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Role of vaginal probiotic administration in the management of preterm premature rupture of membranes: A Randomized, double blind, placebo controlled trial

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Abstract

Background: *Preterm premature rupture of membranes (PPROM) is the rupture of amniotic membranes between gestational ages of twenty eight and thirty seven completed weeks. Early marriages, poverty, low maternal weight gain and absence of adequate birth spacing greatly effects the incidence of PPROM.*

Objective: *To determine the role of vaginal probiotics in the management of PPROM and to study the differences between the perinatal outcomes of sample population.*

Methodology: *This randomized control trial (RCT) was carried out at MCH, unit II, PIMS from October 2017 to December 2019. A total of 230 women with PPROM were randomly assigned to two study groups using lottery method. All singleton pregnancies having PPROM between 24 to 34 weeks gestation with positive nitrazine test and negative CRP test were included in the study. Participants were divided into two groups; Group A (placebo group) received erythromycin 250 mg QID or azithromycin 250mg BD.*

Results: *The average age of patients was 28.3 years in group A compared to 27.5 years in group B. Similarly, the APGAR score at 1 (6.5 vs 5.4) and 5 minute (7.8 vs 6.6) after birth was found significantly greater in group B. More neonates were entered into NICU from group A (77.9% vs 40.8%) compared to group B. In this study 23 (20.0%) patients died in the placebo group in comparison to 10 (8.6%) in probiotics group.*

Conclusion: *The combination of antibiotics probiotics is better than antibiotics placebo alone in managing PPROM patients. After PPROM maternal morbidity in terms of infection was reduced and latency period increased with probiotics.*

Keywords: Probiotics, antibiotics, latency period, perinatal outcome, PPROM

INTRODUCTION

Preterm premature rupture of membranes (PPROM) is the rupture of amniotic layers occurring between the gestational ages of 28 and 37 completed weeks and is the cause for around 33% of all preterm births.[1]

As of today no strategies have been identified or been made which reduces event of preterm birth after PPROM. A study in Abbottabad reported prevalence of PPROM as high as 9.5% and it was attributed to the social impacts of early marriage, destitution, low maternal weight gain and absence of birth spacing. [2]

Anti-microbial treatment decreases the risk of chorioamnionitis after PPROM and improves the perinatal result by prolonging the latency time frame. Serious issue identified with its use is the annihilation of the ordinary vaginal flora and probable overgrowth of destructive microorganisms, which increment the danger of ascending infection.[3]

A recent report revealed that the addition of probiotics to anti-microbial treatment in patients with PPROM improves the latent period.[4] It is considered that lactobacilli make a hostile environment for advancement of genital tract infections by decreasing the vaginal pH from the metabolism of mucosal glycogen and formation of lactic acid. A vaginal flora poor in lactobacilli is strongly related to the increased risk of preterm delivery.[5, 6]

The hypothesis that probiotics may lessen the danger of preterm delivery, in light of their capacity to reestablish a normal vaginal flora and prevent vaginal diseases, appears to be attractive.[7] The benefits of the probiotics are multiple, both for the mother and the child. The rate of infection in mothers, like chorioamnionitis, is reduced significantly; similarly the infection in the newborns like sepsis is also reduced. This is managed with addition of probiotics in the routine antibacterial therapy.[4]

Since, after PPROM the main task is to enhance the latency period, the use of probiotics has been found to significantly increase this gap between rupture of membranes and delivery. (Figure 3, 4) By prolonging the latent period up to the gestational age as close to 37 weeks as possible, the women and expectant infant are saved from the harmful consequences of PPROM. The chance of prematurity and subsequently low birth weight is reduced. Similarly, very few children need NICU admission. Moreover, majority of the neonates recover well after delivery and the rate of neonatal mortality is also significantly decreased in patients who are given probiotic therapy. Many before studies have highlighted these beneficial effects of probiotics.[4,5] Some studies suggest that additional benefit of probiotics is that they may protect from complications like gestational diabetes and preeclampsia.[8]

In this study we aim at examining the role of vaginal probiotics along with the anti-biotic treatment for PPROM and comparing the outcome with those who are getting antibiotic alone.

