

Initiation of a New Frontier in Obstetrics and Gynaecology - The Role of Vaginal Microbiota Dysbiosis in Case of Gynaecological Diseases and the Potential Treatment with Antibiotics, Probiotics and Vaginal Microbiota transplantation - How Practical Will it be - A Systematic Review

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Abstract

Learning from Gut microbiota experience, with the use utilization of probiotics mainly comprised by various *Lactobacillus* species here we tried to review the association of vaginal microbiota impairment possessing the characteristics of loss or absence of predominance of *Lactobacillus* in addition to enhancement of microbial diversity has been observed in the past few years to possess an intricate association with gynaecological diseases. Hence we did a systematic review utilizing the search engine pubmed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms like vaginal microbiota; dysbiosis; candidiasis; trichomoniasis; HIV; HPV Infection; cervical cancer; atrophic vaginitis; bacterial vaginitis; Polycystic ovary syndrome (PCOS) correlation with dysbiosis; uterine fibroids; miscarriage prevention; preterm labour prevention; DUB; Probiotics; lactobacilli spp of vagina; other anaerobes in bacterial vaginitis (BV) from 2005 till date for latest updates in this field. We found a total of 75 articles out of which we selected 57 -4 50 articles for this review. No meta-analysis was done. At present antibiotic as well as probiotics can adequately cure BV, by correction of the Vaginal microbiota as well as escalating the Vaginal environment. Despite them having efficacy, the limitations are drug resistance in addition to high rate of recurrence. Here we have detailed further the significance of altered vaginal along with uterine microbiome in the aetiopathogenesis of certain gynaecological diseases, besides Initiation of miscarriages, preterm labour that brings a new paradigm In the treatment of these diseases like PCOS, uterine fibroids, etc. Further role of Vaginal microbiome transplantation (VMT) is discussed as a therapy in drug resistant chlamydiasis, trichomoniasis, besides escalation of HIV, HPV with disturbed vaginal microbiota that has become markedly prevalent with the correlation of AIDS with greater incidence of these resistant fungal infections. Hence generation of a *Lactobacillus* predominance in both vagina in addition to uterine cavity have been demonstrated to aid in reversal of conditions like PCOS. More randomized controlled trials are required for these to become the mainstay of treating PCOS that has no definite cure till date, besides prevention of acquisition of HPV and cervical cancer.

Keywords: Vaginal Microbiota; Dysbiosis; *Lactobacillus* Predominance; PCOS; VMT

Introduction

An ecosystem comprised of trillions of commensals in the form of bacteria, archaea, protozoa as well as viruses whose collective microbiome is known as microbiota [1,2]. Further we have reviewed in various studies, it has significance that bidirectional gut-brain dialogue occurs via a complicated communication network that is inclusive of the sympathetic as well as parasympathetic branches of the autonomic nervous system (ANS), the hypothalamo-pituitary-adrenal axis (HPA) axis of the endocrine system, the immune system as well as the enteric nervous system (ENS) [3]. Parallel to this the liberation of enteroendocrine hormones can remarkably modulate host physiology. Actually, enteroendocrine hormones cells liberate various hormones like glucagon like peptide 1 (GLP1), peptide-YY (PYY), cholecystokinin (CCK), as well as serotonin (5HT), with a crucial influence on nutrient absorption, metabolism as well as appetite, as well as further manipulate anxiety-like behaviors.

The word probiotic comes from the Greek word, which means 'for life'. Despite 'lot of change in definitions, currently the definition recognized by Food and Agricultural Organization of the United Nations (FAO) [4] and world health organization (WHO) [5] working group experts is that probiotics are live strains of strictly selected microorganisms, which once administered in adequate amounts, give a health benefit to the host [4]. This definition was accepted by the International Scientific Association of Probiotics and Probiotics (ISAPP) in 2013. 21 Though dead bacteria and their components can also show probiotic properties. Most commonly used bacterial strains are *Bifidobacteria* and *Lactobacillus* that exhibit probiotic properties and get included in many functional foods and dietary supplements [6].

Vagina is a significant complicated ecosystem constituted by predominance of *Lactobacillus*, besides consisting of fungi, parasite in addition to a balance of microbial communities are key for health of the female [7,8]. Nevertheless, the microbial balance can get impaired resulting in a variety of infectious diseases possessing the properties of excessive growth of anaerobic bacteria (responsible for BV, AV), *Candida albivans*, etiologica; agent for vulvovaginal candidiasis (VVC), along with infection with *Trichomonas vaginalis* (causing trichomoniasis), *Neisseria gonorrhoea* (etiologica agent for gonorrhoea), *Mycoplasma genitalis* causing cervicitis, Chlamydia

trachomatis (responsible fo PID), different viruses inclusive of HPV (responsible for cervical cancer), herpes simplex virus2 (HSV2)-causes genital ulcers, human immuno deficiency virus (HIV) causes AIDS [8]. Additionally certain noninfectious diseases like abortions that are induced in the presence of bacterial vaginitis (BV) microbiome, infertility with BV microbiome, intrauterine adhesions associated with decreased *Lactobacillus* microbiome, PCOS (associated with decreased *Lactobacillus crispatus* plus escalated Mycoplasma as well as *Prevotella* etc.), uterine fibroids (escalated *Lactobacillus insers*), menstrual problems (with escalated *Gardnerella*, as well as *Prevotella*, *Sneathia*, along with *Vellonella*) further demonstrate correlation with microbial impairment [9-11].

