

Prevention of Recurrent Spontaneous Preterm Delivery by Using Probiotics Including Enterococcus Faecium, Bacillus Subtilis, and Clostridium Butyricum: A Retrospective Study

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ABSTRACT

Aim: The study aims to evaluate the rate of recurrence of spontaneous preterm delivery (sPTD) in pregnant women that have been administered probiotics

Study design: A retrospective study

Place and Duration: This study was conducted at Ghulam Muhammad Mahar Medical College Sukkur, Pakistan from May 2020 to May 2021

Methodology: The study included a total of 102 pregnant women who had a positive history of sPTD. The participants that had been given probiotics before 14 weeks of pregnancy, were selected in the study. The rate of occurrence of sPTD in 510 women who did not take probiotics, was compared with the participants that had taken the probiotics.

Result: The recurrence rate of sPTD was 14 (13.75%) out of 102 women that had taken probiotics. Compared to those women, those who had not taken probiotics showed a recurrence rate of sPTD was 30%. A total of 153 (30%) out of 510 women had sPTD ($p=0.002$).

Conclusion: It is evident from the results that the administration of probiotics significantly reduced the rate of recurrence of spontaneous preterm delivery in pregnancy. The efficacy of probiotics is more if they are taken before the 14th week of gestation compared to if they are taken after the 14th week.

Keywords: Preterm delivery, Clostridium, Recurrent spontaneous preterm delivery, probiotics

Introduction

Preterm delivery can be defined as a delivery that occurs before the completion of 37 weeks of pregnancy. It can be further classified on the basis of duration; extremely preterm in which delivery occurs before 28 weeks, very preterm in which delivery occurs between 28 and 32 weeks, and moderate or late preterm in which delivery occurs between 32 and 37 weeks. The classification of preterm delivery has also been done on the basis of birth weight; low birth weight (LBW) weigh less than 2.5kg, very low birth weight (VLBW) weigh less than 1.5 kg, and extremely low birth weight (ELBW) weight even less than 1 kg. Preterm delivery is either induced or spontaneous. Spontaneous preterm delivery occurs with an intact or ruptured membrane. Spontaneous labor happens in 65-75% of all the cases of preterm delivery and 30- 35% of the cases are induced for a background reason [1].

A positive history of spontaneous preterm delivery (sPTD) accounts for a significant risk factor for its recurrence. The rate of recurrence observed in the case of sPTD is 27% to 34% as per a systemic review [2]. Its rate in a developed country is also very high. An example of such a developed country is Japan where 22.3% of women have shown recurrent sPTD [3]. Hence, the prevention of sPTD is important on a global level. Some of the main causes of sPTD identified are infection and inflammation in the uterus [4]. The severity of sPTD increases in the earlier gestational weeks [5]. The sPTD under 28 weeks of gestation is considered a serious case due to the severe immaturity of the neonate. Such a case demands a high level of care and mostly needs

NICU for survival [6]. A retrospective study was carried out in recent years regarding the prevention of sPTD. According to that study, the use of probiotics has proven a reduction in sPTD. The probiotics include *Enterococcus faecium*, *Bacillus subtilis*, and *Clostridium butyricum*. The probiotics have been seen to be most effective if used before 32 weeks of pregnancy [7].

Out of all the live bacteria used for the prevention of sPTD, *Clostridium* species induces the regulatory T (Treg) cells production [8]. It plays an important role in pregnancy. It is reported in a study that the Treg cells are responsible for the induction of preterm birth [9]. Moreover, the level of *Clostridium* species in the intestinal flora has been reported to be lower in those pregnant women who have sPTD as compared to those that deliver babies on the term [10]. As it can be observed that there is an association of preterm delivery and low level of *Clostridium* species in the intestinal flora, it is obvious that probiotic administration can help in the reduction of recurrence of sPTD.

