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ORIGINAL ARTICLE

Vaginal lactoferrin in prevention of preterm birth in women with bacterial vaginosis

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ABSTRACT

Objective: To evaluate use of vaginal lactoferrin in prevention of preterm birth (PTB) in women with first trimester bacterial vaginosis and prior spontaneous PTB.

Methods: This is a retrospective cohort study of all consecutive singleton gestations with prior PTB, and first trimester diagnosis of bacterial vaginosis. Women who were found to have bacterial vaginosis were recommended lactoferrin 300 mg vaginal tablets daily for 21 days. The primary outcome was the incidence of PTB at less than 37 weeks of gestations. Outcomes were compared in women who received daily lactoferrin with those who did not

Results: During the study period, 847 pregnant women with prior spontaneous PTB were screened for bacterial vaginosis. Of them, 193 were found to have bacterial vaginosis in the first trimester, with an overall incidence of 22.8%. Out of the 193 women, 125 met the inclusion criteria for the study and were analyzed. Sixty of the included women received vaginal lactoferrin, while 65 did not. Women who received supplementation with lactoferrin had a significantly lower rate of PTB < 37 weeks (25.0 versus 44.6%; $p = .02$), lower mean gestational age at delivery (37.7 ± 3.2 versus 35.9 ± 4.1 weeks; $p = .01$), and lower rate of admission for threatened PTL (45.0 versus 70.8%; $p = .04$). No between-group differences were noticed in the other outcomes, including chorioamnionitis, PPROM < 34 weeks, and neonatal outcomes. No cases of late miscarriage were reported in our cohort. No cases of adverse events were reported.

Conclusion: Based on this small single-center retrospective study, supplementation with vaginal lactoferrin in women with first trimester bacterial vaginosis may be an option to reduce the risk of preterm delivery.

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NICU; prematurity; preterm delivery; progesterone; supplementation

Introduction

Prematurity is a leading cause of maternal and neonatal mortality and morbidity, complicating up to 10% of all pregnancies [1]. Mortality and morbidities, including respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC) and sepsis, are inversely associated with gestational age at birth [1,2].

Different strategies have been adopted for prevention of preterm birth (PTB), including cervical pessary, cerclage, and progesterone [3–15]. Observational evidence suggests that vaginal infection is implicated in the genesis of spontaneous preterm labor (PTL), and preterm premature rupture of membranes (PPROM) [16–18]. Bacterial vaginosis in particular is associated with about two to four-fold increased risk of PTB [17]. Therefore, some authors suggest universal screening and treatment for bacterial vaginosis in pregnancy. However, evidence from meta-analyses and randomized trials showed that screening and treatment of bacterial vaginosis in low-risk pregnancies do not reduce the risk of PTB [19–21]. Contrariwise, the effect in women at high risk of preterm delivery for history of prior spontaneous PTB is still a subject of debate [22], although use of antibiotics are not currently recommended. In these patients, a treatment based on vaginal lactoferrin may offered as an alternative and safe approach [23–25] however, evidence of efficacy of lactoferrin in prevention of PTB are still lacking.

Objective

Thus, the aim of this study was to evaluate use of vaginal lactoferrin in prevention of PTB in women

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with first trimester bacterial vaginosis and prior spontaneous PTB.

Materials and methods

Study design

This was a retrospective study using data collected prospectively from clinical records of all consecutive pregnant women with prior PTB who were referred to the University of Naples "Federico II" from January 2016 to January 2019. Only women with singleton gestations and history of prior spontaneous PTB at 16 0/7 – 36 6/7 week of gestation were included in the database. Data were collected with the patient consent and were anonymized before analysis.

Women with prior PTB were screening for bacterial vaginosis using vaginal swab in the first prenatal visit < 13 weeks of gestations. Women who were found to have bacterial vaginosis, based on established diagnostic criteria [26], were included in the study. Women without bacterial vaginosis at the first prenatal visit, and those with first prenatal visit > 13 weeks of gestations were excluded from the study.