Currently the commonest treatment approach utilized for these vaginal dysbiosis associated infections are antibiotics (metronidazole, clotrimazole, azithromycin, etc.), that usually used to have good therapeutic efficacy but lot of resistance in addition to recurrence gets encountered. In the recent past probiotics possessing *Lactobacillus* have demonstrated great advantage for the therapy of infectious diseases (like BV, fungal infections, urinary tract infections [UTI]), besides aid in treatment of non infectious diseases (like preterm, infertility, PCOS). Nevertheless, the outcome of probiotics turns out to be mixed secondary to multiple microbes responsible for infection. What came as an excitement was that in 2019 Abinoam, *et al.* carried out a clinical study of vaginal microbiota transplantation (VMT) in 5 cases with recurrent BV, where they observed 4 of those attained long term remission with vaginal microbiota having predominance of *Lactobacillus*. Hence trying to modulate VM might turnout to be significant in the therapy of a lot of gynaecological diseases.

Earlier we had reviewed on the aetiopathogenesis of obesity, Type 1 diabetes mellitus (T1D) along with role of gut microbiota (GM), besides treatment of same with probiotics. Further we have reviewed with regards to various vaginal infections like trichomoniasis, resistant Vulvo vaginal candidiasis, HIV infection, HPV infection with its correlation with cervical cancer along with oropharyngeal cancer, role of HIV infections [12-23]. Here having the knowledge that a lot of non infectious gynaecological diseases have been linked with vaginal microbiota impairment we attempted to conduct a review on the association of vaginal microbiota impairment with infections gynaecological diseases as well as non in-

fectious gynaecological diseases like Polycystic ovary syndrome (PCOS), uterine fibroids, dysfunctional uterine bleeding like menorrhagia, dysmenorrhea having an association with vaginal microbiota impairment, besides the conventional vaginal infections. Efficacy of antibiotics supplemented probiotics in the treatment of the same besides advantages in obstetrics like avoidance of miscarriage, preterm labour, prevent complications of induced operations, infertility related therapies.

Methods

We utilized search engine pubmed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms like vaginal microbiota; dysbiosis; candidiasis; trichomoniasis; HIV; HPV Infection; cervical cancer; atrophic vaginitis; bacterial vaginitis; PCOS correlation with dysbiosis; uterine fibroids; miscarriage prevention; preterm labour prevention; DUB; Probiotics; *Lactobacilli* spp of vagina; other anaerobes in BV from 2005 till date for latest updates in this field.

Results

We found a total of 75 articles out of which we selected 57 articles for this review. No meta-analysis was done.

Vagina as well as vaginal dysbiosis

Vagina represents a stretchable, duct that is muscular and works to connect uterus to external genitalia, whose physiological function is female coitus, menstrual bleeding, besides fetal delivery [2]. Mucosal system is made of stratified squamous epithelium, besides cervicovaginal fluid (CVF) is essential for sustenance of vaginal health by immune response, antimicrobial by product (like B-defensin), finely tuned microbial communities etc [24]. Of these the ones that can alter to the maximum, besides being at risk as a reaction to internal/external stimuli.

In recent time the make up in detail besides relative high quantities of vaginal microbiota has been estimated with the utilization of high throughput 16S rRNA sequencing, whose properties comprise of 5 microbial community state type (CST), in case of asymptomatic ladies [14]. Of these 4 (CSTI, II, III, V) had a predominance of *Lactobacillus* spp, whereas CSTIV possessed a heterogenous in addition to poly microbial, comprising of lower amount of *Lactobacillus* spp, whereas greater amount of anaerobic bacteria like *Gardnerella*, *Atopobium*, *Mobiluncus*, *Prevotella*, *Streptococcus*, *Mycoplasma*,

Ureaplasma [25]. Till date over 140 *Lactobacillus* spp have got isolated, Nevertheless, the only spp predominantly observed in vaginal microbiota are *Lactobacillus crispatus*, *Lactobacillus gasseri*, *Lactobacillus jensenii*, *L. iners* [20]. These are believed to be vital for Vaginal health, since they possess the capacity of generation of lactic acid, that hydrogen peroxide (H₂O₂), as well as bacteriocins, that results in sustenance of an acidic environment along with avoidance of pathogen growth, stick to the epithelium [8], that aids in other bacterial adhesion getting repelled [24], besides controlling immune as well as inflammatory reactions, that escalates the resistance to diseases. Hence the predominance of *Lactobacillus* is believed to be the hallmark of a healthy Vagina.

