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ORIGINAL RESEARCH ARTICLE

Vaginal streptococcus B colonization is not associated with increased infectious morbidity in labor induction

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Abstract

Introduction: Labor induction rates are increasing and, in Finland today, one of three labors is induced. Group B streptococcus (GBS) is a bacterium found in 10%–30% of pregnant women and it can be transmitted to the neonate during vaginal delivery. Although GBS is rarely harmful in the general population, it is the leading cause of severe neonatal infections such as sepsis, pneumonia, and meningitis. In addition, GBS can cause maternal morbidity. Labor induction in GBS-positive women has not yet been investigated but concerns of infectious morbidity associated with balloon catheters have been raised.

Material and methods: A historical cohort study of 1959 women undergoing labor induction by balloon catheter in Helsinki University Hospital, Finland, between January 1, 2014 and December 31, 2017. Women with viable singleton term pregnancy in cephalic presentation, unfavorable cervix (Bishop score <6), and intact amniotic membranes were included. GBS was screened by rapid qualitative in vitro test (XPert® GBS) from vaginal and perineal culture upon admission for labor induction. All women testing positive received prophylactic antibiotics.

Results: Of the women, 469 (23.9%) were GBS-positive. The rate of maternal intrapartum infection was 7.4%, being lower in the GBS-positive group compared with the GBS-negative group (4.7% vs 8.3%; $p = 0.01$). The rate of maternal postpartum infection was 3.9%, and the rate of neonatal infection was 3.3%, both being similar between the groups. Also, no difference in the rates of other adverse neonatal outcomes was seen. No GBS sepses occurred in the study. In multivariable logistic regression, rupture of membranes to delivery interval ≥12 hours was associated with maternal intrapartum and postpartum infection, as well as neonatal infection. Other risk factors for maternal intrapartum infection were GBS-negativity, nulliparity, prolonged pregnancy (≥41 weeks), and Bishop score <3 at the start of induction. Cesarean section was associated with postpartum endometritis, while nulliparity, gestational diabetes, and maternal intrapartum infection were associated with neonatal infection.

Abbreviations: AUC, area under the curve; BC, balloon catheter; CI, confidence interval; GBS, group B streptococcus; IQR, interquartile range; ROC, receiver operating characteristics.

Conclusions: Regarding maternal and neonatal infectious morbidity, labor induction with balloon catheter appears safe in women colonized with GBS when prophylactic antibiotics are administered at the onset of labor or at membrane rupture.

KEYWORDS
balloon catheter, Foley catheter, group B streptococcus, labor induction, streptococcus B

1 | INTRODUCTION

Rates of labor induction are increasing, and in Finland one of three (32%) labors in 2019 was induced.[1] Labor induction is often started by ripening the cervix mechanically with a balloon catheter (BC) or medically with prostaglandins.

Group B streptococcus (*Streptococcus agalactiae*) (GBS) is a bacterium often found in maternal vaginal and perianal flora that can be transmitted to the neonate during vaginal delivery. The prevalence of GBS in pregnant women ranges between 10% and 30%.[2] Only half of colonized women transmit GBS to their neonates during a vaginal birth, and among these children only 1%–2% have a clinical infection.[3] Although this bacterium is rarely harmful in the general population, it is the leading cause of severe neonatal infections such as sepsis, pneumonia, and meningitis.[4] In addition, GBS can cause maternal morbidity.[5] In women colonized with GBS, the risk of intrapartum chorioamnionitis and postpartum endometritis is twofold compared with GBS-negative women.[5] Antibiotic prophylaxis administered at the onset of labor, preferably at least 4 hours before birth, prevents neonatal sepsis.[6]

Maternal risk factors for severe neonatal infection are preterm delivery, young age, bacteriuria during pregnancy, fever during labor, long interval between rupture of membranes and birth, strong GBS colonization, and a previous GBS-related neonatal infection.[4,7] However, not all severe neonatal infections occur in patients with a high risk for infection, so protocols have changed from selective screening and giving antibiotic prophylaxis to women at high risk to universal screening and giving antibiotic prophylaxis to all GBS-positive women.[7,8] Universal screening programs have decreased the incidence of early-onset GBS neonatal sepsis to 0.22 per 1000 live births.[9] The best way to detect maternal GBS colonization is a rapid screening test on admission to labor ward or before labor induction.[10] As maternal GBS colonization can be permanent or only occasional,[11] traditional rectovaginal culture at 35–37 weeks of gestation does not show the colonization status at labor but rather reflects the past colonization.[12]

Labor induction in GBS-positive women has not yet been investigated but concerns of infectious morbidity associated with BC have been raised.[13] Cervical ripening with BC has been shown to increase the number of bacteria, including GBS, in the cervix,[14] but no evidence of association with clinical infections has yet been presented. Given the maternal and neonatal morbidity associated with GBS, and the high prevalence of labor induction, it is important to assess the safety of cervical ripening by BC in GBS-positive women.

