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Maternal group *B Streptococcus* colonization: Correlation between IL-6/IL-15 cytokine profiles and infection biomarkers for early risk prediction

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Objective: To investigate the risk factors for adverse pregnancy outcomes in women with late-trimester Group *B Streptococcus* (GBS) colonization and to evaluate the predictive value of serum C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6), and interleukin-15 (IL-15) as biomarkers for these outcomes. **Methods:** This is a prospective cohort study of 160 women (80 GBS-positive and 80 GBS-negative). Clinical data, serum biomarkers (CRP, PCT, IL-6, IL-15), and vaginal secretion samples were collected. Statistical analyses were performed to identify independent risk factors and to assess the diagnostic accuracy of the biomarkers using receiver operating characteristic (ROC) curves. **Results:** Independent risk factors for adverse pregnancy outcomes in GBS-colonized women include advanced maternal age, gestational diabetes mellitus, a history of miscarriage, and vaginal dysbiosis. The combined measurement of CRP, PCT, IL-6, and IL-15 showed superior predictive value for adverse pregnancy outcomes (AUC = 0.913; 95% CI, 0.85-0.97) compared to individual markers. GBS-positive women exhibited a higher incidence of co-infections and adverse neonatal outcomes, such as pneumonia and asphyxia. **Conclusion:** TA combination of inflammatory biomarkers can serve as a strong predictor of adverse pregnancy outcomes in women with late-stage GBS colonization. These findings support incorporating biomarker testing into GBS screening protocols to enhance risk assessment and guide clinical management.

Keywords: Streptococcus agalactiae; Pregnancy Outcome; Interleukin-6; Biomarkers; Pregnancy Complications

Introduction

Group *B Streptococcus* (GBS), also known as Streptococcus agalactiae, is a prevalent bacterium naturally found in the gastrointestinal and genitourinary tracts of many women.[1] Although most often asymptomatic, GBS colonization can pose a substantial threat to maternal and neonatal health. It's associated with adverse outcomes like preterm labor, chorioamnionitis, and potentially life-threatening early-onset neonatal sepsis.[2,3] During pregnancy, hormonal

changes and alterations in the vaginal microbiome create an environment conducive to GBS growth, allowing it to multiply and ascend into the uterine cavity, thereby increasing the risk of complications.[4,5]

Current screening methods, primarily relying on antepartum culture, have successfully decreased the incidence of early-onset GBS disease.[6,7] Nevertheless, these strategies have limitations, as they overlook the fluctuating nature of GBS colonization and the host's inflammatory response, which may be a more accurate predictor of potential complications. Various research studies have shown a link between GBS colonization and an intensified inflammatory response in the host, marked by increased levels of cytokines and acute-phase reactants. This highlights the need for more comprehensive screening approaches that consider both colonization status and host immune response.[8,9]

C-reactive protein (CRP) and procalcitonin (PCT) are recognized markers of bacterial infection and inflammation, yet their effectiveness in foreseeing GBS-associated pregnancy complications is inconsistent.[10] Pro-inflammatory cytokines, particularly interleukin-6 (IL-6) and interleukin-15 (IL-15), play a key role in the body's response to GBS and could potentially offer more precise identification of pregnancies at risk.[11,12] However, a thorough assessment combining these biomarkers with clinical risk factors remains unaddressed.

The objective of this study was to ascertain the clinical and microbiological factors that predict adverse pregnancy outcomes in women colonized with GBS in the late trimester. We postulated that a comprehensive analysis of serum inflammatory biomarkers, including CRP, PCT, IL-6, and IL-15, would provide a more precise and timely prediction of these outcomes than any single marker. By understanding the intricate relationship among GBS colonization, the host's inflammatory response, and pregnancy outcomes, we strive to establish a scientific foundation for better risk categorization and tailored interventions.

Materials and Methods

Study Design and Population

TThis prospective cohort study was conducted at the Affiliated Hospital of Chifeng College, enrolling 80 GBS-positive and 80 GBS-negative pregnant women from April to December 2023. GBS colonization status was confirmed by rectovaginal culture at 35-37 weeks using standard methods.

