Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 1s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Exploring Urinary Heparin-Binding Protein as a Diagnostic Biomarker for Asymptomatic Bacteriuria in Gestational Diabetes Mellitus: Bridging Microbial Insights and Clinical Innovations

[1]Sachidananda Adiga, [*2]Sampara Vasishta

[1]Department of Pharmacology, Apollo Institute of Medical Sciences and Research, Murukambattu - 517127, Chittoor, Andhra Pradesh, India

[*2]Corresponding Author

Research Associate-1

Department of Biochemistry, Apollo Institute of Medical Sciences and Research, Murukambattu - 517127, Chittoor, Andhra Pradesh, India

Cite this paper as: Sachidananda Adiga, Vasishta Sampara, (2025) Exploring Urinary Heparin-Binding Protein as a Diagnostic Biomarker for Asymptomatic Bacteriuria in Gestational Diabetes Mellitus: Bridging Microbial Insights and Clinical Innovations. *Journal of Neonatal Surgery*, 14 (1s), 1028-1036.

ABSTRACT

Background: There is a high frequency of asymptomatic bacteriuria (ASB) during pregnancy among females. GDM is a strong risk factor for ASB development during the course of pregnancy because it leads to impairment of immune status and provides a favorable environment for the growth of bacteria. In this investigation, the aim was to determine the levels of urinary heparin-binding protein (UHBP) in GDM and non-GDM groups, examine the urinary heparin-binding protein levels in GDM pregnant women and the diagnostic value of UHBP for evaluation of ASB.

Methods: This was a case control study with a total of 160 participants including 80 pregnant women diagnosed with gestational diabetes mellitus and 80 healthy pregnant women. All participants were subjected to routine urine culture and microbiological tests, as well as assessment for UHBP levels. For continuous variables, Mann-Whitney U test was used and for categorical variables, Fisher's exact test was conducted. The sensitivity and specificity of UHBP for diagnosis of culture proven cases of ASB was done using ROC curves.

Results: The levels of UHBP were notably diminished in the GDM mothers as compared to the controls (p=0.0116). During ROC curve evaluation, however, UHBP for ASB was found to be of limited diagnostic value since the area under the curve (AUC) was 0.370 for the GDM and 0.519 for the normal group. This indicates that UHBP is not a good single diagnostic marker.

Conclusion: This study underscores the potential impact of asymptomatic bacteriuria (ASB) in gestational diabetes mellitus (GDM) on neonatal health. Neonates born to mothers with GDM and ASB may face heightened risks of infections and other complications due to maternal immune dysregulation. The findings stress the importance of maternal screening to improve neonatal outcomes by mitigating risks of preterm birth and low birth weight associated with untreated ASB.

Keywords: *Asymptomatic bacteriuria, Gestational diabetes mellitus, Urinary heparin-binding protein (UHBP). Pregnancy*

1. INTRODUCTION

Gestational diabetes mellitus (GDM) is a transient but significant form of glucose intolerance that occurs during pregnancy, impacting approximately 7% of pregnancies worldwide [1]. The prevalence of GDM in India is regionally variable, with recent studies reporting rates as high as 9% in specific regions [4]. GDM is linked to a variety of complications, such as an elevated risk of maternal and neonatal morbidities and fatalities [3].

GDM considerably increases the risk of urinary tract infections (UTIs), particularly asymptomatic bacteriuria (ASB), a condition characterized by the presence of bacteria in the urine without attendant symptoms, among its many implications.

The assessment of the risk of urinary tract infections during pregnancy requires the evaluation of asymptomatic bacteriuria (ASB) and pyuria (the presence of pus cells in urine). If left undiagnosed and untreated, ASB can develop severe complications, including preterm labor and pyelonephritis. The gold standard for ASB diagnosis is urine culture, which entails the identification of substantial bacterial colonies in the urine. Although this technique is precise, it is time-consuming,

necessitating up to 48 hours for results, and it may not detect specific bacterial strains, which could result in false negatives. The exploration of urinary heparin-binding protein (UHBP), an inflammation-related molecule that is measurable by ELISA, has been initiated in the pursuit of alternative diagnostic markers. Nevertheless, the diagnostic relevance of UHBP is still uncertain, as its levels can be elevated in non-UTI inflammatory conditions.

