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"USE OF PROBIOTICS FOR BACTERIAL VAGINOSIS ASSOCIATED WITH INFERTILITY AND PRETERM BIRTH": A REVIEW ARTICLE

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ABSTRACT

Infertility and preterm births (PTB) are global health concerns. According to World Health Organization (WHO), 15% of reproductive-aged couples worldwide are suffering from infertility.186 million ever-married women seek to have a child believing it to be the only ray of hope in their lives. WHO also states that approximately 1 million children die every year due to complications of preterm birth. One of the reasons for infertility and preterm birth resonates with Bacterial Vaginosis (BV). Treating BV at the earliest is essential in preventing its associated reproductive problems. To date, our understanding of the mechanism and treatment of BV remains scarce. Approved treatment for BV involves antibiotics which are associated with several side effects. In a quest to find an alternate, probiotics are under research and found effective against BV. Probiotics are not approved as a drug for BV even after sufficient research. The question of why probiotics have not been adopted universally is hence crucial to understand. This review summarizes the effect of bacterial vaginosis on infertility and preterm birth and their treatment with probiotics.

KEYWORDS: Probiotics, Bacterial Vaginosis, Infertility, Preterm Birth, Dysbiosis, Recurrent Bacterial Vaginosis.

INTRODUCTION

The increasing research on the vaginal microbiome has opened up a new era for a better understanding of women's health.

Pregnancy is associated with a sudden rise in estrogen and progesterone levels in the body. An increase in progesterone causes dilation of ureter and renal calyces. Enlarged uterus presses on the bladder, ureter, and urethra. Thus, resulting in urinary retention. It also decreases bladder capacity and increases the urinary frequency. Some pregnant women may have vesicoureteral reflux, where urine flows back from the bladder to the kidneys. These physicochemical changes along with reduced immunological actions during pregnancy increases her susceptibility to altered vaginal flora leading to various perinatal complications.[1]

Bacterial vaginosis (BV) is a common genital tract disease in reproductive-aged women.[2] Dysbiosis in the vaginal microbiome is a hallmark of BV. *Lactobacillus* species are predominant in a healthy vaginal microbiota.[3,4] Incidence of menses, pregnancy, overuse of antibiotics, sexual practice, and vaginal douching can all lead to an imbalance in vaginal microbiota.[4] A pungent fishy vaginal odor is the most notable sign of BV. Infections caused due to BV during pregnancy are also a leading cause of premature rupture of membranes, preterm birth, infections in amniotic fluid, wound infections after C-section and spontaneous abortions.[5] The presence of BV is more common in infertile women when in comparison with fertile women.[6]

The only approved treatment for BV is Antibiotics. However, these are associated with several side effects like Multidrug Resistance (MDRs) of microorganisms to antibiotics and disrupting the protective vaginal microbiota. The risk of recurrence of Bacterial Vaginosis increases as a result. An alternative treatment to antibiotics is Probiotics which are not likely to have side effects.[7,8,9]

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.[10] Apart from improving fertility, probiotics confer health benefits in treating urinary tract infections (UTI), Bacterial Vaginosis, and preventing preterm birth. Recently, there has been a rapid increase in the probiotic market with formulations of capsules, powders, gums, pills, chews, and liquid gels for direct installation into the vaginal tract. Very few probiotic formulations have hit the market despite several new formulations.[11]

In recent years, many researchers have been trying to understand the role of vaginal flora in pregnancy outcomes. Even though literature shows a significant relationship between the two, limited data prevents conclusions. Moreover, knowledge on probiotics during pregnancy and their treatment for BV and infertility are also scarce. This demands for more controlled studies with high safety standards to be performed in this field before exploiting probiotics in vulnerable populations such as pregnant women themselves. Therefore, to cover the knowledge gap, we summarize the association of BV with infertility and preterm birth. Further, we discuss the role and effectiveness of probiotics in treating BV associated with infertility and preterm birth.

BACTERIAL VAGINOSIS AND PROBIOTICS

Healthy Vaginal Ecosystem

A commensal, symbiotic, and pathogenic microorganisms colonize the vaginal microbiota (VMB).[12] Most successful pregnancies showed a healthy vaginal microbiome. Thus it is clear that a healthy vaginal microbiome acts as a fertility factor for a successful pregnancy. Yet, our knowledge of the role and diversity of vaginal microbiota in pregnancy is still in its infancy. Thus, it is crucial to understand the vaginal ecosystem during an uncomplicated pregnancy.