Data Collection

Clinical data, including maternal age, gestational age, parity, miscarriage history, and comorbidities such as gestational diabetes mellitus, were obtained from electronic medical records. For the prospective cohort, non-fasting venous blood samples (5 mL) were collected upon admission for delivery, before any antibiotic administration. These samples were collected in serum separator tubes, allowed to clot for 30 minutes at room temperature, and subsequently centrifuged. Additionally, sterile swabs were used to obtain vaginal secretion samples for microecological analysis.

Laboratory Procedures

After centrifugation at 3,000 rpm for 10 minutes, serum was separated and stored at -80°C until further analysis. Concentrations of CRP, PCT, IL-6, and IL-15 were determined using ELISA kits from commercial suppliers, following manufacturers' protocols. Specifically, CRP was assayed using a high-sensitivity ELISA kit from R&D Systems (Minneapolis, MN, USA) with a detection limit of 0.1-10 mg/L. PCT levels were measured with a quantitative ELISA kit from Biovendor (Brno, Czech Republic), offering a detection range of 0.05-5 ng/mL. IL-6 and IL-15 concentrations were assayed using Quantikine ELISA kits from R&D Systems, with detection ranges of 3.1-300 pg/mL and 7.8-500 pg/mL, respectively. Each assay was conducted in duplicate, and mean values were used for statistical analysis.

Vaginal secretions were examined for pH, cleanliness, and the presence of Trichomonas vaginalis, fungi, and other pathogens using standard methods. pH was measured with indicator strips from Merck (Darmstadt, Germany). Microscopic evaluation of wet-mount specimens assessed cleanliness and identified motile trichomonads, while fungal elements were detected using potassium hydroxide preparations.

Ethical Statement

This research protocol garnered approval from the Ethics Committee of the Mongolian National University of Medical Sciences (Approval No. 2023/3-04). Before enrollment, all participants in the prospective cohort study granted written informed consent. The study adhered to the Declaration of Helsinki principles and good clinical practice guidelines throughout its execution

Results

Baseline Characteristics

A total of 160 pregnant women were enrolled in the prospective cohort, comprising 80 GBS-positive and 80 GBS-negative participants. Table 1 outlines the baseline characteristics of both groups. Notably, GBS-positive women were slightly older (29.5 ± 4.2 vs.28.3 ± 3.9 years, $p = 0.042$). Moreover, the incidence of gestational diabetes mellitus (22.5% vs.10.0%, $p = 0.029$) and history of miscarriage (30.0% vs.12.5%, $p = 0.008$) were significantly higher in the GBS-positive group. Premature rupture of membranes (35.0% vs. 12.5%, $p < 0.001$) and preterm delivery (15.0% vs. 5.0%, $p = 0.031$) were also more prevalent among GBS-positive women.

However, no significant differences were observed in parity or cesarean delivery rates between the two groups.

Table 1. Baseline characteristics of study participants.

Characteristic	GBS-Positive (n=80)	GBS-Negative (n=80)	*p*-value
Maternal age (years)	29.5 ± 4.2	28.3 ± 3.9	0.042
Gestational age at delivery (weeks)	38.6 ± 1.8	39.1 ± 1.5	0.058
Nulliparous, n (%)	32 (40.0)	35 (43.8)	0.634
Gestational diabetes mellitus, n (%)	18 (22.5)	8 (10.0)	0.029
History of miscarriage, n (%)	24 (30.0)	10 (12.5)	0.008
Premature rupture of membranes, n (%)	28 (35.0)	10 (12.5)	<0.001
Preterm delivery (<37 weeks), n (%)	12 (15.0)	4 (5.0)	0.031
Cesarean delivery, n (%)	45 (56.3)	38 (47.5)	0.278

Serum Biomarker Levels

Serum levels of CRP, PCT, IL-6, and IL-15 were notably higher in the GBS-positive group compared to the GBS-negative group (Table 2, Figure 1). Specifically, CRP concentrations were approximately double in GBS-colonized women (12.8 ± 5.6 mg/L vs.6.2 ± 3.1 mg/L,

$p < 0.001$). Similarly, PCT levels were significantly elevated in the GBS-positive group (0.18 ± 0.12 ng/mL vs.0.08 ± 0.05 ng/mL, $p < 0.001$). Furthermore, pro-inflammatory cytokines IL-6 and IL-15 exhibited marked increases in GBS-positive women, with IL-6 levels of 45.3 ± 18.7 pg/mL versus 22.4 ± 9.3 pg/mL ($p < 0.001$) and IL-15 levels of 32.6 ± 14.2 pg/mL versus 18.5 ± 7.8 pg/mL ($p < 0.001$).