Key message

Group B streptococcus (GBS) -positive women undergoing labor induction by balloon catheter, with antibiotic prophylaxis administered at the onset of labor or at membrane rupture, had fewer intrapartum infections compared with GBS-negative women. Postpartum infections and neonatal infections did not differ between the groups.

The aim of this study is to evaluate the safety of labor induction by BC in terms of maternal and neonatal infectious morbidity in women with and without GBS colonization.

2 | MATERIAL AND METHODS

This historical cohort study of women undergoing labor induction by BC was carried out in the Department of Obstetrics and Gynecology of Helsinki University Hospital, Finland between January 1, 2014 and December 31, 2017. Women undergoing labor induction with viable singleton term pregnancy in cephalic presentation, unfavorable cervix (Bishop score <6), and intact amniotic membranes were included (Figure 1). According to hospital protocol, GBS testing was performed by rapid qualitative in vitro test (XPert® GBS; Cepheid) from vaginal and perineal culture upon admission for labor induction. All women with a documented positive or negative test result were included in the study. Sometimes the XPert® GBS-test gives an error-signal. If the error-signal is given twice, the test is considered erroneous, uncertain, and the patient is treated as GBS-positive. In this study, women with an erroneous result or no result were excluded (Figure 1). Data on the study population characteristics and labor and delivery outcomes were obtained from individual patient charts in the hospital database.

All GBS-positive women received prophylactic benzylpenicillin 4 million units intravenously followed by 2.5 million units every 4 hours until delivery. In case of penicillin allergy, the women received cefuroxime 1.5 g or clindamycin 900 mg every 8 h intravenously. Prophylaxis was started at the onset of labor or when the membranes were ruptured. All GBS-negative women who received antibiotics received them for suspected infection. In addition, all women undergoing cesarean section received prophylactic antibiotics, but this is not included as antibiotic use in the present study.

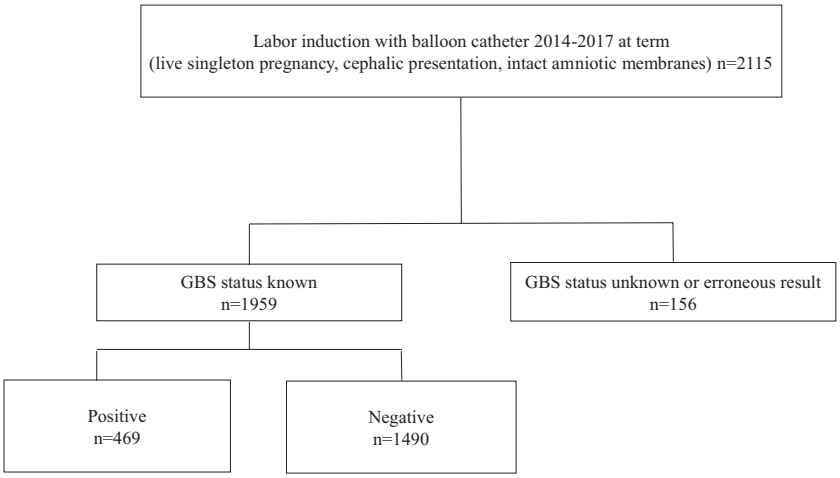

FIGURE 1 Flow chart of the study population

Gestational age was determined by crown-rump length measurement at the time of the first-trimester ultrasound screening. Obesity was defined as severe obesity, with pre-pregnancy body mass index ≥35 kg/m^2. A 2-hour 75 g oral glucose tolerance test was used to diagnose gestational diabetes, and medication-dependent gestational diabetes included both insulin and metformin treatments. Prolonged pregnancy was defined as gestational age ≥41^{+0} weeks and post-term pregnancy was defined as gestational age ≥42^{+0} weeks. Birthweight ≥4500 g defined fetal macrosomia. Indications for labor induction were categorized as post-term pregnancy, diabetes (pregestational or gestational), preeclampsia, and other reasons.

Labor was induced by a single 40–75 mL BC (Rüsh 2-way Foley, Couvelaire tip, catheter size 22 Ch; Teleflex Medical), retained for a maximum of 24 hours. Outpatient protocol was offered for most women at BC insertion, and the women were asked to return to hospital at BC expulsion or after 24 h if the balloon was still in place. In women with an unripe cervix following BC expulsion or removal, sequential misoprostol (Cytotec®; Piramal Healthcare UK Ltd) 50 µg orally or 25 µg vaginally every 4 hours was administered until a Bishop score ≥6 was achieved. Amniotomy was performed when the cervix was favorable (Bishop score ≥6), and oxytocin infusion was started after 2 hours if contractions were inadequate. Continuous fetal cardiotocography was routinely used during labor.