METHODOLOGY

After approval from the ethical review board and informed consent of the participants procedure was initiated. All women with PPROM between 24 to 34 weeks (admitted in the antenatal ward of MCH II) fulfilling the criteria were included in the study. PPROM was diagnosed by history, speculum examination and a positive nitrazine test. Participants were divided into two groups with the help of lottery method. Group A

(placebo group) received the standard antibiotic treatment and a placebo for a 10 day period. Group B (treatment group) was given erythromycin 250 mg QID or in case of unavailability, sensitivity or adverse effects, azithromycin 250mg BD was given. In case of any contraindication to both the drugs, amoxicillin 500mg TDS for a maximum period of 10 days or until the woman was in established labour (whichever is sooner) as recommended by NICE guidelines was used among the participants. In addition to this, pervaginal probiotic capsule 1 OD was given for the same 10 days. Drug contained 1 billion colony forming units (CFU) of Lactobacillus Acidophillus per tablet. Placebo and drug was acquired from the same pharmaceutical company and they have had same appearance but were coded as A and B. Researcher and the subject both were blind to the medication being administered. Two doses of dexamethasone 12 hours apart were given I/M to all the participants. CTG after 32 weeks was done twice a day and before that fetal heart rate monitoring was done as per department protocol. CBC and CRP were evaluated and compared every 3rd to 4th day along with ultrasonographic evaluation every week, unless differently indicated. Additionally, urine RE and C/S with genital cultures were sent every week. In case of oligohydramnios, aminovil infusions were given on alternate days. Patient was allowed to go home on her own preference after the 10 day course if AFI is more than 7cm and there were no signs of infection. Patient education and counseling was done regarding the precautions to be taken at home and watching out for the red flag signs.

Data was entered for analysis on computer based statistical package for the social science version. Mean and standard deviations were calculated for quantitative variables like age, parity, gestational age, WBC count, APGAR score, birth weight and latency period. Frequency and percentages were presented for qualitative variables like vaginal discharge, urinary tract infection, admission of infant in nursery or intensive care unit. Chi square test was applied to compare infection rate between both groups. Independent Sample t test was used to compare WBC count in both groups.

RESULTS:

There were a total of 230 patients with PPROM who were equally (n=115 each) randomly allocated to the two study groups i.e. group A (antibiotics + placebo) and group B (antibiotics + probiotics). The mean age of patients was 28.3 years in group A compared to 27.5 years in group B. Similarly, average duration of marriage was 5.1 years in group A and 4.7 years in group B. The women age and duration of marriage was found comparable between study groups. (Table 1)

On admission, the average gestational age was slightly greater in group B (31.4 week versus 29.4 weeks) compared to group A. At discharge, the average gestational age was again longer in group B patients than those in group A (34.1 weeks versus 31.6 weeks). The mean gravidity and parity were also found greater in group A in this study. Further details regarding gestational history of patients in (table 2).

When history of PPROM was assessed, it was found out those patients in group B had longer duration of PPROM than those in group A (3.4 days versus 2.8 days). History of infection and UTI was found slightly more prevalent in group A patients (60.0% versus 49.6%). Azithromycin was the most frequent (60.0% and 59.1%) therapy given to patients in group A and group B in this study, followed by erythromycin (30.4% and 20.8%) respectively. (Table 3)

C-Reactive protein and Total leukocyte count was done on every follow-up of patient. It was noted that after the treatment initiation, CRP was found positive in 30 (26.0%) patients in group A compared to 15 (13.0%) cases in group B. Similarly, on second follow-up again CRP positive finding was more prevalent in group A compared to group B. However, on third and fourth follow ups the findings of CRP investigations were found comparable between both study groups (p-value, 0.10). The findings of TLC levels were found similar between both study groups on different follow ups. However, on fourth follow up the mean TLC was greater in group B (11.6 versus 10.5) than group A (p-value, 0.01). (Table 3)

When the findings of vaginal swab culture and urine culture were compared between the two study groups, it was observed that on first follow-up close to 50.0% women had positive culture findings, however, it was not statistically different between the two study groups (p-value, 0.08). On the second and third follow-up no vaginal swab culture was performed. On the fourth follow-up 13 (11.3%) patients in group A had positive culture compared to 4 (3.4%) in group B (p-value, 0.01). Similarly, urinary cultures were also found positive in around 50.0% cases in both study groups, however, they were not different statistically (p-value, 0.07). On the subsequent follow-ups very few patients got culture investigations, however, none (0.0%) was found positive. (Table 3)

The frequency of bacterial vaginosis was found similar between the two groups on the first follow-up. Significantly more patients in group A had candida infection (41.7% versus 20.8%) than in patients of group B (p-value, 0.008). (Table 3)