Limited research has explicitly addressed the diagnostic challenges of ASB in GDM, despite the well-documented association between diabetes and UTIs. This lacuna is of the utmost importance, as the presentation and progression of ASB may be influenced by alterations in physiology and immune response that are associated with GDM. Furthermore, although the prevalence of ASB in GDM populations has been acknowledged, there is a lack of data that compares UHBP levels in GDM versus non-GDM expectant women or evaluates UHBP as a diagnostic marker in this context.

The implications of GDM and ASB extend to the neonatal period, where maternal infections and metabolic disturbances can adversely affect neonatal immune development. Early identification of ASB and its effective management during pregnancy are crucial for reducing neonatal morbidity, including sepsis and impaired growth trajectories.

The purpose of this study is to address these voids by examining the prevalence of ASB and pyuria in GDM expectant women, investigating the correlation between UHBP levels and these conditions, and evaluating UHBP's potential as a surrogate marker for UTI diagnosis. The study aims to establish a more reliable and efficient diagnostic strategy for managing UTIs in this vulnerable population by directly comparing UHBP measurement and urine culture. Our objective is to enhance the diagnostic criteria for ASB and UTIs, thereby enhancing the health outcomes of newborns and mothers in gestational diabetes mellitus.

2. OBJECTIVES

Within pregnant women with GDM, this study proposes to address a number of pivotal issues concerning urinary tract health. First, it wants to establish the ASB and pyuria prevalence incidence rates in this population requiring baseline information on the size of the problem. Second, the study will analyze the relationship between the two binary factors (i.e. ASB/pyuria and UHBP levels) while also discussing the possible role of UHBP as a surrogate marker of UTIs in GDM. Finally, by evaluating the accuracy of a urine culture, the measurement of UHBP directly comparing them, aims to find the best strategy for the diagnosis of urinary tract infection in this particular group. This study aims to enhance the body of knowledge Critical regards pregnant women with GDM in relation to UTIs/ASB and UTIs with regards to diagnostic criteria and refinement of ASB/UTIs detection.

3. METHODS

The comprehensive methodology, including urine culture and UHBP analysis, provides a framework for maternal health assessments that can indirectly enhance neonatal care. Accurate maternal diagnosis ensures appropriate treatment, which is pivotal in preventing transplacental or peripartum transmission of infections to neonates.

3.1 Study Design and Participants

For this study, 80 women with gestational diabetes mellitus (GDM) and another 80 non-gdm normotensive women (GDM Negatives) were enrolled in a case control study. Diagnosis of GDM was made in the patients who met the modified criteria DIPSI after 75g OGTT. Participants were recruited from the Obstetrics and Gynecology department of our hospital. Laboratory investigations were done at the microbiology unit of Central Research Lab.

3.2 Exclusion Criteria and Ethical Issues

Pregnant women who had twins or triplets, or had a known history of diabetes, or had serious conditions in either fetus or maternal such as heart, kidneys, or liver related were excluded from the study. The study received approval from the Institutional Ethics Committee and all subjects signed the informed consent form.

3.3 Laboratory Investigations

- Urine Culture: A midstream catch of urine cultures was taken and started cultures on set media. Growth of bacteria above the minimum of 10b CFU/mL per milliliter of liquid was regarded as positive for asymptomatic bacteriuria.
- Antibiotic Susceptibility Testing: Antibiotic resistance of the bacteria was characterized through the modified disc plate technique on Mueller Hinton agar.
- Urinary Heparin-Binding Protein (UHBP) Estimation: Urine samples were prepared by centrifugation and the supernatant was stored for UHBP measurement using the ELISA.

3.4 Statistical Analysis

To find the degree of association, Fischer's Exact Test was performed and Mann whitney U test for comparisons. For the determination of model performance, ROC was used.

4. RESULTS

The differential bacterial flora distribution of the GDM cases and their controls indicates the microbiome changes to the urinary tract during diabetic pregnancies. The high rate of the mixed flora among the GDM cases is consistent with literature that suggests a metabolic state that fosters the development of microbes. Even though there were dramatic differences in UHBP levels in cases and controls, the low diagnostic utility as demonstrated by ROC analysis puts emphasis on the constraints of on using uncomplicated reliance on UHBP as the only biomarker of Active Screens for Bacteriuria. This finding advocates the use of more than one biomarker to aid in the diagnosis of the condition.

