

Association of Vaginal Microbiome Dysbiosis and Serum C-Reactive Protein with the Severity of Gestational Diabetes Mellitus: A Prospective Observational Study

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Abstract

Background

Gestational diabetes mellitus (GDM) is a common metabolic disorder of pregnancy and is associated with increased maternal and neonatal complications. Recent studies suggest that alterations in the vaginal microbiome and chronic low-grade inflammation may contribute to worsening glucose intolerance during pregnancy. However, evidence evaluating the relationship between vaginal microbiome dysbiosis, systemic inflammation, and the severity of GDM remains limited, particularly in the Indian population. We planned this study to assess the association between vaginal microbiome dysbiosis, serum high-sensitivity C-reactive protein (hs-CRP), and disease severity in women with GDM.

Methods

This prospective observational study was conducted in the Department of Obstetrics and Gynaecology at Saveetha Medical College and Hospitals, Chennai. Eighty pregnant women diagnosed with GDM according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria were enrolled. Vaginal microbiome status was assessed using Nugent scoring on Gram-stained vaginal smears. Serum CRP levels, fasting plasma glucose, and glycated haemoglobin (HbA1c) were measured at enrolment. GDM was classified into mild, moderate, and severe categories. Statistical analysis included Chi-square test, one-way ANOVA, Spearman correlation, and multivariable logistic regression.

Results

Among the 80 women included in the study, 27 (33.8%) had mild GDM, 32 (40.0%) had moderate GDM, and 21 (26.2%) had severe GDM. Vaginal dysbiosis (Nugent score ≥ 7) was identified in 38.8% of participants and increased progressively with disease severity, from 11% in mild GDM to 47% in severe GDM ($p < 0.001$). Mean serum CRP levels also increased significantly across vaginal microbiome categories, measuring 4.2 ± 1.1 mg/L in women with normal vaginal flora, 8.7 ± 1.8 mg/L in those with intermediate flora, and 15.3 ± 2.4 mg/L in women with vaginal dysbiosis ($p < 0.001$). A strong positive correlation was observed between Nugent score and serum CRP levels ($\rho = 0.74$, $p < 0.001$). Women with vaginal dysbiosis also had significantly higher rates of preterm birth, neonatal intensive care unit admission, postpartum infection, and macrosomia. On multivariable logistic regression analysis, vaginal dysbiosis and elevated hs-CRP remained independent predictors of severe GDM.

Conclusion

Vaginal microbiome dysbiosis is common among women with gestational diabetes mellitus and is significantly associated with increased systemic inflammation and greater disease severity. Simple and widely available investigations such as Nugent scoring and serum CRP estimation may help identify women at increased risk of severe GDM and adverse pregnancy outcomes. Larger multicentre studies

using molecular microbiome analysis are needed to validate these findings and to evaluate the role of microbiome-based interventions in improving maternal and neonatal outcomes.

Keywords

Gestational diabetes mellitus, High-sensitivity C-reactive protein, Nugent score, , Pregnancy outcomes, , Vaginal dysbiosis , Vaginal microbiome

INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most common medical disorders complicating pregnancy and continues to be a major public health concern across the world. The condition is defined as glucose intolerance that is first detected during pregnancy and is associated with adverse maternal, fetal, and long-term metabolic outcomes.

The clinical importance of GDM extends far beyond abnormal blood glucose values during pregnancy. Women with GDM are at increased risk of hypertensive disorders, polyhydramnios, operative delivery, postpartum haemorrhage, and progression to type 2 diabetes after pregnancy [3]. Similarly, the fetus is exposed to an altered intrauterine metabolic environment that increases the risk of macrosomia, birth trauma, neonatal hypoglycaemia, respiratory distress syndrome, neonatal intensive care admission, and future obesity and diabetes during childhood and adult life.

In recent years, increasing attention has been directed towards the role of systemic inflammation in this process. Elevated inflammatory mediators including tumour necrosis factor- α , interleukin-6, interleukin- 1β , and high-sensitivity C-reactive protein have consistently been associated with impaired insulin signalling and worsening insulin resistance[6]. These inflammatory pathways are now recognised as active contributors to disease progression rather than simple biomarkers of inflammation [3,7].

