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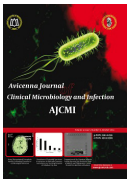

Original Article

Effects of Oral Probiotic Supplements on the Rate of Vaginal Colonization of Group B *Streptococcus* in Pregnant Women: A Clinical Trial Study

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Abstract

Background: Management of Group B *Streptococcus* (GBS) infection in a pregnant woman is one of the serious challenges for gynecologists and infectious disease specialists. The present clinical trial study aimed to investigate the impact of oral probiotic supplements on the rate of vaginal colonization of GBS in pregnant women.

Methods: Overall, 64 pregnant patients with vaginal GBS were selected to participate in this study. They were randomly divided into two groups (n=32/each). The intervention group received a probiotic supplement capsule at a dose of 500 mg daily for 30 days, and the control group received a placebo for 30 days. At the end of the study on day 30, the vaginal sample was retaken with a sterile swab, and all the steps performed at the beginning of the study to diagnose GBS were repeated.

Results: The average mean gestation at the first vaginal sampling was 27.09±2.48 weeks. There was no meaningful difference in age between the two groups of patients ($P=0.47$). Moreover, no considerable difference was found in the body mass index ($P=0.37$), weeks of gestation ($P=0.92$), or number of pregnancies ($P=0.89$) between the two groups. A significant relationship was observed between positive GBS and BMI in pregnant women ($P=0.001$), but this meaningful relationship was not found between GBS and age of patients ($P=0.86$) and age of pregnancy ($P=0.16$). Finally, there was no significant difference between the probiotic and placebo groups in terms of secondary test results for GBS ($P=0.07$).

Conclusion: In the present study, oral probiotic supplementation did not significantly alter GBS in pregnant women, but for a definite opinion, a study with a larger sample size, different vaginal sampling techniques, a higher dose of oral probiotics, and an increase in the length of the intervention period is essential.

Keywords: Group B *Streptococcus*, Probiotics, Pregnancy

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Introduction

Group B *Streptococcus* (GBS) is a bacterial microorganism that often colonizes the lower genital tract (mostly the vagina) and intestines (1). This condition is generally harmless in healthy adults but can be dangerous in conditions such as immunodeficiency, diabetes, liver disease, pregnancy, and the like (1,2). The colonization of this bacterium in the rectum or vagina of a pregnant woman during labor can cause invasive diseases such as meningitis, pneumonia, and septicemia in her newborn (3,4). This condition has also been related to some bad pregnancy outcomes, such as preterm delivery, premature rupture of the amniotic sac, low birth weight, and stillbirth (5,6). Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. They have gained significant attention for their role in promoting gastrointestinal health and modulating the immune system. However, recent studies have also highlighted their potential in supporting vaginal health, particularly by preventing or reducing the colonization of harmful pathogens, including GBS (7).

The primary mechanisms by which probiotics exert

their beneficial effects are through the restoration and maintenance of a healthy microbial balance. In the vaginal environment, a healthy microbiota is predominantly composed of *Lactobacillus* species, which help maintain an acidic pH and produce bacteriocins and lactic acid, inhibiting the growth of pathogenic bacteria (8).

Because of their ability to attach to epithelial cells and create growth inhibitors that suppress pathogenic development as well as the secretion of biosurfactants, vaginal probiotics may thus be useful substitutes for antibiotic treatment. Studies have shown that probiotics, especially those containing *Lactobacillus rhamnosus* and *Lactobacillus reuteri*, may help reduce GBS colonization by competitively inhibiting the pathogen's adherence to vaginal epithelial cells. These strains also enhance the immune response, creating an environment that is less favorable for harmful bacteria to thrive. Furthermore, the use of probiotics as an alternative or adjunct to antibiotics has been suggested to prevent antibiotic resistance and maintain the integrity of the beneficial microbiota in both the mother and newborn (9).

Topical vaginal probiotics could be beneficial, but they are not recommended since they are more intrusive than oral probiotics (10).

In addition to preventing GBS, probiotics have been used to treat other vaginal infections, such as bacterial vaginosis and yeast infections. Their application is not limited to therapeutic settings; probiotics are also employed in preventive healthcare to promote overall vaginal health, especially in women prone to recurrent infections (11).

