

Therapy Effect Comparison of Oral Probiotic to Oral Antibiotic on¹⁵⁴ Reducing The Risk of Premature Birth in Pregnant Women with Bacterial Vaginosis : A Systematic Review

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Abstract

Premature birth is one of the leading cause of neonatus death in the world and in Indonesia. Bacterial vaginosis is one of the risk of preterm birth, therapy can decrease the risk of premature birth. This systematic review was aimed to know the effect of oral probiotic and oral antibiotic to decrease the risk of premature birth in pregnant woman with bacterial vaginosis. Literature search was done using Pubmed, Cinahl, and ScienceDirect, with 'therapy', 'Bacterial Vaginosis', 'pregnancy', and 'premature birth' as the keywords. 1,843 studies were screened using Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA), 5 studies were obtained and analyzed. Datas obtained such as research method, participants, intervention, and outcome such as premature birth risk and side effects were obtained. Based on analysis oral antibiotic therapy is more effective compared to oral probiotic in decreasing premature birth. Therapy using clindamycin is found to be the most effective compared to other oral therapy in this research. Side effect is most minimum using oral probiotic compared to oral antibiotic. The most common side effect found is diarrhea, especially in oral clindamycin usage. Further research using more types of therapy is needed to give better comparison.

Keywords : bacterial vaginosis, pregnancy, preterm birth, therapy

1. Introduction

Premature birth is defined by the World Health Organization (WHO) as a baby born alive before 37 weeks of gestation. Until now, premature birth is still a problem in developed and developing countries. In 2016, premature birth was one of the main causes of death in neonates in the world [13]. Indonesia is one of the countries ranked in the top ten countries with the highest premature birth rate with a figure of 8.7%-11.9% in 2014 [2]. Until now, premature birth is still one of the causes of neonatal death in the world and in Indonesia. According to Sample Registration System (SRS) data conducted by the Indonesian Research and Development Agency (R&D) in 2016, low birth weight (LBW) babies and premature births accounted for 19% of the causes of death in neonates [4]. Premature birth can be caused by various factors and varies according to gestational age. Pathways that can cause premature birth are through maternal or systemic genital infections, placental ischemia or vascular lesions, excessive uterine distension, and stress. Each pathway has differences in mediator and initiator factors, but they have similarities, namely in increasing uterine contractions and premature birth [5]. Factor that can have an impact on premature birth is bacterial vaginosis. Bacterial vaginosis is a condition where there is a decrease in normal flora and an increase in anaerobic bacteria [6]. The mechanism of bacterial vaginosis as a cause of premature birth can be through several mechanisms, namely first by the increase of bacteria from the lower genital tract to the upper genital tract, secondly through the production of proteolytic enzymes produced by the organism so that the structure of the epithelium in the vagina changes, and, thirdly through local innate immunity [11]. A meta-analysis study by Leitich *et al* conducted on 20,232 patients found that bacterial vaginosis increased the risk of preterm birth by more than 2-fold. Bacterial vaginosis in early pregnancy has higher risk factors compared to bacterial vaginosis in late pregnancy. The risk of preterm pregnancy is 7-fold higher in women with BV <16 weeks' gestation and 4-fold higher in women with <20 weeks' gestation [8]. Bacterial vaginosis is caused by a decrease in the number of *Lactobacillus sp.* which is caused by an imbalance in the number of lactic acid-producing bacteria and anaerobic bacteria, resulting in changes in pH in the vagina. Anaerobic bacteria that cause bacterial vaginosis can be caused by *Gardnerella vaginalis*, *Escherichia coli*, *Mycoplasma hominis*, and *Mycoplasma custisii* [9]. A study by Yang *et al* examined the use of oral probiotics in an effort to reduce pro-inflammatory cytokines and chemokynes and reverse dysbiosis of vaginal microorganisms. [15]. Treatment of bacterial vaginosis in pregnant women using antibiotics in some cases can also increase the incidence of premature babies [10]. This research is aimed at finding alternative therapies with fewer side effects but which can provide the same benefits in treating bacterial vaginosis in pregnant women to reduce premature birth. Probiotics are an alternative therapy that can be used in

the treatment of bacterial vaginosis in pregnant women. Therefore, this study aimed to review the effect of giving oral probiotic therapy compared to oral antibiotic therapy on reducing the risk of premature babies in pregnant women suffering from bacterial vaginosis.