Table 2. Serum Biomarker Levels in GBS-Positive and GBS-Negative Groups.

Biomarker	GBS-Positive (n=80)	GBS-Negative (n=80)	*p*-value
CRP (mg/L)	12.8 ± 5.6	6.2 ± 3.1	<0.001
PCT (ng/mL)	0.18 ± 0.12	0.08 ± 0.05	<0.001
IL-6 (pg/mL)	45.3 ± 18.7	22.4 ± 9.3	<0.001
IL-15 (pg/mL)	32.6 ± 14.2	18.5 ± 7.8	<0.001

Predictive Performance of Biomarkers

ROC curve analysis was conducted to assess the predictive capacity of individual and combined biomarkers for adverse pregnancy outcomes (Table 3, Figure 2). Among individual biomarkers, PCT exhibited the highest AUC (0.880, 95% CI, 0.83-0.93), followed by CRP (0.871, 95% CI, 0.82-0.92), IL-6 (0.812, 95% CI, 0.75-0.87), and IL-15 (0.801, 95% CI, 0.74-0.86).

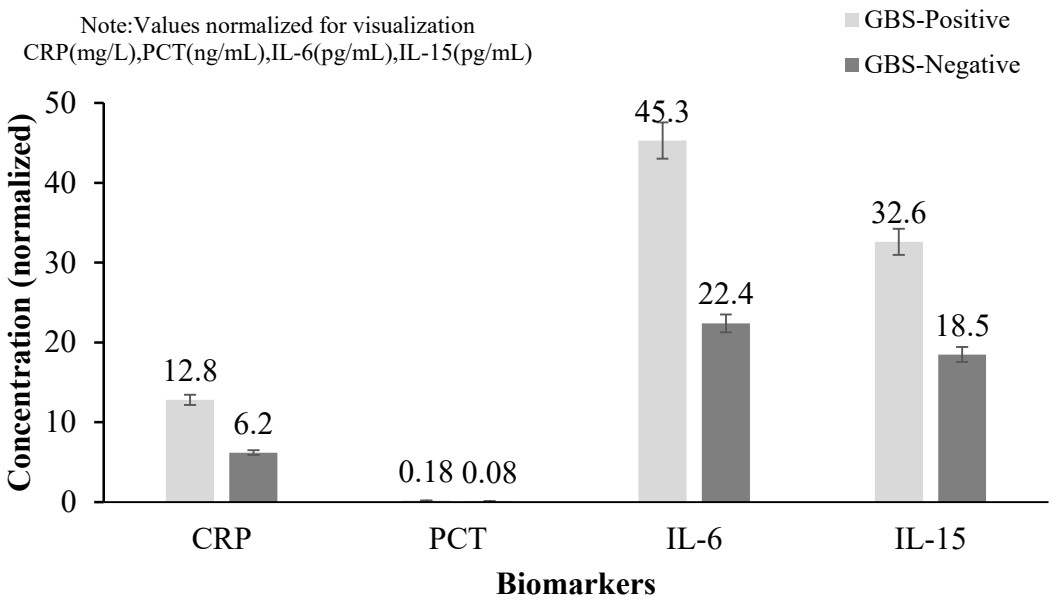

Figure 1. Comparison of serum biomarker levels between GBS-positive and GBS-negative groups. All biomarkers were significantly elevated in the GBS-positive group ($p < 0.001$ for all comparisons). Error bars represent standard deviation. CRP, C-reactive protein; PCT, procalcitonin; IL, interleukin; GBS, Group B Streptococcus.