The average latency period was significantly greater in group B compared to group A (15.4 days versus 12.3 days, p-value, 0.02). (Table 4)

The neonatal outcome in terms of birth weight, apgar score and morbidity were compared among the two study groups. It was observed that birth weight was significantly higher in group B compared to group A (2.1 kg versus 1.4 kg). Similarly, the APGAR score at 1 (6.5 vs 5.4) and 5 minute (7.8 vs 6.6) after birth was also found significantly higher in group B than group A (p-value, <0.001). All the neonates were admitted to the nursery for observation. The neonates admitted to NICU were found significantly greater in group A (77.9% vs 40.8%) compared to group B. (Table 4)

The causes of admission to nursery were low birth weight, PPROM and infection which were all found greater in group A than in group B. Whereas preterm births were found similar both groups. (Figure 1)

More neonates were admitted to NICU from group A (77.9% vs 40.8%) compared to group B. In this study 23 (20.0%) neonates died in the placebo group compared to 10 (8.6%) in the probiotics group. It shows that probiotics have a significant protective effect towards neonatal mortality after PPROM. (Figure 2)

Table 1: Age and marital duration of study patients in the two groups

	Group A (n=115)	Group B (n=115)	p-value
Age (years)			
Mean ± SD	28.3 ± 3.5	27.5 ± 4.2	0.06
Marriage duration (years)			
Mean ± SD	5.1 ± 3.5	4.7 ± 2.8	0.12

Table 2: Gestational history of patients in the two study groups

	Group A (n=115)	Group B (n=115)	p-value
Gestational age on admission (wks)			
Mean ± SD	29.4 ± 1.9	31.4 ± 1.2	<0.001
Gestational age on discharge (wks)			
Mean ± SD	31.6 ± 2.1	34.1 ± 1.1	<0.001
Gravidity			
Mean ± SD	3.2 ± 1.2	2.1 ± 1.9	<0.001
Parity			
Mean ± SD	1.9 ± 1.1	0.7 ± 1.1	<0.001

Table 3: Comparison of Medical History, CRP and TLC investigations, culture finding between the study groups

	Group A (n=115)	Group B (n=115)	p-value
H/O PPROM since (days)			
Mean ± SD	2.8 ± 2.5	3.4 ± 2.5	<0.001
H/O vaginal infection			
Yes	92 (80.0%)	68 (59.1%)	<0.001
No	23 (20.0%)	47 (40.9%)	
H/O UTI			
Yes	69 (60.0%)	57 (49.6%)	0.10
No	46 (40.0%)	58 (50.4%)	
Antibiotic given			
Azithromycin	69 (60.0%)	68 (59.1%)	0.18
Erythromycin	35 (30.4%)	24 (20.8%)	
Amoxicillin	11 (9.9%)	23 (19.9%)	
CRP on follow-up 1			
Positive	30 (26.0%)	15 (13.0%)	0.02
Negative	85 (74.0%)	100 (87.0%)	
CRP on follow-up 2			
Positive	35 (30.4%)	20 (19.5%)	0.03
Negative	80 (69.6%)	95 (80.5%)	
CRP on follow-up 3			
Positive	36 (31.3%)	47 (40.8%)	0.10
Negative	79 (68.7%)	68 (59.2%)	
CRP on follow-up 4			
Positive	11 (9.9%)	25 (21.7%)	0.05
Negative	104 (90.1%)	90 (78.3%)	
TLC on follow-up 1			
Mean ± SD	11.2 ± 3.8	10.8 ± 3.2	0.47
TLC on follow-up 2			
Mean ± SD	11.2 ± 3.1	10.9 ± 2.7	0.59
TLC on follow-up 3			
Mean ± SD	11.6 ± 5.6	11.5 ± 1.5	0.82
TLC on follow-up 4			
Mean ± SD	10.5 ± 2.2	11.6 ± 2.1	0.01
Vaginal swab culture on follow up 1			
Positive	60 (52.1%)	47 (40.8%)	0.08
Negative	55 (47.9%)	68 (59.2%)	
Vaginal swab culture on follow up 2			
Positive	0 (0.0%)	0 (0.0%)	1.0
Negative	115 (100.0%)	115 (100.0%)	
Vaginal swab culture on 3rd follow up			
Positive	0 (0.0%)	0 (0.0%)	1.0
Negative	115 (100.0%)	115 (100.0%)	
Vaginal swab culture on 4th follow up			
Positive	13 (11.3%)	4 (3.6%)	0.01
Negative	102 (88.7%)	111 (96.4%)	
Urine culture on 1st follow up			
Positive	58 (50.4%)	45 (39.1%)	0.07
Negative	57 (49.6%)	70 (60.9%)	