Usually we have the knowledge that the Vaginal microbiota getting disturbed has a great association with different gynaecological diseases, in particular BV, possessing the properties of changes in the Vaginal microbiome from the predominance of *Lactobacillus* towards anaerobic along with facultative anaerobic bacteria (like *Gardnerella*, *Atopobium*, *Prevotella*, *Streptococcus Megaspiera*, *Lep-totrichia*, *Sneathisa* etc.) predominance. BV, has been illustrated to be correlated with different other reproductive tract conditions, that are infertility, preterm birth, cervical cancer, besides acquiring of HIV. Further it has been documented that a lot of sexually transmitted infections (STI), like *Neisseria gonorrhoeae* as well as *Chlamydia trichomatis*, get promoted by Vaginal microbiota dysbiosis as well as possess greater Prevalence in case of bacterial vaginitis (BV)-positive. Additionally, with the advances in Vaginal microbiota research, a lot of studies have correlated vaginal microbiota dysbiosis with several gynaecological non-infectious diseases, of which Liu, *et al.* [26], observed that in contrast to healthy people, Intra uterine adhesions (IUA) patients possessed a lesser percentage of *Lactobacillus*, whereas greater amounts of *Gardnerella*, along with *Prevotella* [10]. Hong, *et al.* [10], observed that in subjects with Polycystic ovary syndrome (PCOS) possessed a lower amount of *Lactobacillus*, whereas greater amounts of *Mycoplasma* in addition to *Prevotella* in contrast to controls [10], while Chen, *et al.* [11], observed that lower amount of *Lactobacillus*, whereas greater amounts of *L. iners* in cases with uterine fibroids in contrast to subjects without fibroids [11].

Thus, balance in vaginal microbiota has a significant part in health of women, as well as strategies for restoration of healthy

microbiota composition might prove to be a good therapy for gynaecological diseases.

Part of microbiota dysbiosis in case of infectious diseases as well as treatment

Uptill now infection is a commonest aetiology of gynaecological diseases, that mostly is correlated with vaginal dysbiosis. Here we discuss common vaginitis, viral infection as well as other infection besides detailing the treatment for restoration of *Lactobacillus* dominated Vaginal microbiota by antibiotic as well as probiotic interventions (Figure 1) [27].

Figure 1: Courtesy ref no-27-Therapy effects of restoring *Lactobacillus*-dominated vaginal microbiota in infectious diseases. First, *Lactobacillus* can produce metabolites including lactate, antimicrobials, and lactic acid to inhibit the proliferation of pathogens. Second, *Lactobacillus* can competitively exclude pathogens from adhering to epithelium and trap pathogens by direct physical contact to prevent the colonization of pathogens. Third, *Lactobacillus* can regulate the immune or inflammatory response, particularly relieving the inflammation by decreasing cytokines like IL-1 β . Fourth, *Lactobacillus* can improve the barrier function by producing lactate, which can increase the mucus viscosity to facilitate viral trapping, and inhibiting pathogens from damaging the DNA of epithelial cells. DNA, deoxyribonucleic acid.

Microbiota dysbiosis as well as interventions in common vaginitis

Microbiota dysbiosis in bacterial vaginitis (BV) as well as interventions

Bacterial vaginitis is the commonest lower Genital Tract disease in case of fertile women that can escalate the susceptibility towards STI along with poor birth results. The main presentation is mucosal inflammation that is inclusive of aberrant vaginal discharge (escalated, yellowish with fishy odour) with itchy sensation in addition to burning [28]. At present use of antibiotic, oral as well as intravaginal antibiotic, mostly clindamycin as well as metronidazole. Nevertheless, longtime use of antibiotic has a probability of generation of antimicrobial resistance, resulting in recurrent infections.

Lot of studies have illustrated that BV occurs secondary to replacement of predominant *Lactobacillus* via multiplication of anaerobic bacteria (like *Gardnerella*, *Atopobium*, *Prevotella*, *Mega-spaera*, *Leptotrichia*, *Sneathisa*) with probiotics basically based on *Lactobacillus* which was controlling microbiota have been demonstrated to be of benefit for treatment of BV. *In vitro* along with clinical studies demonstrated that *Lactobacillus* had the capacity of reduction of the pathogen colonization by avoidance of the pathogen sticking to the epithelium [29], hampering the pathogen growth, by generation of bacteriocins [29], sustenance of the acidic environment by generation of lactic acid, besides relieving the inflammatory reaction, specifically causing significant reduction of the interleukin-1 β (IL-1 β) as well as IL-6 cytokines. Hence antibiotic as well as probiotics can adequately cure BV, by correction of the Vaginal microbiota as well as escalating the Vaginal environment.

Microbiota dysbiosis in vulvovaginal candidiasis (VVC) as well as interventions

Vulvo vaginal candidiasis represents the commonest vaginal fungal infection, classically presenting as mucosal inflammation which is inclusive of curdy cheese like discharge in addition to vulvovaginal burning, itching as well as redness. The standard therapy is antifungal agents inclusive of intravaginal azole or triazole drugs, that can obtain > 80% cure rate [30]. Nevertheless, the accompanying adverse actions (like diarrhea, aberrant urination as well as vaginal burning, itching as well as irritation), drug resistance with escalated recurrence rates which interferes with recovery, posing a threat to health.