In pregnancy, women undergo physiological changes like increased sex hormone levels, physical properties of cervical mucus, behavioural changes like reduced smoking and drinking habits. All these can change the composition of vaginal microbiota resulting in a shift of microbiome that is different from that of non-pregnant women.[13]

Lactobacillus is a dominant genus of a healthy vaginal microbiome during pregnancy. Many studies have concluded the predominance of *Lactobacillus crispatus*.[13,14,15,16,17] Studies have also shown that low diversity and high stability of the vaginal microbiome are the characteristic features of normal pregnancy. Nevertheless, it slightly varies among women depending on factors like ethnicity and gestational age.[14,15]

Estrogen promotes maturation, proliferation, and accumulation of glycogen in the vaginal epithelial cells during pregnancy. *Lactobacillus* present in the vagina then breaks it down to lactic acid, thus, maintaining an acidic environment in the vagina. Consequently inhibits the growth of pathogens.[18] Hence, *Lactobacillus* rich vaginal microbiome decreases the risk of bacterial vaginosis.

Any factor that disturbs vaginal flora increases the risk of BV and associated complications during pregnancy such as infertility, preterm birth, and post- C- section wound infections.[5]

Complications of Bacterial Vaginosis in pregnancy

- Association of Bacterial Vaginosis with Infertility:

Infertility is a global health concern. It is a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse.[19] Many studies have shown that BV is more common in infertile women than fertile women.[6,16,20] This indicates that there is an association between BV and infertility. However, it is difficult to predict if BV is the cause for infertility or infertility causes BV. Pathophysiology of how BV is associated with infertility is also little known. According to a study conducted there are few mechanisms by which BV can cause infertility.

The probable mechanisms proposed are as follows:[20]

1. As part of the body's defense mechanism, an immune response triggers the immune system to recognize a substance as non-self. As a result, antibodies get generated. In the case of BV, increased pathogenic flora of the vagina triggers an immune response that may recognize disease-causing bacteria as foreign and target seminal fluid components as antigens, causing damage to sperms and thus lowering chances of conception.
2. The immune system generates antibodies to produce an inflammatory response in the genital tract resulting in an unsuitable environment for reproduction.
3. Cervical mucus plays an important role during fertilization. It nourishes and protects the sperm during its movement across the female reproductive tract for successful conception. Pathogenic microorganisms release more hydrolyzing enzymes, including mucinases, that break down mucins. The degraded cervical mucus may not nourish or prepare the sperm for successful transport to the egg for fertilization.
4. Dysbiosis decreases *lactobacilli* and increases pH in the vagina, which supports the colonization of infectious bacteria. Thus this increases the risk of Sexually Transmitted Infections like HIV, herpes simplex virus, human papillomavirus, and gonorrhea. These infections are known to cause infertility.[16,20,21]

But more evidence needs to be generated to support the above-mentioned theories.[20] Asymptomatic BV is more common in primary infertility than in secondary infertility.[16] One Study casts doubt on the role of BV in impaired fertility concerning male partners in infertile couples.[22]

- Association of Bacterial Vaginosis with preterm birth:

According to WHO, Preterm is defined as babies born alive before 37 weeks of pregnancy. The annual rate of preterm birth of 15 million is an alarming reason to conduct more studies and identify the most common risk

factor and the possible treatments.[23] Several studies have shown that preterm birth is directly associated with BV.[24,25,26] Mechanism by which BV leads to preterm birth is unclear, although assumptions have been made by Dhanasekar et al. as discussed below:[27]

(a) Pathogens in the vagina ascend to the uterus and release proteolytic enzymes like phospholipase A2 and collagenase. These enzymes increase the levels of prostaglandins and the formation of arachidonic acid. Prostaglandins promote collagen remodeling in the fetal membranes, which leads to uterine contraction and preterm labor.
(b) Pathogens release endotoxins such as Lipopolysaccharides (LPSs) that bind to Toll-like receptor 4 (TLR4) and activate the Nuclear Factor k light-chain-enhancer of activated B cells (NFkB) pathway. This pathway brings about pro-inflammatory cytokine and chemokine in the intrauterine tissues. Prostaglandins production stimulates in the amnion, which promotes parturition leading to preterm labor.