1.2 Material and Methods

This study is a secondary research conducted using systematic review. The study study was aimed for reviewing the effect of giving oral antibiotic therapy and oral probiotic therapy on reducing the risk of premature birth in pregnant women suffering from bacterial vaginosis. Systematic reviews were used to examine several studies that have been extracted and analyzed. All data were obtained from previous studies. Studies chosen for this systematic review were analyzed and sortened using Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) method. Literature search was done using Boolean operators from online databases such as PubMed, Cinahl, and ScienceDirect. Researchers used keywords for study retrieval, keywords used were Therapy AND (bacterial vaginosis OR bv) AND (pregnancy OR pregnant) AND (preterm birth OR premature birth). Data retrieval conducted in 09 August 2022. Datas were collected by comparing oral probiotic and oral antibiotic treatment. Outcomes such as premature birth risk and side effects were obtained then analyzed. Non-research studies such as article and conference paper were excluded. The risk of bias in the literature was calculated using Cochrane's Risk of Bias 2 (RoB2).

1.3 Result

1.3.1 Search Result

The literature search was carried out using e-databases Cinahl, PubMed, and ScienceDirect. From the keyword search, 1843 articles were obtained. In the initial stage, screening was carried out based on the title and abstract. In the first screening, 1678 less relevant articles were excluded. A total of 165 full text articles were then reviewed, at this stage 160 articles were excluded. 50 articles were articles with inconsistent results, 76 articles were articles that could not be accessed in full, 25 articles were articles not in English, 3 articles used samples of pregnant women suffering from bacterial vaginosis with co-infections. 6 articles do not have complete ones. 5 articles were then obtained to be reviewed in this research

