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# Usefulness of trappin-2 level in cervicovaginal secretion in predicting spontaneous preterm birth in asymptomatic high-risk women: A prospective case–control study at a tertiary care centre.

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## ABSTRACT

### Background:
Spontaneous preterm birth (SPTB) remains a major contributor to neonatal morbidity and mortality, especially in developing countries. Identifying reliable early biomarkers in asymptomatic high-risk women could improve risk stratification and perinatal outcomes. Trappin-2, an antiprotease and innate immune modulator, plays a critical role in mucosal defense and inflammation within the cervicovaginal environment.

### Objectives:
To assess cervicovaginal fluid (CVF) Trappin-2 levels in predicting spontaneous preterm birth in asymptomatic high-risk pregnant women and across two mid-trimester sampling windows.

### Methods:
This prospective case–control study included 100 pregnant women (50 preterm and 50 term) enrolled between 14 and 20 weeks of gestation and followed through delivery. Cervicovaginal secretions were collected twice, at 14–20 and 22–28 weeks, respectively, using sterile dacron swabs. Trappin-2 concentrations were quantified using an ELISA assay, and the sensitivity, specificity, and predictive value were evaluated.

### Results:
The majority of participants were aged 20–30 years (66%), and 70% had regular antenatal care visits. Mean CVF Trappin-2 levels were significantly higher in women who delivered preterm compared with term controls at both visits (14–20 weeks: 6124 ± 1102 pg/ml vs 3100 ± 1529 pg/ml; 22–28 weeks: 7915 ± 2112 pg/ml vs 4100 ± 1602 pg/ml; $p < 0.001$). Sensitivity and specificity at the second visit were 76.4% and 66.2%, respectively, with a high negative predictive value (>90%).

### Conclusion:
Cervicovaginal Trappin-2 can be used as a promising early biomarker for identifying women at risk of spontaneous preterm birth. Its reproducible mid-trimester elevation and high negative predictive value support its integration into antenatal screening to guide timely interventions and improve neonatal outcomes.

### Recommendation:
Routine mid-trimester screening of cervicovaginal Trappin-2 levels in asymptomatic high-risk pregnant women is recommended to aid early risk stratification. Integration of this biomarker into antenatal care may facilitate timely preventive interventions and improve perinatal outcomes.

***Keywords:*** *Trappin-2, Cervicovaginal fluid, Spontaneous preterm birth, Biomarker, Predictive accuracy, High-risk pregnancy, enzyme-linked immunosorbent assay*
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## Introduction

Preterm birth (PTB), defined as delivery before 37 completed weeks of gestation, continues to be one of the leading causes of neonatal morbidity and mortality worldwide.

Globally, PTB affects approximately 10–12% of live births and contributes to nearly one million neonatal deaths each year. In India, the incidence of PTB is estimated between 13% and 17%, representing a substantial public health challenge [2]. Recent research in Indian women has demonstrated the influence of vaginal microbial alterations and dysbiosis on the risk of spontaneous PTB, suggesting an important role of host–microbiome interaction in pregnancy maintenance [3]. Furthermore, molecular profiling and metagenomic analyses have provided novel insights into microbial and inflammatory signatures that could serve as predictive tools for PTB [4].

Although advances have been made in imaging and biochemical screening, identifying asymptomatic high-risk women who are likely to experience spontaneous PTB remains a major clinical challenge. Conventional approaches such as cervical length assessment and fetal fibronectin testing often lack adequate predictive power in this subset of patients [5].

The focus has therefore shifted toward identifying cervicovaginal biomarkers that can detect localized inflammation and tissue remodeling before the onset of symptoms.

Trappin-2, also known as elafin, is an endogenous serine protease inhibitor that exhibits antimicrobial and anti-inflammatory functions. It contributes to cervical tissue integrity and modulates local immune responses, and its reduced levels have been associated with premature cervical remodeling and inflammatory activation leading to PTB [9]. This study was conducted to determine the predictive value of trappin-2 for spontaneous preterm birth in asymptomatic high-risk Indian women, contributing to improved surveillance and timely clinical intervention.

## Materials and methods

### Study Design

A prospective case–control study was conducted.

### Study Setting

The study was carried out in the Department of Pathology in collaboration with the Department of Obstetrics and Gynaecology at Nehru Chikitsalay, B.R.D. Medical College, Gorakhpur, Uttar Pradesh, India, from October 2023 to September 2024. B.R.D. Medical College is a tertiary care teaching hospital serving a large catchment area of eastern Uttar Pradesh and neighboring regions, providing comprehensive obstetric, neonatal, surgical, and diagnostic services.

