Role of Microbiome in Reproductive Health: An Expanding Dimension

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Abstract

Trillions of symbiotic microorganisms have evolved with and continue to live on and within human beings, serving an important role in regulating human health and disease. Their omnipresence has a great influence on almost all the physiological functions of the body, and female reproductive system is no exception. As per the Human Microbiome Project, the vaginal microbiota alone makes up about 9% of the total human microbiota. Any internal or external change in this resident microbial population might lead to dysbiosis, further causing disease pathologies. This undesirable shift in microbiota is also strongly associated with stress and lifestyle imbalance, which are directly linked to poor dietary habits and a sedentary routine. Such unfavourable outcomes of vast urbanisation and industrialisation have increased the incidence of major health issues. One such medical condition is infertility, which is currently perceived as a worldwide health problem. Pathophysiological conditions concerning the reproductive system like endometriosis, dysregulated ovarian functions, cervical factors, uterine complications and vaginal infections also affect female fertility to a great extent. Given that these conditions are usually associated with microbial dysbiosis, modulating the microbial population to reinstate eubiosis can certainly alleviate disease symptoms, thereby helping with disease management strategies. Gut microbiota also actively interacts with sex hormones (a concept called

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microgenderome) to regulate the circulating level of the latter and thus affect reproductive health in various ways. Therefore, many microorganisms are now being examined for their potential and promising use in developing various treatment approaches, including probiotics, synbiotics, faecal microbiota transfer (FMT) and vaginal microbiota transfer (VMT). The rationale behind all these options lies in rehabilitating the progenitive niche with a healthy microbial population in order to maintain and regulate the female reproductive system homeostasis.

16.1 Introduction

Humans are born in a virtually germ-free environment. Various microorganisms originating from the mother or other surroundings begin to settle in several body parts shortly after. This early colonisation of bacteria is essential for further development (Kataoka 2016). With time, the human body also referred to as a superorganism (Liang et al. 2018), fosters a tightly populated resident microbial community regulating the functions of their specific residential area. With the advent of high-throughput sequencing techniques and extensive molecular research potential, genital tract microbiota is now being explored in diverse arrays ranging from its identification of taxa to functional capabilities concerning reproductive health, especially in the case of females. The vagina of the female reproductive tract harbours roughly 9% of the human microbial load alone Instances of medical complications in pregnancy and fertility have been associated with a hampered endometrial and cervicovaginal bacterial population. Links have also been identified between infertility and bacterial vaginosis (BV) (Ravel et al. 2021). It is characterised by a transition from *Lactobacillus* spp. dominant bacterial community to a more heterogeneous population comprising mainly of anaerobic bacteria. Women suffering from PCOS, a complex reproductive, neuro-endocrinal and metabolic condition, exhibit a lower α-diversity correlated to higher testosterone concentration and hirsutism score (Thackray 2019). Impaired microbiota structure has also shown links with hyperandrogenism, ovulatory impairment, obesity, insulin resistance and cardiovascular diseases, hence majorly contributing to the pathogenesis of PCOS (He and Li 2020; Torres et al. 2018; Giampaolino et al. 2021). Reproductive health is not only affected by the tiny creatures residing at sites associated with the reproductive system but also by the distant ones present in the gut. Gut microbiota actively communicates with the sex hormones, thereby regulating their levels in circulation. This concept has been termed as “microgenderome” (Flak et al. 2013). Since the *Lactobacillus* species significantly dominate vaginal niche microflora, its role in maintaining reproductive homeostasis and health is also extensively studied. It is the major contributor to the production of antimicrobial factors like lactic acid, hydrogen peroxide, bacteriocins and other organic acids. An indispensable role of microbiota by virtue of its presence all over and inside the human body gives birth to a ray of the possibility of using these commensals for treatment purposes. Different

approaches like probiotics, synbiotics, prebiotics and faecal microbiota transfer (FMT), or a combination of these, are employed to discover the probable hidden effects and establish additional treatment options for diseases in the near future.

16.2 Common Reproductive Problems and Their Microbial Association

16.2.1 Bacterial Vaginosis

The vaginal lumen is a nutrition-rich zone, acting as a favourable niche for a diverse array of microbiota. Though the microbial population in the vaginal milieu keeps fluctuating with different stages of a woman's life, a healthy vaginal microbiota (VMB) of most women is dominated by the Gram-positive, *Lactobacillus* spp capable of maintaining an acidic environment through glycogen fermentation, thereby preventing the overgrowth of exogenous bacteria and viruses. In addition to low pH resulting from the production of lactic acid, the synthesis of biosurfactants and bacteriocins also protects against urinary tract infections and pathogenic microorganisms. Disturbance in the VMB composition (also known as vaginal microbiota dysbiosis) can cause bacterial vaginosis, marked by the loss or a significant decline in the concentration of lactobacilli and an overgrowth of non-lactobacilli, primarily anaerobic bacterial population. The vaginal microbiota is classified into five different categories called as community state types (CSTs) (Ravel et al. 2011). CST I is dominated by *L. crispatus*, CST II by *L. gasseri,* CST III by *L. iners* and CST V by *L. jensenii*. CST IV comprises *Lactobacillus*-deficient type bacteria, most of which are anaerobic and are accountable for causing bacterial vaginosis. A small portion also belongs to partial aerobic bacteria, which are classified by aerobic vaginitis, AV (Gajer et al. 2012). Common microbial genera associated with BV include *Gardnerella*, *Mycoplasma*, *Roseburia*, *Mobiluncus*, *Dialister*, *Prevotella* and *Sneathia* (McMillan et al. 2015; Ceccarani et al. 2019). However, the distinction between a typical/healthy vaginal domain and BV cannot be just based on flora analysis since some bacterial strains are common to both environmental conditions and culturing of the bacterial load alone may result in ambiguous results. Thus, in addition to the vaginal microenvironment analysis, metabolomics also needs to be performed in order to properly characterise the vaginal dysbiosis resulting in diseased states (Vitali et al. 2015). BV most commonly occurs in women of childbearing age but in general, all women/females suffering from BV witness an increased probability of acquiring many gynaecological and obstetric complications like infertility, premature delivery/preterm birth, immature rupture of membranes and miscarriage (Workowski and Bolan 2015; Baqui et al. 2019; Peebles et al. 2019).