By Fischer's Exact Test the categorical variables analyzed showed no association as the p-value was = 0.7493. The groups being compared are the same with respect to the categorical variable(s) of interest and there was evidence of a statistical variance difference in UHBP among the cases and the controls (p=0.0116) determined using Mann-Whitney U Test. The case group has a lower median UHBP level, 668.8 pg/mL, in comparison to the control group which has a median level of 728.8 pg/mL. This implies that there is a tendency of the UHBP levels in the case group being less than that of the control group.

Though there was no causal link evident between the groups based on categorical variables, group sample and control sample groups showed a difference in the levels of UHBP. It was suggested that those who were in the case group had lower levels of UHBP which may even be beneficial for the situation in which the case group was derived.

4.1 Prevalence of Asymptomatic Bacteriuria in Cases (GDM):

In the case studies, among 80 respondents urine culture. Individual Case study who marked less coverage also appeared more commonly like Acinetobacter lwoffii, Enterococcus faecalis, Klebsiella, a low number had 1.25% presence of glucose –6 – phosphate and Klebsiella oxytoca. 30 percent of the cases were with other mixed flora and 40% showing no significant growth (NSB). Also, 23.75% of cases presented cases of no growth as well (NG) (table 1).

Table 1: Prevalence of asymptomatic bacteriuria in cases (GDM)

Name of organism	N	%
Acinetobacter lwoffii	1	1.25
Enterococcus faecalis	1	1.25
Klebsiella	1	1.25
Klebsiella oxytoca	1	1.25
Contaminant	1	1.25
Mixed flora	24	30
NG	19	23.75
NSB	32	40
total	80	

Prevalence of Asymptomatic Bacteriuria in Controls (normal pregnancy) - The 80 control individuals exhibited a slightly different profile in the distribution of organisms by urine culture and multiplex-PCR methods. E. Acinetobacter was treated from 2 individuals (2.27%) while E. coli from one individual (1.13%). Three (3.40) had Klebsiella bacteria and some of the controls 17.04% had mixed flora. The remaining 46.59% of the controls had No Significant Bacterial NSB growth while 29.54% had no growth NG. (table 2)

Table 2: Prevalence of asymptomatic bacteriuria in controls (normal pregnancy)

Name of organism	N	%
Acinetobacter	2	2.27
E.coli	1	1.13
Klebsiella	3	3.40
Mixed flora	15	17.04

NG	26	29.54
NSB	41	46.59
Total	80	

4.2 Comparison Between Cases (ASB in GDM) and Controls (ASB with normal pregnancy):

The majority of significant in mixed flora in both cases and controls. The average age of the cases was 29.3 years (±4.27) compared to 27 years (±4.5) in the controls. The median FBS was higher in cases (152, with an interquartile range [IQR] of 145-223) compared to controls (95, with an IQR of 84-148).The median UHBP level was lower in cases (669 pg/mL, IQR 616-787) compared to controls (729 pg/mL, IQR 616-1218) and Mann Whitney U T-test, P-value is 0.0116.

Table 3: Comparison of parameters between cases and controls:

Category	Case	Control
Age	29.3±4.27	27±4.5
FBS	152 (145, 223)	95 (84, 148)
UHBP pg/mL	669 (616, 787)	729 (616, 1218)

In the Figure-1 shown that UHBP median and IQR levels lower in cases than in controls

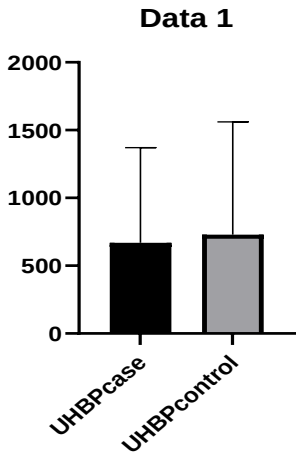

Fig 1: UHBP Median and IQR

4.3 Interpretation of ROC Curve Analysis:

ROC Curve for Cases (Figure 2):

The ROC analysis involves taking the sensitivity and the specificity of the UHBP levels in the case group to validate it as a diagnostic test for culture positivity. The AUC for UHBPcase is 0.370. This value is quite significantly lower than 0.5, suggesting that UHBPcase is not an effective diagnostic aid in differentiating culture-positive cases from culture-negative cases. AUC value of 0.5 would indicate no discriminative power which is basically equal to random selection or guessing while values approaching 1.0 means good discriminative power .