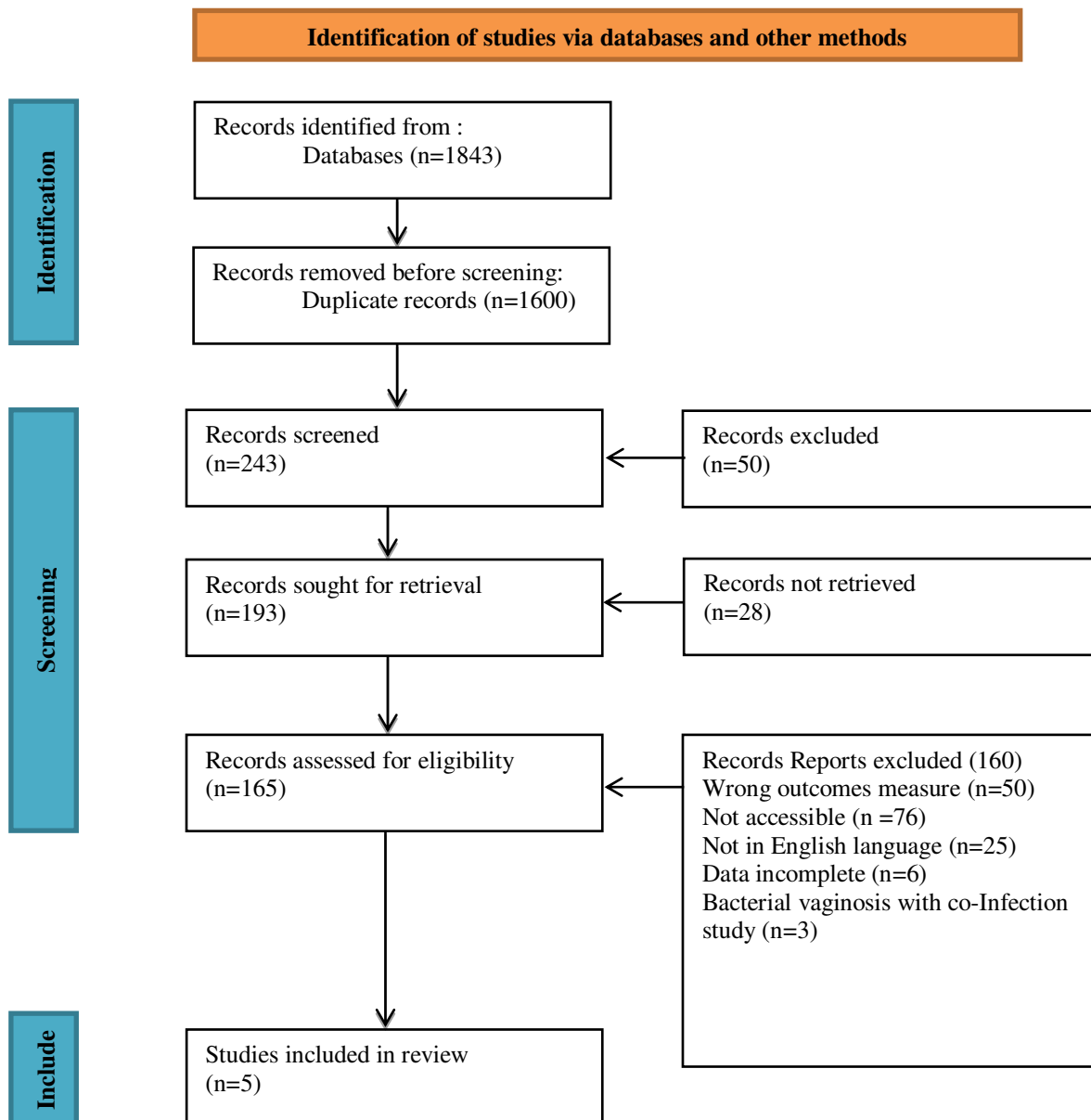


Figure 5.1 PRISMA Research Flow Diagram

1.3.2 Study Characteristics

Data extraction was carried out using a modified Cochrane collection form. The data used in literature data extraction are identity, method, time, sample size, inclusion criteria, exclusion criteria, intervention, diagnosis method, and outcome. Of the 5 articles reviewed, 2 articles were found from the Americas, 2 articles from the European Continent, and 1 article that had no data. The total number of participants obtained from these 5 studies was 96,955.

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|---|---------------|--|-----------------------------|--------|----------------------------------|--------------------|--|---|
| No | Author | Title | Demography | Method | Time | Participant | Intervention | Outcome |
| 1. | Silva 2011 | A randomised controlled trial of probiotics for the prevention of spontaneous preterm delivery associated with bacterial vaginosis: preliminary results | Rio De Janeiro, Brazil | RCT | - | 4204 participants | <i>Lactobacillus rhamnosus</i> GR-1 dan <i>Lactobacillus reuteri</i> RC-14 (10 ⁶ bakteri pada setiap strain) vs Placebo | Spontaneous premature birth Side effects |
| 2. | Ugwumadu 2003 | Effect of early oral clindamycin on late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: a randomised controlled trial | London, Inggris | RCT | 1 November 1996- 1 Februari 1999 | 6120 participants | 300 mg Clindamycin (5 hari) vs placebo | Spontaneous premature birth Side effects |
| 3. | Subtil 2018 | Early clindamycin for bacterial vaginosis in pregnancy (PREMEVA): a multicentre, double-blind, randomised controlled trial | Nord Pas de Calais, Prancis | RCT | 2006-2011 | 84350 participants | Single course clindamycin, triple course clindamycin, placebo | Spontaneous premature birth Side effects |
| 4. | Carey 2000 | Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis | - | RCT | - | 1953 participants | 2g metronidazole (2 dosis) vs placebo | Spontaneous premature birth Side effects |
| 5. | Yang 2020 | Effect of Oral Probiotic <i>Lactobacillus rhamnosus</i> GR-1 and <i>Lactobacillus reuteri</i> RC-14 on the Vaginal Microbiota, Cytokines and Chemokines in Pregnant Women | Toronto, Kanada | RCT | - | 328 participants | <i>Lactobacillus rhamnosus</i> GR-1, <i>Lactobacillus reuteri</i> RC-14 (10 ⁶ bakteri pada setiap strain) vs placebo | Spontaneous premature birth Side effects |

1.3.3 Data Extraction

Table 1. Data of Antibiotic Therapy on Reducing the Risk of Premature Birth in Pregnant Women Suffering from Bacterial Vaginosis

| Researchers, Year | Participant | Therapy | Participant | | Outcomes | | P value |
|--------------------------|-------------|----------------------|-------------|---------|-----------------|-----------------|---------|
| | | | Antibiotic | Placebo | Antibiotic | Placebo | |
| (Ugwumadu., et al. 2003) | 494 | <i>Clindamycin</i> | 249 | 245 | 11/249 (5%) | 28/245 (12%) | 0.001 |
| (Subtil, et al., 2018) | 2860 | <i>Clindamycin</i> | 1904 | 956 | 22/1904 (1.2%) | 10/956 (1.0%) | 0.82 |
| (Carey, et al., 2000) | 1919 | <i>Metronidazole</i> | 966 | 953 | 121/966 (12.5%) | 116/953 (12.2%) | 0.12 |