Lot of studies have illustrated that VVC primarily takes place at the time of vaginal dysbiosis along with immune deficiency, that

was caused secondary escalation of growth of *Candida albicans*, that could result in the epithelial break down via the destruction of the inter cellular, linking in addition to intra cellular mitochondrial structure, besides stimulation of inflammation, Specifically, IL-6 as well as IL-8 cytokines [31,32]. For conferring protection *Lactobacillus* can control the host immune response, hamper the proliferation of *C. albicans* by generation of metabolites like lactate as well as avoidance of colonization of *C. albicans*, treatment directed at adjustment of microbiota can aid in the recovery from VVC [7]. An *in vivo*, study on VVC demonstrated that *Lactobacillus* can control the host immune response by reduction of T-helper1 (Th1) cell/Th2 cell ratio as well as hampering the liberation of proinflammatory cytokines like IL-17 along with Interferon γ (IFN γ) [31]. An *in vitro* study evaluated the capacity of *L. crispatus* for hampering *C. albicans* infecting vaginal epithelial cells VK2/E6E7 Cells [32]. Further a lot of studies pointed that *Lactobacillus* might directly influence antifungal actions by liberation of antimicrobials, enhancement of epithelial barrier by reduction of DNA injury [33]. Subsequently antibiotic with probiotics can result in treatment of VVC as well as avoidance of its initiation by enhancement of microbial, inflammatory in addition to epithelial status.

Microbiota dysbiosis in trichomonal vaginitis as well as therapeutic approaches

Trichomonas Vaginalis, that presents in the form of painful as well as itching intercourse, frothy discharge, with vaginal or cervical bleeding represents the commonest sexually transmitted infections (STI) all over the world that is intricately correlated with pelvic inflammatory disease (PID) or infertility [34]. At present the treatment considered to be standard remains metronidazole or tinidazole, that besides being well efficacious, generate resistance to drugs as well [35]. Etiopathogenesis of Trichomonal Vaginitis is *T. vaginalis*, that is a parasite which is flagellated belonging to the human genital tract which can result in robust injury to epithelial cells by modulation of the lysis of epithelial cells as well as provoke an inflammatory reaction that is inclusive of recruitment of neutrophils to the infected tissue [34]. Studies illustrated that BV specifically with absence of *Lactobacillus*, aided in the *T. vaginalis* getting protected from nucleic acid break down via the generation of polyamines as well as develop biofilms for decreasing drug sensitivity. Hence it has been pointed that restoration of Vaginal microbiota can result in enhancement of the anti trichomoniasis treatment

action. A randomized Clinical study demonstrated that patients consuming probiotics along with metronidazole illustrated earlier clinical resolution in contrast to the patients consuming placebo. Other than leukocyte/epithelial cells ratio, reduction in pH treatment enhanced redox potential of the Vaginal fluid were observed in the probiotic group, that emphasizes the advantageous mode for relief from inflammation, hamper *T. vaginalis* growth, besides damaging the DNA of *T. vaginalis*, respectively. A separate *in vitro* study demonstrated that the aggregation promoting factor (APF) 2 of *L. gasseri* had the capacity of significantly hampering the adherence of *T. vaginalis* to the human ectocervical cells [35]. Hence antibiotic along with probiotics can avoid in addition to treat *T. vaginalis* infection through adjustment of Vaginal microbiota. hampering the growth of *T. vaginalis*, relief of inflammation, in addition to avoidance of colonization with *T. vaginalis*.

Microbiota dysbiosis in atrophic vaginitis as well as therapeutic approaches

Atrophic Vaginitis (AV), secondary to estrogen reduction, besides local immunity subsequent to menopause is common in post menopausal women with the properties of vulvo vaginal dryness, dyspareunia, aberrant vagina discharge. Currently the principles of treatment utilized in treatment of AV are delivery of estrogen for enhancement of vaginal immunity, as well as antibiotics (norfloxacin) for hampering the growth of pathogens. Deficit of estrogen in menopause results in vaginal atrophy, that causes decrease in reduction of epithelial barrier function, besides promotion of pathogens colonization [37]. Brotman., *et al.* [36], illustrated that women with AV possessed lower amounts of *Lactobacillus* along with escalated bacterial diversity *Anaerococcus*, *Peptoniphilus*, *Prevotella* as well as Streptococcus. In view of *Lactobacillus* has been revealed to escalate the total vaginal environment like the vaginal immunity as well as epithelial barrier, utilization of probiotics have been done in combination with estrogen for treatment of AV. A randomized clinical study demonstrated that long time utilization of this combination was enough to escalate the relative clinical factors, sustained the enhanced maturation of vaginal epithelium, as well as avoidance of symptomatic AV relapse [37]. Further it has been pointed that *Lactobacillus* predominant vaginal microbiota has significance of avoidance of AV in post menopausal women, as well as thought to be a successful marker of AV treatment [38]. Hence antibiotic along with probiotics can be utilized in combination with estrogen

for avoidance as well as treatment of AV by escalating the epithelial barrier function in addition to the total vaginal environment.

Microbiota dysbiosis as well as therapeutic approaches in viral infection

Genital HPV, in particular HPV-16 as well as HPV-18 strains are usually sexually transmitted Viruses, besides being the commonest etiology of cervical cancer. Despite 50% of HPV infections get cleared within 6mths, persistence of infections might result in aberrant vaginal bleeding [39]. Conventional therapies for cervical cancer are surgery, chemotherapy as well as radiotherapy, but they don't have the capacity of avoidance, besides plenty of adverse actions like alteration in menstruation in addition to vaginal pain.