Women who were found to have bacterial vaginosis were recommended lactoferrin 300 mg vaginal tablets Medical device (MD) daily for 21 days, starting from January 2018. Before January 2018, women were not recommended any treatment.

Primary and secondary outcomes

The primary outcome was the incidence of PTB at less than 37 weeks of gestations. The secondary outcomes were spontaneous late miscarriage, defined as delivery between 16 and 21 weeks; hospitalization for threatened preterm labor; chorioamnionitis; preterm premature rupture of membranes (PPROM) at less than 34 weeks of gestations; and neonatal outcomes, including birth weight and admission to neonatal intensive care unit (NICU).

Primary and secondary outcomes were compared in women who received vaginal lactoferrin with those who did not.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v. 19.0 (IBM Inc, Armonk, NY, USA). Data were shown as means ± standard deviation or as number (percentage). Univariate comparisons of dichotomous data were performed with the use of the chi-square test with continuity correction. Comparisons between groups were performed with the use of the T-test to test group means by assuming equal within-group variances.

p Values < .05 was considered statistically significant.

Results

During the study period, 847 pregnant women with prior spontaneous PTB were screened for bacterial vaginosis. Of them, 193 were found to have bacterial vaginosis in the first trimester, with an overall incidence of 22.8%. Out of the 193 women, 125 met the inclusion criteria for the study and were analyzed. 60 of the included women received vaginal lactoferrin, while 65 did not.

The two groups were similar in terms of maternal demographics. The mean maternal age was about 28 years, and the mean BMI was about 21. Most of the included women were Caucasian, 53 and 57 in the lactoferrin and in the control group, respectively. Overall 12% (15/125) of the women were smokers. Sixty-one women received progesterone, four received Arabin pessary, and three patients received cervical cerclage (Table 1).

Women who received supplementation with lactoferrin had a significantly lower rate of PTB < 37 weeks (25.0 versus 44.6%; $p = .02$), lower mean gestational age at delivery (37.7 ± 3.2 versus 35.9 ± 4.1 weeks; $p = .01$), and lower rate of admission for threatened PTL (45.0 versus 70.8%; $p = .04$). No between-group differences were noticed in the other outcomes, including chorioamnionitis, PPROM < 34 weeks, and neonatal outcomes. No cases of late miscarriage were reported in our cohort. No cases of adverse events were reported (Table 2).

Discussion

Main findings

This study aimed to evaluate the efficacy of lactoferrin in reducing the incidence of PTB in singleton

Table 1. Maternal demographic characteristics.

	Lactoferrin group $N = 60$	Control group $N = 65$	p-Value
Age (years)	27.6 ± 6.0	28.7 ± 6.3	.32
BMI	21.7 ± 1.8	21.4 ± 1.8	.78
Race			
White	53 (88.3%)	57 (87.7%)	.56
Smoking	7 (11.7%)	8 (12.3%)	.57
Progesterone	52 (86.7%)	59 (90.8%)	.51
Cervical pessary	1 (1.7%)	3 (4.6%)	.34
Cervical cerclage	1 (1.7%)	2 (3.1%)	.53

Data are presented as number (percentage) or as mean ± standard deviation.

gestations with prior PTB, and with first trimester bacterial vaginosis. In our study the incidence of bacterial vaginosis in a cohort of women with prior spontaneous PTB was 22.8%. Women who were recommended lactoferrin 300 mg vaginal tablets daily for 21 days had a significantly lower rate of PTB at less than 37 weeks of gestation. Those women also had less chances to be admitted for threated PTL. We also reported a non-significantly lower incidence of admission to NICU in the lactoferrin group.

The most important limitation of our study is the retrospective, nonrandomized approach. *A priori* power analysis could not be assessed due to its retrospective nature. The number of women included were small due to the restrictive inclusion criteria. Compliance with therapy was not measured. No cost-effectiveness analysis was assessed. The incidence of preterm delivery was higher that expected in our cohort, with an incidence of 44.6% of PTB < 37 weeks, and a 70.8% rate of women admitted inpatient for threatened PLT. Notable, the included women, ie women with prior PTB and with bacterial vaginosis, are patients with high baseline risk of PLT.