Parallel to these developments, research into the human microbiome has transformed our understanding of maternal health during pregnancy. The healthy vaginal microbiome is usually dominated by *Lactobacillus* species. These organisms maintain an acidic vaginal environment through lactic acid production, thereby preventing colonisation by potentially pathogenic microorganisms. Disturbance of this protective microbial ecosystem results in vaginal dysbiosis, characterised by reduced *Lactobacillus* abundance and increased growth of anaerobic bacteria such as *Gardnerella vaginalis*, *Prevotella*, *Mobiluncus*, and *Atopobium vaginae*. Vaginal dysbiosis has traditionally been linked with bacterial vaginosis, preterm birth, premature rupture of membranes, chorioamnionitis, postpartum infections, and adverse neonatal outcomes. More recently, it has also been proposed as a potential contributor to metabolic disorders during pregnancy [8,9].

This inflammatory cascade may further aggravate insulin resistance and endothelial dysfunction, creating a vicious cycle between microbial imbalance, inflammation, and metabolic dysregulation. Experimental and translational studies have suggested that this interaction may influence both maternal glucose metabolism and placental function, thereby affecting pregnancy outcomes. However, the precise relationship between vaginal microbiome alterations and the clinical severity of GDM remains incompletely understood [7,10].

Over the last few years, interest in this field has increased considerably. Cortez et al. reviewed available evidence and highlighted the close interaction between maternal microbiota and glucose metabolism during pregnancy, while Wang et al. demonstrated distinct alterations in maternal and neonatal microbiota among women with GDM. More recently, Rafat et al. reported that vaginal dysbiosis in women with GDM was associated with a higher frequency of adverse perinatal outcomes, suggesting that microbial alterations may have important clinical implications beyond infection alone. Emerging reviews have further proposed that modulation of the maternal microbiome through probiotics, dietary interventions, and microbiome-directed therapies may represent a promising strategy for improving metabolic health during pregnancy. Nevertheless, available evidence remains heterogeneous because of differences in microbiome assessment techniques, study populations, diagnostic criteria, and inflammatory biomarkers evaluated [11,12].

Another important limitation of the existing literature is the scarcity of prospective studies from the Indian subcontinent. Most available reports have evaluated either the vaginal microbiome or

inflammatory biomarkers independently, whereas studies simultaneously examining vaginal microbiome dysbiosis, systemic inflammation, and GDM severity are limited. Furthermore, advanced molecular sequencing techniques are not readily available in many resource-limited settings, making simpler and validated tools such as the Nugent scoring system more practical for routine clinical use. Understanding whether easily measurable markers such as Nugent score and serum CRP reflect disease severity may help identify women at higher risk of adverse maternal and neonatal outcomes during pregnancy.

Keeping these observations in mind, we planned the present prospective observational study to evaluate the association between vaginal microbiome dysbiosis and systemic inflammation in women with gestational diabetes mellitus. We also wanted to examine whether increasing vaginal dysbiosis, assessed using Nugent scoring, was associated with greater disease severity and adverse obstetric outcomes. We believe that identifying such relationships may provide a simple, clinically applicable approach for early risk stratification and may also form the basis for future studies exploring microbiome-targeted interventions as an adjunct in the management of gestational diabetes mellitus. Hence, this study was conducted with the aim of establishing as Association of Vaginal Microbiome Dysbiosis and Serum C-Reactive Protein with the Severity of Gestational Diabetes Mellitus.

MATERIALS AND METHODS

Study design and setting

This conducted a prospective observational study in the Department of Obstetrics and Gynaecology at Saveetha Medical College and Hospitals, Chennai. The study was carried out over a period of 12 months from , 2024 to December 2025. Written informed consent was obtained from all participants before enrolment.

Study population

The study included pregnant women attending the antenatal outpatient department who were diagnosed with gestational diabetes mellitus based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. A total of 80 eligible women were recruited during the study period.

Inclusion criteria

Women were included if they fulfilled all of the following criteria:

- Age between 18 and 45 years.
- Singleton pregnancy.
- Gestational age between 24 and 32 weeks.
- Newly diagnosed gestational diabetes mellitus according to IADPSG criteria.
- Willingness to participate in the study and provide written informed consent.