Studies demonstrated that vaginal microbiota impairment along with reduction in *Lactobacillus* in addition to escalated microbial diversity was intricately correlated with HPV infections pathogenesis [39]. A cohort of 32 sexually active American women demonstrated that women with high amounts of *Gardnerella*, *Atopobium* along with *Prevotella* had the maximum chances of getting infected with HPV as well as had the slowest viral clearance [40]. Other than that the CST IV bacteria were illustrated to escalate the robustness of cervical lesions, facilitate the neoplastic propagation by generation of nitrosamines along with Reactive oxygen species (ROS) for induction of DNA injury in addition to promote HPV infections by damage of the barrier as well as stimulation of chronic inflammation [41]. Mitra, *et al.* [39] reviewed the presently acknowledged mode *Lactobacillus* modulated protective action on cervical health as well as demonstrated that low vaginal pH (that could result in 10% reduction in risk of HPV positivity), lactate (that could escalate the vaginal mucus viscosity, besides escalate the viral trapping) as well as bacteriocins (that could directly implicate the pathogen growth) were the significant modes of conferring protection in addition to enhancement of local immunity as well as inflammation was pointed [39]. Additionally, Palma, *et al.* [42], 2018 evaluated the actions of long as well as short term probiotic utilization in clearance of HPV infection as well as they observed that patients receiving long term probiotic treatment possessed significantly greater viral clearance rate pointing that long term healthy vaginal microbiota was needed to get the ideal therapeutic efficacy. Hence antibiotic along with probiotics can avoid in addition to contribute to treatment of HPV infection by enhancement of microbial balance.

Other viral agents that are common in the reproductive tract are HSV2 as well as HIV, that can present with ulcers as well as AIDS respectively. In view of these viruses can't be deleted in total by the classical utilization of anti viral treatments, hence avoidance is specifically, significantly for sustenance of health. Studies have illustrated that vaginal dysbiosis, in particular BV as well as deletion of *Lactobacillus* could promote HSV2 infection, with a microbiota that confers protection in addition to counteracting HSV2 infection by hampering their proliferation, generation of anti microbials as well as trapping HSV2 particles [24]. Like for HIV a lot of other studies demonstrated that women with CST IV bacteria possess greater HIV infection rate in contrast to women with CST I bacteria, along with a *Lactobacillus* predominant vaginal microbiota could give protection to vagina from HIV infection by sustenance of acidic environment with generation of lactic acid, as well as resulting in reduction in viability of HIV particles [43]. Hence antibiotic along with probiotics can avoid HSV2 as well as HIV infection by correction of the microbial impairment as well as generation of a vaginal environment that is not suitable for viruses.

Microbiota dysbiosis as well as therapeutic approaches in other infections

Neisseria gonorrhoeae, the etiological agent for gonorrhoea, is persistently generating resistance towards anti microbial treatment (ceftriaxone as well as azithromycin) along with thus interfere with recovery. An *in vitro* study demonstrated that *Lactobacillus* possessed the capacity of resulting in reduction of *Neisseria gonococcus* viability by generation of acidic environment, generation of bacteriocins, liberation of biosurfactants, as well as coaggregation with gonococci, resulting in reduction of gonococci adherence to epithelial cells [44]. Hence probiotics can work as adjuvants to antibiotics for the treatment of *Neisseria gonorrhoeae* infection by enhancement of vaginal microbiota.

Mycoplasma genitalium is a ST pathogen which can cause pelvic inflammatory disease (PID) as well as cervicitis [28]. Its 1st line therapy with antibiotics (doxycycline as well as azithromycin) gets compromised secondary to drug resistance. Studies have illustrated that BV might favour *Mycoplasma genitalium* infection [45]. *Lactobacillus* predominant vaginal microbiota might confers protection can counteract the infection by generation of anti microbial as well as sustenance of acidic environment [45]. Hence antibiotic along with probiotics can avoid along with result in treatment of *M.*

genitalium infection by adjustment of microbial structure as well as enhancement of vaginal environment.

Chlamydia trachomatis represents a usual etiology of PID. Its 1st line therapy with antibiotics (doxycycline as well as azithromycin) akin to *M. genitalium* gets compromised secondary to drug resistance [46]. *In vitro* studies illustrated that *Lactobacillus* possesses the capacity of avoidance of colonization by sustenance of acidic environment in addition to glucose consumption, hamper proliferation of Chlamydia at all infection stages, besides hampering the chronicity of infection by avoidance of generation of persistence of trichomatis forms [47]. Hence antibiotic along with probiotics can avoid along with result in efficacious treatment of *C. trachomatis* infection by enhancement of vaginal microbiota.

Part of microbiota dysbiosis in non infectious diseases as well as therapeutic approaches

The part of microbiota in case of non infectious gynaecological diseases had been ignored for long, till currently escalated proof demonstrated its significance. The usual non infectious gynaecological diseases secondary to physical trauma, fertility issues, as well as endocrine condition, besides detailing the actions of restoration of *Lactobacillus*- predominant vaginal microbiota by antibiotic along with probiotic therapeutic approaches (Figure 2).

