

## PREDICTIVE VALUE OF NEUTROPHIL TO LYMPHOCYTE RATIO (NLR) IN EARLY DETECTION OF GESTATIONAL DIABETES MELLITUS (GDM) AMONG PREGNANT WOMEN IN FIRST TRIMESTER OF PREGNANCY

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### Abstract

**Background & Objective:** A substantial number of pregnant women develop gestational diabetes mellitus (GDM). Various biomarkers are being used to diagnose gestational diabetes mellitus. Early detection of GDM can be done by using inflammatory markers like neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) that are rapid, inexpensive and easy to use in different clinical settings. The objective of this study was to evaluate the diagnostic accuracy of raised neutrophil to lymphocyte ratio for the detection of gestational diabetes mellitus taking OGTT as the gold standard.

**Methods:** This was a cross-sectional study held in the Department of Obstetrics and Gynecology CMH Lahore from November, 2018 to May, 2020. After approval from the hospital ethical review committee and taking informed consent, 473 pregnant women enrolled in the first trimester between the ages of 18-35 years, fulfilling the inclusion criteria were included, whereas known diabetics, patients with cardiovascular disorders, previous history of GDM were excluded. Blood samples in a sterilized manner were drawn and sent to the hospital laboratory for analysis of NLR. Then they were screened during 24-28 weeks of gestation for the diagnosis of gestational diabetes mellitus on OGTT. The females were labeled for positive NLR and GDM as per operational definition. Diagnostic accuracy of NLR was calculated for the development of gestational diabetes mellitus.

**Results:** Mean age of females was  $26.72 \pm 4.90$  years and mean gestational age was  $15.50 \pm 1.67$  weeks. 94 (19.9%) females had a raised neutrophil to lymphocyte ratio while 397 (80.1%) females had a normal neutrophil to lymphocyte ratio and there were 90 (19%) females who had gestational diabetes mellitus while the rest of 383 (81%) did not have gestational diabetes mellitus. The sensitivity, specificity, positive predictive value, negative predictive value and overall diagnostic accuracy of NLR were 95.56%, 97.91%, 91.49%, 98.94% and 97.46%, respectively.

**Conclusion:** The study concluded that a raised neutrophil to lymphocyte ratio is significantly high among gestational diabetes mellitus and NLR has a high diagnostic accuracy for predicting gestational diabetes mellitus.

**Key words:** GDM, Gestational diabetes mellitus, neutrophil-to-lymphocyte ratio, OGTT, pregnancy.

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Gestational diabetes mellitus (GDM) is a metabolic disorder which can occur during pregnancy for the first time or it is present before pregnancy that has not been diagnosed previously.<sup>1</sup> A substantial number of pregnancies are complicated by GDM and there is a uniform consensus that in pregnant women with GDM an excellent glycaemic control along with diet and wherever the use of oral hypoglycemics drugs alone or with insulin results in improved perinatal outcomes. There is a substantial reduction of serious

neonatal morbidity along with routine prenatal care.<sup>2</sup> Gestational diabetes incidence rate varies from 2%-13% depending on several factors and socioeconomic status of countries and their diagnostic criteria for GDM.<sup>1,3</sup> The prevalence rate of GDM in Pakistan is reported as high as 14.8%.<sup>4</sup>

One of the most common metabolic disorders, gestational diabetes occurring in pregnancy and understanding its pathophysiology and screening mothers at risk of GDM and its related major complications during or after pregnancy is of great importance for effective management and prevention of complications as a sequelae.<sup>5</sup> However, in developing countries the standard antenatal care provided in public and private sector and lack of understanding the pathophysiology of complications is very limited. The risk prediction in gestational diabetes mellitus (GDM) in low to middle income countries mostly rely on maternal history and identification of clinical risk factors, this strategy may not be able to identify high risk pregnancies.<sup>5</sup>

However, if pregnant women who are at risk of developing GDM are screened for earlier detection of women might allow prompt intervention that could not only potentially reduce delayed diagnosis of GDM but also prevent its complications and other associated morbidities. Early diagnosis of GDM especially in the first trimester between 12–16 weeks of pregnancy can prevent its complications and subsequent morbidities.<sup>6</sup> It would therefore be sensible to evaluate other tests that are predictive at early state and could aid the antenatal care provider to identify potential pregnant women at high risk to this metabolic abnormality especially during early pregnancy. Various biomarkers are being investigated and in use for diagnosis of GDM especially the inflammatory markers like neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR). The use of these markers for diagnosis of GDM can aid in diagnosis quickly, with ease and relatively are inexpensive. NLR and PLR have previously been used as markers of inflammation in chronic diseases like inflammatory bowel disease and or in cancer metastasis<sup>7</sup> also they are used in prognosis of ischemic heart diseases.<sup>8,9</sup> NLR and PLR has been extensively

used as screening tests for complications associated with DM,<sup>9</sup> and like other biomarkers its use in diagnosis of GDM has recently been evaluated for its ability to predict GDM.<sup>10,11</sup> In a study by Yilmaz et al (2014) showed that a cut off value of NLR > 2.93 had a sensitivity and a specificity of 76.2% and 94.1% in early detection of GDM especially in first trimester.<sup>10</sup>