Exclusion criteria

Women with any of the following were excluded:

- Pre-existing type 1 or type 2 diabetes mellitus.
- Multiple pregnancy.
- Current treatment for vaginal infection.
- Antibiotic or probiotic use within the previous four weeks.
- Human immunodeficiency virus infection or other chronic immunocompromised conditions.
- Any major medical illness that could affect inflammatory marker levels or vaginal microbiome composition.

Sample size

The study included 80 pregnant women who fulfilled the eligibility criteria during the study period. Consecutive eligible patients were recruited until the required sample size was achieved.

Data collection

After enrolment, demographic details including maternal age, parity, gestational age, body mass index (BMI), and relevant obstetric history were recorded using a structured proforma. Clinical examination

was performed in all participants, and routine antenatal investigations were reviewed from the hospital records.

Fasting plasma glucose and glycated haemoglobin (HbA1c) values were recorded to assess glycaemic status. Based on fasting plasma glucose, HbA1c values, and requirement of insulin therapy, participants were grouped into mild, moderate, and severe gestational diabetes mellitus.

Vaginal microbiome assessment

A high vaginal swab was collected from each participant during sterile speculum examination before starting any treatment for vaginal infection. The samples were immediately transported to the microbiology laboratory and processed according to standard laboratory procedures.

Gram-stained smears were examined, and the vaginal microbiome was assessed using the Nugent scoring system. Nugent scores of 0–3 were considered normal Lactobacillus-dominant flora, scores of 4–6 were considered intermediate flora, and scores of 7–10 indicated vaginal dysbiosis consistent with bacterial vaginosis.

To minimise observer bias, the microbiologist reporting the Nugent score was unaware of the participant's glycaemic status and severity of gestational diabetes.

Assessment of inflammatory marker

Fasting venous blood samples were collected from all participants on the same day as vaginal swab collection. Serum C-reactive protein levels were measured using an automated nephelometric method in the central biochemistry laboratory following standard quality control procedures.

Outcome measures

The primary outcome of the study was to determine the association between vaginal microbiome dysbiosis and the severity of gestational diabetes mellitus.

The secondary outcomes included:

- Association between Nugent score and serum CRP levels.
- Distribution of vaginal dysbiosis across different grades of gestational diabetes.
- Maternal and neonatal outcomes including preterm birth, macrosomia, neonatal intensive care unit admission, and postpartum infection.

Statistical analysis

All collected data were entered into Microsoft Excel and analysed using IBM SPSS Statistics version 26. Continuous variables were expressed as mean $\pm$ standard deviation, while categorical variables were presented as frequency and percentage.

The Chi-square test was used to compare categorical variables. Independent Student's *t*-test or one-way analysis of variance (ANOVA) was used for comparison of continuous variables depending on the number of groups. Spearman's rank correlation test was used to assess the relationship between Nugent score and serum CRP levels.

A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

Participant characteristics

A total of 80 pregnant women diagnosed with gestational diabetes mellitus (GDM) were included in this prospective observational study. Based on the predefined clinical criteria, 27 women (33.8%) had mild GDM, 32 (40.0%) had moderate GDM, and 21 (26.2%) had severe GDM.

The overall mean maternal age was **27.4 $\pm$ 4.1 years**, while the mean gestational age at recruitment was **27.6 $\pm$ 2.8 weeks**. The mean pre-pregnancy body mass index (BMI) was **24.8 $\pm$ 4.3 kg/m²**. Primigravidae accounted for 45% of the study population.

Women with severe GDM were older and had a higher mean BMI compared with those in the mild and moderate groups. Mean fasting plasma glucose, HbA1c, and serum CRP levels also increased with increasing disease severity (Table 1).