Microbiota dysbiosis as well as therapeutic approaches secondary to physical trauma

Abortion that gets Induced is quite frequent gynaecological procedure attempted world over, be it drug stimulated or surgical stimulation it can result in lot of trauma to the female reproductive tract as well as escalate the probability of serious complications like incomplete abortion, heavy bleeding, infection, scarring of endometrium, adhesions of the uterine cavity as well as cervix, along with endometriosis. Of these upper genital tract infection is the one that is most bothering as well as usual clinical problem that can subsequently result in endometritis, salpingitis in addition to infertility [9].

Studies have illustrated that post abortal infection was usually secondary to pathogens from the lower genital tract like *Chlamydia*, *Mycoplasma* as well as *Neisseria gonorrhoeae* along with BV associated bacteria, passing via the cervix to the uterine cavity as well as to the fallopian tubes, resulting in infections, as well as inflamma-

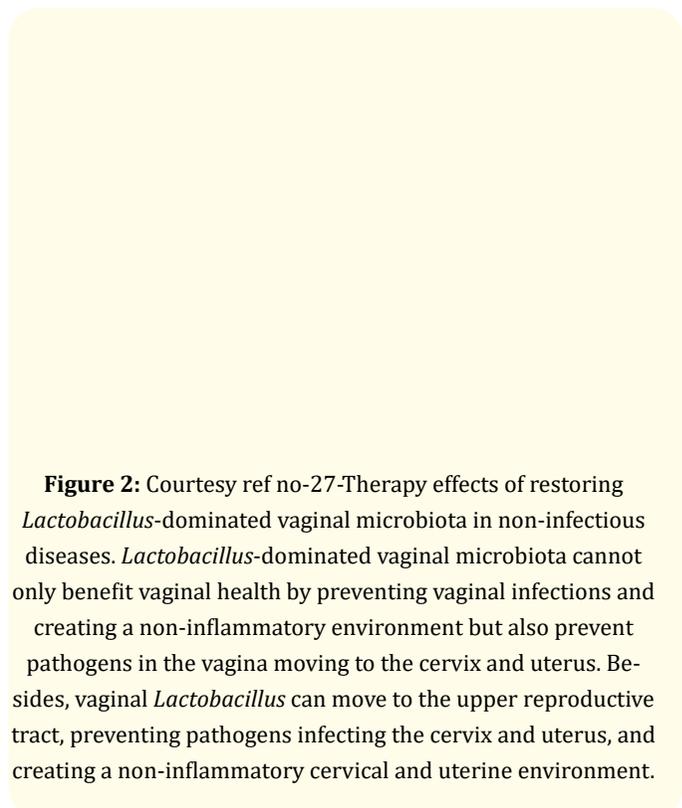


Figure 2: Courtesy ref no-27-Therapy effects of restoring *Lactobacillus*-dominated vaginal microbiota in non-infectious diseases. *Lactobacillus*-dominated vaginal microbiota cannot only benefit vaginal health by preventing vaginal infections and creating a non-inflammatory environment but also prevent pathogens in the vagina moving to the cervix and uterus. Besides, vaginal *Lactobacillus* can move to the upper reproductive tract, preventing pathogens infecting the cervix and uterus, and creating a non-inflammatory cervical and uterine environment.

tion of the whole reproductive system [49]. With this context WHO advocated the utilization of antibiotic prophylaxis for avoidance of abortion stimulated infection, with a meta-analysis of randomized clinical studies demonstrated that preoperative antibiotic (metro, nitroimidazoles) could decrease the risk of post abortal infection by 50% [48]. Nevertheless, if the homeostasis of the uterus does not get totally restored, it remaining fertile for microbial disorders, antibiotics can't avoid reinfection [50]. Hence with probiotics possessing a lot of potential for restoration of the normal vaginal microbiota, besides enhancement of the uterine environment, perioperative utilization of antibiotic in addition to probiotics can avoid the post abortal infection.

Intra uterine adhesions (IUI) is a disorder where the scar tissues generate within the uterine cavity, that in a lot of situations would result in a lot of cases with adhesions of the opposing endometrium. Despite the probability of removal of these adhesions can be done by utilization of transcervical resection, the postoperative

recurrence rate is a lot. Aberrant vaginal microbiota was demonstrated in a clinical study in IUA patients, with lower *Lactobacillus*, whereas escalated *Gardnerella*, *Atopobium*, *Prevotella* that might facilitate uterine pathology.

Microbiota dysbiosis as well as therapeutic approaches secondary to fertility issues

Miscarriage that by definition is a loss of a spontaneous pregnancy prior to the anticipated point represents a maximum Prevalent pregnancy complications. There are a lot of causes, being mostly secondary to other conditions like uterine malformations, infection, chromosomal aberrations in addition to hormone deficiency (like progesterone) [51]. In this context, the avoidable along with curative approaches objective is to tackle the primary etiologies [51].

