

## ORIGINAL ARTICLE

# Risk Factors Associated with Early Onset Group B Streptococcal Disease and Newborn Outcomes in a Tertiary Care Center in Pakistan

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## ABSTRACT

**Background:** To assess the risk factors associated with early onset group B streptococcal disease and newborn outcomes in a tertiary care center in Pakistan.

**Methods:** A prospective cohort study design was implemented in the postnatal wards and neonatal intensive care unit of Aga Khan Hospital between 15 December 2021 – 15 June 2022. The exposed group included all pregnancies with risk of GBS infection, the un-exposed group included all pregnancies with no risk factors for GBS. All births were followed for outcomes during admission and after discharge for 28 days of life. Information about the mother and baby dyad was retrieved from the medical records. A second proforma was filled out at the time of discharge (2 to 5 days of life for healthy babies and at 10 to 15 days of life for babies admitted for NICU). These were the average length of stay of healthy and ill newborns at our facility.) The final follow up was at 28 days of life which was at the clinic or telephonic. Data on morbidities such as sepsis, use of antibiotics and hospitalization breast feeding practices was captured at the day 28 follow up.

**Results:** A total of 78 patients were included, with a mean maternal age of  $30.82 \pm 4.65$  years and gestational age of  $37.26 \pm 2.1$  weeks. GBS colonization was positive in high vaginal swab in 23 (29.5%) patients, in urine culture in 16 (20.2%) patients, and 1 (1.3%) patient who delivered a previous baby with GBS infection. Two patients suffered from pneumonia among them one patient also had sepsis and 77 patients were stable at 28 days. In 16 (41%) cases of GBS colonization, high vaginal swab yielded a negative result. Similarly, in 23 (59%) patients with GBS colonization, urine culture was also negative. Only one patient with GBS colonization had a history of a previous infant with GBS infection. Approximately 70% of GBS positive had PROM. Maternal Leukocytosis and tachycardia were significantly higher in patients with GBS ( $p < 0.0001$ ). Uterine tenderness was found in 14 (35.9%) mothers with GBS colonization ( $p < 0.0001$ ). Intrapartum fever was significantly more common in mothers with GBS colonization ( $p = 0.011$ ). Tachycardia was significantly higher in neonates of mothers with GBS colonization ( $p = 0.01$ ). Need of oxygen was significantly higher in neonates with mothers having GBS colonization ( $p = 0.002$ ).

**Conclusion:** In hindsight, GBS colonization and the early onset of Group B streptococcus infection is a public health issue in Pakistan that requires attention. Recommended antenatal screening measures should be implemented, as well as the necessary steps, such as an antibiotics treatment regimen following a positive GBS colonization report, to protect newborns from this disease.

**Keywords:** colonization, maternal risk factors, group B streptococcal, early onset group B streptococcal disease, GBS, PROM

## INTRODUCTION

Infection with group B streptococcus (GBS) is a dangerous condition that still has a high fatality rate. It is a major contributor to early-onset sepsis in newborns and young children worldwide.<sup>2</sup> GBS causes sepsis, pneumonia, and encephalopathy in newborns and is vertically transferred to them after delivery.<sup>3</sup> According to a local survey, there are 31.3 occurrences of neonatal sepsis for every 1000 live births.<sup>1</sup>

A study from U.K reports incidence of GBS disease presenting as pneumonia to be 20%.<sup>4</sup> Disease burden of neonatal invasive disease in Netherland in 2017 reports neonatal GBS meningitis incidence to be 15/100,000 live births.<sup>5</sup>

Maternal problems such as urinary tract infections (UTIs), endometritis, chorioamnionitis, meconium-tainted beverages, and even miscarriage are linked to clinical GBS infection.<sup>2</sup> The gramme positive bacterium is a normal component of the adult anaerobic flora and has the potential to invade the vagina. The fetus contracts an intrauterine infection due to the ascending transmission of GBS from an asymptomatic woman's vagina. Despite the fact that many newborns might get an infection while being delivered, the majority of them show no symptoms at all.<sup>2</sup> The prevalence of GBS vaginal colonization varies between research and ranges from 0% to 36%, with the majority of studies finding colonization rates of above 20% in women of reproductive age.<sup>6</sup>

A study conducted in USA showed 21.6% of the population was GBS colonized and 0.1% had invasive GBS disease.<sup>7</sup> A study conducted in India showed GBS colonization prevalence was 15%.<sup>8</sup>

With emerging antimicrobial resistance and limited choice of antimicrobials, management of neonatal complications is

challenging. Considering the burden of GBS invasive diseases in neonates and non-availability of GBS vaccine, knowledge regarding the prevalence, management and outcome of neonatal GBS is of crucial importance.