Given these benefits, probiotic supplementation represents a promising, non-invasive, and affordable approach for reducing GBS colonization during pregnancy, which could potentially reduce the need for antibiotic use during labor and its associated risks.

To prevent vaginal GBS colonization, prophylactic intravenous antibiotics are currently administered to 20%–35% of childbearing women during labor. Intravenous antibiotics after childbirth interfere with the early growth of beneficial bacteria in the infant's stomach and lead to the emergence of antibiotic-resistant bacteria (12). In Iran, various investigations have reported different statistics on the prevalence of GBS in pregnant women, but according to a meta-analysis published by Verani et al, the prevalence of this bacterium was 9.8% (13).

Management of GBS infection in a pregnant woman and prevention of early or late complications in her baby are among the serious challenges for gynecologists and infectious disease specialists. One of the routine treatments for this purpose is the injection of intravenous antibiotics in labor to reduce the chances of transmission to the newborn (14). The adverse side effects of the aforementioned therapeutic approach are the increase in resistance to antibiotics, the disturbance of the early growth of useful bacteria in the newborn's gastrointestinal tract, and the disruption of the bifidobacteria and lactobacilli counts in the mother's milk after delivery (15-17). It has been reported in some surveys that pregnant women with more vaginal *Lactobacillus* were less likely to be exposed to GBS colonization (18,19). It has been proposed that one means to increase the rate of *Lactobacillus* colonization is to take probiotic oral supplements. The present clinical trial study seeks to investigate the impact of oral probiotic supplements on the rate of vaginal colonization of GBS in pregnant women.

Materials and Methods

Study Design and Patients

The present trial study was accepted by the Department of Infectious Diseases, School of Medicine, Isfahan University of Medical Sciences (IUMS), Isfahan, Iran, and the main purpose of the researchers was to evaluate the impact of oral probiotic supplements on the rate of vaginal colonization of GBS in pregnant women. The Ethics Committee of IUMS approved this study (IR.MUI.MED.REC.1399.513). In addition, the approval of the University Ethics Committee to conduct the present study is available at the Internet address (http://ethics.Research.ac.ir/IR.MUI.MED.REC.1399.513).

The current study was performed from September 2020 to February 2021 at Alzahra Hospital of IUMS, Isfahan, Iran. The patients were selected from pregnant women with GBS who were referred to our department during the 20th to 33rd week of pregnancy. At the beginning of the study, the objectives and method of the study were explained to the patients, and if they agreed to participate in the study, informed consent was obtained from them. They were requested to write their demographic information, weight, height, and body mass index (BMI) in separate forms. The vaginal sample was taken using a sterile swab and sent to the laboratory for the definitive diagnosis of GBS. The acceptable criteria for patients to enter the study were patient consent to participate in this study, pregnant women over 18 years of age who were diagnosed with GBS based on physical examinations, clinical and laboratory signs, a culture of positive vaginal/rectal secretions for GBS, and gestational age between 20 and 33 weeks. On the other hand, the exclusion criteria were antibiotic consumption during the intervention and one week before, absolute bed rest of the patient, diagnosis of preeclampsia or gestational diabetes, BMI more than 40, and age less than 20 years or more than 45 years.

Based on the inclusion and exclusion criteria, 64 patients with GBS were chosen to participate in this study by convenience sampling. For sample collection and bacterial identification, one sterile cotton swab from the vaginal (the lower third vagina) was collected from each participant according to the Centers for Disease Control and Prevention guidelines (13). Then, it was placed into the Amies transport medium (HiMedia, India) without charcoal and transmitted within 4 hours to the bacteriological laboratory of the Isfahan Infectious Diseases and Tropical Medicine Research Center.