Earlier studies have illustrated that pregnant women with BV possessed 2 fold greater risk of miscarriage in contrast to those without BV correlated bacteria from the vagina to the uterus resulting in endometritis, deciduitis, chorioamnionitis, as well as amniotic fluid infection. Studies that have evaluated the particular modes of BV that promoted miscarriage demonstrated that the BV- correlated bacteria could generate lytic enzymes (proteases, phospholipases etc.) to result in lysis of the fetal membranes as well as result in the generation of prostaglandin, that could facilitate the uterine muscle contraction, reduction in the cervical resistance, along with stimulation of liberation of Matrix Metallo proteinases (MMP's) for the breakdown of chorio amniotic membranes. Other than that the amount of the inflammatory cytokines IL-6 as well as IL-8 were further escalated in the amniotic fluid of pregnant women with BV. A randomized controlled trial illustrated that the pregnant women that received treatment with clindamycin for BV possessed 5 fold lesser chances of miscarriage in contrast to any given placebo. This points that early screening in addition to treatment of BV can result in avoidance of infection associated miscarriage. Additionally, a Clinical study pointed that hydrogen peroxide (H₂O₂) generating *Lactobacillus* in the vagina could besides aiding in vaginal health by enhancement of the microbial along with inflammatory status, generated a uterine microenvironment for implantation in addition to placentation. Hence perioperative utilization of antibiotic in addition to probiotics can avoid along with treat the infection-stimulated miscarriage by restoration of the vaginal microbiota in addition to the enhancement of uterine microenvironment.

A lot of proof illustrated that BV could further escalate the risk of preterm along with infertility, basically by promoting STI as well as stimulation of the Intra uterine inflammation [9]. Recent studies demonstrated that *Lactobacillus*- predominant vaginal microbiota had a negative correlation with preterm along with infertility, as well as can avoid poor fertility results in women by modulation of vaginal microbiota in addition to inflammatory cytokines IL-4 as well as IL-10 [9]. Hence antibiotic in addition to probiotics can avoid preterm along with infertility by enhancement of vaginal as well as uterine microbiota along with eubiosis.

Microbiota dysbiosis as well as therapeutic approaches secondary to endocrine condition

Polycystic ovary syndrome represent one of most common endocrine condition in case of reproductive women, that mostly presents in the form of a menstrual disorder, hirsutism, infertility [10]. Despite lot of therapies exist like utilization of Oral contraceptives to hamper the maturation of ovarian follicles in the form of long time PCOS treatment, besides ovulation induction for those PCOS patients needing fertility, they cant cure it. Till now lifestyle modifications (like weight reduction) continues to be the 1st line, besides the mainstay of treatment [52]. A case controlled study of 39 PCOS patients as well as 40 healthy controls demonstrated that the vaginal microbiota of PCOS patients were significantly separate in contrast to healthy controls, having the properties of escalated diversity in addition to relatively excess of Mycoplasma along with *Prevotella* in addition to reduction of the relative amounts of *L. crispatus* [10]. This points that Dysbiosis of vaginal microbiota might participate as well as aid in the PCOS pathology, with treatments targeted at enhancement of vaginal microbiota appear attractive. A systematic review implicating 855 PCOS patients evaluation of the actions of probiotics (*Lactobacillus*) in treating PCOS, with the outcomes demonstrated that probiotics delivery in PCOS ladies significantly escalated their hormonal index by reduction of free androgen index (FAI), in addition to enhancement of sex hormone binding globulin (SHBG), along with their inflammatory index by escalation of plasma nitric oxide (NO), in addition to reduction of malondialdehyde (MDA) [53]. Further Shamashi, *et al.* [53], also found that those patients who received probiotics had escalated total glutathione (GSH) as well as total antioxidant capacity (TAC), besides reduction in testosterone (T), (Dehydro epi androsterone sulphate (DHEAS), hormonal index) highsensitive C Reactive Pro-

tein (hsCRP, inflammatory index) in addition to hirsutism score in contrast to placebo. Since utilization of antibiotic in addition to probiotics is for restoration of normal vaginal microbiota, besides enhancement of environment of the reproductive system as well as beyond, they might be used for the treatment of PCOS symptoms along with facilitate the recovery by enhancement of their hormonal in addition to inflammatory amounts.

Recently aberrant microbiota have further been illustrated in association with uterine fibroids along with menstrual disorders (menorrhagia as well as dysmenorrhea, having the characteristics of relative escalated vaginal *L. insers*, besides relative escalated uterine *Gardnerella*, *Sneathisa*, *Prevotella* along with *Veillonella* respectively [54]. Thus, antibiotic in addition to probiotics might be attractive treatment in uterine fibroids along with menstrual disorders.

Conclusions and Future Suggestions for the Treatment of Vaginal Dysbacteriosis

Getting the inspiration with the utilization of fecal microbiota transplantation (FMT), Vaginal microbiota transplantation (VMT) has been posited for the treatment of Vaginal Dysbacteriosis, that implicates transplantation of the total vaginal microbiota from a healthy donor into the Vagina of the patient for restoration of the total diversity, stability, besides normal composition of the microbiota [55]. The procedure is illustrated in figure 3. Chen., *et al.* [11]. demonstrated in 2017 that transplantation of healthy rat vaginal microbiota into the vagina of BV rat models resulted in restoration of the morphology of uterine tissue in addition to reduction of inflammatory factors like IL-6, IL-8 as well as tumor necrosis factor alpha (TNF α), that demonstrated clear recovery action on Vaginal infection that occurred secondary to the BV, impairment of vaginal microbiota. Lev Sagai A., *et al.* [56], in 2019 further documented that VMT possessed a great action on long term recovery from recurrent, antibiotic unresponsive along with refractory BV. Here 4/5 BV patients that got treatment with VMT recovered Subsequent to 5 - 21 months of treatment with VMT, with efficacy, that demonstrated significant enhancement of symptoms, negative Ansel criteria, with *Lactobacillus*- predominant vaginal fluid under the microscope, with a cure rate uptill 80%. Further Lev Sagai A., *et al.* [56] observed long term resolution of BV possessed illustrated significant alteration in microbiota composition in the first mth Sub-