The primary outcomes were the rates of maternal intrapartum and postpartum infections and neonatal infections. The secondary outcomes were other adverse neonatal outcomes (5-minute Apgar-score <7, umbilical artery pH <7.05, or base excess <−12, and neonatal intensive care unit admission).

Maternal intrapartum infection was diagnosed if two of the following were observed: fever ≥38°C, fetal heart rate >160 bpm, total white cell count ≥15 e9/L, uterine tenderness, or purulent discharge.[15] Maternal postpartum infection included endometritis (diagnosed if at least two of the following were observed: fever ≥38°C, total white cell count ≥15 e9/L, uterine tenderness, or purulent vaginal discharge), clinical wound infection in cesarean or episiotomy wound, septicemia, abdominal or pelvic infection, urinary tract infection, or puerperal fever of unknown origin within 1 week of delivery.[16] A neonatologist categorized and confirmed all neonatal infections as blood-culture-positive sepsis, clinical sepsis, suspected sepsis, and other suspected infections. If blood culture remained negative when the neonate presented symptoms and signs of sepsis (fever, respiratory distress or apnea, tachycardia, poor perfusion, low blood pressure, seizures, hypo- or hyperglycemia, feeding problems, lethargy or irritability), had abnormal blood values (leukocytosis, leukopenia, increased neutrophil precursors, thrombocytopenia, or C-reactive protein >20 mg/L), and had a positive response to a minimum of 5 days of antibiotic treatment, the infection was considered clinical sepsis. If the neonate presented at least one symptom of sepsis, had at least one abnormal blood value, and responded positively to antibiotic treatment, the infection was considered suspected sepsis.

Interval between insertion of the BC and birth defined the induction to delivery interval. Onset of labor was defined as regular contractions every 3–5 minutes with cervical change or dilatation of ≥6 cm. Failure to progress in labor with ruptured membranes, oxytocin infusion for ≥12 hours, and cervical dilatation <6 cm defined failed labor induction.[17] Labor arrest was diagnosed in the first stage of labor if no progress was observed at cervical dilatation ≥6 cm with ruptured membranes and adequate contractions for ≥4 hours,[17] and in the second stage of labor if delivery was failed at cervical dilatation of 10 cm despite ≥1 hours of active pushing or by failed operative vaginal delivery.[17]

2.1 | Statistical analyses

Analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM). Data with categorical variables were compared by Pearson's chi-squared test. Unpaired comparisons of continuous variables were carried out by Student's *t*-test when the data were normally distributed and by Mann–Whitney *U* test when the data did not follow a normal distribution. Logistic regression analyses were performed to assess odds ratios for maternal or neonatal infection. Adjusted odd ratios with 95% CI were calculated by modelling the data to control for possible confounding factors (GBS-positivity, previous cesarean section, maternal age ≥37 years, in vitro fertilization, smoking, nulliparity, body mass index ≥35 kg/m^2, gestational diabetes, prolonged pregnancy, Bishop score <3, rupture of membranes to delivery interval ≥12 hours, cesarean section, and maternal intrapartum infection). Stepwise logistic

regression was used to choose factors included in the final multivariable analyses. Only univariable analyses are presented when small sample size did not allow multivariable analysis. All variables used in the final multivariable analyses are shown in the tables with respective univariable analyses. A p value <0.05 was considered statistically significant. R software was used to perform receiver operating characteristic (ROC) curve analyses to find cut-off values for continuous time factors predicting infection, and using Youden criterion, area under the ROC curve (AUC) >0.75 was considered significant.[18]

2.2 | Ethical approval

The study protocol was approved by the institutional review board of the hospital region (Helsinki and Uusimaa Hospital District Committee for Obstetrics and Gynecology, nr. HUS/400/2016, December 9, 2016). Due to the historic nature of the study, written informed consent was waived by the institutional review board according to national legislation (Medical Research Act 488/1999, chapter 2 a [23.4.2004/295], sections 5 and 10a).

3 | RESULTS

A total of 1959 women were included in the study, of whom 469 (23.9%) were GBS-positive.

Table 1 presents the characteristics of the study population. The mean age of the women was 31.4 years (standard deviation 5.4 years), the median weight was 66.0 kg (interquartile range [IQR] 19.0 kg), and the median body mass index was 24.0 kg/m^2 (IQR