Table 1. Baseline clinical characteristics according to GDM severity

Variable	Mild (n=27)	Moderate (n=32)	Severe (n=21)	p value
Age (years)	26.1 $\pm$ 3.8	27.4 $\pm$ 4.2	29.0 $\pm$ 4.3	<0.05
BMI (kg/m ²)	23.4 $\pm$ 3.1	25.1 $\pm$ 4.4	27.2 $\pm$ 5.1	<0.01

Fasting plasma glucose (mg/dL)	94.3 ± 7.2	122.6 ± 9.4	158.4 ± 14.7	<0.001
HbA1c (%)	5.9 ± 0.3	7.0 ± 0.4	8.1 ± 0.6	<0.001
Serum CRP (mg/L)	4.6 ± 1.3	9.2 ± 2.1	16.8 ± 3.1	<0.001

Vaginal microbiome pattern according to disease severity

The vaginal microbiome differed across the three GDM severity groups. Women with mild disease were more likely to have a normal Lactobacillus-dominant vaginal flora, whereas vaginal dysbiosis became progressively more common with increasing disease severity.

Overall, **31 women (38.8%)** had Nugent scores of **7 or above**, indicating vaginal dysbiosis. The proportion of women with dysbiosis increased from **11%** in the mild GDM group to **25%** in the moderate group and **47%** in the severe group.

The association between Nugent score category and GDM severity was statistically significant ($\chi^2 = 19.4$, $p < 0.001$) (Table 2).

Table 2. Distribution of vaginal microbiome according to GDM severity

Nugent category	Mild	Moderate	Severe	Total
Dysbiosis (7–10)	11%	25%	47%	38.8%

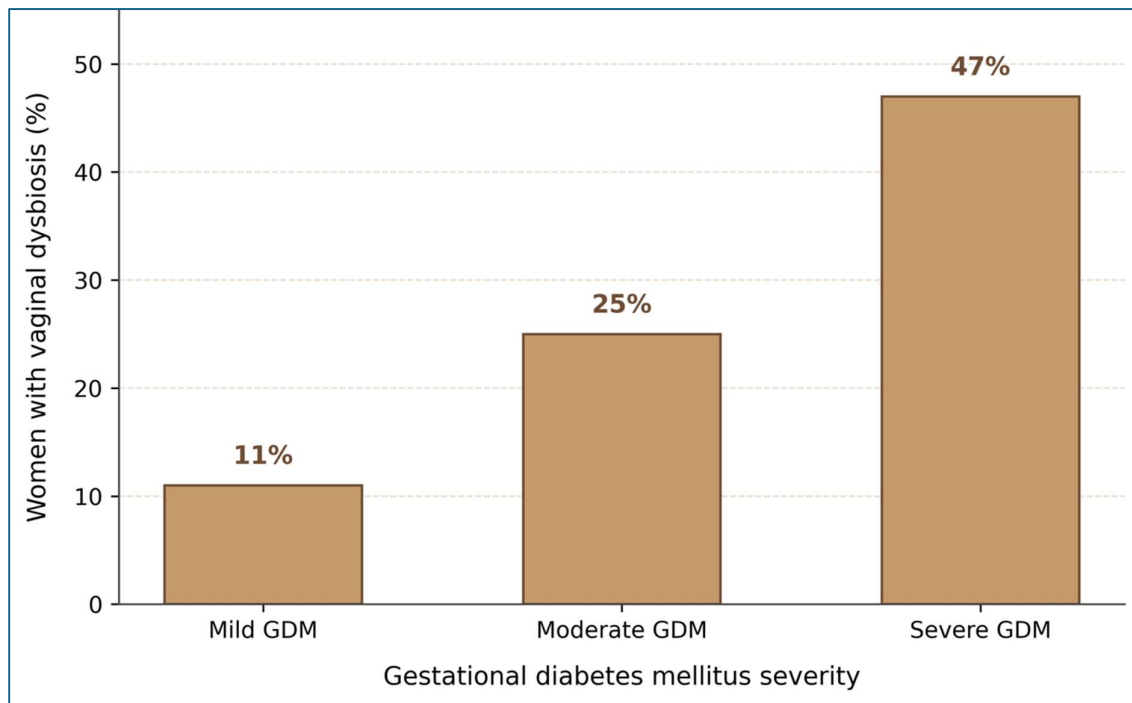


Figure 1. Vaginal dysbiosis across GDM severity

Association between vaginal dysbiosis and inflammatory marker

Serum CRP levels showed a gradual increase with worsening vaginal microbiome status.

The difference in CRP levels among the three microbiome groups was statistically significant (ANOVA, $p < 0.001$) (Table 3).