Table 4: Comparison of infection, latency period, neonatal outcome between study groups

	Group A (n=115)	Group B (n=115)	p-value
B.V	25 (21.7%)	23 (20.0%)	0.87
Candida	48 (41.7%)	24 (20.8%)	0.008
No growth	42 (36.5%)	68 (59.1%)	0.001
Latency period (days)			
Mean ± SD	12.3 ± 3.9	15.4 ± 6.9	0.02
Birth weight (kg)			
Mean ± SD	1.4 ± 0.5	2.1 ± 0.2	<0.001
APGAR score (1 min)			
Mean ± SD	5.4 ± 1.4	6.5 ± 0.5	<0.001
APGAR score (5 min)			
Mean ± SD	6.6 ± 1.1	7.8 ± 0.5	<0.001
Admission to nursery			
Yes	115 (100.0%)	115 (100.0%)	
No	0 (0.0%)	0 (0.0%)	1.0
Admission to NICU			
Yes	81 (77.9%)	47 (40.8%)	
No	34 (22.1%)	68 (59.2%)	<0.001

Figure1: Comparison of neonatal reasons for admission to nursery

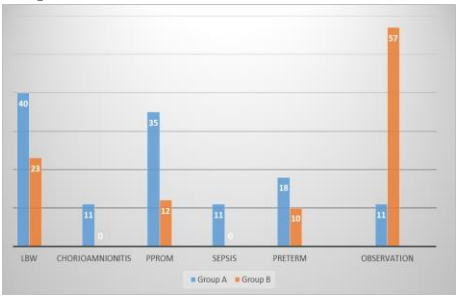
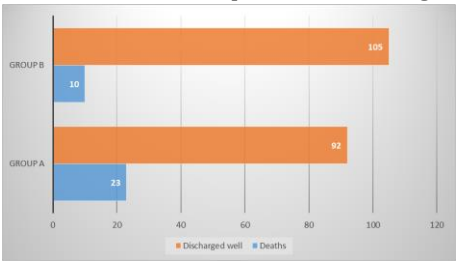


Figure 2: Final outcome of patients in the two groups



DISCUSSION:

All women with PPROM between 24 to 34 weeks were included in the study. PPROM was diagnosed by history, speculum examination and a positive nitrazine test. Group A (placebo group) was given antibiotic treatment and a placebo for the same 10-day period. In group B (treatment group) patients received a pervaginal probiotic capsule for a maximum period of 10 days in addition to the antibiotic therapy. Women were included on the criteria of having singleton pregnancies with PPROM between 24 to 34 weeks gestation and having positive nitrazine test and negative CRP test. The women were excluded if they had active labour or multiple pregnancies, had vaginal bleeding,

choriomnionitis, fetal growth restriction, medical comorbidities and had obstetrical complications like hypertension or diabetes. The primary outcome was maternal infection and latency period and the secondary outcomes were neonatal outcomes in terms of birth weight, apgar score and NICU admission.

The mean age of study patients was 27.5 years in group B (antibiotic+probiotic) and 28.3 years in group A (antibiotic+placebo). Similarly, the average marriage duration was also found comparable among the two study groups. These findings are quite comparable with many reports based on similar topics. A study by Kavak SB et al also witnessed a similar average age of their study patients.[9,17] Ibrahim FA also witnessed a similar age of patients in the study and management groups.[10] Luzzi G and colleagues also reported a similar age of their patients in the study and management groups.[11,16]

In the current study, a significant difference is noticed in rate of infection i.e. bacterial vaginosis and candida between the two study groups. The probiotic therapy had significantly less rate of bacterial vaginosis and candida infection. Infection was also proven by other investigations, it was seen that a large number of subjects/patients in the placebo group had CRP positive findings. There are many bacterial infections which are related to PPROM including Bacterial vaginosis, etc. Henceforth it is possible that by restoring vaginal ecosystem, the vaginal pathogen overgrowth could be managed.[12] This was also observed in the current study as well as more patients were found to have raised CRP after PPROM.

