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Original Research Paper

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COMPARATIVE CROSS-SECTIONAL OBSERVATIONAL STUDY OF NEUTROPHIL TO LYMPHOCYTE RATIO (NLR) AND PLATELET TO LYMPHOCYTE RATIO(PLR) BETWEEN NON-DIABETIC ANTENATAL CASES AND THOSE WITH GESTATIONAL DIABETES MELLITUS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Background: Gestational Diabetes Mellitus (GDM) is one of the most common metabolic disorders in pregnant women. It is associated with adverse pregnancy and foetal outcomes. GDM is defined as glucose intolerance, with first recognition arising during pregnancy mostly in the second trimester between the 24th and 28th week of gestation and resolves after pregnancy. **Objective:** To determine the relationship between elevated plasma glucose levels on NLR and PLR in antenatal cases diagnosed with Gestational Diabetes Mellitus in comparison with non-diabetic antenatal cases. **Methods:** This Hospital based Comparative Cross-Sectional Observational Study was conducted among 108 antenatal cases of 24-28 weeks of gestation with and without Gestational Diabetes Mellitus at Niloufer Hospital & Modern Government Maternity Hospital, Hyderabad, Telangana**.** Duration of study was 2 years. **Result:** There was a positive correlation of NLR and PLR with elevated plasma glucose levels. Mean NLR values were above the normal range in GDM cases and are higher when compared with controls. Mean PLR were in the normal range but were higher in GDM when compared with controls. Mean NLR values and Mean PLR values between GDM and controls were statistically significant. When correlated with GDM, the sensitivity and specificity of increased NLR are 77.78% and 77.78% respectively. The Positive Predictive Value PPV and Negative Predictive Value NPV are 77.78% and 77.78% respectively. When correlated with GDM, PLR values were increased in GDM cases when compared with controls but they were in the normal range. **Conclusion:** There is increased NLR and increased PLR in pregnancies complicated by GDM when compared with normal pregnant females. Combined use of NLR and PLR not only helps in early diagnosis of inflammatory status, but also helps in predicting the severity and outcome of GDM.

KEYWORDS : Neutrophil To Lymphocyte Ratio (NLR), Platelet to Lymphocyte Ratio (PLR), Non-Diabetic Antenatal, Gestational Diabetes Mellitus

INTRODUCTION:

Gestational Diabetes Mellitus (GDM) is a major cause for maternal, perinatal and neonatal morbidity.[1,2] Therefore, screening for GDM is important to determine the risks both during and after pregnancy and to prevent potential complications.[1,3]

GDM is a significant health issue globally, affecting approximately 5% to 7% of pregnancies in high-income countries. In India, GDM impacts a substantial number of women, estimated at around 5 million annually. The prevalence of GDM in India varies widely, ranging from 4% to 18%, reflecting diverse demographic and regional factors influencing health outcomes. Recent studies indicate an increasing trend in GDM incidence over the past decade, with potentially higher rates among specific ethnic or racial groups. Furthermore, experiencing GDM increases the likelihood of recurrence in future pregnancies and raises the risk of developing Type 2 Diabetes mellitus (T2DM) and cardiovascular diseases later in life.

Pregnancy is a diabetogenic state and a pro-inflammatory state where many inflammatory markers are raised in the body.[1,3] Previous studies have shown that inflammation plays a role in the development of GDM and T2DM. Association between GDM and T2DM with markers such as Interleukins (ILs), Tumour Necrosis Factor- Alpha, C-reactive protein (CRP) was demonstrated. However, their widespread use is limited due to cost and technical complexities.[1,2]

The need of the hour is to identify a biomarker that will facilitate early diagnosis and permit monitoring in GDM. A sensitive, swift, inexpensive tool accessible to all will support appropriate and timely management as well as alleviate potential foetal and maternal complications. Among these, the Neutrophil to Lymphocyte ratio (NLR) and Platelet to Lymphocyte ratio (PLR) stand out as simple, rapid, and cost-effective inflammatory biomarkers.[3] The study aims at determining the relationship between elevated plasma glucose levels on NLR and PLR in antenatal cases diagnosed with Gestational Diabetes Mellitus in comparison with non-diabetic antenatal cases.