16.2.2 Polycystic Ovary Syndrome (PCOS)

PCOS is a highly complex heterogeneous endocrine disease and is one of the most common causes of female endocrine infertility. The worldwide prevalence of PCOS in women of childbearing age varies between 6% and 15%. Urban regions witness more PCOS patients because of improper dietary habits and lifestyle (Deswal et al. 2019). Timely diagnosis and prevention of PCOS are very important in order to combat its rising prevalence (Deswal et al. 2020). This syndrome is mainly characterised by chronic anovulation, hyperandrogenism, insulin resistance and obesity (Apridonidze et al. 2005; Bozdag et al. 2016; Bhatnager et al. 2018). Hyperandrogenism further leads to many dermatological issues like hirsutism, acne, and androgenic alopecia. Irregular ovarian folliculogenesis and alteration of the hypothalamus–pituitary–gonadal axis, on the other hand, cause severe menstrual abnormalities (Azziz et al. 2016). Although the exact aetiology of PCOS is still unclear, several factors have been identified that are suggested to disrupt the hormonal and metabolic balance and contribute to the pathogenesis of this syndrome. One of such important and critical factors is microbiota. A bidirectional relationship between gut microbiota and sex hormones is seen, which involves the modulation of enterohepatic androgen circulation. Elevated concentration of bacterial genera like *Escherichia*, *Shigella* and *Streptococcus* has also been correlated to decreased levels of gut hormones like PYY and Ghrelin (Batra et al. 2022). The widely accepted hypothesis states that this disease originates due to interactions between genetic and environmental factors. Genes regulating folliculogenesis, steroidogenesis, insulin resistance and adipocyte differentiation all might play a critical role in disease development (Franks et al. 2006). Apart from genetic, neuroendocrine, and metabolic factors, gut barrier integrity, endotoxemia and inflammation have been analysed as well. Lower diversity and an altered phylogenetic composition have been observed in the stool samples of PCOS patients. Differences in taxa abundance were also observed that varied with the metabolic factors and did not follow a single transition trend. For example, the concentration of some Gram-negative bacteria mainly belonging to the genera Bacteroides and Escherichia/Shigella significantly amplified in the gut of obese PCOS women. In such cases, lipopolysaccharides produced by these microorganisms induce obesity, insulin resistance and chronic inflammation (Liu et al. 2017), thereby worsening the symptoms of PCOS.

16.2.3 Endometrial Complications

Miscarriage or infertility is also associated with specific endometrial microbiota composition. With next-generation sequencing technologies and the possibility to culture even less than 1% of microorganisms (Wade 2002), the concept of the sterile womb hypothesis has been challenged. Primary studies concerning endometrial microbiota indicate its association with different gynaecological conditions like chronic endometritis (CE) (Moreno et al. 2018), dysfunctional endometrial bleeding

(Pelzer et al. 2018), endometriosis (Wee et al. 2018), endometrial polyps (Fang et al. 2016) and endometrial cancer (Walther-António et al. 2016). The primary cause of CE is a microbial infection in the uterine cavity. The microorganisms frequently detected in the endometrium with CE are *Escherichia coli*, *staphylococcus species Streptococcus species*, *Enterococcus faecalis*, *proteus species*, *Pseudomonas aeruginosa*, *Gardnerella vaginalis*, mycoplasma/ureaplasma species (*Mycoplasma hominis*, *Mycoplasma genitalium* and *Ureaplasma urealyticum*), *Corynebacterium*, *Klebsiella pneumoniae* and yeasts Cicinelli et al. 2008; Cicinelli et al. 2009; Kitaya et al. 2017). This microbiota structure is widely affected by factors like BMI, diet, physical activity, abnormal fluctuation in the levels of circulating hormones, and menstrual cycle irregularities (Dominianni et al. 2015; Claesson et al. 2012; Lynch and Pedersen 2016; Bracewell-Milnes et al. 2018; Wilson et al. 2007). Still, an active debate goes on about whether a unique microbiota resides in the uterine environment or not (Winters et al. 2019) since various technical challenges prevail that make it difficult to study samples with low biomass and to differentiate microorganisms between the ones that actually reside in small quantities from those that arise as a result of contamination/infection (Weyrich et al. 2019). Thus, more extensive research is needed to confirm whether dysbiosis in the uterus is a cause or consequence of disease pathology.

16.3 Pathophysiology

16.3.1 Microgenderome

Recently, the concept of "microgenderome" has come into play. It signifies the bidirectional interactions that take place between sex hormones and gut microbiota. Gut microbiota regulates sex hormone levels by means of interactions among its metabolites, the immune system and some nerve–endocrine axes, such as the gut–brain axis (He et al. 2021). The gut microbiome shows β-glucuronidase enzyme activity (Beaud et al. 2005). This enzyme prevents oestrogen from binding with glucuronic acid as a result of which, the oestrogen concentration increases in the body. Some studies also indicate the involvement of enterohepatic circulation (Liu et al. 2021). In this process, the β-glucuronidase activity shown by the bacterial species in the gut causes deconjugation of conjugated oestrogens that take place in the liver for excretion through bile. Such enhanced levels of oestrogen can further cause a surge in the migration and adhesion capabilities of the cells having oestrogen receptor, thereby contributing to the colonisation and metastasis of ovarian cancer (Wallace et al. 2010). Thus, it can be said that gut microbiota may play an indirect role in the development of ovarian cancer and other such oestrogen-driven diseases by regulating the amount of active oestrogen circulation (Shen et al. 2012). Microorganisms containing genes for β-glucuronidase also affect androgens in a similar way. These bacteria carry out side-chain cleavage of glucocorticoids, converting them into androgens, causing their elevation in the body and hence participating in the pathogenesis of PCOS. *Edwardsiella*, *Bacteroides*, *Collinsella*,

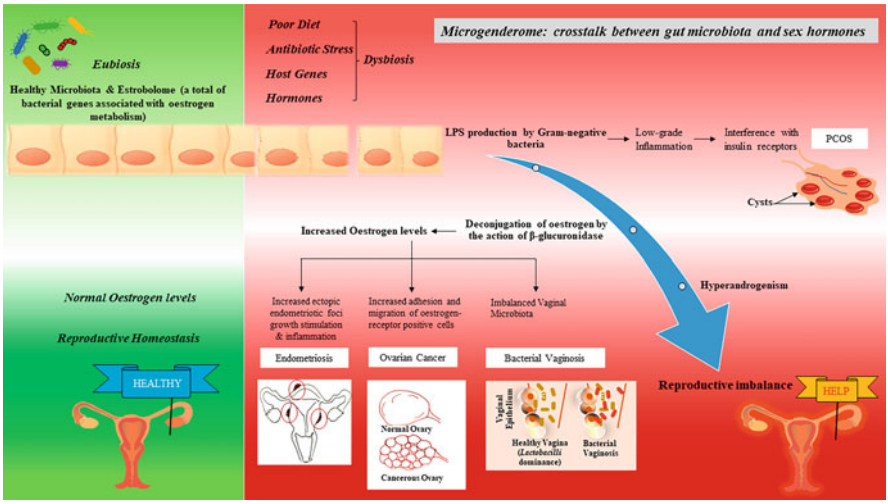

Fig. 16.1 Microgenderome: crosstalk between gut microbiota and sex hormones

Propionibacterium, *Bifidobacterium*, *Escherichia Clostridium*, *Faecalibacterium*, *Alistipes*, *Lactobacillus*, *Roseburia*, *Citrobacter*, etc., are some of the examples of such bacteria (Kwa et al. 2016). Figure 16.1 provides an overview of how microgenderome affects the reproductive health of a female.