Upon arrival at the bacteriological laboratory at the Isfahan Infectious Diseases and Tropical Medicine Research Center, the samples were transferred to Trans-Vag selective and enrichment media (Todd Hewitt Broth supplemented with 8 µg/mL gentamicin and 15 µg/mL nalidixic acid) for incubation at 37 °C for 24 hours. After enrichment, the broth was streaked onto defibrinated sheep blood agar plates and incubated for an additional 24 hours at 37 °C to promote the growth of bacterial colonies. GBS was identified using the following tests:

1. Gram-staining: Gram-positive cocci in chains were observed.
2. Catalase test: Negative catalase activity was confirmed, which is the characteristic of GBS.
3. Christie, Atkinson, Munch, Peterson (CAMP) test: A positive CAMP test (characterized by enhanced hemolysis near *Staphylococcus aureus* colonies) confirmed the presence of GBS.
4. Sodium hippurate hydrolysis test: The ability to hydrolyze sodium hippurate was used to differentiate GBS from other Streptococcus species.
5. Polymerase chain reaction (PCR) amplification of the *cfb* gene: As a final confirmatory step, PCR was utilized to amplify the *cfb* gene, a specific marker for GBS. This test was performed using primers targeting the *cfb* gene following the protocol described by Ke et al (20).

Colonies that were Gram-positive, catalase-negative, CAMP-positive, and PCR-positive for the *cfb* gene were confirmed as GBS. This detailed process ensures the accurate isolation and identification of GBS, providing reliability in diagnosing the colonization of GBS in the participants.

Pregnant women with positive reports of GBS were randomly divided into two groups (n = 32/each); the intervention group received a probiotic supplement capsule (Familact, Iran) at a dose of 500 mg daily for 30 days, while the control group received a placebo for 30 days. The placebo was quite similar in shape and color to the drug pill and was made of corn starch. The probiotic used in our study, Familact (Iran), was selected based on several considerations:

1. Previous research support: Familact contains strains of *Lactobacillus* species, which have been shown in previous studies to be beneficial in maintaining vaginal health. *Lactobacillus* strains, particularly *Lactobacillus rhamnosus* and *Lactobacillus reuteri*, are commonly used for their ability to adhere to vaginal epithelial cells and inhibit pathogen adhesion, including GBS (21). Several studies, such as Borges et al and Guerra-Ordaz et al, have highlighted the role of *Lactobacillus* in promoting vaginal health and preventing GBS colonization (9, 22).
2. Local availability and safety: Familact is a widely available and commonly used probiotic supplement in Iran, and its safety profile is well-established. Since the probiotic strains included in Familact have been extensively utilized in clinical settings for gastrointestinal and vaginal health, it was deemed an appropriate and safe choice for this study in a pregnant population.
3. Practicality: Given the study's location, Familact was readily available for procurement, making it a feasible option for the intervention. Moreover, the dose regimen of 500 mg daily for 30 days was based on previous clinical studies that assessed the efficacy of similar dosing in achieving beneficial outcomes for vaginal flora.
4. Consistency with other studies: The strains in Familact are similar to those used in other international trials investigating the role of probiotics in reducing GBS colonization. This allowed us to compare our findings with the existing literature and contribute to the growing body of evidence.

Regarding the choice not to use other probiotics, while other strains such as *Bifidobacterium* could also have been considered, this study focused on *Lactobacillus* due to its direct relevance to vaginal health and its established role in combating GBS. Additionally, choosing a single probiotic formulation allowed us to maintain consistency in the study and avoid introducing additional variables that might complicate the analysis of results.

In our study, all participants, including those in the control and placebo groups, received standard medical care to ensure the safety of both the mother and the fetus. The following are specifically the medical standard care:

Prophylactic antibiotics: For mothers who tested positive for GBS after the second test (day 30), prophylactic intravenous antibiotics [injectable ampicillin (2 g at first, then 1 g every 4 hours) or vancomycin (1 g every 12 hours until delivery)] were administered during labor to reduce the risk of neonatal transmission of GBS. The specific antibiotic regimen followed the Centers for Disease Control and Prevention guidelines to prevent early-onset GBS disease in newborns. This process was followed irrespective of whether the patient was in the probiotic or placebo group.

Follow-up and monitoring: Throughout the study, regular follow-ups and monitoring were conducted to ensure maternal and fetal well-being. Any signs of complications were immediately addressed by the attending medical team.

Cesarean section cases: For participants who underwent cesarean sections before labor, antibiotics were not administered as the risk of GBS transmission was mitigated by the surgical procedure. This approach ensured that both groups, including the placebo group, received the necessary precautions to minimize the risk of GBS transmission to the newborn, while also enabling us to assess the potential benefits of probiotic supplementation in comparison to the placebo (23).

