrand, L., Schuppe-Koistinen, I., & Nielsen, H. S. (2022). The microbiome in reproductive health: protocol for a systems biology approach using a prospective, observational study design. *Human reproduction open*, *2022*(2), hoac015. https://doi.org/10.1093/hropen/hoac015

[135] Chen, J., Chen, J., Fang, Y., Shen, Q., Zhao, K., Liu, C., & Zhang, H. (2023). Microbiology and immune mechanisms associated with male infertility. *Frontiers in immunology*, *14*, 1139450. https://doi.org/10.3389/fimmu.2023.1139450

[136] Fuzail MA, Ahmed B, Burke DL, et al. Microbiome research potential for developing holistic approaches to improve refugee health. *Journal of Global Health Reports.* 2021;5:e2021094. doi:10.29392/001c.28997 (https://doi.org/10.29392/001c.28997)