TABLE 1 Characteristics of the study population; N = 1959

	GBS-positive		GBS-negative		
	n = 469	23.9%	n = 1490	76.1%	P value
Nulliparous	232	49.5	801	53.8	0.10
Maternal age ≥37 years	97	20.7	233	15.6	0.01
Body mass index ≥35 kg/m^2	46[a]	9.8	92[b]	6.2	0.01
Previous cesarean section	61	13.0	200	13.4	0.82
Smoking	48	10.2	165	11.1	0.61
In vitro fertilization	22	4.7	75	5.0	0.77
Diabetes type 1	5	1.1	5	0.3	0.05
Gestational diabetes	142	30.3	444	29.8	0.84
Medication-dependent gestational diabetes	40	8.5	128	8.6	0.97
Prolonged pregnancy (≥41 weeks)	240	51.2	762	51.1	0.99
Post-term pregnancy (≥42 weeks)	95	20.3	298	20.0	0.90
Bishop score at the start of labor induction <3	193	41.2	611[c]	41.2	0.99
Indication for labor induction					
Post-term pregnancy	203	43.3	636	42.7	0.83
Diabetes	68	14.5	192	12.9	0.39
Preeclampsia	55	11.7	162	10.9	0.61
Other	143[d]	30.5	500[e]	33.6	0.24

Abbreviation: GBS, group B streptococcus.

[a]Missing values n = 1.

[b]Missing values n = 7.

[c]Missing values n = 7.

[d]Psychosocial reasons n = 30, intrahepatic cholestasis of pregnancy n = 30, oligohydramnios n = 20, intrauterine growth restriction n = 19, complications in previous pregnancy n = 16, non-diabetic fetal macrosomia n = 8, fetal anomalies n = 7, reduced fetal movements n = 5, maternal medical condition unrelated to pregnancy n = 4, Rhesus immunization n = 2, non-reassuring cardiotocograph n = 1, prevention of fetal malposition after successful external cephalic version n = 1.

[e]Psychosocial reasons n = 112, intrahepatic cholestasis of pregnancy n = 96, oligohydramnios n = 79, intrauterine growth restriction n = 76, complications in previous pregnancy n = 34, non-diabetic fetal macrosomia n = 31, fetal anomalies n = 14, reduced fetal movements n = 24, maternal medical condition unrelated to pregnancy n = 19, Rhesus immunization n = 6, non-reassuring cardiotocograph n = 4, prevention of fetal malposition after successful external cephalic version n = 3, fetal arrhythmia n = 1, polyhydramnios n = 1.

6.7 kg/m^2). GBS-positive women were older and more obese than GBS-negative women (Table 1). Mean gestational age at the start of labor induction was 40.6 weeks (standard deviation 1.4 weeks).

Table 2 presents the delivery outcomes. The overall rate of maternal intrapartum infection was 7.4%, being lower in the GBS-positive group compared with the GBS-negative group (4.7% vs 8.3%; p = 0.01) (Table 2). There were seven cases of intrapartum sepsis, all in the GBS-negative group. Pathogens in blood culture were *Staphylococcus aureus* (n = 2), GBS (n = 1), *Enterococcus faecalis* (n = 1), *Granulicatella elegans* (n = 1), *Staphylococcus epidermidis* (n = 1), and *Streptococcus anginosus* (n = 1). The overall rate of maternal postpartum infection was 3.9%, and no difference between the groups was seen (Table 2). No cases of postpartum septicemia occurred.

There were no differences between the groups in BC insertion to expulsion interval, induction to delivery interval, or rupture of

TABLE 2 Delivery outcomes and infectious morbidity in women; N = 1959

	GBS-positive		GBS-negative		
	n = 469	23.9%	n = 1490	76.1%	p value
Sequential use of misoprostol	91	19.4	307	20.6	0.57
Sequential use of oxytocin in induction	239	51.0	718	48.2	0.30
Epidural or spinal analgesia	362	77.2	1203	80.7	0.09
Mode of delivery					
Spontaneous vaginal delivery	296	63.1	964	64.7	0.53
Operative vaginal delivery	61	13.0	165	11.1	0.25
Cesarean section	112	23.9	361	24.2	0.88
Cesarean section indication					
Fetal distress	41	8.7	127	8.5	0.78
Failed induction or failure to progress	60	12.8	172	11.5	0.27
Suspected infection	6	1.3	34	2.3	0.18
Other	5[b]	1.1	28[c]	1.9	0.23
Placental retention	11	2.3	65	4.4	0.05
Sphincter injury	10[d]	2.1	36	2.4	0.72
Postpartum hemorrhage ≥1000 mL	68[e]	14.5	222[f]	14.9	0.83
Uterine rupture	1	0.2	2	0.1	0.56
Intrapartum infection	22	4.7	123	8.3	0.01
Postpartum infection	14	3.0	63	4.2	0.23
Endometritis	10	2.1	34	2.3	0.71
Clinical wound infection	1	0.2	17	1.1	0.06
Other	3 [g]	0.6	12 [h]	0.8	0.77
Balloon catheter retention (h), median (IQR)	5.4[a]	(6.8)	5.8	(7.0)	0.78
Induction to delivery interval (h), median (IQR)	24.8	(20.4)	23.5	(21.8)	0.83
Duration of ruptured membranes (h), median (IQR)	9.9	(11.6)	10.5	(11.1)	0.41

Abbreviations: GBS, group B streptococcus; IQR, interquartile range.