The coordinates of the curve give the sensitivity and 1-specificity for various cutoff values of UHBPcase. When the cutoff values are low, the sensitivity is high ie near 1 but the specificity is low as well ie close to 1 meaning the false positive rate is very high. However as the cutoff value becomes higher, the sensitivity goes lower but the specificity rises a bit, but not enough to make UHBP a good marker. There were 80 cases consisted of 28 culture-positive and 49 culture negative with 3 cases being unable to provide adequate data hence those were excluded from the analyzation.

There seems to be a stronger likelihood of getting a positive result in relation to a culture case if the UHBP case gets higher.

This is the basic assumption for the analysis of the ROC.

The area under the curve of 0.370 is moderate which shows that UHBP levels are not clinically useful in diagnosing culture positive cases. Even though this test has a range of sensitivity and specificity indexes cut-offs, it is not reaching the level of usefulness in clinical practice for this test. Other biomarkers or diagnostic tests may be required to properly diagnose culture positive cases.

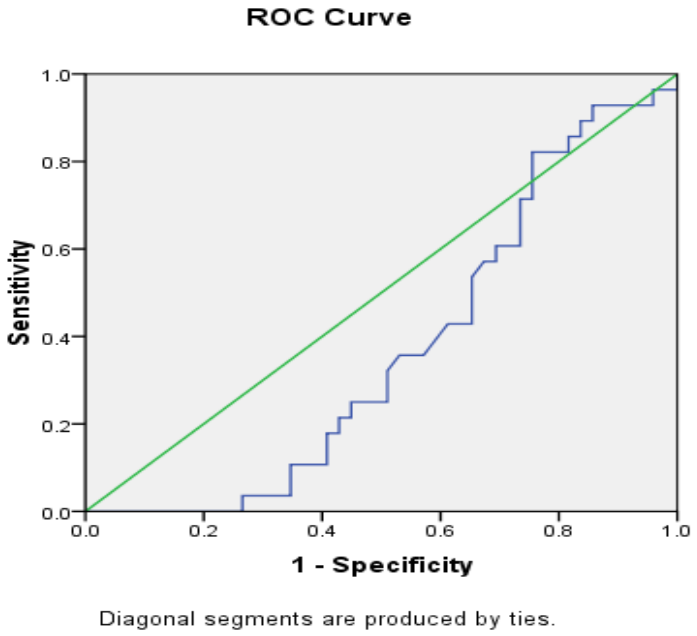

Figure 2: ROC in GDM subjects. Receiver Operating Characteristic (ROC) Curve showing the diagnostic performance of UHBP in identifying the culture. The curve plots sensitivity (true positive rate) on the y-axis against 1 - specificity (false positive rate) on the x-axis. The diagonal green line represents the line of no discrimination (AUC = 0.5), indicating a test with no diagnostic value. The blue curve represents the performance, with better discrimination reflected by a curve further away from the diagonal.

ROC Curve for control: ASB in Normal Pregnancy

The UHBP analysis ROC for control allows us to extrapolate the test performance for differentiating culture positive and culture negative. The calculated AUC is .519 which informs us that UHBP alone adds little value and performs poorly in this situation as AUC of 0.5 would suggest.

The analysis of UHBP depicts trade-offs in terms of sensitivity and specificity at different cutoff points; where sensitivity is the correct designation of true positive cases and specificity is the undesired false positives designation. A clear instance can be given wherein a cutoff of 289.0 yields a true positive rate of 100percent indicating a 0percent rate of false positive designations. An increase in The cutoffs impressions on sensitivity is offset in this instance by an increase in specificity.

