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Original Article

Biochemistry Section

# Alterations in Inflammatory Markers in Women with and Without Gestational Diabetes Mellitus: A Case-control Study

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## ABSTRACT

**Introduction:** Gestational Diabetes Mellitus (GDM) is diagnosed when pregnant women develop hyperglycaemia. GDM during pregnancy causes many complications in the mother and the foetus. Until now, GDM is diagnosed by an Oral Glucose Tolerance Test (OGTT) that becomes positive in the second trimester of pregnancy. Widespread inflammation is present in GDM. Inflammatory markers could help diagnose GDM.

**Aim:** To evaluate the levels of inflammatory markers in women with GDM.

**Materials and Methods:** The present case-control study was conducted at the Department of Biochemistry, SRIHER, Chennai, Tamil Nadu, India. The data were collected from medical records from January 2022 to December 2023. Data on plasma glucose and Complete Blood Count (CBC) were collected. Inflammatory indices such as Neutrophil Lymphocyte Ratio (NLR), Monocyte Lymphocyte Ratio (MLR), Platelet Lymphocyte Ratio (PLR), Systemic Immune-inflammation Index (SII), Systemic Inflammation Response Index (SIRI) were calculated. Pregnant women between the ages of 20 and 40 years without diabetes (n=119) and pregnant women with GDM (n=118) were included. Pregnant women with pre-existing diabetes mellitus, gestational hypertension, and inflammatory disorders were excluded. The obtained data were subjected to the normality of distribution. Student's t-test and Chi-square test were used. The Pearson correlation coefficient was used to compare the variables. The p-value ≤0.05 was considered statistically significant.

**Results:** The mean age of women in non-diabetic group was 32.5±7.51 years and in diabetic group was 30.9±8.9 years (p=0.13). Among the White Blood Cells (WBC), only monocyte count (%) showed a statistically significant difference (p=0.03) between the groups. All the derived variables showed statistically significant differences between the groups NLR (p=0.007), MLR (p=0.007), PLR (p=0.03), SII (p=0.03), and SIRI (p=0.02). Fasting plasma glucose, 1-hr OGTT, and 2-hr OGTT were positively correlated with RBC, PLR, and SII, which were statistically significant.

**Conclusion:** All the derived variables, such as NLR, MLR, PLR, SII, and SIRI, showed higher values in GDM individuals than non-diabetic pregnant women. Plasma glucose was correlated with the systemic immune inflammation index and platelet-to-lymphocyte ratio. Thus, inflammatory markers (NLR, MLR, PLR, SII, and SIRI) could serve as potential diagnostic markers of GDM.


**Keywords:** Glucose tolerance test, Hyperglycaemia, Inflammation, Neutrophil, Plasma glucose

## INTRODUCTION

The GDM is the glucose intolerance with the onset or first recognition during pregnancy [1]. According to the International Diabetes Federation (IDF) Atlas, 537 million people had diabetes worldwide in 2021, and it will rise to 783 million in 2045 [2]. Roughly 21.3 million were estimated to be women affected by hyperglycaemia during pregnancy, of which 18.4 million of these cases were due to GDM [3]. Approximately, 14% of pregnancies in the world are affected by GDM yearly [4]. GDM is a high-risk disorder during pregnancy, increasing the risks of both maternal and foetal complications and outcomes [5].

Diabetes mellitus in pregnancy is diagnosed by the 2006 World Health Organisation (WHO) criteria for diabetes if one or more of the following criteria are met: fasting plasma glucose ≥126 mg/ dL, and/or 2-hour plasma glucose ≥200 mg/dL following a 75 g oral glucose load or random plasma glucose ≥200 mg/ dL in the presence of diabetes symptoms [6]. Currently, screening and diagnosis of GDM is based on a one-step or two-step procedure, which is done during 24-28 weeks of pregnancy [7]. The 2-step system is currently recommended in the United States. A 50g, 1-hour Glucose Challenge Test (GCT) is followed by a 100 g, 3-hour OGTT for those with an abnormal screening result. For high-risk women, a 1-step approach can be used by proceeding directly to 100 g, 3-hour OGTT. The sensitivity of OGTT depends on the threshold values used [8]. The ADA recommends using either the 1-step or the 2-step screening method, advising that both tests are acceptable screens [9].

During pregnancy, women with GDM experience heightened inflammation triggered by the increased blood levels of glucose, leading to elevated levels of cytokines and other inflammatory markers and chronic subclinical inflammation results in gestational hyperglycaemia [10]. In GDM, the levels of haematological parameters such as Red Blood Cells (RBC), WBC, haemoglobin (Hb), and platelets are altered from the first trimester onwards [11]. The role of NLR, MLR, PLR, SII, SIRI in screening GDM has been evaluated [12].