[a]Missing values n = 1.

[b]Preeclampsia n = 3, umbilical cord prolapse n = 1, maternal request n = 1.

[c]Preeclampsia n = 12, fetal presentation n = 3, decision of planned cesarean in early stage of induction n = 4, umbilical cord prolapse n = 2, maternal request n = 2, placental abruption n = 2, epilepsy n = 1, suspicion of uterine rupture n = 1, hemorrhage n = 1.

[d]In addition one patient with fourth-degree tear.

[e]Missing values n = 1.

[f]Missing values n = 3.

[g]Episiotomy wound infection n = 1, fever of unknown reason n = 1, urinary tract infection n = 1.

[h]Episiotomy wound infection n = 4, mastitis n = 2, urinary tract infection n = 2, intra-abdominal abscess (pathogen unknown) n = 2, pneumonia n = 1, periappendicular abscess n = 1.

TABLE 3 Neonatal outcomes; *N* = 1959

	GBS-positive		GBS-negative		
	n = 469	23.9%	*n* = 1490	76.1%	*p* value
Female	226	48.2	699	46.9	0.63
Birthweight, mean (SD)	3611.8	515.6	3592.3[a]	499.9	0.47
Macrosomia (≥4500 g)	21	4.5	46[a]	3.1	0.15
Apgar at 5 min <7	21[b]	4.5	45[c]	3.0	0.13
Umbilical artery pH <7.05	9[d]	1.9	26[e]	1.7	0.80
Umbilical artery BE <−12.0	13[f]	2.8	34[g]	2.3	0.55
Neonatal intensive care unit admission	5	1.1	16	1.1	1.00
Infection	14	3.0	51	3.4	0.66
Blood-culture-positive sepsis	0		1	0.1	
Clinical sepsis	2	0.4	9	0.6	1.00
Suspected sepsis	6	1.3	28	1.9	0.55
Other suspected infection	6	1.3	13	0.9	0.32

Abbreviations: BE, base excess; GBS, group B streptococcus.

[a]Missing values *n* = 1.

[b]Missing values *n* = 7.

[c]Missing values *n* = 20.

[d]Missing values *n* = 12.

[e]Missing values *n* = 35.

[f]Missing values *n* = 12.

[g]Missing values *n* = 43.

membranes to delivery interval (Table 2). The median duration of labor was 6.6 hours (IQR 2.3 hours) in women who delivered vaginally, and no difference between GBS-positive and GBS-negative women was observed (6.2 hours, IQR 6.0 hours for GBS-positive women; 6.7 hours, IQR 6.3 hours for GBS-negative women, $p = 0.41$). The rate of cesarean section was 24.1% ($n = 473$) (Table 2).

Table 3 presents the neonatal outcomes. The rate of neonatal infection was 3.3% ($n = 65$), and the rates did not differ between the GBS-positive and GBS-negative groups (Table 3). There was one case (0.05%) of blood-culture-positive sepsis (unspecified coagulase-negative staphylococcus) in the GBS-negative group. No difference in the rates of other adverse neonatal outcomes was seen between the groups (Table 3). Of the neonates, 21 (1.1%) were admitted to the neonatal intensive care unit, 35 (1.8%) had an umbilical artery blood pH <7.05 at birth, and 66 (3.3%) had a 5-minute Apgar score <7.

Overall, antibiotics were administered to 465 (99.1%) GBS-positive women, and 404 (86.1%) of these women received GBS prophylaxis at least 4 hours before delivery. Antibiotics administered were most often benzylpenicillin ($n = 360$, 76.8%), cefuroxime ($n = 81$, 17.2%), and clindamycin ($n = 17$, 3.6%). Of the GBS-negative women, 219 (14.7%) received antibiotics during labor ($p < 0.001$).

In multivariable logistic regression analysis, the risk factors associated with maternal intrapartum infection were nulliparity, prolonged pregnancy (≥41^{+0} weeks), Bishop score <3 at the start of induction, and rupture of membranes to delivery interval ≥12 hours (Table 4A). In univariable logistic regression analysis of the subgroup of GBS-positive women, nulliparity was a risk factor for intrapartum infection (Table 4A). In multivariable logistic regression analysis of the subgroup of GBS-negative women, the associations remained the same as in analysis of all women (Table 4A). The adjusted odds ratio of GBS-negativity for intrapartum infection was 1.8 (95% CI 1.1–2.9; $p = 0.02$). Among the nulliparous women who delivered vaginally, those with intrapartum infection had longer duration of labor than those with no infection (median duration 13.0 hours vs 8.7 hours, $p < 0.001$). Also, the nulliparous women with intrapartum infection more often had prolonged labor induction of ≥24 hours (70.4% vs 52.8, $p = 0.02$) and longer duration of ruptured membranes of ≥12 hours (68.2% vs 49.5%, $p = 0.02$) than nulliparous women with no infection.