Table 3. Serum CRP according to vaginal microbiome status

Vaginal microbiome	Mean CRP (mg/L)
Normal	4.2 ± 1.1
Intermediate	8.7 ± 1.8
Dysbiosis	15.3 ± 2.4

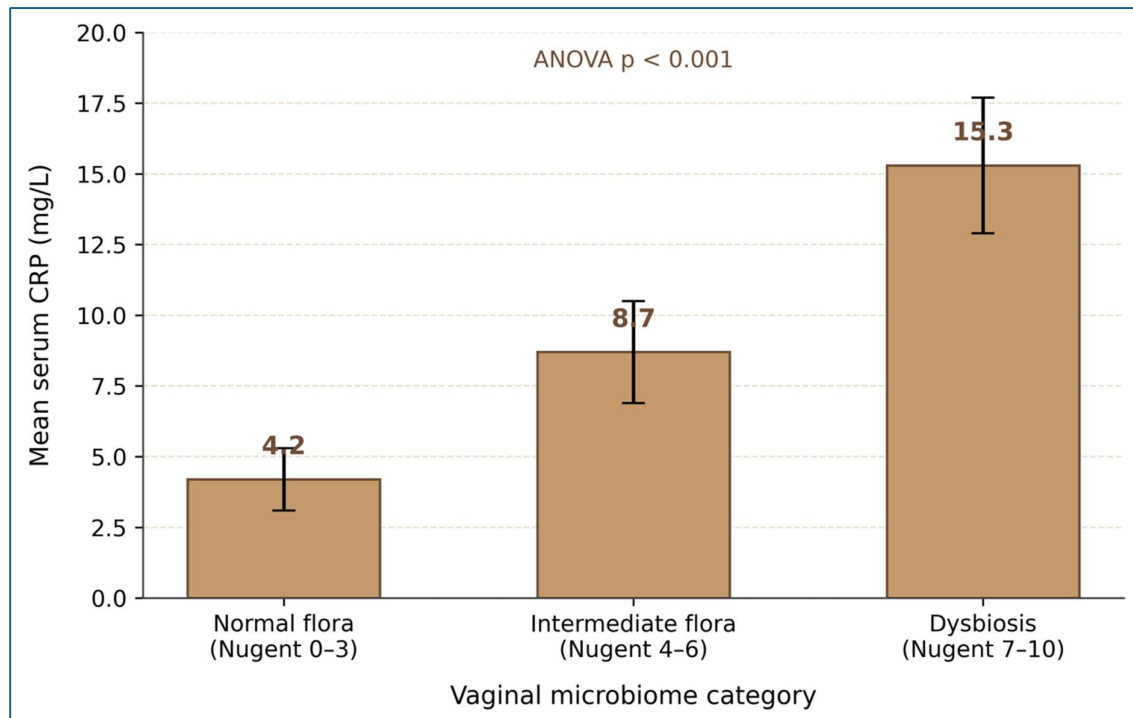


Figure 2 . Serum CRP by vaginal microbiome status

Correlation between Nugent score and serum CRP

A significant positive correlation was observed between Nugent score and serum hs-CRP levels.

Adverse pregnancy outcomes

Women with vaginal dysbiosis experienced adverse pregnancy outcomes more frequently than women with a normal vaginal microbiome.

Preterm birth occurred in 24% of women with dysbiosis compared with 5% among women with a normal microbiome ($p = 0.008$). Similarly, neonatal intensive care unit admission was more common in women with vaginal dysbiosis (31% vs 8%, $p = 0.003$). (Table 5).

Table 5. Pregnancy outcomes according to vaginal microbiome status

Outcome	Normal microbiome	Dysbiosis	p value
Preterm birth	5%	24%	0.008
NICU admission	8%	31%	0.003
Macrosomia	14%	22%	0.040
Postpartum infection	6%	38%	<0.001

Table 6. Multivariable logistic regression analysis for factors associated with severe gestational diabetes mellitus

Variable	Adjusted Odds Ratio (aOR)	95% Confidence Interval	p value
Maternal age (per year increase)	1.08	0.98–1.20	0.112
Body mass index (per kg/m ² increase)	1.18	1.04–1.35	0.014*
Serum hs-CRP (per mg/L increase)	1.29	1.13–1.48	<0.001*
Vaginal dysbiosis (Nugent score ≥ 7)	3.74	1.46–9.61	0.006*
Primigravida	1.31	0.55–3.09	0.542