Implications

Bacterial vaginosis is characterized by a dysbiosis of the vaginal microbiota where protective Lactobacillus spp. are replaced by a mixed anaerobic microbiota, including *Gardnerella vaginalis* and *Mobiluncus* spp. morphotypes [27,28]. Symptoms of bacterial vaginosis include vaginal discharge and fishy odor, but most of the women are asymptomatic. One problem with bacterial vaginosis, is the inconsistencies in the diagnosis. Initially, it was diagnosed with Amsel criteria, then largely replaced by the Nugent criteria [26,27,29]. Recently, polymerase chain reaction (PCR) of bacterium-specific 16S rDNA has been used to detect bacteria associated with bacterial vaginosis [28–30].

Table 2. Primary and secondary outcomes.

	Lactoferrin group $N = 60$	Control group $N = 65$	*p*-Value
PTB < 37 weeks	15 (25.0%)	29 (44.6%)	**.02**
GA at delivery (weeks)	37.7 ± 3.2	35.9 ± 4.1	**.01**
Late miscarriage	0	0	–
Threatened PTL	27 (45.0%)	46 (70.8%)	**.04**
Chorioamnionitis	2 (3.3%)	6 (9.2%)	.27
PPROM < 34 weeks	1 (1.7%)	2 (3.1%)	.53
Birth weight (grams)	2,808 ± 719	2,625 ± 831	.19
Admission to NICU	5 (8.3%)	14 (21.5%)	.05

Data are presented as number (percentage) or as mean ± standard deviation.
PTB: preterm birth; GA: gestational age; PTL preterm labor; NICU: neonatal intensive care unitBoldface data, statistically significant.

Bacterial vaginosis, especially when present in early pregnancy, has been associated with an increased risk of preterm delivery, early pregnancy loss, low birth weight, increased neonatal morbidity, and higher rates of postpartum endometritis. Despite the strength of evidence linking infection with preterm labor and delivery and perinatal complication, most of the efforts to prevent these complications with antibiotics have been not successful [19–21,31–33]. Romero and other experts suggest that this may be explained by the fact that PTB is a syndrome and the infection is only one of its causes, and by the fact that the odds ratio for PTB in women with bacterial vaginosis is low [31–33].

Notably, antimicrobial agents are drugs that alter the microbial ecosystems, including the vaginal microbiome. Antibiotic administration may alter the vaginal flora and predispose to vaginal candidiasis and other infections, and can affect intestinal, urinary tract, and periodontal flora. These theories may also explain the increased risk in preterm labor in women receiving antibiotics compared to placebo in several randomized trials [19–21]. For these reasons, other nonantibiotic agents have been studies in order to reduce the risk of PTB in women with bacterial vaginosis.

Gardnerella vaginalis proliferation is dependent on iron, whereas lactobacilli require manganese [29]. Lactoferrin is an iron-binding protein that is elevated in the vaginal discharge of patients with bacterial vaginosis. This suggests that the increased lactoferrin production may be a host response to limit proliferation of iron-requiring bacteria [29]. Moreover, in animal model, human lactoferrin showed a potential to suppress uterine cervical ripening [25]. Therefore, supplementation with oral or vaginal lactoferrin has been proposed as an alternative approach for pregnant women with bacterial vaginosis [23,24]. To the best of our knowledge, this study may be the first clinical observational cohort study showing efficacy of vaginal lactoferrin in reducing the risk of PTB in women with bacterial vaginosis.

Conclusions

In summary, based on this small single-center retrospective study, supplementation with lactoferrin in women with first trimester bacterial vaginosis may be a safe option to reduce the risk of preterm delivery.

Disclosure statement

No potential conflict of interest was reported by the authors.

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