The risk factors associated with maternal postpartum endometritis in multivariable logistic regression analysis were rupture of membranes to delivery interval ≥12 hours and cesarean section (Table 4B). In univariable logistic regression analysis of the subgroup of GBS-positive women, postpartum endometritis was associated with cesarean section alone, whereas in the subgroup of GBS-negative women, in multivariable logistic regression analysis, the associations remained the same as in the analysis of all women (Table 4B).

In multivariable logistic regression analysis, the risk factors associated with neonatal infection were nulliparity, gestational diabetes, rupture of membranes to delivery interval ≥12 hours, and maternal intrapartum infection (Table 4C). In univariable logistic regression analysis of the subgroup of GBS-positive women, the risk factors associated with neonatal infection were prolonged

TABLE 4 (A–C) Risk factors for (A) maternal intrapartum infection (n = 145), (B) maternal postpartum endometritis (n = 44), and (C) neonatal infection (n = 65)

	All women						GBS-positive (n = 22)			GBS-negative (n = 123)					
	Unadjusted			Adjusted			Unadjusted			Unadjusted			Adjusted		
(A) Intrapartum infection	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
GBS-positivity	0.5	0.3–0.9	0.01	0.6	0.3–0.9	0.02									
Previous cesarean section	1.0	0.6–1.6	0.94	2.0	1.0–4.1	0.06	0.7	0.2–2.9	0.58	1.0	0.6–1.8	0.89	2.2	1.0–4.9	0.06
Maternal age ≥37 years	0.7	0.4–1.1	0.14	0.8	0.5–1.4	0.52	0.8	0.3–2.6	0.77	0.7	0.4–1.2	0.18	0.8	0.4–1.4	0.40
In vitro fertilization	0.8	0.4–1.9	0.64	0.7	0.3–1.6	0.39	1.0	0.1–7.5	0.97	0.8	0.3–2.0	0.61	0.7	0.3–1.8	0.46
Smoking	1.4	0.9–2.3	0.15	1.3	0.8–2.2	0.27	2.8	1.0–7.9	0.06	1.2	0.7–2.1	0.48	1.1	0.4–2.1	0.65
Nulliparity	3.0	2.1–4.5	<0.001	2.7	1.5–4.9	0.001	2.9	1.1–7.4	0.03	3.0	2.0–4.7	<0.001	2.7	1.4–5.4	0.004
Body mass index ≥35 kg/m^2	0.9	0.4–1.7	0.76	1.0	0.5–2.1	1.0	1.0	0-	1.0	1.2	0.6–2.5	0.58	1.3	0.6–2.7	0.55
Gestational diabetes	1.1	0.7–1.5	0.76	1.3	0.9–2.0	0.17	1.3	0.5–3.3	0.53	1.0	0.7–1.5	0.94	1.3	0.8–2.0	0.29
Prolonged pregnancy (≥41 weeks)	1.8	1.3–2.6	0.001	1.6	1.1–2.3	0.02	1.4	0.6–3.3	0.45	1.9	1.3–2.9	<0.001	1.5	1.1–2.6	0.02
Bishop score at the start of labor induction <3	1.7	1.2–2.4	0.002	1.6	1.1–2.3	0.007	1.2	0.5–2.8	0.68	1.9	1.3–2.7	0.001	1.7	1.2–2.6	0.007
Rupture of membranes to delivery interval ≥12 h	5.1	3.4–7.5	<0.001	3.6	2.4–5.5	<0.001	1.2	0.5–2.9	0.64	7.2	4.5–11.6	<0.001	5.1	3.1–8.4	<0.001

	All women						GBS-positive (n = 10)			GBS-negative (n = 34)					
	Unadjusted			Adjusted			Unadjusted			Unadjusted			Adjusted		
(B) Postpartum endometritis	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
GBS-positivity	0.9	0.5–1.9	0.85	0.9	0.4–1.9	0.83									
Body mass index ≥35 kg/m^2	1.3	0.5–3.8	0.60	1.9	0.6–6.1	0.28	0.7	0.09–5.5	0.73	1.6	0.7–3.9	0.27	2.1	0.5–7.8	0.29
Gestational diabetes	1.3	0.7–2.5	0.35	1.8	0.9–3.4	0.10	1.3	0.4–3.9	0.65	1.3	0.75–2.2	0.37	1.7	0.8–3.7	0.17
Rupture of membranes to delivery interval ≥12 h	3.8	1.9–7.4	<0.001	2.6	1.3–5.2	0.01	2.7	0.9–8.2	0.08	4.2	2.4–7.5	<0.001	3.8	1.6–9.1	0.003
Cesarean section	3.9	2.1–7.2	<0.001	3.0	1.6–5.7	<0.001	3.3	1.1–9.7	0.03	5.6	3.3–9.4	<0.001	2.5	1.2–5.1	0.02