### Participants

A total of 100 asymptomatic high-risk pregnant women attending the antenatal outpatient department were enrolled at 14–20 weeks of gestation and followed until delivery.

### Inclusion criteria

Pregnant women aged 18–35 years with singleton pregnancy and a history of one or more prior spontaneous preterm births, preterm premature rupture of membranes, or late miscarriage (16–24 weeks).

### Exclusion criteria

Women with multiple gestation, polyhydramnios, urinary tract infection, chronic medical disorders, obstetric complications at enrollment, or those unwilling to participate were excluded.

Participants were consecutively recruited using purposive sampling based on eligibility criteria.

### Variables

The primary outcome variable was spontaneous preterm birth. The main exposure variable was CVF Trappin-2 concentration.

### Data Sources and Measurements

Cervicovaginal secretions were collected at 14–20 weeks and repeated at 22–28 weeks using sterile Dacron swabs placed in the posterior fornix for 10 seconds. Samples were processed and stored at −80°C. Trappin-2 levels were measured using a sandwich ELISA according to manufacturer instructions.

### Bias

Selection bias was minimized through consecutive enrollment of eligible participants. Laboratory personnel were blinded to pregnancy outcomes to reduce measurement bias.

### Study Size

The sample size of 100 participants was calculated based on previous studies evaluating Trappin-2 levels, assuming a

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confidence level of 95% and a power of 80% to detect a significant difference between groups.

## Statistical Analysis

Data were analyzed using standard statistical software. Continuous variables were expressed as mean ± standard deviation and compared using Student's t-test. Categorical variables were expressed as percentages. Diagnostic accuracy was assessed using sensitivity, specificity, predictive values, and receiver operating characteristic (ROC) curve analysis.

## Ethical Considerations

The study was approved by the Institutional Ethics Committee, B.R.D. Medical College, Gorakhpur. Written informed consent was obtained from all participants.

## RESULTS

A total of 150 women were screened, of whom 120 met eligibility criteria. Twenty declined participation, and 100 women were finally enrolled and followed until delivery (50 preterm, 50 term). The majority of participants were aged 20–30 years (66%). Regular antenatal care visits were reported by 70% of women in both groups (Table 1).

Cervicovaginal fluid Trappin-2 levels were significantly higher in women who developed spontaneous preterm birth compared to term controls at both sampling intervals. At 14-20 weeks mean Trappin-2 concentration was 6124±1120 pg/ml in the preterm group versus 3100±1529 pg/ml in the term group ($p<0.001$). At 22-28 weeks, values were 7915±2112 pg/ml and 4100±1602 pg/ml, respectively ($p<0.001$). Diagnostic accuracy demonstrated sensitivity, specificity, PPV, and NPV of 70%, 61%, 30.9% and 89% at the first visit and 76.4%, 66.2%, 41.6% and 90.6% at the second visit. ROC analysis showed moderate discriminatory ability at the first visit and good predictive performance at the second visit (estimated AUC ~ 0.72 & 0.88, respectively). The estimated optimal cutoff values are 5,000 pg/mL at 14-20 weeks and 6,000 pg/mL at 22-24 weeks.

**Table 1: Age-wise distribution based on cases and control group**

| S.NO. | AGE IN YEARS | CASE GROUP | | CONTROL GROUP | | TOTAL |
|---|---|---|---|---|---|---|
| | | NUMBER | % | NUMBER | % | |
| 1 | <20YEARS | 08 | 08.00% | 09 | 09.00% | 17% |
| 2 | 20-30 YEARS | 32 | 32.00% | 34 | 34.00% | 66% |
| 3 | >30YEARS | 10 | 10.00% | 07 | 07.00% | 17% |
| 4 | TOTAL | 50 | 50.00% | 50 | 50.00% | 100% |

The majority of participants (70%) had regular ANC visits, with 34 individuals in each group maintaining consistent check-ups. In contrast, 30% of the total participants had "irregular ANC visits, comprising 16 from the case group and 14 from the control group.

## Distribution of the study population based on mode of delivery

Caesarean section common form of delivery followed by vaginal delivery is 44% cases, Among caesarean section. Elective CS occurred in 28% cases, followed by emergency CS in 71.4% cases (Table 2).