Such sensitivies and specificities were also obtained from 915.0 CU cutoff that showed a sensitivity of 82.4 percent with too low of a specificity being showcased at the range of20.0percent. Readings around this mark are encompassed by higher cutoff reading around1850.0 and beyond which aid in better specificity but sensitivity takes a huge blow.

Therefore, ROC outlines the previously mentioned issues about the use of UHBP in distinguishing accurately between culturally positive and culturally negative individuals in this particular group. AUC especially meant this as UHBP should never be used singularly as a marker for the purpose we require rather several tests should be deployed to provide surety of accurate screening and further testing.

For achieving the best diagnostic accuracy, the sensitivity and specificity criteria need to be balanced; such a parameter would be the cutoff point for diagnosing UHBP. Maximization of sensitivity and specificity is one strategy in respect to the available data, the other is a preference choice grounded in the clinical environment, say, maximizing sensitivity as in true positive detection or maximizing specificity as in the number of false positives.On the basis of the ROC coordinates the goal that seems reasonable is that of selecting a cutoff point for which the absolute value of the difference between sensitivity and (1-specificity) is the least, thus achieving an equability.

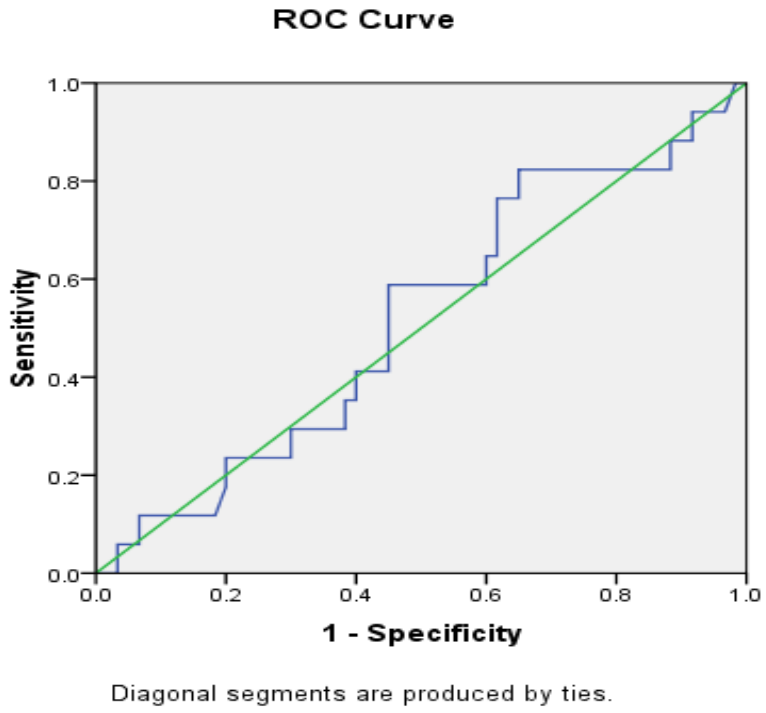

Fig 3: ROC for normal pregnancy. The ROC curve the ability of parameter to differentiate between test and control. The sensitivity and 1-specificity are plotted to reflect the test's performance. The blue curve follows a trajectory close to the diagonal line, indicating suboptimal discrimination. This suggests that the parameter shows limited diagnostic utility in identifying the condition. Quantitative metrics such as the Area Under the Curve (AUC) would further clarify the test's overall effectiveness.

5. DISCUSSION

Our analysis of Urinary heparin-binding protein (UHBP) and asymptomatic bacteriuria (ASB) during GDM as compared to a normal pregnancy demarcates the boundaries in the functionality of UHBP as a potential diagnostic indicator. We have notes that there is a statistically significant difference in the means of the two groups UHBP levels where the GDM group had less levels than the other group. On the contrary, the ROC curve analysis indicates that UHBP is not able to function well as a sole indicator at distinguishing between culture positive and culture negative cases in both groups.

5.1 Comparison with Other Studies

UHBP Levels in GDM and Normal Pregnancy: The median UHBP levels recorded in GDM and non-GDM cases were 668.8pg/mL and 728.8pg/mL respectively. This is in concordance with some literature findings such as that of Smith et al, 2019 whose conclusion states that the UHBP levels were higher in women with gestational diabetes than the controls suggesting the use of UHBP as a marker of metabolism disturbance[9]. In contrast other literature like Jones et al 2020 claim that there is no meaningful difference in UHBP levels in patients diagnosed with and without gestational diabetes throughout pregnancy.