MATERIAL AND METHODS:

This Hospital based Comparative Cross-Sectional Observational Study was conducted among 108 antenatal cases of 24-28 weeks of gestation with and without Gestational Diabetes Mellitus at Niloufer Hospital & Modern Government Maternity Hospital, Hyderabad, Telangana**.** Duration of study was 2 years.

Sample Size: 108

Inclusion Criteria:

- Patients who are giving valid consent for the study.
- Antenatal cases of 24-28 weeks of gestation diagnosed with

GDM and without GDM

Exclusion Criteria:

- Patients not willing to participate in the study.
- Antenatal cases with Overt Diabetes Mellitus.
- Antenatal cases with Impaired Glucose Tolerance.
- Pregnant women on any medication altering platelets (aspirin, heparin).
- Pregnant women with other comorbidities like Pregnancy Induced Hypertension, Urinary tract infections.

Study Tools:

Patients, Relevant Investigation reports (plasma glucose levels) with clinical diagnosis, EDTA Vacutainers, 5-part haematology analysers and High- Performance Liquid Chromatography (HPLC).

Methodology:

- Antenatal cases of 24-28 weeks presenting to the Obstetric out-patient service and those admitted to the antenatal wards were included in the present study
- The data was recorded from each subject with an in-person interview by administering a specific questionnaire
- After obtaining informed consent, 2ml of venous blood is collected in a EDTA vacutainer.
- EDTA samples are processed and evaluated in 5-part haematology analyser for Complete blood picture, in which WBC parameters-TLC, DLC, ANC, ALC and Platelet count are analysed.
- NLR and PLR values are calculated.

NLR and PLR values are compared with the glucose levels of the study subjects.

Statistical Analysis:

Statistical data is collected. Data is entered in MS Excel sheet. The data was represented in Descriptive manner, histograms, bar diagrams, tables and pie-charts. Appropriate tests of statistical significance were used.

RESULTS:

This is a comparative cross-sectional observational study. The study population consisted of 108 antenatal cases who had fulfilled the inclusion and exclusion criteria. Based on IADPSG criteria, study population is divided into two groups.

Group A: 54 antenatal cases with GDM

Group B: 54 antenatal cases without GDM - Control

The mean value for each parameter like age, FBS, PPBS, HbA1c, TLC, ANC, ALC, platelet count, NLR and PLR were calculated and compared between the groups.

The age distribution is categorized into three age groups: 20-25, 25-30 and above 30years. In the 20-25 years age group, there are 3 individuals with GDM and 17 individuals in the control group. For the 25-30 years age group, there are 48 individuals with GDM and 26 in the control group. In the above 30 years age group, there are 3 individuals with GDM and 10 in the control group. In this study, the majority of GDM cases fall within the 25-30 age group, while the control group has a more balanced distribution across the different age ranges.

Table 1: Mean Age With Standard Deviation In GDM Cases And Controls

GROUP	MEAN AGE	STANDARD DEVIATION
GDM	26.83	1.65
CONTROL	26.7	3.63

In the present study, mean age of GDM group and control is similar i.e, 27 years.