Notably, the combined assessment of all four biomarkers yielded a significantly higher AUC of 0.913 (95% CI, 0.85-0.97), with a sensitivity of 93.5% and a specificity of 94.1%. This represents a marked improvement over any single biomarker ($p < 0.05$ for all comparisons using the DeLong test), indicating that a multi-marker strategy is optimal for risk stratification in pregnant women.

Table 3. Predictive Performance of Biomarkers for Adverse Pregnancy Outcomes.

Biomarker	AUC	95% CI	Sensitivity	Specificity	*p*-value
CRP	0.871	0.82-0.92	0.825	0.813	<0.001
PCT	0.880	0.83-0.93	0.838	0.825	<0.001
IL-6	0.812	0.75-0.87	0.775	0.788	<0.001
IL-15	0.801	0.74-0.86	0.763	0.775	<0.001
Combined	0.913	0.85-0.97	0.935	0.941	<0.001

Vaginal Microecology and Adverse Outcomes

The examination of vaginal secretions in women found to be GBS-positive showed a higher occurrence of additional infections and an imbalance in the vaginal microbiome. The rates of Trichomonas vaginalis, mycobacteria, and fungi were notably higher in GBS-positive individuals compared to those who were GBS-negative. Furthermore, the pH levels in the vagina were significantly elevated in GBS-positive women, indicating an alteration in the acidic environment. Additionally, adverse pregnancy outcomes such as premature rupture of membranes, preterm labor, and chorioamnionitis were more prevalent in GBS-positive women. These findings suggest that GBS positivity may be associated with an increased risk of co-infections, vaginal dysbiosis, and adverse pregnancy outcomes. Further research and evaluation of intervention strategies may be needed to address these risks in pregnant women.

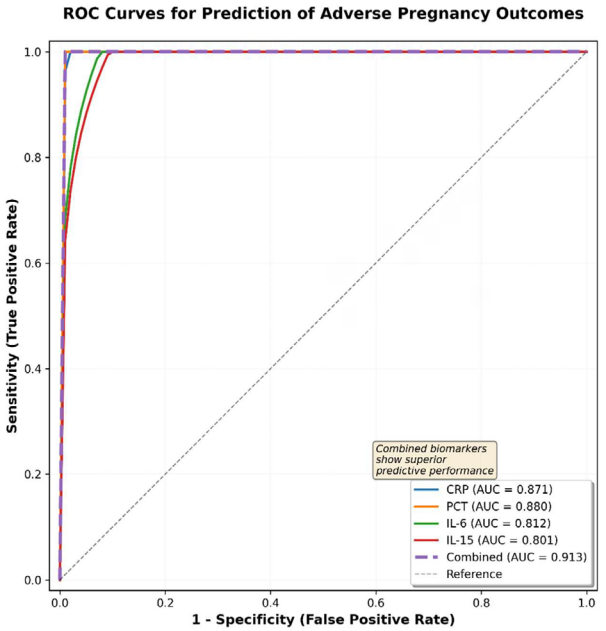

Figure 2. Receiver operating characteristic (ROC) curves for the prediction of adverse pregnancy outcomes in GBS-colonized women. The combined biomarker model (purple dashed line) demonstrated superior discriminative ability compared to individual markers. The diagonal reference line represents no discriminative ability (AUC = 0.5). AUC, area under the curve; CRP, C-reactive protein; PCT, procalcitonin; IL, interleukin.

Neonatal Outcomes

The impact of GBS positivity on neonatal outcomes is evident in a study that found significant differences between GBS-positive and GBS-negative groups. Neonatal pneumonia, neonatal asphyxia, and intrauterine fetal distress were all more prevalent in the GBS-positive group compared to the GBS-negative group. Specifically, the incidence of neonatal pneumonia was 12.5% in GBS-positive cases versus 2.5% in GBS-negative cases. Similarly, neonatal asphyxia and intrauterine fetal distress were more common in GBS-positive cases. The mean Apgar score at 5 minutes was also lower in neonates born to GBS-positive mothers. However, there were no significant differences in the incidence of low birth weight or mean birth weight between the two groups. These findings highlight the importance of GBS screening and management during pregnancy to improve neonatal outcomes.