The current study is designed to evaluate diagnostic accuracy of NLR in for prediction of gestational diabetes mellitus as there is no local study done in our setting so far and international data is also limited for NLR diagnostic accuracy and there is growing consensus in medical literature that in the pathophysiology of gestational diabetes mellitus inflammation plays a pivotal role. Neutrophil-to-lymphocyte ratio (NLR) is a simple inexpensive method for the assessment of inflammatory status and can aid in diagnosis of GDM and this can help clinicians for an early diagnosis and prompt treatment of the condition among women who are at risk for GDM. This will not only aid in early intervention but will also potentially reduce a delayed diagnosis and its associated morbidities of GDM, especially when diagnosed early in first trimester of pregnancy.

The objective of the study was to evaluate diagnostic accuracy of raised neutrophil to lymphocyte ratio for early detection of gestational diabetes mellitus taking OGTT as gold standard.

## METHODS

We conducted a cross-sectional study at Department of Obstetrics and Gynaecology CMH Lahore, from November, 2018–May, 2020. A sample size of 473 females was calculated from win-pepi ver: 11.15, with 95% confidence level, using sensitivity of NLR > 2.93 as 76.2% at 10% margin of error and specificity as 94.1% with 5% margin of error. A prevalence of 14.8% GDM was assumed from Yilmaz et al study.<sup>10</sup> A non-probability consecutive sampling technique was used and pregnant women enrolled in first trimester between age 18–35 years fulfilling the inclusion criteria were included and known diabetics, patients with cardiovascular disorders, previous history of GDM were excluded. Additional cardiovascular risk factors such as coronary artery disease, hypertension, hyperlipidemia that may affect ratio of any subset of white blood cells and drugs e.g corticosteroids, acetyl-

salicylic acid, and condition like active infections chronic smoking, recent trauma and impaired liver and kidney functions were also excluded. A 5 ml blood samples in sterilized manner was drawn and was sent to hospital laboratory for analysis of NLR and screened during 24-28 weeks of gestation and NLR of  $>2.93$  was taken as cut off for raised NLR. Diagnosis of gestational diabetes mellitus on OGGT at 2 hours, a blood sugar level of 140 mg/dL or greater was considered as gestational diabetes. Data was entered and analyzed using SPSS version 22. Descriptive statistics such as mean $\pm$ S.D was used for quantitative data. To calculate diagnostic accuracy (sensitivity, specificity, PPV, NPV) of NLR a  $2\times 2$  table was made taking GDM as gold standard.

## RESULTS

The mean age of females was  $26.72 \pm 4.90$  years with minimum and maximum age as 18 and 35 years. The mean gestational age was  $15.50 \pm 1.67$  weeks and 258(54.5%) females who had parity 1-2 and 215(45.5%) females had parity 3-5. There were 63(13.3%) obese and 410(86.7%) non obese females were non-obese. (Table no:1). 94(19.9%) females who had raised neutrophil to lymphocyte ratio while 397(80.1%) females had normal neutrophil to lymphocyte ratio and 90(19%) females who had gestational diabetes mellitus while rests of 383(81%) did not have gestational diabetes mellitus. There were 86 females who had raised NLR and were diagnosed of gestational diabetes mellitus, 375 females had normal NRL and did not have gestational diabetes mellitus while there were 8 females who had raised NRL but did not have gestational diabetes mellitus while 4 females had normal NRL but they had gestational diabetes mellitus(Table 2). The sensitivity, specificity, positive predictive value, negative predictive value and overall diagnostic accuracy of NRL was 95.56%, 97.91%, 91.49%, 98.94% and 97.46%.

## DISCUSSION

During pregnancy there is relative insulin resistance and increased placental secretion of diabetogenic

hormones like growth hormone, placental lactogen, progesterone, and corticotropin-releasing hormone

**Table 1:** Demographic and clinical characteristics of patients

Variables (n= 473 )	Frequency / Mean $\pm$ SD	Percentage
Age (Mean $\pm$ SD)	26.72 $\pm$ 4.90	
Gestational Age (Mean $\pm$ SD)	15.50 $\pm$ 1.67	
<b>Parity</b>		
1 -3	258	54.5
3-5	215	45.5
<b>Obese</b>		
Yes	63)	13.3
No	410	86.7

**Table 2:** Diagnostic accuracy of NLR

Raised NLR( $>2.1$ )	Gestational Diabetes Mellitus		Total
	Yes	No	
Yes	86 (95.6%)	8 (2.1%)	94 (19.9%)
No	4 (4.7%)	375 (97.9%)	379 (80.1%)
Total	90 (100.0%)	383(100.0%)	473 (100.0%)

and as a consequence there is occurrence of GDM due to compromised function of pancreas. Several researches have demonstrated the role of inflammation in the development type 2 DM and GDM. Other studies have shown an association between C-reactive protein (CRP, tissue necrosis factor-alpha (TNF- $\alpha$ ), interleukins (ILs), interferon  $\gamma$ , adiponectin, leptin, transforming growth factor- $\beta$ , visfatin and resistin with development of type 2 diabetes mellitus and GDM.<sup>11,12</sup>