Role of Probiotics in BV associated Infertility and Preterm Birth

Approved treatments for Bacterial Vaginosis presently involve "antibiotics" administered orally or intravaginally. The route of administration is proven to have a minor impact in treating BV.[28,29] Studies with extended re-examining first-line drugs show 50% recurrence in 6-12 months.[30,31] Reasons for Recurrent Bacterial Vaginosis (RBV) could be the resistance to drugs, the endurance of the remaining infection, or reinfection from male or female partners.[30] It appears evident that antibiotic treatment is effective in treating Bacterial Vaginosis but is associated with severe side effects, especially in pregnant women, and risks of RBV. Antibiotics disrupt vaginal microbiota and increase the risk of urinary tract infections (UTI) and Bacterial Vaginosis. Therefore, a switch from antibiotics to probiotic treatment is more focused on present-day research. Studies show oral or vaginal administration of Lactobacillus may help prevent recurrent infections.[32] Mechanism of probiotics in the containment of BV includes.[7,33]

i) Competing against pathogens for nutrition
ii) Obstruct adhesion of the pathogen
iii) Produce lactic acid, thus maintaining low pH.
iv) Produce hydrogen peroxide, bacteriocins, and biosurfactants
v) Regulate vaginal mucosal immunity
vi) Avert colonization of exogenous pathogens (biofilms)

In 2004, the FDA approved a pH buffering tampon by the brand "ELANEE," which works as a regular tampon and releases lactic acid and citric acid, which can help treat vaginosis. Approval for this drug is not yet received; thus, further trials (large scale clinical trials) are underway to determine its effect in treating BV.[34,35]

- Probiotics for BV associated Preterm birth (PTB):

Probiotics are studied for a balanced microbiota and to treat/prevent several infections and inflammatory diseases.[36] These reduce the number of harmful bacteria and promote the growth of good bacteria. A study with probiotics containing Streptococcus faecalis, Clostridium butyricum, and Bacillus mesentericus administered for preventive treatment of BV in pregnant women significantly suppressed preterm birth.[37,38] On the other hand, if Lactobacillus rhamnosus GR1 and Lactobacillus reuteri RC14 are administered at or before 20 weeks of gestational age, show their benefits for use in pregnancy to prevent PTB.[27]

Based on Randomized Control Trials (RCTs) reviews, many neonate clinics in high-income countries have adopted probiotics as a conventional cure for preterm neonates.[39] Prophylaxis of probiotics has a significant effect on decreasing the morbidity and mortality of preterm neonates.[40,41,42]

- Probiotics for BV associated Infertility:

Conception rates in Assisted Reproductive Treatments (ART) remain disturbingly low. These rates were related to the disturbance of bacterial flora, a hallmark of BV.[42,43] The risk of developing Sexually Transmitted Diseases (STD) is high with the occurrence of BV and hence relates to reproductive failure.[44] One study believed in the idea of colonizing *L. crispatus* with the transfer-catheter tip at the time of In Vitro Fertilization-Embryo Transfer (IVF-ET) to increase implantation rates.[45] Although most available results on administering probiotics for treating BV are positive[32,46,47,48], there is no guaranteed approval for its usage. Thus this makes it even hard to confirm probiotics for treating BV-related infertility.

A systematic review by Corbett et al. concluded the effect of oral administration of probiotics in males with enhanced sperm motility but did not improve women's fertility.[49]

CONCLUSION

A shift in the normal vaginal microbiome caused due to infection in the vagina is a characteristic of Bacterial Vaginosis. It has become one of the most common vaginal problems in the world. Inability to prevent relapse of BV is a sign of our lack of knowledge on BV.

BV is associated with other reproductive problems such as infertility and preterm birth. However, our understanding of the mechanism by which these problems occur is still vague and needs more focus. It is crucial to understand the vaginal ecosystem during an uncomplicated pregnancy.

Treating BV at earlier stages is believed to reduce its related health problems. Approved treatment for BV presently includes antibiotics which cause several side effects. On the other hand, probiotics have shown

significant results in treating BV. Although much research on the impact of probiotics on BV has a positive outlook, they are not approved as a drug for treating BV. The question of why probiotics have not been adopted universally is hence crucial to understand.

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