Table 2: Mean Values And Standard Deviation Of Fasting, Post Prandial, HbA1c, NLR and PLR

PARAMETER	GDM		Control	
	Mean	Standard Deviation	Mean	Standard Deviation
Fasting	106.0	6.9	77.2	5.7
Post Prandial	164.9	7.2	111.4	6.4
Hba1C	6.8	0.4	5.2	0.2
NLR	3.6	0.7	2.9	0.3
PLR	165.5	55.1	119.3	24.5

The parameters measured include fasting blood glucose levels, postprandial blood glucose levels, HbA1C, NLR, and PLR. In the GDM group, the mean fasting blood glucose level is 106.0 mg/dL with a standard deviation of 6.9, while in the Control group, it is 77.2 mg/dL with a standard deviation of 5.7. The mean postprandial blood glucose level in the GDM group is 164.9 mg/dL with a standard deviation of 7.2, compared to 111.4 mg/dL with a standard deviation of 6.4 in the Control group. The mean HbA1C in the GDM group is 6.8% with a standard deviation of 0.4, whereas in the Control group it is 5.2% with a standard deviation of 0.2. The mean NLR in the GDM group is 3.6 with a standard deviation of 0.7, compared to 2.9 with a standard deviation of 0.3 in the Control group. Lastly, the mean PLR in the GDM group is 165.5 with a standard deviation of 55.1, while in the Control group it is 119.3 with a standard deviation of 24.5.

Table 3: Descriptive Statistics Between GDM And Control In Relation To NLR

GDM		Control	
Mean	3.623559222	Mean	2.892047
Standard Error	0.099362486	Standard Error	0.043678
Median	3.387804878	Median	2.833333
Mode	4.411764706	Mode	3
Standard Deviation	0.730162167	Standard Deviation	0.320965
Sample Variance	0.53313679	Sample Variance	0.103019
Kurtosis	-0.924985775	Kurtosis	2.589271
Skewness	0.397412612	Skewness	1.427416
Range	2.749092819	Range	1.571038
Minimum	2.452205882	Minimum	2.5
Maximum	5.201298701	Maximum	4.071038
Sum	195.672198	Sum	156.1705
Count	54	Count	54
Largest (1)	5.201298701	Largest (1)	4.071038
Smallest (1)	2.452205882	Smallest (1)	2.5
Confidence Level (95.0%)	0.199295907	Confidence Level (95.0%)	0.087607

The data compares the Neutrophil-to-Lymphocyte Ratio (NLR) between individuals with Gestational Diabetes Mellitus (GDM) and a control group. For the GDM group, the mean NLR is 3.62 with a standard error of 0.099 and a standard deviation of 0.73, based on 54 observations. The median NLR for this group is 3.39, and the mode is 4.41. The sample variance is 0.53, with a range of 2.75, spanning from a minimum of 2.45 to a maximum of 5.20. The kurtosis is -0.92, indicating a relatively flat distribution compared to a normal distribution, while the skewness is 0.40, suggesting a slight right skew. The 95% confidence level is 0.20.

In contrast, the control group has a mean NLR of 2.89 with a standard error of 0.044 and a standard deviation of 0.32, also based on 54 observations. The median NLR for this group is 2.83, and the mode is 3. The sample variance is 0.10, with a range of 1.57, spanning from a minimum of 2.50 to a maximum of 4.07. The kurtosis is 2.59, indicating a peaked distribution compared to a normal distribution, while the skewness is 1.43, suggesting a strong right skew. The 95% confidence level is 0.088.

Overall, the GDM group shows higher mean NLR values and a wider range compared to the control group, indicating more variability and higher levels of inflammation in the GDM group. The control group's data is more normally distributed with less variability and lower overall NLR values.

The mean PLR in the GDM group is 165.5, which is significantly higher than the mean PLR in the Control group at 119.3. The standard deviation is also higher in the GDM group (55.1) compared to the Control group (24.5), indicating more variability in the GDM group. The confidence intervals at 95% show that there is a clear difference between the two groups, with the GDM group showing higher PLR values.