16.3.2 Gut–Brain Axis

The gut and brain are very well interconnected through highly characterised channels of communication. Endocrine, neural, and inflammatory mechanisms are tightly integrated to make these channels work. Variations in the small intestinal permeability and blood–brain barrier may modulate this communication network. Another factor that tends to regulate this axis is brain–gut microbiome interaction (Osadchiy et al. 2019). The gut microbiome connects to the central nervous system via its metabolic intermediates such as short-chain fatty acids (SCFAs), secondary bile acids (2BAs), and tryptophan metabolites. 90–95% of colonic SCFAs include acetate, butyrate and propionate. They maintain a lower pH, favouring the growth of bacteria that promote a state of homeostasis, such as *Bifidobacteria* and *Lactobacillus,* and hinder the establishment of opportunistic pathogenic bacteria, including *Clostridium* and *E. coli*. SCFAs also aid in preserving the function of the gut barrier (Amabebe and Anumba 2020). These components stimulate the regeneration of epithelial cells and the production of mucus and antimicrobial peptides. This inhibits the translocation of toxins and bacteria into the bloodstream, preventing infections. The gut microbiome can regulate the activation of pathways leading to inflammation, brain–gut peptide secretion and proliferation of islet cell, which may result in

abnormal or excessive fat accumulation, compensatory hyperinsulinemia and insulin resistance in case of dysbiosis (Vrieze et al. 2010; Barber et al. 2016). Food intake control is also modulated by these SCFAs via an increase in the production of hunger-suppressing hormones, like peptide YY, glucagon-like peptide-1 and leptin, eventually reducing excessive food intake. On the other hand, reduced production of SCFAs is associated with obesogenic and pro-inflammatory mechanisms (Larraufie et al. 2018). Obese PCOS women have an abnormal proportion of brain–gut axis intermediaries, which has been linked to PCOS-related clinical phenotypes. Gram-negative bacteria also produce lipopolysaccharides that pass through the gut wall, enter the circulation and cause low-grade inflammation. Immune system activation then interferes with the insulin receptors, elevating the insulin levels, which further increase testosterone production in the ovary, contributing to PCOS. Thus, it is important to avoid gut microbiota dysbiosis, which might take a toll on the reproductive health of women (Tremellen and Pearce 2012).

16.3.3 Prenatal Episodes of Microbiota Exposures

With the advent of new techniques, the placenta has now been shown to harbour microorganisms that affect the growth and development of the foetus (Cao et al. 2014). Several studies illustrate a unique microbial profile associated with the placenta, thereby opening the possibility for the maternal–foetal spread of commensal microorganisms, leading to colonisation of a microbial community at a prenatal stage. Through research done on samples from infant and maternal faeces, amniotic fluid, placenta, meconium and colostrum from mother–infant pairs, it was noted that a less abundant and less diverse microbiota with a predominance of Proteobacteria is present in placenta and amniotic fluid. Further, infant meconium displays shared features in the microbiota composition, thereby pointing towards a microbial transmission from mother to foetus. 3–4 days after birth, a newborn's gut microbiota structure resembles that of colostrum, thus outlining the stepwise establishment of the gut microbiome (Collado et al. 2016). Studies indicate a relationship between infections and inflammation with preterm births (PTBs). It has been assumed that infections that cause PTB initiate in the reproductive or genitourinary tract from where they rise upward via the cervix and breach the placental barrier. (Cao et al. 2014). Therefore, it is essential to shift our focus on the microbial ecology of the placenta and amniotic fluid, in particular, to avoid any malfunctioning of these sites and ensure proper growth and development of the foetus. Many eminent scientists favour the traditional belief and not the studies claiming microbiota colonisation of these parts of the human body. This is because most of these studies have identified the fragments of microbial DNA, their metabolites and some pathogenic strains, which might be translocated or leaked from maternal tissues into the so-called privileged sites, thus crossing the placental barrier and affecting the growth of the foetus. No clear evidence has been provided to assure the presence of live microbiota that has established a proper colony/niche with well-defined host–microbe interactions and their related functional outcomes. The presence of germ-free mice

again points to sterility (Blaser et al. 2021). Thus, it can be said that actual microbiota is still in the process of being discovered in such germ-free habitats. New findings undoubtedly lay a foundational base for further research and help open up the gate to an altogether different direction that might bring out changes highly beneficial for society in the future. Hence, it can be said that there exists some association, direct or indirect, though way more exploration is required to understand the underlying interaction comprehensively and the magnitude of these connections affecting the in utero generations.

16.3.4 An Indispensable Role of Lactobacilli

In healthy reproductive-aged women, vaginal microenvironment and eubiosis are mainly characterised by the *Lactobacillus* species-dominated microbial population. These bacteria serve as active players in the game of reproductive homeostasis (Mendling 2016). Figure 16.2 provides a simple illustration of the establishment of Lactobacilli species in the vagina and the importance of lactic acid produced by them.

The rationale behind Lactobacillus dominance in VMB lies in the fact that these bacteria produce an ample amount of lactic acid as a result of glycogen fermentation, maintaining a pH $<$ 4.5 and producing many other antimicrobial factors that help fight against infections. Some of these factors include the following:

1. *Lactic Acid:* The bactericidal action of this acid is facilitated in its protonated form (active at pH $<$ 3.9) and not as a lactate anion (O'Hanlon et al. 2011). The latter anionic form is less membrane-permeant and requires the use of GPR81 receptor (Ahmed et al. 2009) or monocarboxylate transporters (Kuchiiwa et al.

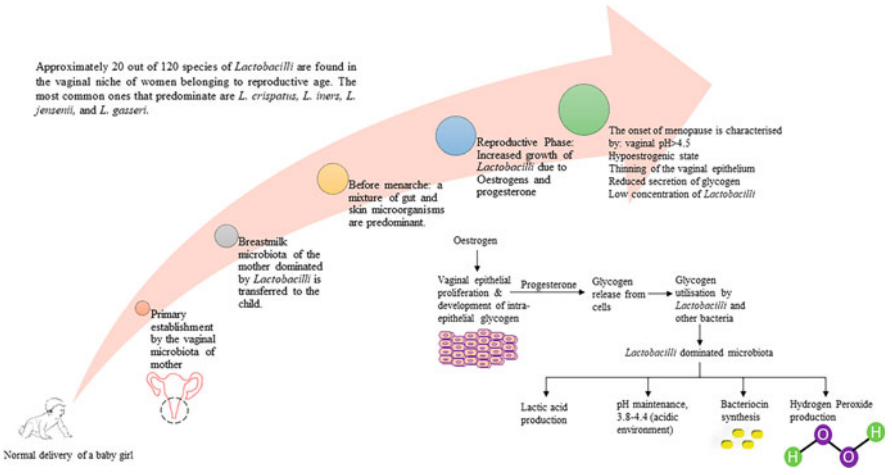

Fig. 16.2 Vaginal microbiota colonization and role of Lactobacilli

2011). This kind of complex lactate shuttle is not seen in the case of the protonated form of lactic acid, which, upon cell entry, acidifies the cytosol, interfering with the cellular metabolism and leading to cell death (Kashket 1987). Production of lactic acid alone by species like *L. gasseri* and *L. crispatus* can inhibit the infections caused by *Neisseria gonorrhoeae* (Graver and Wade 2011), *Chlamydia trachomatis* (Gong et al. 2014) and *Escherichia coli* (Valore et al. 2002). These pathogenic strains were seen to be inactivated in vitro. The acidic environment sustained in the vaginal niche also inhibits the growth and colonisation of pathogenic microorganisms. Lactic acid also exhibits virucidal activity. Reduced rate of viral shedding into the lower female reproductive tract has been seen in HIV-positive women harbouring Lactobacillus-enriched microbiota (Mitchell et al. 2013). The potential inactivation of HIV-1 in such cases is multifactorial that involves modulating the viral lipid envelop integrity, affecting the viral surface proteins and negating the viral core protein functionality (Tachedjian et al. 2017). This genus also makes women less likely to get infected with other viruses like herpes simplex virus 2 (HSV-2) (Borgdorff et al. 2014). Lactobacilli either indirectly prevent this disease by inhibiting viral entry, replication and reducing adhesion capacity or by directly exerting effects via lactic acid (Conti et al. 2009).