On the basis of the inference that probiotics including the *Clostridium* species, can induce Treg cells production and hence prevent the rate of recurrence of sPTD, we administered probiotics including *Enterococcus faecium*, *Bacillus subtilis*, and *Clostridium butyricum* to pregnant women with a positive history of sPTD. This was done to prevent sPTD and for the investigation of recurrence rate in the following pregnancy.

Methodology

The study includes a total of 102 subjects in the test group. The study was conducted in the Gynecology and Obstetrics department of our hospital. It was a retrospective study. Permission was taken from the ethical review committee of the institute. The records of the participants were collected from the patient data bank saved in the hospital record. The records of those pregnant women were acquired who had taken probiotics for the prevention of the recurrent sPTD. Those patients who had delivered through labor pains, or through clinical chorioamnionitis (c-CAM) [16] or had been diagnosed with chorioamnionitis (h-CAM) [17] by means of pathological investigation, were thought to have sPTD. An exclusion criterion was set before choosing the participants according to which those patients who had a uterine malformation, conization

history, steroid use history, placental abruption, multiple pregnancies, hypertensive disorders, placenta Previa, gestational diabetes, fetal anomaly, insufficient amniotic fluid, eclampsia, growth of the fetus and excessive amniotic fluid, were not included in the study. The data regarding sPTD in women who had not been taking probiotics were also collected for the sake of comparison. The variables which were included in the data were the age of the mother, gravidity, parity, the number of sPTD, and delivery weeks of sPTD. After that, the probiotics and non- probiotics groups were compared.

In the 102 participants included in the study, oral probiotics including *Enterococcus faecium*, *Bacillus subtilis*, and *Clostridium butyricum* was administered before the fourteen weeks of pregnancy. The dose of the probiotics in one tablet given is as follows; 2 mg *Enterococcus faecium*, 10 mg *Bacillus subtilis*, and 10 mg *Clostridium butyricum*. The patients have been prescribed two tablets three times in one day. Hence, a total of six tablets of each probiotic was taken by the patient in one day for 36 weeks. Informed consent was taken from the participants of the study before the administration of the probiotics.

A prophylactic Shirodkar cerclage was done on the participants who had cervical insufficiency along with the formation of the bag within 12 weeks to 16 weeks. Moreover, those women who had developed a bag before 28 weeks of pregnancy or had a short cervix (<25mm), were treated by application of McDonald's cerclage. When the participants were diagnosed to have preterm labor, ritodrine hydrochloride and magnesium sulfate were given in intravenous fluids. The dose of ritodrine hydrochloride was 200 µg/min and the dose of magnesium sulfate was 2.0 g/h. A maintenance dose of tocolysis for decreasing the rate of contractions was also given afterward.

The data was recorded and analyzed in the IBM SPSS version 26. Mann–Whitney U test or χ^2 - test was applied. The p-value of less than 0.05 was considered to be significant.

Results

In the present study, 102 women had a history of sPTD and they had been taking probiotics. Before the selection of the participants, some of them were excluded due to more than 15 weeks of probiotics, history of steroids intake, uterine malformation, and cervical conization. Hence, the remaining 102 patients were included in the study and had been administered probiotics before the 14th week of gestation. Among those 102 patients, cervical cerclage was done in 20

cases. Shirodkar cerclage was done on 14 patients and McDonald's cerclage was done on 6 patients. 14 patients were treated with tocolysis.

The comparison of characteristics of the patients has been given in Table 1. The number of participants in the probiotics group was 102 and the number of cases considered in the non-probiotics group was 510. The age of the patients included in the probiotics group (mean age = 33 years) was lower when compared to the non-probiotics group (mean age = 34 years). The gravidity and parity of the probiotics group were significantly larger than the non-probiotics group. The weeks of delivery of sPTD in past pregnancy was lower in the probiotics group than that of the non-probiotics group ($p < 0.001$)

The comparison of the prognosis sPTD in the pregnant women in both groups has been shown in Table 2. The rate of recurrence was significantly lesser in the probiotics group compared to the non-probiotics group. Moreover, the rate of late sPTD was also greatly lesser in the probiotics group compared to that of the non-probiotics group.