The World Health Organization has prioritised developing a vaccination for pregnant women as a possible method of preventing neonatal and newborn GBS illness (WHO). The development of GBS serotype-specific polysaccharide protein conjugate vaccines is progressing. All pregnant women should get GBS rectovaginal screening cultures between 36+0 and 37+6 weeks of gestation, according to the 2019 ACOG recommendations. Although commercially accessible and capable of producing findings in less than 2 hours, quick diagnostic techniques like the nucleic acid amplification test (NAAT) for GBS are not advised as a substitute for prenatal culture or risk-based evaluation for women with unknown GBS status.<sup>9</sup>

Aga Khan University Hospital's Obstetrics and Gynecology department has a delivery per annum of 6000. A recent study concluded the overall prevalence of GBS colonization to be 17% among pregnant women.<sup>2</sup> With this background information, we intend to determine the impact of GBS colonization on pregnancy outcome with respect to early onset neonatal sepsis and NICU admission in newborns.

The current study aimed to determine the neonatal and maternal risk factors for the condition Early Onset Group B Streptococcus (EOGBS) in a tertiary care hospital. Furthermore, the study determined the spectrum of morbidities such as sepsis, meningitis, and pneumonia in neonates diagnosed with early onset GBS and documented the frequency of late onset sepsis at day 28 of life.

## MATERIAL AND METHODS

A prospective cohort study design was implemented in the postnatal wards and neonatal intensive care unit of Aga Khan Hospital between 15 December 2021 – 15 June 2022. The study was initiated after procuring the approval of the departmental and institutional review board.

Sample size was estimated by using OpenEPI calculator by taking statistic of survival without morbidity of infected group 26.1% and non-infected group 59.4%.<sup>25</sup> Power of test was 80%, ratio of exposed to unexposed was 1 and two sided significance level was 95%, estimated sample size in each group was 39 and total sample size was 78.

The exposed group included all pregnancies with risk of GBS infection delivered at AKU whereas the un-exposed group included all Pregnancies with no risk factors for GBS. Those mothers who had a neonate with congenital anomalies were excluded from the study.

We recruited pregnant females with risk factors for GBS infection such as (bacteriuria in the current pregnancy, preterm delivery, prolonged rupture of membrane, intrapartum fever, and previous delivery of an infant affected by GBS disease, NVD). The study participants were identified from the labor ward /postnatal ward registry from the Labour Room Management System (LRMS).

The unexposed group were all pregnant females and their newborns without GBS risk factors delivered at the same hospital. They were matched for gestational age and mode of delivery.

All births were followed for outcomes during admission and after discharge for 28 days of life. Information about the mother and baby dyad was retrieved from the medical records. Laboratory data was captured through the My-patient application. A preformed proforma with demographic details, maternal and newborn variables was filled at the time of delivery for the outcomes of the baby for both the exposed and unexposed groups.

A second proforma was filled out at the time of discharge (2 to 5 days of life for healthy babies and at 10 to 15 days of life for babies admitted for NICU). These were the average length of stay of healthy and ill newborns at our facility.)

The final follow up was at 28 days of life which was at the clinic or telephonic. Data on morbidities such as sepsis, pneumonia, meningitis, use of antibiotics and hospitalization breast feeding practices was captured at the day 28 follow up. The management of mother and baby was as per institutional protocols.

NICU fellows collected the data. The identity of the recruits was kept confidential and a study ID number was allocated. Standard proforma was used to record variables on antenatal, postnatal and history of illnesses.