Apart from antimicrobial activities, lactic acid showcases *immunomodulatory properties* too. Studies have shown that treating cervicovaginal cells with the protonated form of lactic acid can result in a dampening effect on the production of pro-inflammatory cytokines and chemokines stimulated by Toll-like receptor 1/2 agonist Pam3CSK that mimics the bacterial and viral pathogen-associated molecular patterns (PAMPs) of BV-associated bacteria and HIV (i.e. gp120) (Hearps et al. 2014; Hearps et al. 2017). The mucus lining of the inner epithelium of the female genital tract acts as the first line of defence against pathogenic invasions. When any microorganism disrupts and makes its way across this layer, the epithelial cells identify the organism by using pattern recognition receptors and producing an inflammatory response. To maintain the immune equilibrium, lactic acid induces the production of anti-inflammatory cytokines like IL-10 to lower the production of pro-inflammatory cytokine IL-12 in dendritic cells (DCs) and reduces the cytotoxicity of natural killer cells. The presence of other organic acids produced by vaginal microbiota also favours the anti-inflammatory activity of lactic acid. A slight reduction in the production of other pro-inflammatory factors, for example, cytokine IL-6, IL-1 and macrophage inflammatory protein three alpha (MIP-3α), has also been documented (Li et al. 2020).

2. *Hydrogen Peroxide (H_2O_2):* It is another compound having antimicrobial properties. 94–95% of the strains of *L. crispatus* and *L. jensenii* produce H_2O_2 (Antonio et al. 1999). Hydrogen peroxide alone is microbicidal for many bacterial species. This microbicidal activity is 10- to 100-fold greater when combined with chloride anion and myeloperoxidase, both of which are found in the vagina (Ravel et al. 2011; Gajer et al. 2012). This vaginal antimicrobial defence system (H_2O_2, chloride anion and myeloperoxidase) has potent in vitro activity against *E. coli* and other microorganisms (Stapleton 2017). Using H_2O_2 resulted in

eliminating some major symptoms of BV like malodorous leucoxanthorrhoea in 89% of women under study. It also fostered the clue cells and anaerobic pathogenic flora to disappear from the vaginal smears and vaginal secretions in 100% of the cases (Cardone et al. 2003). Since the levels of dissolved O_2 are low in the vaginal compartment, high concentrations of (H_2O_2) cannot just be detrimental to the growth of lactobacillus species. Still, they might favour the growth of bacteria responsible for dysbiosis, causing gynaecological infections (O'Hanlon et al. 2011).

3. *Bacteriocins:* Bacteriocins are proteinaceous substances secreted by some bacteria and pose bactericidal activities to halt and prevent the growth and colonisation by microorganisms that are usually closely related to the microorganism producing the bacteriocins (Stoyancheva et al. 2014). Bacteriocins are mainly classified into two types. Class I constitutes lanthionine-containing bacteriocins (lantibiotics) and class II contains non-lanthionine-containing peptides. Class I elements cause pore formation, resulting in the uncontrolled efflux of small metabolites from the sensitive cells or inhibit enzyme activities, while class II types are active by inducing permeabilisation of membrane gains, causing the leakage of internal metabolites from target bacteria (Cotter et al. 2005). These are synthesised by *Lactobacillus* species, specifically *L. gasseri* and *L. crispatus*. These bacteria encode genes corresponding to antimicrobial bacteriocins like acidocin F221A, J46, IIa, IIc, type A lantibiotic and gassericin T (Stoyancheva et al. 2014). Bacteriocin production is one of the chief antagonistic mechanisms for avoiding undesirable microbial colonisation.
4. *Biosurfactants (BS):* Some microorganisms produce amphiphilic compounds called biosurfactants that either remain anchored to their surface or are secreted outside into the surrounding environment. These compounds are mostly secondary metabolites and are characterised by excellent emulsifying properties (Van Hamme et al. 2006). These molecules facilitate nutrient transportation to support the producer microorganism survival and actively fight against opportunistic and pathogenic microorganisms by serving as anti-adhesive, antimicrobial and anti-biofilm agents (Satpute et al. 2016; Sharma and Saharan 2016; Sambanthamoorthy et al. 2014). A non-homogenous lipopeptide molecule (BS) isolated from vaginal *L. crispatus* has been shown to reduce the growth of *Candida* spp. by interfering with its ability to adhere to the cervical epithelial wall and thus alleviating the mucosal damage caused during vulvovaginal candidiasis (VVC) (De Gregorio et al. 2020).

16.4 Microbiota in Therapeutics: An Evolving Concept!

An indispensable role of microbiota, by virtue of its presence all over and inside the human body, gives birth to a ray of the possibility of using these commensals for treatment purposes as well. Much research, including clinical and randomised controlled trials on various diseases, is being carried out to explore any possible therapeutic function of a microorganism if present. Different approaches like

probiotics, faecal microbiota transfer (FMT), synbiotics, prebiotics or a combination of these are employed to discover the probable hidden effects and establish additional treatment options for diseases in the near future. Despite being characterised by differences in their constituents, nature, mode of administration and factors affecting the efficacy, the basic principle behind all these methods mentioned above lies in the ultimate aim to recover the typical microbial environment that has been imbalanced. These therapeutic options are usually used as adjuvant therapies and not straightaway as the first or only line of treatment.

Probiotics Probiotics are "live microorganisms, which when consumed in adequate amounts, confer a health benefit on the host" (FAO/WHO 2001). It is important to note that whether a probiotic contains a single microorganism or a consortium of microbial strains, and the composition is always defined/known with well-established viability and efficacy. Also, probiotics should not be confused with commensal microorganisms. In gynaecology and obstetrics, probiotics are living, beneficial microorganisms, mainly consisting of *Lactobacillus* species given in adequate quantity to restore physiological vaginal microflora to treat BV and other reproductive tract disorders (Buggio et al. 2019). *Lactobacillus* spp, owing to their capability of potentiating the effect of antibiotics, can act as effective antimicrobial adjuvants (Larsson et al. 2011). Different species of *Lactobacillus* like *Lactobacillus rhamnosus* (E21 and L3), *Lactobacillus salivarius* (N30) (Pino et al. 2019), *Lactobacillus* strain (SQ0048) (Niu et al. 2019), *Lactobacillus rhamnosus* GR1, *Lactobacillus buchneri* (DSM 32407) (Peter et al. 2018) and many other have remarkable properties that make them capable of regulating and maintain reproductive health. Some characteristics include tolerance to low pH/maintenance of low pH, ability to colonise both intestinal and vaginal epithelia, production of hydrogen peroxide, bacteriocins and organic acids and skill to co-aggregate and prevent the growth of pathogenic microorganisms. Some strains like *Lactobacillus rhamnosus* CECT8361 and *Bifidobacterium longum* CECT7347 also have anti-inflammatory and antioxidant activities (Valcarce et al. 2017). Other genera, for example, *Bifidobacterium lactis* V9 and Bacillus species (*B. clausii*, *B. subtilis and B. coagulans*), also showcase such probiotic effects. Further functional properties comprising tolerance to bile salts, acids and lysozyme are also essential for such microorganisms to get through the gastrointestinal tract and reach the target site of action (Hashem and Gonzalez-Bulnes 2022). Since glycogen is an energy source for lactobacilli, a combination (Gynoflor) of low-dose oestriol and live lactobacillus has been reported for glycogen production and re-establishment of normal vaginal microbiota (Ozkinay et al. 2005). Several studies have suggested that using probiotics helps decrease metabolic intestinal endotoxemia, insulin resistance and the production of inflammatory mediators and improves glycaemic control in women with PCOS (Akbari and Hendijani 2016; Ruan et al. 2015). Oral capsules containing *L. reuteri* (formerly *L. fermentum*) and *L. casei var. rhamnosus* significantly modulate the vaginal flora, resulting in a good percentage of treatment success rate (Reid et al. 2003). Oral feeding of *Bifidobacterium longum* NK49 and *Lactobacillus plantarum* NK3 alleviates *Gardnerella vaginalis* (GV)-induced vaginosis in female mice.