Nagelkerke $R^2 = 0.42$, Hosmer–Lemeshow goodness-of-fit test: $p = 0.71$

Overall model classification accuracy = 82.5%

Table 7. Correlation analysis between study variables

Variables	Correlation coefficient (r/q)	p value
Nugent score vs hs-CRP	0.74	<0.001
Nugent score vs HbA1c	0.56	<0.001
Nugent score vs FPG	0.49	<0.001
hs-CRP vs HbA1c	0.62	<0.001
hs-CRP vs BMI	0.39	0.001

This study showed that vaginal microbiome dysbiosis was common among women with gestational diabetes mellitus and became more frequent with increasing disease severity. Higher Nugent scores were associated with significantly elevated serum hs-CRP levels and a greater occurrence of adverse pregnancy outcomes. A strong positive correlation between Nugent score and CRP further supports the relationship between vaginal dysbiosis and systemic inflammation in women with GDM.

DISCUSSION

In this study, we observed that vaginal microbiome dysbiosis was common among women with gestational diabetes mellitus and its frequency increased as GDM became more severe. Women with severe GDM had a higher proportion of Nugent score ≥ 7 compared with women having mild and moderate disease. We also found that serum CRP levels increased along with worsening Nugent score. This suggests that vaginal dysbiosis and systemic inflammation may be closely linked in women with GDM.

Rafat et al. also reported that vaginal dysbiosis in women with GDM was associated with adverse perinatal outcomes, supporting our finding that dysbiosis is not only a local vaginal finding but may also have wider pregnancy-related effects [1]. Cortez et al. described that maternal microbiome changes may influence metabolic function during pregnancy, and our study adds to this observation by showing a clear association between dysbiosis, CRP, and GDM severity [2]. Wang et al. also found altered maternal and neonatal microbiota in pregnancies complicated by GDM, which supports the possibility that microbial imbalance may be linked with the metabolic environment of pregnancy [3]. In this study, the prevalence of vaginal dysbiosis increased from 11% in mild GDM to 25% in moderate GDM and 47% in severe GDM. This stepwise rise is important. It indicates that worsening glycaemic status may be associated with progressive disturbance in vaginal flora. A healthy vaginal microbiome is usually Lactobacillus-dominant. Lactobacilli help maintain acidic vaginal pH and reduce overgrowth of anaerobic organisms. When this balance is disturbed, organisms such as Gardnerella, Prevotella and Mobiluncus may increase, leading to dysbiosis. Similar microbiome shifts have been described in pregnancy-related metabolic disturbances in previous studies [2,3,7].

Another important finding in our study was the rise in hs-CRP levels with increasing vaginal dysbiosis. Mean hs-CRP was 4.2 ± 1.1 mg/L in women with normal vaginal flora, 8.7 ± 1.8 mg/L in women with intermediate flora, and 15.3 ± 2.4 mg/L in women with dysbiosis. This shows a clear inflammatory gradient. CRP is a simple and commonly available inflammatory marker. Earlier studies have shown that high CRP levels are linked with insulin resistance and later development of GDM [8–11]. Our study supports this inflammatory hypothesis and shows that women with vaginal dysbiosis had much higher CRP values than those with normal flora.

The possible biological explanation is that vaginal dysbiosis may increase local and systemic inflammatory activity. Anaerobic bacteria can produce endotoxins and other bacterial products that stimulate immune pathways. This may lead to increased production of inflammatory cytokines and CRP. In pregnancy, where insulin resistance is already physiologically increased, this additional inflammatory burden may worsen glycaemic control. This may explain why women with higher Nugent scores in our study also had higher CRP and more severe GDM.