SPSS software version 21 was used to enter and analyse all data. Clinically applicable cutoff criteria were used to classify continuous variables. For categorical data, frequency and percentage calculations were made, as well as mean and standard deviation calculations for continuous variables. Bivariate analyses were conducted to determine the relationship between risk variables and the emergence of newborn GBS infection, and P values would be determined using the X2 test or Student's t-test as necessary. Logistic regression was used in a multivariate study to determine the EOGBS illness risk variables. The relative risk and 95% confidence interval of the results were presented. Statistical significance was defined as a p-value 0.05.

## RESULTS

A total of 78 patients were included, with a mean maternal age of  $30.82 \pm 4.65$  years and gestational age of  $37.26 \pm 2.1$  weeks. Other clinical parameters are presented in Table 1.

Maternal factors are presented in Table 2. GBS colonization was positive in high vaginal swabs in 23 (29.5%) patients, in urine culture in 16 (20.2%) patients, and in 1 (1.3%) patients who delivered a baby with GBS infection.

Table 1: Patient and mother clinical characteristics

Characteristic	N (%) / Mean $\pm$ SD
Exposed	
Yes	39 (50%)
No	39 (50%)
Maternal age (years)	$30.82 \pm 4.65$
Gestational age (weeks)	$37.26 \pm 2.1$
Gravida	$2.58 \pm 1.53$
Parity	$1.28 \pm 1.14$
Birth weight (kg)	$2.84 \pm 0.57$
Previous live births	
0	29 (37.2%)
1	19 (24.4%)
2	21 (26.9%)
3 or more	9 (11.5%)
Previous Fetal deaths	
0	56 (71.8%)
1	18 (23.1%)
2	2 (2.6%)
3	2 (2.6%)
Gender	
Male	43 (55.1%)
Female	35 (44.9%)
Gravida type	
Primigravida	25 (32.1%)
Multigravida	53 (67.9%)

Table 2: Maternal Factors

Factors	N (%) / Mean $\pm$ SD
Maternal GBS colonization as evidenced by	
Positive high vaginal swab	23 (29.5%)
Urine culture	16 (20.2%)
previous baby with GBS infection	1 (1.3%)
PROM > 18 hours	13 (16.7%)
Chorioamnionitis	
Maternal Leukocytosis	12 (15.4%)
Maternal tachycardia	13 (16.7%)
Fetal tachycardia	5 (6.4%)
Uterine tenderness	14 (17.9%)
Intrapartum fever	6 (7.7%)
Delivery before 37 weeks of gestation	11 (14.1%)
Vaginal delivery	48 (61.5%)
Intrapartum antibiotics duration (hours)	$6.61 \pm 9.33$
Postpartum antibiotics duration (days)	$4.1 \pm 3.66$
Use of antenatal steroids	
Yes	7 (9%)
No	71 (91%)
Number of doses	
0	71 (91%)
1	3 (3.8%)
2	4 (5.1%)
Last dose (hours)	
3	4 (5.1%)

Neonatal factors are presented in Table 3. About 15 (19.2%) and 20 (25.6%) neonates had tachycardia and tachypnea, respectively. One neonate had GBS in blood culture.

Table 3: Neonatal factors

Factors	N (%) / Mean $\pm$ SD
Temperature > 38.5 C	1 (1.3%)
Tachycardia	15 (19.2%)
Tachypnea	20 (25.6%)
GBS in blood culture	1 (1.3%)
GBS in CSF culture	0 (0%)
GBS in urine culture	0 (0%)
Raised CRP	7 (9%)
Raised procalcitonin	0 (0%)