These bacteria exhibit anti-inflammatory activities by inhibiting the excessive expression of TNF-α and NF-κB activation in the vagina and uterus with a simultaneous decrease in the vaginal GV population (Kim et al. 2019). This example again reflects upon the importance of gut microbiota restoration in maintaining a homeostatic reproductive environment. However, the guidelines on using probiotic formulations for gynaecological concerns differ between countries since there is no universal background, and the presence of inconsistencies in results has led to inconclusiveness (Barrientos-Durán et al. 2020).

Prefilled vaginal applicators also use such species to encourage a favourable community state type. Post-antibiotic administration of *L crispatus* CTV-05 (Lactin-V, Osel) in women suffering from BV resulted in a lower rate of BV recurrence at 3 months compared to the placebo group (Cohen et al. 2020). Use of topical gels containing lactic acid has been assessed for tolerability and efficacy when administered as an adjuvant to metronidazole in a study concerning BV treatment. Gels like Lactacyd vaginal gel (LVG) contained lactic acid (225 mg) and prebiotic glycogen (5 g) to promote the growth of *Lactobacillus*. The combination was superior to antibiotic treatment alone (Decena et al. 2006).

Prebiotics Prebiotics can be defined as nutrients that promote the growth and activities of probiotic microorganisms, specifically favouring Lactobacilli and Bifidobacteria over potentially harmful bacteria, which may be proteolytic and putrefactive in nature. This way, prebiotics intend to deliver health benefits to the host and are gaining considerable interest in developing new therapeutic approaches. The most commonly known prebiotic nutrient components are inulin, fructooligosaccharides (FOS), lactulose and galactooligosaccharides (GOS). By favouring the growth of "good" bacteria, these prebiotics help reduce fasting glucose, total cholesterol, LDL cholesterol, HDL cholesterol and serum TG levels (Altun and Yıldız 2017). Some prebiotics also control hyperglycaemia and HOMA-IR (Fernandes et al. 2017). In women with PCOS, resident dextrin consumption may improve hirsutism, androgen levels and menstrual cycle irregularities (Gholizadeh Shamasbi et al. 2019). Considering the role of probiotics and prebiotics, if these components are combined, then what we would get will be a *synbiotic* featuring the advantages of both, resulting in coactive effects. Antibiotics also form a part of the strategic group, but it has been seen to reduce the bacterial diversity even of desired residents because of broad-spectrum activity, thereby disturbing communal harmony.

Faecal Microbiota Transfer (FMT) Lately, interest in using FMT to treat chronic gastrointestinal infections and inflammatory bowel diseases has been increasing. FMT involves the faecal microbiota transfer from a healthy donor into the recipient's (patient) intestinal tract (Smits et al. 2013). It helps transmit and increase the concentration of good bacteria at the disturbed site in the recipient and lower the severity of symptoms in ways such as restoring community structure and functions through engraftment or refurbishing the lost metabolome. However, the exact mechanisms are unclear (Libertucci and Young 2019). Recent findings suggest

FMT's promising role in managing female genital disorders associated with microbiota alterations. Crosstalk between the resident bacterial strains of the gut and vagina results in local and systemic immune regulation. Concerning this fact, genetic engineering of particular commensal bacterial species can be done to develop oral vectors proficient in eliciting immune responses to prevent or alleviate disease symptoms. These vectors can express specific antigenic proteins, thereby triggering a local immune response and the production of antibodies. Successful intravaginal immunization of mice against human papillomavirus infection suggests that mucosal colonisation with commensal recombinant bacteria can sure pave the way for developing new vaccines to fight sexually transmitted diseases (STDs) (Medaglini et al. 1997). In addition, rectal boosting, that is, administration of live attenuated strains, may also cause the cervicovaginal environment to become immunologically stimulated (Kutteh et al. 2001). Furthermore, faecal microbiota transfer poses an alternative to bacterial vectors and a better option since, with only one or a few more faecal microbiota infusions, an enormous number of bacteria along with their metabolites can be transferred, all of which are capable for volunteering to induce the local and systemic immune responses (Quaranta et al. 2019). An intervention of FMT from healthy rats into PCOS-induced rat models resulted in restored gut microbial profile, characterised by an increased *Clostridium* and *Lactobacillus* and a decreased *Prevotella* population indicating that the gut microbiota dysbiosis plays an important role in the pathogenesis of PCOS (Guo et al. 2016).

Vaginal Microbiota Transfer (VMT) It involves the transfer of healthy vaginal microbiota isolated from a healthy donor into the patient's (recipient's) vagina to retract dysbiosis and promote overall microbial diversity and stability. Since VMT has substantial uncertainty, whether it will always reinstate the beneficial microbiota or not still needs to be researched (DeLong et al. 2019). Table 16.1 lists different therapeutic interventions done using microbiota-targeted approaches to treat various female reproductive health-related conditions.

16.5 Conclusion

Human microbiome causes a significant impact on human health, regulating the metabolism at all levels and in all parts of the body. The past decade has provided evidence that the female reproductive system also harbours a specific microbial community and that a balance (eubiosis) among different populations is critical to reproductive fitness. Undesirable changes in the microbial community design can lead to dysbiosis and cause reproductive failure. Since these microorganisms form an essential part of the metabolism, immunity and many physiological interactions, manipulating these tiny residents can provide a great platform to manage disease pathologies and alleviate symptoms. Reinstating the favourable microbial population and establishing a state of eubiosis can lay the immense potential to not just serve as an adjunct therapy but also to provide a permanent solution to combat various female reproductive health conditions like infertility, PCOS and BV, which

Table 16.1 Therapeutic interventions using microbiota-targeted approaches to treat female reproductive health-related conditions