Table 4: Descriptive Statistics Between GDM And Control In Relation To PLR

GDM-PLR		CONTROL-PLR	
Mean	165.459923	Mean	119.2945488
Standard Error	7.492141019	Standard Error	3.338264982
Median	169.1022444	Median	114.8859555
Mode	127.8772379	Mode	N/A
Standard Deviation	55.05576773	Standard Deviation	24.53113749
Kurtosis	2.546959101	Kurtosis	-0.226224446
Skewness	1.078823154	Skewness	0.516135371
Range	286.1771011	Range	103.3868017
Minimum	78.56454021	Minimum	75.74658006
Maximum	364.7416413	Maximum	179.1333817
Sum	8934.835844	Sum	6441.905633
Count	54	Count	54
Largest (1)	364.7416413	Largest (1)	179.1333817
Smallest (1)	78.56454021	Smallest (1)	75.74658006
Confidence Level (95.0%)	15.02733184	Confidence Level (95.0%)	6.695711618

The skewness and kurtosis values indicate that both distributions are slightly skewed to the right and have relatively high peaks, with the GDM group being more skewed and having a higher kurtosis.

These differences suggest that individuals with GDM have higher PLR levels, which could indicate increased inflammatory responses compared to the Control group.

Table 5: Statistical Test For NLR And PLR

Independent Samples Test							
		Levene's Test for Equality of Variances					
		F	Sig.	t	df	95% Confidence Interval of the Difference	
						Lower	Upper
NLR	Equal variances assumed	50.505	.001	-6.740	106	-.94670	-.51632
PLR	Equal variances assumed	18.270	.001	-5.628	106	-62.42705	-29.90370

The Independent Samples Test compares the Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) between the GDM group and the control group, assuming equal variances.

For NLR:

Levene's Test for Equality of Variances: The F value is 50.505 with a p-value of 0.001, indicating a significant difference in variances between the two groups.

t-test for Equality of Means: The t value is -6.740 with 106 degrees of freedom (df). The 95% Confidence Interval (CI) of the difference ranges from -0.94670 to -0.51632. This suggests that the mean NLR in the GDM group is significantly higher than in the control group.

For PLR:

Levene's Test for Equality of Variances: The F value is 18.270 with a significance (Sig.) of 0.001, also indicating a significant difference in variances between the two groups.

t-test for Equality of Means: The t value is -5.628 with 106 degrees of freedom (df). The 95% Confidence Interval (CI) of the difference ranges from -62.42705 to -29.90370. This suggests that the mean PLR in the GDM group is significantly higher than in the control group.

Overall, these results show that both NLR and PLR are significantly higher in the GDM group compared to the control group, indicating higher levels of inflammation in individuals with GDM. The significant Levene's Test results for both parameters suggest that the variances in the two groups are not equal, adding robustness to the observed differences.

DISCUSSION:

The mean age of participants with GDM across most studies is typically around 29-31 years. Control group participants generally have a mean age slightly lower than those with GDM, typically around 27-30 years. In study by Liu et al. 2020[4] the mean ages are similar between GDM (29.8 years) and control (30.2 years) groups. In study by Fashami et al. 2019[5], the mean age of the GDM group (29.3 years) is higher than the control group (27.9 years). In study by Sargin et al. 2016[2], the GDM group has a higher mean age (30.9 years) compared to the control group (27.51 years). In study by Aktulay et al. 2015[6], the mean age of the GDM group (29.3 years) is higher than the control group (27.0 years). In study by Yilmaz et al. 2014[7], the GDM group (30.4 years) has a significantly higher mean age than the control group (26.75 years). In present study, the mean ages are very close between the GDM (26.83 years) and control (26.70 years) groups.

Some studies show a notable difference in mean age between GDM and control groups (e.g., Sargin et al[2]. 2016, Yilmaz et al. 2014) [7], while others show minimal differences (e.g., Liu et al. 2020[4], Present Study). The data indicates a trend where women with GDM tend to be slightly older than the control group, though the age differences vary across studies. The present study shows the least age difference between the GDM and control groups, suggesting that age might be less of a distinguishing factor in this specific sample compared to others. The sample distribution across various studies comparing Gestational Diabetes Mellitus (GDM) to control groups shows significant variation in size and balance. Some studies, like Fashami et al. 2019 and the present study, have equal sample sizes for both groups, while others, such as Sargin et al[2]. 2016, have a much larger control group compared to the GDM group. The sample sizes range from as small as 29 participants per group in Aktulay et al. 2015 to as large as 144 GDM and 304 control participants in Sargin et al[2]. 2016. This variability in sample size and balance can affect the reliability and generalizability of the study findings.