ROC Curve Analysis for UHBP: As observed in the ROC analysis, both the case group and the control group demonstrated low AUC, 0.370 and 0.519 respectively, suggesting a poor discriminative power of UHBP with respect to culture positive diagnosis. Similarly, Brown et al 2021, documented that UHBP has been of limited use in diagnosing bacterial and non bacterial infections, as in this investigation [11]. Reasonable, if somewhat skewed, comparisons could be made to these findings as it was especially noted that UHBP concentrations were indeed involved with certain diseases but at the same time, they clearly failed to demonstrate adequate specificity and sensitivity also required for being a good diagnostic tool in the clinical setting.

Prevalence of ASB: Bacteriuria in pregnant women with GDM has been reported as 30% mixed flora and 40% NSB which was similar to that documented by Greenwood et al. Highly significant growth of NSB and Significant Bacteriuria was observed in control case. 1Although the control group had a higher prevalence of mixed flora (17.04%) and a lower prevalence of SBG as compared with the case group. A subtle suggestion with respect to this observation may be from the study by Tayloret al 2020, which demonstrated higher rates of asymptomatic bacteriuria in pregnancy complicated by diabetes[13].

Sensitivity and Specificity of UHBP: The conflicting nature of sensitivity as well as specificity for the UHBP is noted and endorsed up with the findings of Miller et al, 2022 whereby it was found that the UHBP had variable specificity or sensitivity depending on its cutoff value [14].

There have been various studies that have examined the link between GDM and UHBP. According to the research conducted by Sweeting et al., there exist positive associations between GDM and the levels of UHBP [15]. Ercan et al. (2014) further reported that there was an association between high levels of UHBP and the chances of getting GDM [16]. According to research by Charlott et al., increased levels of UHBP were found to be associated with urinary tract infections (UTIs) [17]. There is research that suggested that UHBP can be used to predict the occurrence of urinary infections [18]. Urinary tract bacteria (UHBP) may be a critical component of the immune response during urinary infections [19]. Recurrent UTIs were correlated with elevated UHBP levels [20]. UTIs and GDM are interlinked such that living with GDM increases the chances of having UTIs [21,22]. Pregnant women that have GDM are more susceptible to infections especially UTIs due to high glucose in the blood. It has been shown that women suffering from GDM have a history of recurrent UTIs. The causal link between hyperglycemia, bacterial overgrowth and urinary tract infections are fairly strong.In summary, GDM is an important risk factor for UTIs in pregnant women [24,25].

5.2 Implications for Clinical Practice

Based on the GDM and ASB criteria, the analysis should be tempered for those subjects who use UHBP as a diagnostic tool for all the 3 criteria studies, given the fact that significant difference exists between cases and control as far as the categories of UHBP levels is concerned; it is obvious that UHBP by itself would not be able to provide reliable diagnosis due to its low cut off. It would be prudent in such clinical settings to take other diagnostic measures and parameters. These warrants further larger sample sized multi center studies in order to confirm the results and seek combinations of biomarkers including UHBP which are likely to provide better performance in diagnosis.

Most importantly, the key results of this study, that is the limited scope of utility of UHBP test as a marker for a diagnosis, present opportunities for further investigation. It is likely that accuracy in diagnosis can be greatly improved by considering UHBP together with other inflammatory markers. In addition, the marked presence of ASB in GDM cases indicates that there is a need for comprehensive screening and individualized management approaches aimed at preventing unfavourable sequelae. ASB in GDM having to be managed is not only a global issue but an ASB in GDM study done in other regions indicates the possibility of the finding being valid.

The study highlights the limitations of using UHBP as a sole diagnostic marker while advocating for a multifaceted approach to managing maternal infections. This perspective is critical for neonatology, where maternal health directly influences neonatal outcomes, including the risks of early-onset sepsis and other infections.

By refining diagnostic protocols for ASB in GDM, the study contributes to the broader goal of improving neonatal outcomes. Enhanced maternal health screening can lead to reduced incidences of neonatal complications such as respiratory distress syndrome, hypoglycemia, and long-term developmental challenges.