Study design	Location	Probiotic strains	Disease/ condition	Number of participants	Duration of intervention	Inference	Reference
Randomised double-blind Placebo-controlled trial	Auckland and Wellington, New Zealand	*Lactobacillus rhamnosus* HN001	Postpartum Symptoms of depression and anxiety	423 women (recruited at 14–16 weeks of gestation) Probiotic: 212 Placebo:211	From enrolment until 6 months postpartum if breastfeeding	Significant reduction in depression and anxiety scores	Slykerman et al. (2017)
Prospective double-blind randomised controlled trial	Brisbane, Australia	*Lactobacillus rhamnosus* and *Bifidobacterium animalis* subspecies *lactis*	Gestational diabetes mellitus (GDM)	411 overweight and obese women	From second trimester until 28 weeks gestation	Rates of GDM were not lowered in the probiotic group	Callaway et al. (2019)
Randomised, double-blind, placebo-controlled trial	Bangkok, Thailand	*Bifidobacterium* and *lactobacillus*	Insulin resistance in pregnant women (diet-controlled (GDM)	Women at 24–28 weeks of gestation Probiotic: 28 Placebo: 29	Four consecutive weeks	Glucose metabolism improved significantly	Kijmanawat et al. (2019)
Randomised, double-blinded, placebo-controlled clinical trial		*Lactobacillus acidophilus, lactobacillus reuteri, lactobacillus fermentum* and *Bifidobacterium bifidum* plus 200 μg/day selenium	Polycystic ovary syndrome	60 subjects (18–40 years old)	12 weeks	An improvement in mental health parameters, total serum testosterone and hirsutism was observed post-co-administration of the probiotic with selenium. MDA, GSH and TAC levels also improved	Jamilian et al. (2018)
Double-blind placebo-controlled	Iran	*Lactobacillus acidophilus* LA-5, *Bifidobacterium* BB-12, *streptococcus*	Inflammation and oxidative stress	64 pregnant women with GDM	Eight consecutive weeks	Statistically, significant improvement was observed in	Hajifaraji et al. (2018)

randomised clinical trial		*Thermophilus* STY-31 and *lactobacillus delbrueckii bulgaricus* LBY-27	biomarkers in GDM			C-reactive protein, tumour necrosis factor-α, erythrocyte glutathione peroxidase and malondialdehyde, glutathione reductase levels	
Two-Centre double-blind, randomised, placebo-controlled parallel	Auckland and Wellington, New Zealand	Lactobacillus rhamnosus HN001 (HN001)	GDM	Pregnant women (with a personal or partner history of atopic disease) randomised at 14–16 weeks' gestation. Participants (*n* 423) randomised to the HN001 (*n* 212) placebo group: (*n* 211)	From enrolment throughout pregnancy and until 6 months post birth if still breastfeeding	Probiotic supplementation might reduce the prevalence of GDM, especially in older women and women with a history of GDM	Wickens et al. (2017)
Randomised, blinded, placebo-controlled clinical trial	Rwanda	Lactobacillus rhamnosus GR-1 and lactobacillus reuteri RC-14	Microbiota and metabolomic analysis of vaginal samples	Healthy pregnant women (aged 18–55 years) with a gestational age <36 weeks	1 month	According to microbiota and metabolomics data, low diversity and lactobacillus dominance were seen to be associated with a healthy vagina, and these women were less likely to give preterm births	McMillan et al. (2018)
A randomised (1:1) double-blind, placebo-controlled trial	Poznan University of Medical Sciences, Poland	2 strains of *Bifidobacterium lactis* (W51 and W52), *lactobacillus acidophilus* (W22),	Polycystic ovary syndrome	65 women with PCOS and BMI > 25	Evaluations first performed at baseline and then repeated after	8% decrease in the BMI of the symbiotic-supplemented group was noted	Chudzicka-Strugała et al. (2021)

(continued)

Table 16.1 (continued)

Study design	Location	Probiotic strains	Disease/ condition	Number of participants	Duration of intervention	Inference	Reference
		lactobacillus paracasei (W20), *lactobacillus plantarum* (W21), *lactobacillus salivarius* (W24) and *lactobacillus lactis* (W19) and the prebiotics fructooligosaccharides and inulin			3 months of intervention	with a reduction in the circumference of the waist, hip and thighs as well. Testosterone levels also lowered significantly post-symbiotic administration	
Randomised double-blind, placebo-controlled trial		*Lactobacillus acidophilus*, *lactobacillus casei* and *Bifidobacterium bifidum* plus 0.8 g inulin	Polycystic ovary syndrome	60 women diagnosed with PCOS Synbiotic: 30 Placebo: 30	12 weeks	A substantial increase in the plasma nitric oxide (NO) levels, serum sex hormone-binding globulin (SHBG) and a decrease in Ferriman Gallwey (mF-G) scores and serum high-sensitivity C-reactive protein (hs-CRP) was observed indicating beneficial effects on these parameters. No effect was seen on other oxidative biomarkers	Nasri et al. (2018)

Prospective, randomised, double-blind, placebo-controlled trial	Kashan, Iran	*Lactobacillus acidophilus* strain T16 (IBRC-M10785), *lactobacillus casei* strain T2 (IBRC-M10783) and *Bifidobacterium bifidum* strain T1 (IBRC-M10771) plus 800 mg inulin	Glycaemic control, lipid profile and atherogenic index (AIP) of women suffering from PCOS	60 patients with PCOS (aged 18–40 years) Synbiotic: 30 Placebo: 30	12 weeks	A substantial decrease in the following parameters was observed: Triglycerides, AIP and VLDL cholesterol levels. Lipid profiles were not much affected by the treatment	Samimi et al. (2019)
Randomised, controlled, triple-blinded, parallel trial study	Iran	SPJ: Inulin and lactobacillus per week, for 8 weeks PJ: Pomegranate juice per week, for 8 weeks SB: Synbiotic beverage per week, for 8 weeks, (each litre of the beverage contains 1 L of water +20 g of inulin +2 × 10^8 CFU/g lactobacillus + pomegranate flavouring)	Sex hormone, glycaemic profiles and anthropometric indices in women with PCOS	92 PCOS patients (aged 15–48 years) 3 treatment groups (23 subjects each) Synbiotic pomegranate juice (SPJ) Pomegranate juice (PJ) Synbiotic beverage (SB) 1 control group (water + pomegranate flavouring)	2 L of beverage weekly	The new beverage SPJ can improve insulin, insulin resistance, BMI, weight and testosterone levels	Esmaeilinezhad et al. (2019)
Randomised double-blinded placebo-controlled clinical trial	Tabriz, Iran	Each synbiotic capsule contained seven strains (*lactobacillus casei*, *lactobacillus rhamnosus lactobacillus bulgaricus*, *lactobacillus acidophilus*, *Bifidobacterium longum* and *Streptococcus*	Metabolic factors and obesity values in women PCOS	68 overweight or obese women with PCOS (aged 20–44 years); 34 subjects in synbiotic and placebo groups each	8 weeks	Serum fasting glucose, insulin, BMI, waist and hip circumference decreased significantly. An increase in HDL cholesterol was also observed	Darvishi et al. (2021)

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Table 16.1 (continued)