Table 2. Data of Probiotic Therapy on Reducing the Risk of Premature Birth in Pregnant Women Suffering from Bacterial Vaginosis

| Researchers, Year | Participant | Therapy | Participant | | Outcomes | |
|------------------------|-------------|---|-------------|---------|--------------|---------------|
| | | | Probiotic | Placebo | Probiotic | Placebo |
| (Yang., et al. 2020) | 84 | <i>Lactobacillus rhamnosus GR-1</i> , <i>Lactobacillus reuteri RC-14</i> | 41 | 43 | 2/41 (4.9%) | 0/43 (0%) |
| (Silva, et al., 2011) | 636 | <i>Lactobacillus rhamnosus GR-1</i> , <i>Lactobacillus reuteri RC-14</i> | 322 | 314 | 6/322 (1.8%) | 13/314 (4.1%) |

1.3.4 Data Analysis

1.3.4.1 Analysis of Antibiotic Therapy on Reducing the Risk of Premature Birth in Pregnant Women Suffering from Bacterial Vaginosis

Based on the research obtained, 3 studies were obtained that could be observed. Research by Ugwumadu., et al (2003), with a total of 494 participants, with clindamycin antibiotic therapy. It was found that 11/249 (5%) premature births occurred in pregnant women suffering from bacterial vaginosis, 28/245 (12%) premature births occurred in participants receiving placebo therapy, with a p value of 0.001. The difference in premature births in the Ugwumadu study between the Clindamycin and placebo treatment groups was quite significant. Clindamycin therapy in research by Ugwumadu et al (2003)

showed a reduction in premature births in pregnant women suffering from bacterial vaginosis. However, this is different from the research of Subtil *et al* in 2018, with the administration of a similar antibiotic, namely Clindamycin. Subtil *et al*'s (2018) research was conducted on the largest number of participants, a total of 2860 participants. Premature birth was experienced in pregnant women suffering from bacterial vaginosis 22/1904 (1.2%) with oral antibiotic Clindamycin therapy. Meanwhile, 10/956 (1.0%) of the placebo group experienced premature birth, with a p value between groups of 0.82. Research by Subtil, *et al* (2018) did not show any significant differences between the two oral Clindamycin therapy groups and the placebo group. Administration of the oral antibiotic Metronidazole also did not show any reduction in premature births in pregnant women suffering from bacterial vaginosis. A study by Carey, *et al* (2000) conducted on 1919 participants showed no significant difference in the reduction of premature births in participants receiving oral Metronidazole and participants receiving placebo. 121/966 (12.5%) participants who received oral Metronidazole therapy experienced premature birth, 116/953 (12.2%) participants who received placebo experienced premature birth, with a p value of 0.12. In 3 studies, antibiotic therapy with oral Clindamycin showed better results in reducing the risk of premature birth in pregnant women suffering from bacterial vaginosis compared to other antibiotics such as Metronidazole.

1.3.4.2 Analysis of Probiotic Therapy on Reducing the Risk of Premature Birth in Pregnant Women Suffering from Bacterial Vaginosis

Based on the research obtained, 2 studies were obtained that could be observed. The study by Yang, *et al* (2020) and the study by Silva, *et al* (2011) show different results. In a study by Yang, *et al* (2020), it was found that the group that received oral probiotic therapy experienced 2/41 (4.9%) premature births, while the group that received placebo did not experience 0/43 (0%). Meanwhile, in research by Silva, *et al* (2011) giving oral probiotic therapy can reduce the risk of premature birth, 6/322 (1.8%) of oral probiotic therapy participants experienced premature birth, 13/314 (4.1%) of placebo therapy participants experienced birth premature. Silva, *et al* (2011) had a larger number of participants than Yang, *et al* (2020).