sequent to VMT, that had a *Lactobacillus*- predominant in addition to reduction of Bifidobacterium (intricately correlated with *Gardnerella*), *Fannyhessea* along with *Prevotella*. Chen., *et al.* [57], In 2021 demonstrated the validity of VMT in animal models trying to evaluate the modes [57]. The outcomes illustrated that utilization of vaginal secretions from healthy rats could aid in the treatment of impairment of vaginal microbiota, as well as avoid the recurrence in rats, which particularly manifested as the reduction of inflammatory cells, proinflammatory cytokines, along with apoptotic factors in the uterine wall, besides the restoration of the vaginal microbiota diversity. Initial studies on VMT have shown the probability of utilization of VMT for the treatment of BV, illustrating advantageous actions. In contrast to other treatment of BV, VMT can result in restoration of the vaginal microbiota to a healthy state, hence illustrating better curative actions in contrast to the conventional antibiotic in addition to probiotics, while evaluation for drug resistance, recurrence, adverse actions correlated with antibiotic therapy [57]. Having the knowledge that apart from BV, vaginal microbiota impairment had a comprehensive association with propagation of gynaecological diseases, along with enhancement of vaginal microbiota, antibiotic in addition to probiotics, illustrated good treatment actions, restoration of the vaginal microbiota by VMT might possess further good treatment actions in different gynaecological infectious as well as non infectious diseases.

Nevertheless, the Clinical translation of VMT is faced by a lot of hurdles, like inadequate Clinical trials (Just one research comprising of 5 subjects), absence of any Standard protocol, transmission of pathogens that can't be identified in addition to antimicrobial resistance, unintended pregnancy, immune rejection, besides unknown long term actions. Hence the enhancement of the VMT needs multidisciplinary cooperation. The concerned personnel need to develop VMT screening guidelines as early as feasible, keep exploring the application probability of VMT in the treatment of BV in addition to other gynaecological diseases, generation of a safe as well as efficacious new treatment regimen, besides generation of safety analysis criteria. Hopefully, safe standard as well as effective VMT will evoke new hope to the patients with gynaecological diseases, besides having a good probability of application.

Having reviewed the role of GM in obesity and DM, besides finding that altered gut microbiome exists there, further even in

Figure 3: Courtesy ref no-27-Schematic diagram of VMT operation. As for donors, first, donors are recruited, preferably from the recipients' first and second relatives. Second, collect blood/ CVF/urine samples of donors and conduct a series of screening by questionnaire, PCR, blood, and urine analysis machines, cultures, microscopy, and NGS. Third, collect CVF sample from qualified healthy donor and process it. It is then transplanted into the recipient's vagina. As for recipients, first, recipients undergo the same screening process for diagnosis and basic health assessment. Second, recipients are given intravaginal antibiotics to prepare for transplantation. Third, transplant the prepared CVF solution from healthy donor into the recipient's vagina. Fourth, follow-up studies are carried out on recipients to assess the treatment outcome and adverse effects. VMT, vaginal microbiota transplantation; CVF, cervicovaginal fluid; PCR, polymerase chain reaction; NGS, next-generation sequencing.

neuropsychiatric diseases it had been revealed that abnormal GM was implicated in inflammatory conditions of bowel, besides in NPD like ASD, Schizophrenia etc. further it was demonstrated to have an association as has been witnessed in case of correlation of vaginal microbiota with not only vaginal infection but other gynaecological diseases. Extrapolating from this knowledge it forces us to rethink how evolutionarily the significance of symbiosis with these microbes has been done with the host with these microbes essential for maintenance of pH along with certain other functions in the respective area like In GIT, in maintaining integrity of mucosal wall control of pH digestion of oligosaccharides, prevention of infection by clostridial infection although some group of clostridia like *Faecalibacterium prausnitzii*, is essential for certain intestinal

function. In vagina it is *Lactobacillus* predominance preventing any infections like BV other VVC and opportunistic infections besides avoidance of viral infections like HPV virus and alteration in vaginal and uterine environment has been correlated with generation of disease like PCOD, infertility, uterine fibroids etc. Similarly it appears the organisms in the nose, eye, mouth further might have a similar role that one needs to look into for the generation of a lot of diseases that might aid in revolutionizing therapies. Biggest disadvantage of allopathy is with use of antibiotics a lot of natural ecoflora gets altered influencing the generation of further superadded viral infections etc. Thus we need to respect the god designed symbiotic system in whole body where mutual utilization of each others aid benefit 's each other.

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