Diagnosis of gestational diabetes with use of inflammatory markers like neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) are inflammatory markers that can be useful in certain clinical situations where other tests are inconclusive. NLR can be performed with ease, in short time and is relatively inexpensive. NLR and PLR, these two markers have been used in inflammatory disease conditions, cancer metastasis, inflammatory bowel diseases. In diabetes mellitus associated complications and ischemic heart disease NLR is used as prognostic markers and as screening tests.<sup>13</sup>

In conditions like preeclampsia and determining its grade, hyperemesis gravidarum and ability to pre-

dict GDM, NLR has also been investigated to determine pathophysiology and diagnosis.<sup>10-13</sup>

Our study the sensitivity, specificity of 95.56% and 97.91% along with a positive, negative predictive value and overall diagnostic accuracy of NRL of 91.49%, 98.94% and 97.46% respectively which is high as compared to the Yilmaz et al study who with NLR > 2.93 cut-off showed a sensitivity of 76.2 % and a specificity of 94.1 % in detection of GDM. The study also showed a significant higher mean NLR in GDM women of  $3.00 \pm 0.83$  as compared to controls  $2.26 \pm 0.43$  ( $p < 0.001$ ), with an odds ratio of elevated NLR of 5.512, (95% CI: 1.352-22.475). ( $p = 0.017$ ) and NLR being an independent variable detecting GDM in pregnant women.<sup>10</sup> The current study also had higher diagnostic accuracy and predictive ability for detecting GDM.

In another study women with gestational diabetes mellitus ( $n = 52$ ) and pregnant women with normal glucose tolerance ( $n = 50$ ) were compared for CBC, serum glucose and serum soluble interleukin-2 receptor. The result has showed that in terms of age pregnant women had age of  $31 \pm 6$  years that were older than controls  $25 \pm 5.3$  years, also a low mean platelet volume was seen in pregnant women with GDM  $10.3 \pm 1.4$  fL as compared to control group  $10.8 \pm 1$  fL and there a statistically non-significant difference was seen between neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, serum glucose concentration, CBC, neutrophil count, platelet count, lymphocyte count, hemoglobin concentration and serum soluble interleukin-2 receptor concentration were statistically significant.<sup>14</sup>

Similarly another study aimed to investigate whether the NLR and platelet-to-lymphocyte ratio (PLR) for screening of GDM among pregnant women in first trimester of pregnancy and inflammatory markers like leukocyte, neutrophil, and lymphocyte counts that were statistically significant as compared to control group ( $P < 0.01$ ). The study also showed a statistically non-significant differences for NLR and PLR ( $P > 0.05$ ).<sup>15</sup>

Other researchers also evaluated NLR and LMR for predicting GDM and their correlation with other metabolic parameters in pregnant women with GDM.

The study compared, NLR and LMR, homeostatic model assessment of insulin resistance (HOMA-IR) scores, highly sensitive C-reactive protein (hs-CRP), fasting blood glucose (FBG), fasting insulin. A significant higher levels are seen among pregnant women with GDM women as compared to controls suggesting role of inflammation plays in pathogenesis of GDM and these markers can be helpful in early detection of GDM.<sup>16,18</sup>

Similarly in another research to investigate pathophysiology of gestational diabetes mellitus (GDM) and role of inflammation by comparing serum levels of neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and human chitinase-3-like protein 1 (YKL-40) in GDM and control subjects a statistically significant higher values of NLR and PLR were seen as compared to control group. These studies and our study concluded that high levels of NLR indicate inflammatory status and can be used in diagnosis and prognosis of GDM.<sup>18</sup>

However these inflammatory markers use in early detection and diagnosis is limited due to the costs and technical difficulties associated with detection in every day clinical practice especially in clinical settings in developing countries where diagnostic facilities lack expertise and resources are scarce. There are also technical issue in screening for GDM in pregnancy women in early trimester. Henceforth, it is important to develop a more feasible approach for screening which should be low-cost for detection of GDM it is readily available and applicable in primary health care setting especially in low income countries.<sup>12</sup>

## CONCLUSION

It is concluded that NLR has high diagnostic accuracy for predicting gestational diabetes mellitus. Early detection of women who are at risk for GDM, measuring the neutrophil-to-lymphocyte ratio (NLR) can aid in diagnosis and hence management of GDM. Hence all pregnant females at 12–16 weeks should be screened for possible development of gestational diabetes mellitus. If they found with raised NLR then

they must be considered to reduce the risk of GDM through preventive strategies or through medication.

**Conflict of Interest** *None*

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