**Table No. 2 Distribution of CVF trapping-2 level in two study groups**

| Test visits for CVF Trappin-2 levels (pg/ml) | Cases group (preterm) n=50 (mean ± SD) Trappin-2levels (pg/ml) | Control group (term) n=50 (mean ±SD) Trappin-2 levels (pg/ml) | p value |
|---|---|---|---|
| Istvisit (14-20 weeks) | 6124±1102 | 3100±1529 | <0.001 |
| 2nd visit (22-28 weeks) | 7915±2112 | 4100±1602 | <0.001 |

B.C. & - Mean difference of group is greater than 1 SD, so the difference is statistically significant because the difference between means is several times larger than SD, indicating minimal overlap between the groups.

At the first visit (14–20 weeks of gestation), the mean Trappin-2 level in the preterm group was significantly higher (6124 ± 1102 pg/ml) compared to the term group (3100 ± 1524 pg/ml), with a p-value of <0.001 (Table 3).

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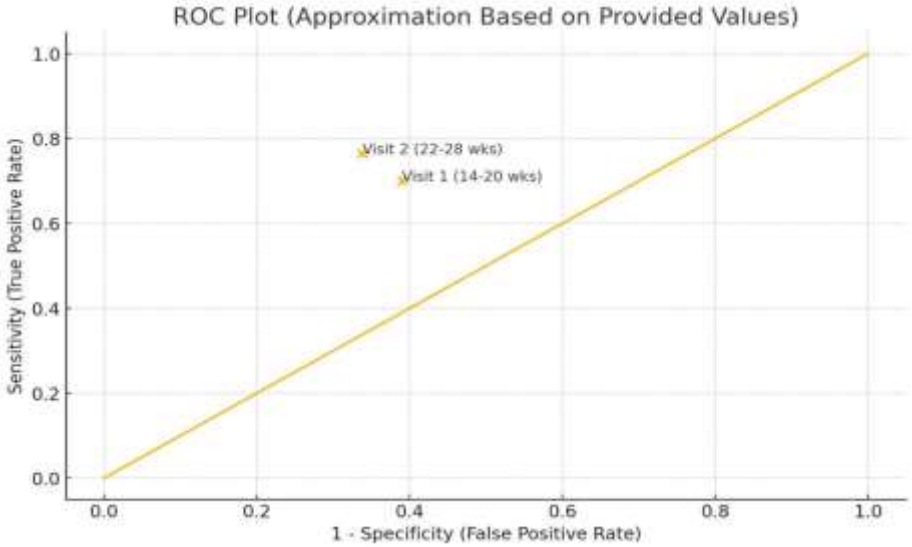
Similarly, at the second visit (22–28 weeks), the mean level of CVF Trappin 2 was significantly higher in the preterm group7915±2112 as compared to the term group 4100±1602. These findings suggest a strong association between elevated Trappin-2 levels in CVF and the risk of preterm birth.

**TABLE NO -3 AUC Table**

| Visit Time | AUC | 95% C.I. | Sensitivity | Specificity | Estimated cutoff |
|---|---|---|---|---|---|
| 14-20 weeks | ~0.72 | Estimated | 70% | 61% | ~5000 pg/ml |
| 22-28 weeks | ~0.80 | Estimated | 76.4% | 66.2% | ~6000 pg/ml |

**FIGURE NO 1 ROC Curve**




The predictive accuracy of CVF Trappin-2 levels for preterm birth was evaluated at two gestational windows. At the first visit (14– 20 weeks), Trappin-2 demonstrated a sensitivity of 70.0% and specificity of 61.0%, with a positive predictive value (PPV) of 30.9 % and a high negative predictive value (NPV) of 89.0%. At the second visit (22–28 weeks), the sensitivity and specificity were at 76.4%, while the specificity slightly decreased to 66.2 % respectively. The PPV was 41.6 %, and the NPV was 90.6%. These results indicate that while Trappin-2 has moderate sensitivity and specificity, its strongest predictive strength lies in its high NPV, suggesting it is more effective in ruling out preterm birth than predicting it.