	All women						GBS-positive (n = 14)			GBS-negative (n = 51)					
	Unadjusted			Adjusted			Unadjusted			Unadjusted			Adjusted		
(C) Neonatal infection	OR	(95%CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
GBS-positivity	0.9	0.5–1.6	0.65	1.1	0.6–2.1	0.76									

(Continues)

TABLE 4 (Continued)

	All women						GBS-positive (n = 14)			GBS-negative (n = 51)				
	Unadjusted			Adjusted			Unadjusted			Unadjusted			Adjusted		
(C) Neonatal infection	OR	(95%CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Nulliparity	3.7	2.0–6.9	<0.001	2.2	1.2–4.3	0.02	2.6	0.8–8.5	0.11	4.2	2.0–8.6	<0.001	2.8	1.3–6.1	0.008
Body mass index ≥35 kg/m^2	0.2	0.03–1.5	0.11	0.2	0.03–1.4	0.10	1.0	0-	1.0	0.3	0.04–2.2	0.23	0.2	0.03–1.7	0.15
Gestational diabetes	1.4	0.8–2.3	0.21	1.9	1.1–3.3	0.03	0.6	0.2–2.3	0.47	1.7	1.0–3.0	0.07	2.2	1.2–4.2	0.01
Prolonged pregnancy (≥41 weeks)	2.0	1.2–3.5	0.008	1.6	0.9–2.9	0.11	13.1	1.7–100.6	0.01	1.5	0.8–2.7	0.16	1.2	0.6–2.2	0.60
Rupture of membranes to delivery interval ≥12 h	3.5	2.0–6.0	<0.001	1.9	1.1–3.5	0.03	2.7	0.9–8.2	0.08	3.7	2.0–7.0	<0.001	2.1	1.0–4.0	0.04
Maternal intrapartum infection	10.7	6.3–18.1	<0.001	7.3	4.2–12.7	<0.001	29.3	9.1–94.2	<0.001	8.4	4.6–15.2	<0.001	5.5	2.9–10.4	<0.001

Note: All variables shown in the Table were included as confounding factors in the multivariable analysis.
In the subgroup of GBS-positive women, only univariable analyses were performed and presented due to small sample size.
Abbreviations: GBS, group B streptococcus; OR, odds ratio.

pregnancy and maternal intrapartum infection (Table 4C). In multivariable logistic regression analysis of the subgroup of GBS-negative women, the risk factors remained the same as in the analysis of all women (Table 4C).

Interval from BC insertion to expulsion was not associated with infectious morbidity, but in GBS-positive women, an interval of >6.5 hours showed an association towards (no statistical significance) postpartum endometritis in the ROC curve with AUC 0.73 (Figure 2A). No clinically relevant cut-off value for increased risk for infection was found for induction to delivery interval or duration of labor. Rupture of membranes to delivery interval >13.3 hours showed some association (no statistical significance) to intrapartum infection with AUC 0.72 (Figure 2B) in all women. In GBS-negative women, the cut-off value was 12.7 hours with AUC 0.76, but in GBS-positive women, no correlation was found.

4 | DISCUSSION

Labor induction by BC appears safe in GBS-positive women when prophylactic antibiotics are administered at the onset of labor or at rupture of membranes. Controversially, the rates of maternal and neonatal infections were lower in the GBS-positive women compared with the GBS-negative women. The 7% rate of maternal intrapartum infection, the 4% rate of postpartum endometritis, and the 3% rate of neonatal infection in our study are consistent with the rates reported by previous studies.[16,19]

To our knowledge, no other studies currently exist on the use of BC in GBS-positive women, and the data on safety regarding infectious morbidity in GBS-positive women undergoing cervical ripening by BC are lacking. A previous study suggested that membrane stripping, a mechanical procedure often performed before induction of labor with similar mechanical and biochemical cervical effect as BC, is safe in women colonized with GBS.[20] This is in accordance with our results. Another older study reported an increase in cervical pathogenic microbes, such as GBS, *Candida albicans*, *Candida glabrata*, and *Gardnerella vaginalis* during BC retention.[14] In our study, the duration of BC retention was not linked to infectious intrapartum or neonatal morbidity, but retention time of 6.5 hours or more was slightly associated with a higher risk for postpartum endometritis in GBS-positive women.