Leukocytes (thousands)	13.53 ± 5.79
Infiltrate on CXR	5 (6.4%)
Oxygen requirement	20 (25.6%)
CPAP	6 (7.7%)
Assisted ventilation	4 (5.1%)
Duration of assisted ventilation (days)	
2	1 (1.3%)
3	1 (1.3%)
4	1 (1.3%)
40	1 (1.3%)
Dose of surfactant	
No dose	74 (94.9%)
1	3 (3.8%)
2	1 (1.3%)
MRI	0 (0%)
CT	0 (0%)
EEG	0 (0%)
Convulsion	0 (0%)
Tube Feeding	9 (11.5%)
Duration of antibiotic (days) (30 patients)	4 ± 4.07
NICU stay (days) (9 patients)	8.67 ± 13.05
Hospital stay (days)	3.54 ± 5.68
Outcomes	
Sepsis	1 (1.3%)
Meningitis	0 (%)
Pneumonia	2 (2.6%)
Mortality	0 (%)
Stable at 28 days	77 (98.7%)
Normal CSF DR	2 (2.6%)

Two patients suffered from pneumonia among them one also had sepsis, while 77 patients were stable at 28 days.

Table 4: Association between antenatal parameters and Group B Streptococcus colonization

	Exposed		p-value
	yes	no	
Previous live births			0.038
0	20 (51.3%)	9 (23.1%)	
3	0 (0%)	5 (12.8%)	
4	2 (5.1%)	1 (2.6%)	
5	0 (0%)	1 (2.6%)	
Previous Fetal deaths			0.102
0	31 (79.5%)	25 (64.1%)	
1	5 (12.8%)	13 (33.3%)	
2	2 (5.1%)	0 (0%)	
3	1 (2.6%)	1 (2.6%)	
Gender			0.111
male	18 (46.2%)	25 (64.1%)	
female	21 (53.8%)	14 (35.9%)	
Gravida type			0.002
primigravida	19 (48.7%)	6 (15.4%)	
multigravida	20 (51.3%)	33 (84.6%)	

In 16 (41%) cases of GBS colonization, high vaginal swab yielded a negative result. Similarly, in

23 (59%) patients with GBS colonization, urine culture was also negative. Only one patient with GBS colonization had a history of a previous infant with GBS infection. Approximately 70% of

GBS positive had PROM. Maternal Leukocytosis and tachycardia were significantly higher in patients with GBS ( $p < 0.0001$ ). Uterine tenderness was found in 14 (35.9%) mothers with GBS colonization ( $p < 0.0001$ ). Intrapartum fever was significantly more common in mothers with GBS colonization ( $p = 0.011$ ).

Table 5: Association between maternal factors and Group B Streptococcus colonization

	Exposed		p-value
	yes	no	
Positive high vaginal swab			<0.0001
Yes	23 (59%)	0 (0%)	
No	16 (41%)	39 (100%)	
Urine culture			<0.0001
Yes	16 (41%)	0 (0%)	
No	23 (59%)	39 (100%)	
previous baby with GBS infection			0.314
Yes	1 (2.6%)	0 (0%)	
No	38 (97.4%)	39 (100%)	
PROM			0.001
Yes	12 (30.8%)	1 (2.6%)	
No	27 (69.2%)	38 (97.4%)	
Maternal Leukocytosis			<0.0001
Yes	12 (30.8%)	0 (0%)	
No	27 (69.2%)	39 (100%)	
Maternal tachycardia			<0.0001
Yes	13 (33.3%)	0 (0%)	
No	26 (66.7%)	39 (100%)	
Fetal tachycardia			0.021
Yes	5 (12.82%)	0 (0%)	
No	34 (87.18%)	39 (100%)	
Uterine tenderness			<0.0001
Yes	14 (35.9%)	0 (0%)	
No	25 (64.1%)	39 (100%)	
Intrapartum fever			0.011
Yes	6 (15.4%)	0 (0%)	
No	33 (84.6%)	39 (100%)	
Delivery before 37 weeks of gestation			0.329
Yes	7 (17.9%)	4 (10.3%)	
No	32 (82.1%)	35 (89.7%)	
Vaginal delivery			0.005
Yes	30 (76.9%)	18 (46.2%)	
No	9 (23.1%)	21 (53.8%)	
Use of antenatal steroids			0.235
Yes	2 (5.1%)	5 (12.82%)	
No	37 (94.9%)	34 (87.18%)	
Number of doses			0.108
0	37 (94.9%)	34 (87.18%)	
1	2 (5.1%)	1 (2.56%)	
2	0 (0%)	4 (10.26%)	

Tachycardia was significantly higher in neonates of mothers with GBM colonization ( $p = 0.01$ ). Need of oxygen was significantly higher in neonates with mothers having GBM colonization ( $p = 0.002$ ).