1.4 Discussion

1.4.1 Effect of Oral Clindamycin Therapy on Reducing the Risk of Premature Birth

In this systematic review, 2 studies were obtained (Ugwumadu, *et al.*, 2003; Subtil, *et al.*, 2018) which assessed the effect of oral clindamycin therapy on reducing the risk of premature birth. Clindamycin is a macrolide antibiotic, macrolide antibiotics are used as a broad spectrum treatment. Macrolides have the unique property of fighting the inflammatory response caused by infection. Macrolide drugs such as clindamycin are used to treat bacterial vaginosis in pregnant women. Bacterial vaginosis can cause an inflammatory response due to the body's response to fighting infection which can cause premature contractions and cause premature birth. Both studies compared the effects of oral clindamycin with placebo, but found several differences. One study used oral clindamycin therapy 300 mg 3 times a day for 5 days and placebo 2 times a day for 5 days. Other studies divide therapy administration based on low-risk groups and high-risk groups. The therapy given to the low risk group was divided into a single course of clindamycin 600 mg for 4 days with placebo 2x a day for 4 days, clindamycin 600 mg 3x a day for 4 days, placebo 3x a day for 4 days. Therapy in the high risk group is divided into a single course of clindamycin 600 mg for 4 days and clindamycin 600 mg 3 times a day for 4 days. A study by Ugwumadu stated that oral clindamycin can reduce the risk of premature birth, patients on clindamycin therapy had a 5% preterm birth, while placebo 12%, $p = 0.001$). The incidence of premature birth in pregnant women with asymptomatic bacterial vaginosis who were given oral therapy with clindamycin 300 mg twice a day for 5 days had a significantly lower incidence of prematurity, namely 13 of 244 (5.3%) compared to participants who were given placebo, namely 38 of 241 (15.7%) [13]. In contrast to the results of a study by Subtil *et al* in 2018 which found that 22 of 1904 participants with low risk pregnancies experienced premature birth after being given oral clindamycin therapy, 10 of 956 participants with low risk pregnancies experienced premature birth after being given placebo. Meanwhile, in high-risk pregnancies, 8 out of 236 participants who were given single-course oral clindamycin therapy experienced premature birth and 5 out of 236 participants experienced premature birth after receiving triple-course clindamycin therapy [12]. The study by Subtil *et al* did not show a reduced risk of premature birth in pregnant women with bacterial vaginosis in the first trimester. The side effects of clindamycin therapy were also studied by Ugwumadu, *et al.* and Subtil, *et al.* Administration of clindamycin to pregnant women in both studies showed that side effects occurred more frequently in the group of pregnant women undergoing clindamycin therapy compared to the placebo group. In the study by Ugwumadu, side effects occurred in 17/239 (7%) women in the clindamycin group, and 8/239 (3%) women in the placebo group. Side effects reported included digestive disorders ($n=15$, 10 in the placebo group, 5 in the clindamycin group), nausea, vomiting, diarrhea, abdominal pain, or a combination of these complaints, and rash ($n=2$, one placebo group, one clindamycin group) throat irritation ($n=1$, in the placebo group), and headache ($n=5$, one in the placebo group, 4 in the clindamycin group), 11/244(5%). The study by Ugwumadu *et al* also showed the presence of eclampsia in the clindamycin therapy group.

A study by Subtil *et al* showed that side effects were found more frequently in the group of pregnant women undergoing clindamycin therapy. Clindamycin therapy was divided into two groups in the study by Subtil *et al*. High risk group and low risk group, with single course oral clindamycin and triple course oral clindamycin. 25/941 (23.7%) experienced side effects in the single oral clindamycin group, 33/963 (3.4%) experienced side effects in the triple course oral clindamycin. With a total of 58/1904 (3.0%) experiencing side effects in the oral clindamycin therapy group, 12/956 (1.3%) in the placebo group experienced side effects. Diarrhea was a side effect that was more frequently experienced in the clindamycin therapy group, 30/1904 (1.6%), other side effects experienced in the clindamycin group were abdominal pain, 9/1904 (0.4%), and other symptoms 24/1904 (1.3%). Meanwhile, in the placebo group, side effects other than stomach pain and diarrhea were experienced more often. In the placebo group, no one experienced abdominal pain, 4/956 (0.4%) experienced diarrhea, 8/956 (0.8%) experienced other symptoms. Both studies show that there are side effects from administering oral clindamycin therapy, although these side effects are not high risk, administering clindamycin therapy to pregnant women suffering from bacterial vaginosis still needs further consideration.