Table 1. Comparison of characteristics of probiotics group and non-probiotics group

Variables	Probiotics group (n=102)	Non-probiotics group (n=510)	p-value
Age (years)	33 ± 7	34 ± 9 years	0.025
Gravidity	3 ± 3	2 ± 4	< 0.001
Parity	2 ± 2	1 ± 6	0.007
Number of sPTD	1 ± 1	1 ± 1	0.924
Delivery weeks	26 ± 9	34 ± 3	< 0.001

Table 2. Comparison of prognosis of sPTD in the probiotics group and non-probiotics group

Variables	Probiotics group (n=102)	Non-probiotics group (n=510)	p-value
sPTD	10 (9.81%)	158 (30.98%)	0.002

sPTD < 34 weeks	6 (5.88%)	58 (11.37%)	0.266
Late sPTD	4 (3.92%)	100 (19.61%)	0.007
Term delivery	92 (90.19%)	352 (69.02%)	0.008

Discussion

The prevalence of preterm births in Pakistan is 15.7%, whereas, it is 9.6% on a global level [11]. However, the rate identified in our study is 9.8%. The rate of reduction of recurrent preterm deliveries reduced by means of probiotics and other management protocols such as cervical cerclage was 22.3%. For the investigation of effectivity of probiotics as a preventive measure, the data regarding the cases of sPTD in which probiotics were not given, was also obtained. After a thorough comparison, it was observed that a significantly lower rate of recurrence of sPTD was present in the probiotics group compared to the non-probiotics group. These results are evidence that the use of probiotics is effective for the prevention of sPTD. However, some studies suggest that the use of probiotics alone is not helpful in the reduction of the rate of preterm birth [12].

The study of Gogfrey et al included a total of 585 pregnant women who had undergone multiple interventions including probiotics, Myo-inositol, and supplements of micronutrients. They all proved to be efficient in the prevention of preterm deliveries, late preterm deliveries as well as preterm and premature rupture of the membranes. The results were compared to the control group [13]. The etiological factors by which sPTD is seen are multifactorial. Similarly, the mechanism of prevention of sPTD by using probiotics is also not clear. However, probiotics play a great role in the maintenance of appropriate gestational health [14].

According to the study conducted by Arango et al, the administration of probiotics can assist in the regulation of the balance of microflora composition which is present in diabetic and obese pregnant women. The effect of probiotic supplements on pregnant women was seen in their study. Probiotics also have a protective effect against preeclampsia, vaginal infections during pregnancy, allergic diseases, gestational diabetes mellitus, and infant weight. Hence, their study suggested that probiotics have multiple benefits during pregnancy [15].

The study of Myhre et al included a total of 950 participants. The study was a cohort study. It had been observed in the study that pregnant women who used to take dairy products containing probiotics were at a reduced risk of SPTD [16]. Similarly, according to the study of Lindsay et al that included 189 articles, a potential benefit of probiotics in the prevention of sPTD has been demonstrated. The incidence of preeclampsia and gestational diabetes mellitus was also reduced. The level of C-reactive proteins seems to be decreased in the pregnant women who had been taking probiotics. It is considered a therapeutic tool to combat the recurrence of sPTD [16].

The most significant strength of the present study is that it has demonstrated the preventive impacts of probiotics. There are a few such studies available in this regard.

Conclusion

It is evident from the results that the administration of probiotics significantly reduced the rate of recurrence of spontaneous preterm delivery in pregnancy. The efficacy of probiotics is more if they are taken before the 14th week of gestation compared to if they are taken after the 14th week.

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There was not a specific source of funding

Conflict of interest

The present study did not have any kind of conflicts of interest

Permission

Permission was asked and taken from the ethical committee of the institute

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