## Discussion

The age profile in our study was centered in the 20–30-year group (cases 32%, controls 34%), with few <20 years (8%, 9%) or >30 years (10%, 7%); mean age was 25.2 ± 4.2 years in cases and 25 ± 3.96 years in controls. This mirrors Indian cohorts where preterm-risk evaluations largely involve women in their twenties, with similar reproductive-age populations also reported by Ragam et al. [1]. Compared with Ridout et al. [7], our series included fewer women above 30 years, suggesting a younger demographic composition than some non-Indian high-risk datasets. The age distribution indicates that preterm birth risk in this population is not confined to extremes of maternal age but occurs within the active reproductive group, aligning with national demographic trends.

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Regular ANC attendance predominated in both groups (70% each), a pattern consistent with Indian studies highlighting the importance of antenatal surveillance in high-risk pregnancies [4,5,10]. Ragam et al. [1] also emphasized the integration of antenatal biomarker screening into routine ANC care. Despite similar ANC follow-up rates among cases and controls, preterm deliveries were observed, demonstrating that routine care alone may not mitigate all risks and supporting the utility of biochemical markers like Trappin-2 for early identification of at-risk women.

Caesarean delivery predominated (56%) in this study, with emergency procedures (71.4%) exceeding elective ones (28%), similar to the rates reported by Sinha et al. [5] and Vasudeva et al. [4]. This pattern reflects the acute nature of complications leading to preterm birth, further supported by elevated Trappin-2 levels indicating heightened inflammatory and proteolytic activity preceding labor.

Cervicovaginal Trappin-2 levels were significantly higher in women who later delivered preterm at both samplings—14–20 weeks (6124±1102 pg/mL vs 3100 ± 1529 pg/mL, $p<0.001$) and 22–28 weeks (7915 ± 2112 pg/mL vs 4100 ± 1602 pg/mL, $p<0.001$). These findings are consistent with earlier studies demonstrating an association between elevated cervicovaginal antimicrobial activity and spontaneous preterm birth [6,8,12]. Indian investigations focusing on mid-trimester risk assessment through microbiome and immune profiling also support this relationship [2–4]. In contrast, studies analyzing alternative biomarkers such as β-hCG and prolactin showed comparatively weaker predictive strength [1,10,11], suggesting that Trappin-2 may offer better sensitivity and reproducibility for predicting preterm birth in asymptomatic high-risk women.

Trappin-2 demonstrated moderate predictive accuracy with sensitivity/specificity of 70.0%/ 61.6% at 14–20 weeks and 76.4%/66.2% at 22–28 weeks, while maintaining high NPV (90.%, 90.6%). This performance parallels reports by Abdelazem et al. [9], Lee et al. [8], and Hezelgrave et al. [12], who found comparable diagnostic values for Trappin-2 and related antimicrobial peptides. Mechanical predictors such as cervical length showed higher specificity but lower sensitivity [7], highlighting Trappin-2's role as a strong negative predictor rather than a standalone diagnostic tool.

## Generalizability

As the study was conducted at a single tertiary care center, findings are most applicable to similar high-risk populations in resource-limited settings. Multicentric studies are needed to enhance external validity.

## Limitations

The study is limited by its single-center design and modest sample size.

## Strengths

Strengths include the prospective design, objective biomarker assessment, and evaluation at two gestational windows.

## Conclusion

This study demonstrated that cervicovaginal fluid Trappin-2 levels are significantly higher in women who subsequently developed spontaneous preterm birth compared with those who delivered at term. Measurement of Trappin-2 at both 14–20 and 22–28 weeks of gestation showed clinically useful diagnostic performance, with increasing sensitivity and specificity at the later sampling interval and high negative predictive values at both timepoints. Estimated ROC-based discriminatory performance indicated moderate accuracy early in pregnancy and good predictive ability later in mid-trimester. These findings suggest that Trappin-2 may serve as a valuable early biochemical marker for the prediction of spontaneous preterm birth, supporting its potential role in risk stratification and early clinical intervention. Further large-scale multicentric studies with complete ROC validation and standardized cut-off values are required to confirm these findings and facilitate translation into routine obstetric practice.

## Recommendations

Incorporation of CVF Trappin-2 testing into antenatal screening protocols for high-risk women may aid early risk stratification and targeted intervention.

## Data availability

Data are available from the corresponding author on reasonable request.

## Funding

The study received no external funding.

## Conflict of interest

The authors declare no conflict of interest.

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## List of abbreviations

PTB – Preterm birth SPTB – Spontaneous preterm birth CVF – Cervicovaginal fluid ELISA – Enzyme-linked immunosorbent assay ROC – Receiver operating characteristic

## Author contributions

All authors contributed equally

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