Study design	Location	Probiotic strains	Disease/ condition	Number of participants	Duration of intervention	Inference	Reference
		thermophilus) and inulin-type prebiotics (Fructooligosaccharides (FOS))					
A pilot randomised controlled trial	Sydney, Australia	*Lactobacillus rhamnosus* GR-1 (GR-1) *and lactobacillus fermentum/reuteri* RC-14 (RC-14)	Group B streptococcal colonisation rates in vagina of pregnant women	34 women (36 weeks pregnant) positive for GBS Control group: 13 Intervention group: 21	Oral dose (daily for 3 weeks or until they gave birth)	More number of vaginal commensals found in probiotic group. Still, expected results not achieved Probable reasons: Problem might lie in the length of intervention, concentration of dosage, selection of probiotic strain, inadequate sample size or route of administration	Olsen et al. (2018)
Prospective pilot clinical assay	Spain	*L. salivarius* CECT 9145	Rectal and vaginal eradication of *Streptococcus agalactiae* (GBS)	57 pregnant women with age between 25 and 36 years (39 vaginal and rectal GBS positive and 18 rectal and vaginal GBS negative)	Week 26 to week 38 of pregnancy	Probiotic intervention caused 68% and 72% of the women to be GBS negative as analysed from in the vaginal and rectal samples, respectively	Martín et al. (2019)

Double-blind, placebo-controlled study	Finland	*Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* Bb12	Pregnancy outcome; prenatal and postnatal growth	256 women at first trimester of pregnancy	First trimester of pregnancy to the end of exclusive breastfeeding	Frequency of GDM reduced post-probiotic treatment; no adverse events occurred in mother or child	Luoto et al. (2010)
Phase I placebo-controlled, randomised, double-blind study, dose-ranging safety trial	San Francisco (UCSF), USA	Lactobacillus crispatus CTV-05 (LACTIN-V) (vaginal applicator)	Safety trial for bacterial vaginosis	Twelve healthy volunteers	Product used for 5 consecutive days; follow-up on days 7 and 14. Phone interviews on days 2 and 35	31 mild and 4 moderate adverse events occurred out of which the moderate ones were unrelated to product use. Colposcopy findings and laboratory parameters were within normal limits. The product was well-tolerated and accepted	Hemmerling et al. (2009)
Phase 2a (randomised, double-blind, placebo-controlled trial)	San Francisco (UCSF), USA	Lactobacillus crispatus CTV-05 (LACTIN-V) administered by a vaginal applicator	Safety trial for bacterial vaginosis	24 women with BV Group receiving product: 18 Placebo: 6	Once daily for 5 days (days 1–5) followed by once weekly for 2 weeks (days 12 and 19)	Grade 3 or 4 adverse events not observed. No deep epithelial disruption seen during colposcopy. The product was well-tolerated, safe and accepted by women with BV	Hemmerling et al. (2010)

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Table 16.1 (continued)

Study design	Location	Probiotic strains	Disease/ condition	Number of participants	Duration of intervention	Inference	Reference
Prospective, randomised, single-blinded clinical trial	Kashan, Iran	Probiotic yoghurt containing *lactobacillus acidophilus* La5 and *Bifidobacterium animalis* BB12	Inflammatory factors in pregnant women	Primigravida and singleton pregnant women (18–30 years) Probiotic yoghurt group: 37 Conventional yoghurt group: 33	28–37 weeks of gestation	Probiotic yoghurt caused significant decrease in hs-CRP levels, but no effect was seen on TNF-alpha levels	Asemi et al. (2011)
Randomised double-blind, placebo-controlled trial	Arak, Iran	*Lactobacillus acidophilus*, *L. casei* and *Bifidobacterium bifidum*	Glycaemic control and lipid profiles in gestational diabetes	Sixty primigravida pregnant women (18–40 years of age) Probiotic group: 30 Placebo: 30	6 weeks	Serum insulin homoeostasis model assessment (HOMA) for insulin resistance and for β-cell function fasting plasma glucose levels significantly decreased. VLDL cholesterol and serum triglyceride levels also reduced. However, no changes were found in lipid profiles	Karamali et al. (2016)
Double-blind, placebo-controlled, randomised trial	Italy	4 strains of lactobacilli (*L. acidophilus* DSM 24735, *L. plantarum* DSM 24730, *L. paracasei* DSM 24733, *L. delbrueckii* subsp. bulgaricus DSM 24734), 3 strains of	Breast milk composition	66 women Probiotic: 33 Placebo: 33	36th week of pregnancy until 4 weeks after giving birth	The concentration of both lactobacilli and Bifidobacteria was higher in colostrum and mature milk of women taking probiotics. This	Mastromarino et al. (2015)

		Bifidobacteria (*B. longum* DSM 24736, *B. breve* DSM 24732, *B. infantis* DSM 24737) and 1 strain of *Streptococcus thermophilus* (DSM 24731)				study also indicates that modulation of breast milk composition probably occurs through a systemic effect	
Randomised placebo-controlled clinical trial	Iran	Probiotic *lactobacillus sporogenes* (1×10^7 CFU), 0.04 g inulin as prebiotic with 0.38 g isomalt, 0.36 g sorbitol and 0.05 g stevia as sweetener per 1 g	Glycaemic status and serum hs-CRP in pregnant women	52 pregnant women (primigravida), aged 18–35 years Control: 26 Synbiotic: 26	9 weeks	Substantial reduction in serum insulin levels with a significant rise in QUICKI score. No effect on FPG and serum hs-CRP levels	Taghizadeh and Asemi (2014)
Randomised, double-blind, placebo-controlled study	Malaysia	*L. Plantarum* LP115, *L. helveticus* LA25, *L. rhamnosus* LRH10, *L. paracasei* LPC12, *L. fermentum* LF26 and *L. delbrueckii* subsp. *lactis* LDL114 (mixture ratio of LP115: LA25: LRH10: LPC12: LF26: LDL114 = 3: 3: 3: 6: 1: 3)	Vaginal candidiasis in pregnant women	78 pregnant women with VC (lactobacilli, $n = 39$; placebo, $n = 39$)	8 weeks	Probiotic supplementation proved to be beneficial in alleviating the vulvovaginal symptoms (irritation, discharge and burning) and recurrences of VC. Social and emotional distress related to VC also reduced	Ang et al. (2022)
Prospective, double-blind randomised clinical trial	Taiwan	*Lactobacillus rhamnosus* GR-1 and *lactobacillus reuteri* RC-14	Group B streptococcus (GBS) colonisation in	10 group B streptococcus (GBS)-positive subjects (pregnant, at	From the time of recruitment until delivery	Probiotic administration could reduce the rate of vaginal and	Ho et al. (2016)

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Table 16.1 (continued)