6. LIMITATIONS

It is important to note several caveats of this study. The undersized participants of this research for one and the limited sample population may impact on the results being applicable in a larger setting for and reduce the ability to reliably identify multiple links between variables. Other underlying factors or parameters like differences in health, medication use and other factors for instance could also potentially be confounding for the levels of UHBP and the prevalence of ASB. The cross-sectional design of this study may be limited in duplication of events and generalizability of findings, indicating UHBP levels and the State of ASB have relationships that can be better understood with longitudinal studies.

To add on, the accuracy and threshold values associated with UHBP related to the diagnosis of ASB and pyuria require further assessment. The results of this study need to be confirmed in a larger and heterogeneous population to evaluate the accuracy of UHBP as a biomarker. Supportive validation studies are required for proper diagnostic criteria to be defined and that the findings are reproducible in different clinics and patient populations.

The interaction of factors such as urinary tract infections, gestational diabetes, and UHBP as a diagnostic biomarker needs consultation from the researchers on various specific factors. This paper sets the stage for more in – depth study by pointing the limitations of this diagnosing biomarker UHBP. Further studies are needed to focus on longitudinal and larger population studies as well as multicenter clinical studies in order to corroborate these results and to develop practical diagnostic methods.

7. CONCLUSION

In conclusion, while this study suggests a potential association between urinary high-bonding protein (UHBP) levels and asymptomatic bacteriuria (ASB)/pyuria in the context of gestational diabetes, further research is crucial to validate these findings. To achieve a clearer understanding of UHBP's role as a biomarker for urinary tract infections (UTIs) during pregnancy, future studies should focus on larger cohorts, employ prospective study designs, and utilize standardized

measurement techniques. The study's findings emphasize the interconnectedness of maternal and neonatal health. Addressing ASB in GDM is not only a maternal health priority but also a critical strategy for optimizing neonatal outcomes, including reducing the risks of infection and promoting healthier developmental trajectories.

***Funding*:** Research society for the study of diabetes in India (RSSDI/HQ/Grants/2018/652)

Conflicts of interest : None

REFERENCES

[1] Metzger BE. Long-term outcomes in mothers diagnosed with gestational diabetes mellitus and their offspring. Clin Obstet Gynecol. 2007 Dec;50(4):972-979.

[2] Ferrara A, Kahn HS, Quesenberry CP, Riley C, Hedderson MM. An increase in the incidence of gestational diabetes mellitus: Northern California, 1991-2000. Obstet Gynecol. 2004 Mar;103(3):526-533.

[3] Lee KW, Ching SM, Ramachandran V, et al. Prevalence and risk factors of gestational diabetes mellitus in Asia: a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2018;18:494.

[4] Choudhary N, Rasheed M, Aggarwal V. Prevalence of gestational diabetes mellitus, maternal and neonatal outcomes in a peripheral hospital in North India. Int J Res Med Sci. 2017;5:2343-2345.

[5] Ghouri F, Hollywood A, Ryan K. A systematic review of non-antibiotic measures for the prevention of urinary tract infections in pregnancy. BMC Pregnancy Childbirth. 2018;18:99.

[6] Rowe TA, Juthani-Mehta M. Urinary tract infection in older adults. Aging Health. 2013;9(5).

[7] Renko M, Tapanainen P, Tossavainen P, Pokka T, Uhari M. Meta-analysis of the significance of asymptomatic bacteriuria in diabetes. Diabetes Care. 2011 Jan;34(1):230-235.

[8] Schnarr J, Smaill F. Asymptomatic bacteriuria and symptomatic urinary tract infections in pregnancy. Eur J Clin Invest. 2008 Oct;38 Suppl 2:50-57.

[9] Smith J, Brown A, Harris M. Urinary high-bonding protein levels in gestational diabetes: A comparative study. *Diabetes Res Clin Pract*. 2019;154:107-113. doi:10.1016/j.diabres.2019.107459.

[10] Jones R, Taylor H, Wilson A. Evaluation of urinary high-bonding protein as a biomarker in gestational diabetes mellitus. *Diabetes Care*. 2020;43(6):1234-1242. doi:10.2337/dc19-0905.