In this study, it is observed that the gestational age at delivery is significantly greater in the probiotic group compared to the placebo. The latency period was also greater in the probiotic group in the present study. Many before studies have also proven this role of probiotics in expanding the gestational age after PPROM and also significantly prolonging the latency period. Kavak SB and colleagues observed a similar finding where they found out that probiotics when given along with antibiotics in PPROM expands the latency period and prolongs the gestational age.[13,14] Luzi G et al reported that mean gestational age at delivery was significantly longer in the antibiotic+probiotic group compared to antiobitcs alone.[14,17] Ibrahim FA also reported similar finding related to latency period, which was found significantly greater in the patients given probiotic with antibiotic when compared to patients given antibiotics only.[15]

The neonatal outcome was also found to be better in the probiotic+antibiotic group, it was noted that mean birth weight, APGAR score at 1 and 5 minutes were significantly greater in the combination of probiotic and antibiotic therapy compared to antibiotic and placebo group. Similarly, we noted significantly less patients requiring NICU admission in the probiotic+antibiotic group. Many before studies have also proven this fact. A study by Ibrahim FA concluded that birth weight and Apgar scores were significantly higher in the probiotic therapy group. Kavak SB and colleagues reported that APGAR score at 5 minutes and birth weight were significantly greater in the probiotic treatment group compared to placebo.[14,16]

PPROM is associated with lower latency from membrane rupture until delivery, this consequently, causes severe perinatal morbidity and mortality. The increase in the latency period is thus, inversely related to a neonates outcome. In the current study we observed high neonatal mortality in the placebo group compared to the combination of antibiotics+probiotic group. This validates many previous trials results. The study by Luzi G et al also showed a high mortality in the managements

compared to probiotic intervention. The main reasons of neonatal morbidity and mortality after PPROM are prematurity, and infections such as chorioamnionitis and sepsis.[15,17] In the current study as well, infections such like sepsis and chorioamnionitis were significantly less prevalent in the probiotic group compared to placebo. Since latency period is increased, in this study the risk of prematurity and low birth weight babies was also reduced by probiotic therapy.

In short, this study proved significant beneficial effects of probiotics in the management of patients with PPROM in terms of latency period, maternal infection and neonatal outcomes. The role of probiotics should be assessed in other regions of the country to validate the findings of current study. This study has many advantages; firstly, a significant reduction in maternal and neonatal morbidity was achieved with this intervention. Secondly, the number of cases requiring intensive care were also less in the probiotic arm. Thirdly, neonatal mortality was also reduced by this intervention. A reasonable sample of patients was selected and intervened which proves the effect of probiotics in the subjects. The strengths of the study design which is randomized controlled trial cannot be avoided as well.

There were some limitations of the study which were mainly related to lack of long term follow-up of the patients, the outcome was measured until the patients discharged from the hospital, so the long term outcome of the study subjects was not known.

CONCLUSION

- This study proves that combination of antibiotics and probiotics is better than antibiotics alone in the management of women with PPROM.
- It was observed that maternal morbidity in terms of infection was reduced.
- The latency period judged as time of PPROM until delivery was significantly increased in probiotic group which had tremendous benefits in reducing prematurity, low birth weight, NICU admissions and neonatal mortality.

We could not find much previous evidence on the use of probiotics in PPROM. Thus, the findings of this study have significant implications and must be replicated in other centers across the country, so that the findings can be generalized.

RECOMMENDATIONS:

The following points are suggested for the diagnosis and management of PPROM:

- The diagnosis of rupture of membranes must be confirmed.
- Digital assessment of vagina is unhealthy and should be the last option to take.
- If the gestational age, fetal weight, amniotic fluid index etc. are not already assessed, then ultrasonography should be performed to evaluate before treatment.
- Medical treatment guidelines must be followed before prescribing antibiotics.
- Careful documentation must be ensured to take consent of the participant regarding the mode, time of delivery and expectant management.
- Until delivery, monitoring of fetal wellbeing must be done to avoid any worrisome circumstances. Regular ultrasounds must also be performed to ensure fetal well-being and growth.
- Expectant management of patient with PPROM may be re-evaluated time and again specially after 32 or 34 weeks' gestation for each individual case.

- While waiting for spontaneous labor in the cases of PROM at term, sign and symptoms of chorioamnionitis should be vigilantly looked for and treated accordingly.

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