The prevalence of GBS in the study population was 24%, which is in line with previous research.[2,21] In this study, some characteristics of GBS-positive women, such as obesity, were in line with previous studies,[22] but some, such as advanced maternal age, contradicted previous research.[21] The factors associated with infectious intrapartum morbidity in our study, including nulliparity, prolonged pregnancy, and Bishop score <3 at the start of labor induction, were in line with previous research.[23,24] In the current study, cesarean section was associated with postpartum endometritis, as also noted previously.[25,26] Furthermore, maternal intrapartum infection was associated with neonatal infectious morbidity, as were nulliparity and gestational diabetes.[27,28]

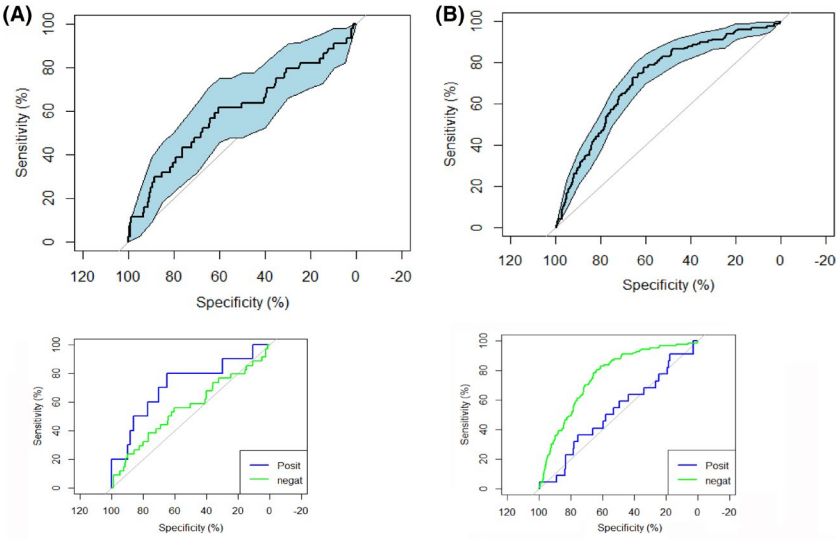

FIGURE 2 (A) ROC curve, effect of balloon insertion to expulsion interval to postpartum endometritis in all women (AUC 0.60) and in GBS-positive and GBS-negative women (AUC 0.72 and 0.56). (B) ROC curve, effect of rupture of membranes to delivery interval to intrapartum infection in all women (AUC 0.72) and in GBS-positive and GBS-negative women (AUC 0.52 and 0.76). AUC, area under the curve; GBS, group B streptococcus; ROC, receiver operating characteristics

Our results are comparable with the 2014 meta-analysis of antibiotic prophylaxis for term or near-term premature rupture of membranes, in which women who received antibiotics had a lower rate of chorioamnionitis and endometritis than women who received antibiotics only in case of latency of 12 hours or more from premature rupture of membranes to delivery.[29] The higher maternal intrapartum infection rate of GBS-negative women in our study suggests that prophylactic antibiotics given to the GBS-positive women may have a protective effect for intrapartum infection, as there were no differences in duration of ruptured membranes, duration of labor, or the induction to delivery interval between the groups. This protective effect may also partly explain why duration of ruptured membranes of 12 hours or more was associated with an increased risk for maternal postpartum endometritis and neonatal infection only in GBS-negative women but not in GBS-positive women. We aimed to investigate optimal cut-off values for significant rise in the infection rates during labor induction, and ≥12 hour interval of ruptured membranes to delivery may be a candidate by this model.

In our study, 99% of GBS-positive women received prophylactic antibiotics. In 1% of the women, the prevention guidelines were not met because these women delivered shortly after admission to the labor ward before the antibiotic administration was started. Of the GBS-negative women, 15% received antibiotics for suspected infection. The criteria for intrapartum infection was met for 56% of these women, the others received antibiotics at the discretion of the treating obstetrician, for elevated body temperature or elevated infection markers (leukocytes, C-reactive protein). Antibiotic use affects both maternal and neonatal microbiomes and possibly even long-term health.[30] As GBS-negative women, however, had a higher risk for maternal and neonatal infections, antibiotic prophylaxis in the case of ruptured membranes of ≥12 hours duration may be beneficial for them. Further research regarding this subject is warranted.

The strengths of our study are the relatively large sample size, which adds to the limited data available, universal rapid screening testing for GBS, comprehensive antibiotic prophylaxis, and the detailed medical records. The major limitation of this study is the retrospective design. Additionally, excluding those women who underwent labor induction by misoprostol may be a potential bias, because some women regarded as having a high risk for infection may have been treated with misoprostol instead of BC.

5 | CONCLUSION

Our results suggest that with regard to maternal and neonatal infectious morbidity, labor induction with BC is safe in women colonized with GBS when prophylactic antibiotics are administered at the onset of labor or at membrane rupture. Careful attention should be given to GBS-negative women with prolonged duration of ruptured membranes. However, future studies, preferably randomized trials, are needed to substantiate these findings.

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CONFLICT OF INTEREST

None.

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