The choice of diagnostic criteria for Gestational Diabetes Mellitus (GDM) can indeed affect the comparability of study results. The International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria and the Carpenter and Coustan criteria have different thresholds and diagnostic approaches, which can lead to variations in the identification and classification of GDM cases. The IADPSG criteria generally have a lower threshold for diagnosing GDM, which might lead to identifying more cases compared to the Carpenter and Coustan criteria (C & C). This difference can impact the study outcomes, prevalence rates, and the assessment of treatment effectiveness. When comparing studies that use different criteria, it's essential to consider these variations and how they might influence the findings

and conclusions.

In studies by Liu et al. 2020[4] and Fashami et al. 2019[5], IADPSG criteria was used, while Sargin et al. 2016, and Yilmaz et al[7]. 2014 used the Carpenter and Coustan criteria. In present study IADPSG criteria has been considered.

In Liu et al. 2020[7], the GDM group had an NLR of 3.4±0.9 compared to the control group with 3.00±0.8, showing a significant difference. Fashami et al. 2019 reported NLRs of 3.2±1.9 for GDM and 3.06±1.04 for the control, which was not significant. Sargin et al[2]. 2016 found NLRs of 3.5±1.2 in the GDM group and 3.44±1.19 in the control group, also not significant. Yilmaz et al[7]. 2014 showed NLRs of 3.0±0.8 for GDM and 2.26±0.43 for the control, with a significant difference. The present study reports an NLR of 3.6±0.7 for GDM and 2.9±0.3 for the control, also showing a significant difference.

Fashami et al[5]. 2019 found a significant difference, with the GDM group showing a PLR of 103.9±60.0, compared to 81.4±29.0 in the control group. Sargin et al[2]. 2016 reported no significant difference, with PLRs of 119.83±45.31 for GDM and 117.88±37.26 for the control group. The present study also identified a significant difference, with the GDM group having a PLR of 165.5±55.1 compared to 119.3±24.5 in the control group. Most studies indicate a significant difference in PLR between GDM and control groups, except for Sargin et al[2]. 2016, which found no significant difference.

In the comparative analysis of diagnostic performance between Yilmaz et al. (2014) and the present study, distinct differences in sensitivity and specificity are evident. Yilmaz et al[7]. (2014) reported a sensitivity of 76.2% and a specificity of 94.1%. Sensitivity refers to the test's ability to correctly identify individuals with the condition (true positives), while specificity measures the test's ability to correctly identify individuals without the condition (true negatives). The high specificity of Yilmaz et al[7].'s study indicates a robust ability to correctly identify non-cases, minimizing false positives. However, the sensitivity of 76.2% suggests that the test may miss a significant proportion of actual cases, potentially leading to false negatives.

In contrast, the present study shows an improvement in sensitivity at 77.78%, indicating a slightly better capacity to detect true positives compared to Yilmaz et al[7]. However, this improvement comes with a notable trade-off: the specificity has decreased to 77.78%. This reduction in specificity implies a higher rate of false positives, which means that the test may be less effective at correctly identifying non-cases.

CONCLUSION:

This study provides evidence supporting that there in increased NLR and increased PLR in pregnancies complicated by GDM when compared with normal pregnant females. Combined use of NLR and PLR not only helps in early diagnosis of inflammatory status, but also helps in predicting the severity and outcome of GDM. But, as NLR and PLR are non specific markers they only serve in detecting the inflammatory status in patient but cannot be used as sole markers for screening. Further studies are needed to define their clinical utility and validity and to provide robust physiological evidence casually linking the NLR and PLR to GDM and its clinical outcomes.

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