Follow-up Procedure and Data Extraction

Patients were followed up by phone contact every week to

control them in terms of taking supplements and placebo. The patients were excluded from the study if they did not take more than 10% of the total supplement. At the end of the study on day 30, the vaginal sample was taken again with a sterile swab, and all the steps performed at the beginning of the study to diagnose GBS were repeated. The samples were transferred to the laboratory for secondary testing for GBS.

Statistical Analysis

Finally, all data were entered into SPSS software (version 19; SPSS Inc., Chicago, IL, USA) and underwent statistical analysis. Absolute and relative frequencies were calculated for qualitative variables. For quantitative variables, means and standard deviations were calculated, and their normal distribution was examined by the Kolmogorov-Smirnov test. In addition, the t-test and chi-square test were used to compare the variables in the two groups, and a $P<0.05$ was considered a statistically significant difference.

Results

Pregnant women with a definitive diagnosis of GBS (n = 64) were assigned to intervention (probiotic supplement) and control (placebo) groups (n = 32/each). Based on the statistical analysis, the average mean gestation at the time of the first vaginal sampling was 27.09 ± 2.48 weeks. Considering that the inclusion criteria were 20–33 weeks of gestation, all study participants completed the intervention period, which was assessed through weekly follow-ups and telephone contact with patients. Further, none of the patients were excluded from the study due to absolute bed rest or preterm delivery.

The collected demographic variables between the intervention and control groups were compared and summarized in Table 1. There was no meaningful difference between ages in the two groups of patients ($P=0.47$). Furthermore, no considerable difference was observed in BMI ($P=0.37$), weeks of gestation ($P=0.92$), or number of pregnancies ($P=0.89$) between the two groups. The number of days between the first and second vaginal sampling was one month, and there was no difference between the two intervention and control groups. The aforementioned results indicated that both groups in our trial had a degree of homogeneity.

According to our analysis, there was a significant relationship between positive GBS and BMI in pregnant women ($P=0.001$), but this meaningful relationship was not observed between GBS and age of patients ($P=0.86$) and age of pregnancy ($P=0.16$). This finding suggests that high BMI in pregnant women may be associated with increased GBS resistance to probiotics.

Among the patients in the intervention group, 50% (16/32) had a negative GBS secondary test result, while 50% (16/32) had a positive test result. In the control group, 28.1% (9/32) had a negative GBS secondary test result, whereas 71.9% (23/32) had a positive test result. Based on data analysis, there was no significant difference between the probiotic and placebo groups in terms of secondary test results for GBS ($P=0.07$).

Table 1. Differences in Demographic Variables in the Two Groups Under Study

Variable	Control Group (n = 32)	Intervention Group (n = 32)	*P* Value
Age	29.69 ± 5.19	30.66 ± 5.67	0.47
BMI	29.81 ± 2.81	30.49 ± 3.19	0.37
Age of gestation	27.13 ± 2.52	27.96 ± 2.48	0.92
Number of pregnancies	1.88 ± 0.87	1.84 ± 0.95	0.89

Note. BMI: Body mass index.

Discussion

Probiotics are a group of active bacteria, and their regular consumption plays an important role in improving the function of various organs (7). In recent years, the use of probiotics to combat GBS has increased, and many researchers have investigated the preventive or therapeutic effects of such supplements (12,24,25). It has been proposed that probiotics, especially lactobacilli, decrease the rate of GBS colonization by inhibiting the adhesion of GBS to the epithelium of the vaginal wall (26). Due to the sharp increase in cases of positive GBS among pregnant women and its bad consequences for the mother and her baby, affordable and non-invasive approaches such as probiotic therapy would be useful for the management of this condition.

In the present study, there was no significant difference between the probiotic and placebo groups in terms of secondary test results for GBS. However, it should be noted that in our study, the number of patients with positive tests for GBS after completing the study was lower in the probiotic group than in the placebo group. Our findings are in line with those of Olsen et al. They investigated the impact of oral probiotics on the vaginal GBS colonization rate during pregnancy (12) and found that oral probiotics did not have a significant effect on reducing the rate of GBS colonization. In a recent study, Namugongo et al evaluated the potential positive effect of oral probiotics to eliminate vaginal GBS colonization in pregnant women (24). Nonetheless, their findings did not support the theory that oral probiotic supplements can eliminate GBS during the third trimester of pregnancy, which conforms to our study results.