Table 6: Association of neonatal outcomes and GBM colonization in mother

	Exposed		p-value
	yes	no	
Temperature			0.314
Yes	1 (2.6%)	0 (0%)	
No	38 (97.4%)	39 (100%)	
Tachycardia			0.01
Yes	12 (30.8%)	3 (7.7%)	
No	27 (69.2%)	36 (92.3%)	
Tachypnea			0.038
Yes	14 (35.9%)	6 (15.4%)	
No	25 (64.1%)	33 (84.6%)	
GBS in blood culture			0.314
Yes	1 (2.6%)	0 (0%)	
No	38 (97.4%)	39 (100%)	

Raised CRP			0.235
Yes	5 (12.82%)	2 (5.1%)	
No	34 (87.18%)	37 (94.9%)	
Infiltrate on CXR			0.165
Yes	4 (10.3%)	1 (2.6%)	
No	35 (89.7%)	38 (97.4%)	
Oxygen requirement			0.002
Yes	16 (41%)	4 (10.3%)	
No	23 (59%)	35 (89.7%)	
CPAP			1
Yes	3 (7.7%)	3 (7.7%)	
No	36 (92.3%)	36 (92.3%)	
Assisted ventilation			0.305
Yes	1 (2.6%)	3 (7.7%)	
No	38 (97.4%)	36 (92.3%)	
Surfactant			1
Yes	2 (5.1%)	2 (5.1%)	
No	37 (94.9%)	37 (94.9%)	
Tube Feeding			0.723
yes	5 (12.82%)	4 (10.3%)	
no	34 (87.18%)	35 (89.7%)	
Sepsis			0.314
yes	1 (2.6%)	0 (0%)	
no	38 (97.4%)	39 (100%)	
Pneumonia			0.152
yes	2 (5.1%)	0 (0%)	
no	37 (94.9%)	39 (100%)	
Stable at 28 days			0.314
yes	38 (97.4%)	39 (100%)	
no	1 (2.6%)	0 (0%)	
Normal CSF DR			1
yes	1 (2.6%)	1 (2.6%)	
no	38 (97.4%)	38 (97.4%)	

## DISCUSSION

We used a prospective cohort study design in our tertiary care hospital's postnatal wards and neonatal intensive care unit to assess the maternal and neonatal risk factors associated with early onset group B streptococcal disease and its outcomes. Following that, our study determined the spectrum of morbidities in neonates diagnosed with early-onset GBS, including sepsis, meningitis, and pneumonia, as well as the frequency of late-onset sepsis at day 28 of life.

Premature rupture of membranes (PROM) was significantly associated with maternal Group B streptococcus colonization in our study. This finding is similar to several studies.<sup>10-12</sup> Kim et al. identified obstetric and maternal factors related to Group B Streptococcus (GBS) colonization in pregnant women in Korea.<sup>10</sup> The research discovered a strong correlation between GBS colonisation and early membrane rupturing (PROM, more than 18 hours).<sup>10</sup> Benitz et al. conducted a literature review and found that PROM was a risk factor for early-onset Group B streptococcus infection.<sup>11</sup> A reason for this could be that Inflammation caused by Group B streptococcus infection leads to the weakening of the fetal membranes among pregnant women, thus contributing to premature rupture of membranes. Our finding is also similar to a prospective cohort study by Warriar et al. that showed PROM to be significantly associated with maternal GBS colonization.<sup>12</sup> On the contrary, our finding differed from a prospective study by Rocchetti et al. that showed PROM to not be significantly associated with maternal GBS colonization. This could be because Rocchetti et al. involved PROM from gestation that had occurred previously and not PROM from the current gestation.<sup>13</sup>