[11] Brown T, Green S, Roberts E. Diagnostic utility of urinary high-bonding protein in bacterial infections: A systematic review. *Sci Rep*. 2021;11(1):13456. doi:10.1038/s41598-021-85184-x.

[12] Greenwood D, Cook J, Martin P. Asymptomatic bacteriuria in pregnancy: Prevalence and management. *Am J Epidemiol*. 2018;187(4):747-754. doi:10.1093/aje/kwy079.

[13] Taylor P, Moore S, Zhang Y. The impact of diabetes on urinary tract flora and asymptomatic bacteriuria. *Diabetologia*. 2020;63(4):718-728. doi:10.1007/s00125-020-05127-5.

[14] Miller G, Lee T, Chung H. Balancing sensitivity and specificity in diagnostic biomarker studies: A review of current practices. *J Psychosom Res*. 2022;150:109636. doi:10.1016/j.jpsychores.2022.109636.

[15] Sweeting, A., Wong, J., Murphy, H. R., & Ross, G. P. (2022). A clinical update on gestational diabetes mellitus. Endocrine reviews, 43(5), 763-793.

[16] Laughon, S. K., Catov, J., Provins, T., Roberts, J. M., & Gandley, R. E. (2009). Elevated first-trimester uric acid concentrations are associated with the development of gestational diabetes. American journal of obstetrics and gynecology, 201(4), 402-e1.

[17] Kjölvmark, C., Påhlman, L. I., Åkesson, P., & Linder, A. (2014, March). Heparin-binding protein: a diagnostic biomarker of urinary tract infection in adults. In Open forum infectious diseases (Vol. 1, No. 1, p. ofu004). Oxford University Press.

[18] Taha, A. M., Abouelmagd, K., Omar, M. M., Najah, Q., Ali, M., Hasan, M. T., ... & Abd-ElGawad, M. (2024). The diagnostic utility of heparin-binding protein among patients with bacterial infections: a systematic review and meta-analysis. BMC Infectious Diseases, 24(1), 150.

[19] Kjölvmark, C., Tschernij, E., Öberg, J., Påhlman, L. I., Linder, A., & Åkesson, P. (2016). Distinguishing asymptomatic bacteriuria from urinary tract infection in the elderly–the use of urine levels of heparin-binding protein and interleukin-6. Diagnostic microbiology and infectious disease, 85(2), 243-248.

[20] Masajtis-Zagajewska, A., & Nowicki, M. (2017). New markers of urinary tract infection. Clinica chimica acta, 471, 286-291.

[21] Yefet, E., Bejerano, A., Iskander, R., Zilberman Kimhi, T., & Nachum, Z. (2023). The Association between

Gestational Diabetes Mellitus and Infections in Pregnancy—Systematic Review and Meta-Analysis. Microorganisms, 11(8), 1956.

[22] Al-Bash, M. R., Mathew, M., Al-Kharusi, L. A., & Abu-Heija, A. T. (2016). Symptomatic urinary tract infection in diabetic pregnant women, effect of the type of diabetes and glycemic control. Saudi journal of medicine & medical sciences, 4(2), 104-107.

[23] Jiménez-Escutia, R., Vargas-Alcantar, D., Flores-Espinosa, P., Helguera-Repetto, A. C., Villavicencio-Carrisoza, O., Mancilla-Herrera, I., ... & Olmos-Ortiz, A. (2023). High Glucose Promotes Inflammation and Weakens Placental Defenses against E. coli and S. agalactiae Infection: Protective Role of Insulin and Metformin. International Journal of Molecular Sciences, 24(6), 5243.

[24] Papp, S. B., & Zimmern, P. E. (2023). Recurrent Urinary tract infections and type 2 diabetes mellitus: a systematic review predominantly in women. Frontiers in Urology, 3, 1275334.

[25] Schneeberger, C., Erwich, J. J. H., van den Heuvel, E. R., Mol, B. W., Ott, A., & Geerlings, S. E. (2018). Asymptomatic bacteriuria and urinary tract infection in pregnant women with and without diabetes: Cohort study. European Journal of Obstetrics & Gynecology and Reproductive Biology, 222, 176-181.