Discussion

This study delves into the potential of utilizing a combination of serum inflammatory biomarkers as a reliable predictor of adverse pregnancy outcomes for women with late-trimester GBS colonization. Through our research, we have identified CRP, PCT, IL-6, and IL-15 as biomarkers that are notably elevated in GBS-positive women. When these markers are analyzed collectively, they exhibit greater predictive accuracy than when assessed individually. These compelling results indicate that incorporating biomarker-based risk stratification alongside conventional culture-based screening could enhance clinical decision-making and facilitate more personalized interventions for pregnant women at risk of adverse outcomes. This study sheds light on the importance of using multiple biomarkers to improve the prediction and management of pregnancy complications.

The development of adverse pregnancy outcomes in cases of GBS infection is a complex process involving both the direct impact of the bacteria and the response of the host immune system. GBS can travel from the lower genital tract to the amniotic cavity, leading to infection and inflammation inside the uterus. The immune system's response to GBS involves the production of pro-inflammatory cytokines, such as IL-6 and IL-15, which are crucial for triggering labor and may lead to complications such as preterm birth and chorioamnionitis.[13-16] Our findings of elevated levels of IL-6 and IL-15 in GBS-positive pregnant women support previous research highlighting the role of these cytokines in infection-induced preterm labor. These observations shed light on the intricate mechanisms behind GBS-related adverse pregnancy outcomes.

CRP and PCT are commonly used to identify bacterial infections. The liver produces CRP in response to IL-6 and other pro-inflammatory mediators, whereas PCT is produced by various cells in response to bacterial toxins.[17,18] Studies have revealed heightened levels of CRP and PCT in women with intrauterine infections and adverse pregnancy outcomes.[19,20] Our research expands on this, showing that CRP and PCT levels are also increased in women colonized with GBS, even without obvious signs of infection. This suggests that hidden inflammation may play a critical role in GBS-related complications, underscoring the importance of monitoring these markers in prenatal care to enable early intervention and prevention.

The combined biomarker model demonstrates superior predictive performance, with an AUC of 0.913, compared with individual markers alone. This highlights the importance of using a multi-marker approach to assess adverse pregnancy outcomes. Complicated interactions between various pathophysiological processes contribute to these outcomes, making it essential to consider multiple biomarkers for a comprehensive evaluation.[21] With a high sensitivity of 93.5% and specificity of 94.1%, the combined model shows promise for accurately identifying high-risk pregnancies. This suggests potential benefits, including enhanced fetal surveillance, earlier hospital admission, and modified antibiotic prophylaxis regimens to enable proactive interventions. Overall, a multi-marker approach offers significant advances in the management and monitoring of pregnancy complications.

Our research emphasizes the vital role of vaginal microecology in understanding GBS colonization. We found that women who tested positive for GBS were more likely to have co-infections with Trichomonas vaginalis, mycobacteria, and fungi, as well as higher vaginal pH levels. This indicates that GBS colonization can disrupt the normal balance of vaginal microbiota, potentially paving the way for other harmful organisms to thrive.[4,22-24] Moreover, this imbalance may exacerbate inflammation and increase the likelihood of ascending infections. It follows that interventions geared towards restoring vaginal microbiome equilibrium, such as probiotics or targeted antimicrobial treatments, could play a pivotal role in mitigating GBS-related complications. Future investigations should delve into whether such interventions can enhance pregnancy outcomes for GBS-colonized individuals, underscoring the importance of maintaining a healthy vaginal microenvironment for overall well-being.

Our study found that neonates born to mothers with GBS colonization were more likely to experience neonatal pneumonia, asphyxia, and intrauterine distress, indicating the importance of identifying and managing at-risk pregnancies.[25-28] Surprisingly, there was no significant difference in the incidence of low birth weight between GBS-positive and GBS-negative groups, suggesting that GBS colonization may impact acute neonatal outcomes rather than fetal growth. This aligns with the nature of GBS infection, which typically causes acute inflammation rather than chronic placental insufficiency. The findings highlight the critical need for early detection and intervention in pregnancies where maternal GBS colonization is present to prevent adverse neonatal outcomes. It underscores the importance of comprehensive prenatal care to ensure the health and well-being of both the mother and the newborn.