The strength of this study is that we assessed vaginal microbiome status and systemic inflammation together in the same group of women with GDM. We also classified GDM severity and looked at

pregnancy outcomes, which gives the study a broader clinical value. Another strength is the use of Nugent scoring, which is simple, low-cost and feasible in routine hospital settings. This is especially useful in Indian clinical practice, where advanced 16S rRNA sequencing may not be easily available. This study has some limitations. It was conducted in a single centre with a relatively small sample size. We used Nugent scoring rather than molecular sequencing, so we could not identify specific bacterial species in detail. We assessed hs-CRP as the main inflammatory marker, but we did not measure cytokines such as IL-6, TNF-alpha or IL-1 β . Also, as this was an observational study, we cannot prove causation. We can only say that vaginal dysbiosis and raised CRP were associated with greater GDM severity.

Overall, this study suggests that vaginal microbiome dysbiosis may be an important associated factor in women with GDM, especially in those with severe disease. The combination of Nugent score and hs-CRP may help in identifying women who need closer monitoring. Future multicentre studies with larger sample size, molecular microbiome analysis and longitudinal follow-up are needed to confirm these findings and to explore whether microbiome-based interventions can improve GDM-related outcomes.

CONCLUSION

In this study, we found that vaginal microbiome dysbiosis was common among women with gestational diabetes mellitus and became more frequent with increasing disease severity. Women with vaginal dysbiosis had significantly higher serum CRP levels, suggesting a close association between altered vaginal flora and systemic inflammation. We also observed that adverse pregnancy outcomes, including preterm birth, NICU admission, macrosomia and postpartum infection, were more common among women with vaginal dysbiosis.

Our findings indicate that simple and inexpensive tools such as Nugent scoring and serum CRP estimation may help identify women with GDM who are at a higher risk of severe disease and poor pregnancy outcomes. Although a causal relationship cannot be established from this observational study, the results support the growing evidence that the vaginal microbiome may play an important role in the pathophysiology of gestational diabetes mellitus.

Further multicentre studies involving larger study populations and molecular microbiome analysis are required to validate these findings. Future research should also evaluate whether microbiome-based interventions, including probiotics and dietary modification, can improve maternal glycaemic control and pregnancy outcomes.

STRENGTHS OF THE STUDY

This study has several strengths. First, it was conducted using a prospective observational design, which allowed systematic collection of clinical and laboratory data during pregnancy. Second, we evaluated vaginal microbiome status and systemic inflammation together, providing a more comprehensive assessment of their relationship with gestational diabetes mellitus. Third, we used Nugent scoring, which is a simple, validated, and cost-effective method that can be easily implemented in routine clinical practice, especially in resource-limited settings. Finally, we also assessed important maternal and neonatal outcomes, thereby improving the clinical relevance of our findings.

LIMITATIONS

This study has certain limitations. It was conducted at a single tertiary care centre with a relatively small sample size, which may limit the generalisability of the findings. Vaginal microbiome assessment was based on Nugent scoring rather than molecular sequencing techniques; therefore, individual bacterial species and microbial diversity could not be evaluated. Only serum CRP was assessed as an inflammatory marker, while other cytokines such as interleukin-6 and tumour necrosis factor-alpha were not measured. As this was an observational study, a cause-and-effect relationship between vaginal dysbiosis and gestational diabetes mellitus cannot be established. Long-term follow-up of mothers and infants was also beyond the scope of the present study.

CLINICAL IMPLICATIONS

The findings of our study suggest that assessment of vaginal microbiome status may provide additional information during the evaluation of women with gestational diabetes mellitus. Nugent scoring is

inexpensive, widely available, and can be performed in most microbiology laboratories without specialised equipment. When combined with serum hs-CRP measurement, it may help identify women who require closer antenatal surveillance and early intervention. These findings also support further research into microbiome-based preventive and therapeutic strategies in gestational diabetes mellitus.

FUTURE DIRECTIONS

Future multicentre prospective studies with larger sample sizes are needed to confirm our findings. Molecular techniques such as 16S rRNA gene sequencing and metagenomic analysis should be used to identify specific bacterial communities associated with gestational diabetes mellitus. Long-term follow-up studies evaluating maternal metabolic health and childhood outcomes will provide better understanding of the clinical significance of vaginal microbiome alterations. Randomised controlled trials investigating probiotics, prebiotics, dietary interventions, and other microbiome-targeted therapies may help determine whether correction of vaginal dysbiosis improves pregnancy outcomes in women with gestational diabetes mellitus.

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