1.4.2 The Effect of Metronidazole Therapy on Reducing the Risk of Premature Birth

In this systematic review, 1 study was found regarding the effect of administering metronidazole on reducing the risk of premature birth. Metronidazole is the prototype of nitroimidazole, this drug was initially introduced to treat *T. vaginalis*, but is currently used to treat anaerobic and protozoal infections. Nitroimidazole is bactericidal through toxic metabolism which can cause DNA strand damage. A study by Carey *et al* in 2000 showed that the results were not significantly different in participants who were given metronidazole therapy 250 mg x 2 a day compared to participants who were given lactose placebo. In this study, 188 of 845 women who were given metronidazole therapy still experienced bacterial vaginosis, while 538 of 859 women who were given placebo experienced bacterial vaginosis [1]. Administration of metronidazole does not reduce the birth rate of premature babies. The metronidazole therapy group and the placebo group did not have significant differences. Preterm birth occurred in 121/953 (12.5%) patients in the metronidazole group, the incidence of premature birth in the placebo group was 116/966 (12.2%). Metronidazole therapy does not reduce the incidence of spontaneous labor, spontaneous membrane rupture, intra-amniotic infections, postpartum infections, and neonatal sepsis. Although treatment with metronidazole has shown effectiveness in treating bacterial vaginosis, its role in reducing preterm birth is less effective. Therefore, antibiotic therapy containing anti-inflammatory properties may be needed to reduce premature birth.

Based on a study by Carey *et al*, side effects were experienced more in the metronidazole therapy group than in the placebo group. The side effects that often occurred were gastrointestinal symptoms, 19.7% in the metronidazole therapy group and 7.5% in the placebo group. The most common gastrointestinal symptom is vomiting.

1.4.3 The Effect of Probiotic Therapy on Reducing the Risk of Premature Birth

Bacterial vaginosis is a modification of the environmental conditions of the vaginal flora which is described by a reduction or absence of normal vaginal flora in the form of lactobili, resulting in a change in pH which causes increased colonization by facultative and anaerobic microorganisms, including *Gardnerella vaginalis*, *Bacteroides sp.*, *Mobiluncus sp.*, *Prevotella sp.*, genital mycoplasma, and gram-positive cocci. The presence of increased concentrations of the chemokine IL-8 and the pro-inflammatory cytokine interleukin (IL)-1 β is often associated with bacterial vaginosis, both of which are also found to be increased in the cervical fluid and amniotic fluid of women with premature birth and microbial invasion of the amniotic cavity. Previous research discussed that different results were obtained when administering antibiotics as a treatment for bacterial vaginosis to reduce premature birth. The probiotics in this study are intended as an alternative to antibiotic treatment for bacterial vaginosis. Probiotics are defined as live microorganisms, which when given in sufficient quantities can provide benefits to the health of the host [3].

There were 2 studies that assessed the effect of giving probiotics on reducing the risk of premature birth in pregnant women suffering from bacterial vaginosis. A study conducted in 2011 by Silva *et al* showed less significant differences in reducing the risk of premature birth in pregnant women suffering from bacterial vaginosis without a history of premature pregnancy [7]. The study said the results could not be assessed for efficacy in preventing premature birth due to insufficient data. A study of the effect of antibiotics was also carried out by Yang *et al* in 2020. The study used oral probiotics *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 at a dose of 106 for each strain. Yang *et al* compared the effect of probiotics with placebo on reducing the risk of premature birth in women suffering from bacterial vaginosis. However, Yang's study also did not have sufficient data to determine whether probiotics had an effect on reducing premature births [14]. Studies with higher doses of oral probiotics in pregnant women suffering from bacterial vaginosis are needed to find a relationship between antibiotic therapy and a reduced risk of prematurity.

Side effects from probiotic and placebo therapy in both studies were minimal. Based on a study by Silva *et al*, 5/317 in the probiotic therapy group, 8/323 in the placebo group experienced side effects. Side effects that are often found are vomiting and diarrhea. This is different from the study by Yang *et al* which stated that no side effects were found in the probiotic therapy group and the placebo therapy group.

1.5 Strength and Limitation

This study utilized recent researches regarding oral probiotic and antibiotic therapy in decreasing the risk factor of premature birth in pregnant women with bacterial vaginosis, however this research also have limitation, there were still no RCT head to head comparative studies between antibiotic therapy and probiotic therapy.

1.6 Conclusion

Based on the findings in this research oral antibiotic therapy is better than oral probiotic therapy in reducing the risk of premature birth in pregnant women suffering from bacterial vaginosis, clindamycin is better than metronidazole in decreasing the risk of premature birth. Based on studies analyzed, oral probiotic gave less frequency of side effects from therapy, side effects that often found were gastrointestinal symptoms, such as diarrhea. Side effects frequently found in women given clindamycin oral therapy.

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