So far, many studies have focused on assessing the relationship between the BMI of pregnant women and GBS rate colonization. Based on the results of the current study, there was a significant relationship between positive GBS and BMI in pregnant women. Namugongo et al reported that high BMI was related to the colonization of GBS in the anovaginal regions of pregnant women (24). Furthermore, they declared that pregnant women with a BMI of more than 30 were four times more likely to be colonized with GBS in their anovaginal regions compared to women with a BMI less than 30. In another study by Stapleton et al, high BMI was suggested as one of the risk factors for GBS in women (25). The main link between obesity and GBS in

pregnant women is not known, and different studies have expressed different views in this regard, but what is the most likely cause is that obesity increases the incidence of GBS during pregnancy by altering the natural microbial flora of the genital area (26).

In addition to our findings regarding the use of oral probiotics for reducing GBS colonization, it is essential to consider the body of research surrounding vaginal probiotic formulations, such as ointments, creams, and gels. Several studies have explored these topical applications, demonstrating their potential effectiveness in promoting vaginal health and reducing the incidence of infections, including GBS.

For instance, Stojanović et al examined the use of vaginal probiotic gels containing *Lactobacillus* species and found significant reductions in bacterial vaginosis and other urogenital infections. Similarly, a randomized controlled trial by Treven et al reported that vaginal probiotics significantly decreased the colonization of GBS when compared to a placebo group. These findings indicate that topical applications may provide a more direct method of delivering beneficial bacteria to the vaginal microbiota, potentially resulting in quicker and more localized effects (10,18). In contrast, our study focused on the administration of oral probiotics, which, while being non-invasive and convenient, may have a delayed effect due to the digestive process involved in absorption. Oral probiotics rely on their ability to survive the gastrointestinal tract and then reach the vaginal microbiota, which may limit their efficacy in reducing GBS colonization compared to direct application methods. Furthermore, some studies suggest that vaginal probiotics may not only alter the vaginal microbiome but also have immunomodulatory effects, enhancing local immunity and providing an additional layer of protection against pathogenic bacteria, including GBS. This aspect may not be fully realized with oral probiotic supplementation (27). Despite the potential advantages of vaginal probiotics, it is crucial to consider their acceptability and practicality for patients. Many women may prefer oral probiotics due to their ease of use and reduced invasiveness, making them a more appealing option in certain populations.

Important further studies should be performed about "how much probiotic is needed to survive and change vaginal flora, as well as whether oral or vaginal probiotics are the most effective and whether the regimen would be well-tolerated" (28).

The present study encountered several limitations. One of the limitations of our study was the small sample size. What is certain is that a larger sample size is needed to make a definite statement about whether a treatment is effective or not. The second limitation was the single center of the study; naturally, multicenter studies are more valid. In addition, our study coincided with the coronavirus disease 19 epidemic in Iran, and in this situation, it was difficult to communicate with the patient and even convince her to participate in the project. As mentioned earlier, the results of the present study demonstrated no difference between the two probiotic and placebo groups. Factors such as short treatment duration, low-dose probiotic supplementation, or low efficacy of oral probiotics to combat genital GBS can play a role in achieving these results, but the issue is open to discussion. On the other hand, one of the strengths of the present study was the sensitivity in terms of the inclusion and exclusion criteria. In other words, by eliminating confounding variables such as gestational diabetes, liver disease, use of antibiotics, BMI more than 40, and the like, it was possible to reduce unwanted bias in the results of the study. The patients' continuous follow-up by telephone also confirmed the accuracy of the study.

Conclusion

In the present study, oral probiotic supplementation did not significantly alter GBS in pregnant women, but for a definite alternative, further studies with larger sample sizes, different vaginal sampling methods, higher doses of oral probiotics, and an increase in the length of the intervention period are necessary. Given that GBS is a crucial issue for pregnant women worldwide, more investigations to prevent GBS colonization before birth are necessary.

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Authors' Contribution

Conceptualization: Kiana Shirani, Behrooz Ataei, Elahe Zarean, Soodabeh Rostami.
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Competing Interests

The authors declared that they have no conflict of interests.

Ethical Approval

The study design was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1399.513), and during the study, the authors disclosed any ethical concerns.

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