Our research findings strongly advocate for incorporating biomarker testing as a standard part of GBS screening procedures. Currently, guidelines recommend universal GBS screening for all pregnant women between 35 and 37 weeks of gestation, with subsequent antibiotic treatment for those who test positive. However, this one-size-fits-all approach fails to account for differences in risk levels among expectant mothers. By introducing biomarker testing, healthcare providers could individualize risk assessments, offering targeted monitoring, timelier interventions, or alternative care plans based on each woman's unique profile. For instance, pregnant individuals with elevated biomarker levels might require increased prenatal check-ups, more frequent ultrasounds, or even the option of earlier delivery, especially if other risk factors are at play. Ultimately, integrating biomarker testing into routine screening protocols holds promise for enhancing maternal and fetal health outcomes by tailoring care to each woman's specific needs.

It is important to note several limitations of our study. Firstly, the sample size of our prospective cohort was relatively small, which may restrict the generalizability of our findings and the accuracy of our estimates. To ensure the reliability of the combined biomarker model, larger multicenter studies encompassing diverse populations with varying demographic and clinical characteristics are recommended. Additionally, we did not conduct serial measurements of biomarkers throughout pregnancy, which could have provided insight into the temporal progression of the inflammatory response. We helped determine the optimal timing for biomarker assessment.

Furthermore, we did not explore the impact of intrapartum antibiotic prophylaxis on biomarker levels or pregnancy outcomes, a crucial consideration for clinical decision-making. Antibiotic administration may alter the inflammatory response and, consequently, affect the predictive value of the biomarkers. Moreover, our study was limited to a single institution in China, and the results may not be directly applicable to different healthcare settings with diverse patient demographics, clinical practices, or GBS serotype distributions. Lastly, we did not carry out GBS serotyping or virulence factor analysis, which could have provided deeper insights into the mechanisms underlying the associations observed in our study. Overall, these limitations highlight the importance of further research to enhance the validity and applicability of our findings.

Our study has highlighted the potential benefits of a multi-biomarker approach in predicting adverse pregnancy outcomes in women colonized with GBS. Moving forward, it is essential to conduct large-scale validation studies to validate further the effectiveness of the combined biomarker model across different population groups. Establishing standardized cut-off values for clinical use is also a crucial step in improving prediction accuracy. Prospective interventional studies are needed to assess whether biomarker-guided management strategies could lead to better maternal and neonatal outcomes compared to standard care practices. Additionally, mechanistic studies delving into the molecular pathways linking GBS colonization, inflammatory biomarkers, and adverse pregnancy outcomes may reveal new therapeutic targets and guide the development of preventive strategies. Exploring the role of vaginal microbiome modulation in reducing GBS-related complications through randomized controlled trials of probiotics or other microbiome-targeted interventions will further enhance our understanding in this area. Lastly, conducting cost-effectiveness analyses will help determine whether integrating biomarker testing into routine clinical practice is economically feasible. By addressing these key areas, we can potentially improve the management and outcomes of pregnancies affected by GBS colonization.

This research underscores the significant elevation of serum levels of CRP, PCT, IL-6, and IL-15 in women with late-trimester GBS colonization, indicating a correlation with adverse pregnancy outcomes. The combined evaluation of these biomarkers offers enhanced predictive value, with an impressive AUC of 0.913 and high sensitivity (93.5%) and specificity (94.1%), surpassing the efficacy of individual markers. These results endorse the implementation of biomarker testing in GBS screening protocols, paving the way for more personalized risk assessment and clinical intervention. Early detection of high-risk pregnancies can lead to tailored interventions, including intensified fetal monitoring, optimized antibiotic use, and timely delivery planning, ultimately improving outcomes for both mothers and newborns. Moreover, the links identified among GBS colonization, vaginal dysbiosis, and adverse effects underscore the potential benefits of microbiome-targeted approaches as a supportive measure to prevent GBS-related complications.

Conflict of Interest

The authors declare no competing interests.

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All authors reviewed the manuscript.

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