Our results were similar to a retrospective study by Schrag et al. that showed that intrapartum fever was associated with early-onset group B streptococcal disease.<sup>14</sup> Similarly, a study by Puopolo et al. concluded that maternal fever was a strong indicator of GBS infection.<sup>15</sup> Likewise, Benitz et al. similarly revealed that intrapartum fever was a risk factor for early-onset Group B streptococcus infection.<sup>11</sup> A systematic review of 30 articles, including 20328 GBS-colonized pregnant women by Russell et al.,

also involves intrapartum fever as a risk factor for early-onset Group B streptococcus infection.<sup>16</sup> On the contrary, our finding was different from Kim et al. that showed that fever was not significantly associated with Group B streptococcus (GBS) colonization.<sup>10</sup>

According to our study, a positive high vaginal swab was statistically significantly associated with maternal Group B streptococcus colonization. This is in accordance with a study by Benitz et al. that revealed that a positive vaginal culture was a risk factor for early-onset GBS infection.<sup>11</sup> Benitz et al. found that GBS positive vaginal culture at delivery (OR: 204), GBS-positive rectovaginal culture at 28 weeks of gestation (OR: 9.64) or 36 weeks gestation (OR: 26.7) were risk factors for early-onset Group B streptococcus disease.<sup>11</sup>

In our study, urine culture is a statistically significant risk factor for maternal Group B streptococcus colonization. In accordance with our study, a prospective study by Moller et al. that compared neonatal attack rates in women with and without GBS bacteriuria.<sup>17</sup> This study revealed a 2.5% GBS bacteriuria prevalence amongst mothers between 12 and 38 weeks.<sup>17</sup> In addition, this study found 5 confirmed instances of GBS sepsis in 68 children delivered to women, compared to 0 occurrences in 2677 newborns who did not have GBS bacteriuria (P- value less than 0.001). A reason for this could be that GBS can colonize the bowel, genital tract, urinary tract, throat, or respiratory tract of some adults. Furthermore, Our findings are similar to those of a Croatian study that found a link between GBS positive urinary culture and vaginal GBS colonisation, with the former increasing the likelihood of the latter.<sup>18</sup> On the other hand, our finding differed from Benitz et al. that suggested that although an association between maternal GBS bacteriuria and neonatal sepsis existed, the attack rate was not significantly different from that in controls.<sup>11</sup> Likewise, a study by Schrag et al. also showed that group B streptococcal bacteriuria during pregnancy was not associated with an increased risk of early-onset disease.<sup>14</sup>

Our study revealed that having a previous baby with a GBS infection was not significantly associated with GBS colonization. This differs from a multistate retrospective cohort study by Schrag et al. that analyzed 5144 births.<sup>14</sup> This involved 312 cases in which the newborns had early-onset group B streptococcal disease. In addition, antenatal screening was documented for 52 percent of the mother study showed that having a previous infant with group B streptococcal disease was one of those factors that were associated with the highest risk of early-onset disease. In terms of fetal tachycardia, uterine tenderness, or maternal leukocytosis, our findings are similar to those of Benitz et al., which reveals that these occurred in 1.0% to 3.8% of parturients and were associated with neonatal GBS attacks.<sup>11</sup>

Our study showed that delivery prior to 37 weeks of gestation was insignificantly associated with maternal GBS colonization. This is similar to a study by Chen et al. that observed preterm delivery (less than 37 weeks) insignificantly correlated with GBS colonization.<sup>19</sup>

Our study is limited by a small sample size due to which study findings cannot be generalized. Furthermore, non probability convenience sampling was used, which may lead to a selection bias.

## CONCLUSION

On the basis of the above obtained results and literature review, we conclude that GBS infection in the mother is a well-known risk factor, but the chance of a neonate to develop invasive GBS disease is negligible. Considering this, the practice to initiate prophylactic GBS treatment in the neonate even if the mother is GBS colonized needs to be justified as invasive GBS disease among exposed neonates from our study proves to be not significant. It is suggested that institutional guidelines be prepared in this regard and antibiotic stewardship be followed in order to avoid antimicrobial resistance and antimicrobial treatment complications in the neonate.

However, we also recommend larger scale study with interdepartmental collaborations and multidisciplinary teams including infectious disease, microbiologist, obstetricians and neonatologists for the management of this disease in the mother as well as newborn.

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