Study design	Location	Probiotic strains	Disease/ condition	Number of participants	Duration of intervention	Inference	Reference
			pregnant women	35–37 weeks of gestation)		rectal GBS colonisation in pregnant women	
Randomised, double-blind, placebo-controlled trial	Iran	*Lactobacillus acidophilus*, *lactobacillus casei* and *Bifidobacterium bifidum* (2×10^9 colony-forming units/g each) plus 800 mg inulin	Insulin metabolisms and lipid profile in patients with GDM	70 patients with GDM (ages 18–40 years) Synbiotic group: 35 Placebo group: 35	6 weeks	Significant reduction serum TAG and VLDL cholesterol concentrations and serum insulin levels homoeostatic model assessment for insulin resistance and homoeostatic model assessment for β-cell function	Ahmadi et al. (2016)
Randomised single-blinded controlled clinical trial	Kashan, Iran	Commercially available yoghurt prepared with the starter cultures of *Streptococcus thermophilus* and *lactobacillus bulgaricus*, enriched with the probiotic culture of two strains of lactobacilli (*lactobacillus acidophilus* LA5) and bifidobacteria (*Bifidobacterium animalis* BB12) with a	Insulin resistance in pregnant women	Pregnant women, primigravida, aged 18–30 years old (singleton pregnancy at their third trimester) Probiotic yoghurt (n ¼ 37) Conventional yoghurt (n ¼ 33)	9 weeks	Daily consumption of probiotic yoghurt-maintained serum insulin levels. Therefore, it might help pregnant women prevent the development of insulin resistance	Asemi et al. (2013)

		total of min 1×10^7 colony-forming units					
Observational, prospective study	Belgrade	*Lactobacillus rhamnosus* BMX 54 (vaginal application)	Abnormal vaginal flora in pregnant women	60 pregnant women 30 in each group (treated and untreated)	12 weeks	Application of probiotic capsule prevented the development of an abnormal vaginal flora. It also lowered the chances of preterm delivery	Stojanović et al. (2012)
Pilot study (open-label, two-group quasi-experiment)	Midwest region, United States	Florajen3 ($>7.5 \times 10^9$ *L. acidophilus*, $> 6.0 \times 10^9$ *B. lactis* and $>1.5 \times 10^9$ *B. longum*)	GBS colonisation	10 pregnant women (at 28 ± 2-week gestation) received probiotic; 10 served as control	From the start of intervention till 36 ± 2 weeks gestation	No AEs or even minor side effects seen in the intervention group. One half of these participants presented improved gastrointestinal symptoms. Lower quantitative GBS colony counts found in the probiotic group	Hanson et al. (2014)
An open-label, double-blind, placebo-controlled, parallel-group randomised clinical trial	Tehran, Iran	Probiotic yoghurt contained *lactobacillus bulgaricus*, *Streptococcus thermophilus*, *probiotic lactobacillus* and *Bifidobacterium lactis*. And clindamycin	BV in pregnant women	310 pregnant women (third trimester) with BV	Twice a day for 1 week	Some women administered with probiotic yoghurt should pH decrease and those receiving both probiotic yoghurt and clindamycin, reported complete symptomatic cure	Hantoushzadeh et al. (2012)

(continued)

Table 16.1 (continued)

Study design	Location	Probiotic strains	Disease/ condition	Number of participants	Duration of intervention	Inference	Reference
Prospective, multicentre, double-blind, randomised phase III trial	Paris	*Lactobacillus crispatus* IP174178* (Lc)	Bacterial vaginosis	Probiotic group: 39 Placebo group: 39	Vaginal capsule of Lc or placebo: Once daily for 14 days over first two menstrual cycles and again the same treatment for 14 days for the following two menstrual cycles	Administration of Lc probiotic could lower the rate of BV recurrences and increase the time of recurrence	Bohbot et al. (2018)
Multicentre, randomised, double-blind, placebo-controlled, parallel–group study	Poland	*L. gasseri* 57C, *L. fermentum* 57A and *L. plantarum* 57B in a total number of $\geq 10^8$ c.f.u. with standard metronidazole treatment	Bacterial vaginosis and aerobic vaginitis	600 women with regular menstruation and histories of recurrent BV; 18–50-year-old (probiotic group, $n = 285$; placebo group, $n = 293$)	Antibiotic taken together with probiotic or placebo twice daily for 10 days	Oral probiotic treatment increased the remission time in patients with recurrent AV/BV. Clinical and microbiological parameters were also improved	Heczko et al. (2015)
Open-label, parallel-group, randomised, cross-over and controlled trial	Israel	5×10^9 *lactobacilli* (L.) *Rhamnosus* GR-1 and *L. reuteri* RC-14	Vaginal colonisation in pregnant women at high risk for preterm birth	40 participants (pregnant; normal vaginal flora) Probiotic: 20 No treatment: 20	Two oral capsules/ day for 2 months. Treatment crossed over for additional 2 months	No significant difference in the end points of the two groups. Oral administration of probiotics did not increase the vaginal lactobacilli colonisation rates	Yefet et al. (2020)
	Tehran, Iran	Symbiotic capsule (*lactobacillus*	PCOS	Women with PCOS (aged 19–37 years)	12 weeks	Beneficial effects on LDL and HDL	Karimi et al. (2020)

Double-blind placebo-controlled trial		*acidophilus* 3×10^{10} CFU/g, *lactobacillus casei* 3×10^{9} CFU/g, *lactobacillus bulgaricus* 5×10^{8} CFU/g, *lactobacillus rhamnosus* 7×10^{9} CFU/g, *Bifidobacterium longum* 1×10^{9} CFU/g, *Bifidobacterium breve* 2×10^{10} CFU/g, *Streptococcus thermophilus*) 3×10^{8} CFU/g) and prebiotic inulin (fructooligosaccharide)		Synbiotic supplement ($n = 50$) Placebo ($n = 49$)		cholesterol were observed. No differences in anthropometric indices between groups were found	
Phase 2 randomised (1:1 allocation ratio) interventional parallel-group prospective placebo-controlled multicentre clinical study	Ukraine	1 capsule of the verum (5.4 billion lactobacillus crispatus LMG S-29995, lactobacillus brevis and lactobacillus acidophilus in proportion of 60%, 20% and 20%, respectively)	Symptomatic bacterial vaginosis	Women with recent symptomatic BV cured with metronidazole. 18 to 45 years old Supplement group: 82 Placebo: 82	1 capsule of the verum or the placebo two times daily for the first 7 days and one time daily for the next 8 to 120 days	Recurrences of BV significantly reduced in women treated with probiotic supplement	Reznichenko et al. (2020)
Randomised, double-blind, placebo-controlled clinical trial	Tehran, Iran	*Lactobacillus acidophilus* strain T16 (IBRC-M10785), *L. casei* strain T2 (IBRC-M10783) and *Bifidobacterium bifidum* strain T1 (IBRC-	Pregnancy outcomes in gestational diabetes	60 pregnant women (with GDM; aged 18–40 years) Synbiotic group: 30 Placebo group: 28	One capsule daily for 6 weeks	No effect on plasma nitric oxide levels observed post-symbiotic supplementation. However, symbiotic	Karamali et al. (2018)

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Table 16.1 (continued)

Study design	Location	Probiotic strains	Disease/ condition	Number of participants	Duration of intervention	Inference	Reference
		M10771) (2×10^9 CFU/ g each) plus 800 mg inulin				treatment showed beneficial effects on plasma TAC, GSH and MDA and serum hs-CRP levels	
Randomised, placebo-controlled, triple-blind, parallel-group trial	Germany	Oral supplementation with *lactobacillus rhamnosus* GR-1 and *L reuteri* RC-14 (10^9 colony-forming units)	Vaginal health in pregnancy	320 subjects enrolled with <12 completed weeks of pregnancy	8 weeks	No effect on vaginal health observed. Other routes of administration might be more effective in regulating the vaginal health	Gille et al. (2016)

are commonly seen to be associated with disturbed microbial taxa abundances. Hence, the microbiome indeed leads to an altogether different yet intricate dynamic horizon, expanding the dimensions of reproductive health and research.

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