The primary objective of the study was to evaluate the levels of NLR, MLR, PLR, SII and SIRI in women with GDM and the secondary objectives of the study were to compare the levels of NLR, MLR, PLR, SII and SIRI in women with and without GDM and to find the correlation among the variables in the study participants.

**Null hypothesis:** The inflammatory markers do not get altered in women with GDM.

**Alternate hypothesis:** The inflammatory markers get altered in women with GDM.

## MATERIALS AND METHODS

The present case-control study was conducted in the Department of Biochemistry at Sri Ramachandra Institute of Higher Education and Research, Chennai, India. The data on plasma glucose and CBC were collected from medical records from January 2022 to December 2023. The Institutional Ethics Committee approved the study (CSP-MED/24.JAN/97/13, dated 30-01-2024). Since the

patients were treated and discharged from the hospital, a waiver of informed consent was obtained.

**Sample size calculation:** Based on the article by Zhang Y et al., 2021 the sample size was calculated as follows:

At two-side significance level: 0.05; Power (1- beta): 0.8; ratio of sample size, first group/ second group: 1; expected mean in first group: 10.34; expected mean in second group: 9.51; population standard deviation: 2.28 [13].

Non-diabetics (n=119); Diabetics (n=118); total (N=237)

**Inclusion criteria:**

- Control group:

  Pregnant women between the ages of 20 and 40 years were included;

  Twin pregnancies were included.
- Case group:

  Pregnant women between the ages of 20 and 40 years diagnosed to have diabetes during pregnancy were included.

**Exclusion criteria:**

- Control group:

  Pregnant women with pre-existing diabetes mellitus, gestational hypertension, infection, chronic inflammatory and autoimmune disorders, disorders of the kidney, lung, and heart were excluded.
- Case group:

  Pregnant women with pre-existing diabetes mellitus, gestational hypertension, infection, chronic inflammatory and autoimmune disorders, disorders of kidney, lung and heart were excluded.

### Study Procedure

Plasma glucose was analysed using the hexokinase method in a Roche Cobas C 702 analyser, CBC was analysed by the impedance method, and differential count was analysed by fluorescence flow cytometry (Sysmex XN-3100 six-part CBC analyser, Sysmex Corporation, Japan).

Derived indices were calculated as follows [12]:

Neutrophil to Lymphocyte Ratio (NLR)=Neutrophil count/ Lymphocyte count

Monocyte to Lymphocyte Ratio (MLR)=Monocyte count/Lymphocyte count

Platelet to Lymphocyte Ratio (PLR)=Platelet count/Lymphocyte count

Systemic Immune Inflammation Index (SII)=(Platelet × Neutrophil)/ Lymphocyte

SIRI=(Monocyte × Neutrophil)/ Lymphocyte

## STATISTICAL ANALYSIS

The obtained data were analysed using Statistical Package for Social Sciences (SPSS) software version 16. The obtained data were subjected to the normality of distribution. Since the data was normally distributed, continuous variables were expressed in mean and standard deviation and categorical data were expressed as frequency and percentage. Continuous variables were compared using Student's t-test and categorical variables were compared using Chi-square test. Peason's correlation was done among glucose, CBC and derived parameters such as NLR, PLR, MLR, SII, and SIRI. P≤0.05 was considered statistically significant.

## RESULTS

The present study included women who were diagnosed with GDM (n=118) and normal pregnant women (n=119), for a total of 237 participants. The participants were age and gravida-matched in both groups. [Table/Fig-1] shows the comparison of the variables between the two groups.

| Variables | Non-diabetics (n=119) | Diabetics (n=118) | t-/Chi-square value | p-value |
|---|---|---|---|---|
| **Age (years)** | 32.5±7.51 | 30.9±8.9 | 1.49 | 0.13 |
| **Gravida #** | | | | |
| Primigravida n (%) | 65 (55) | 75 (64) | 1.52# | 0.16 |
| Multigravida n (%) | 54 (45) | 43 (36) | | |
| **Plasma glucose (mg/dL)** | | | | |
| Fasting | 80.85±7.51 | 95.42±22.50 | 6.67 | <0.001** |
| 1-hr OGTT | 126.26±20.33 | 192.03±40.78 | 15.69 | <0.001** |
| 2-h OGTT | 110.40±16.94 | 174.96±52.43 | 12.73 | <0.001** |
| **Hb (g/dL)** | 11.34±1.04 | 11.54±1.03 | 1.48 | 0.14 |
| **RBC (X $10^6$ cells/µL)** | 4.05±0.45 | 4.17±0.43 | 2.09 | 0.03* |
| **MCV (fL)** | 88.10±6.57 | 86.48±5.78 | 2.01 | 0.04* |
| **MCH (pg)** | 28.59±2.43 | 27.83±2.38 | 2.43 | 0.01* |
| **MCHC (g/dL)** | 32.31±1.19 | 31.92±1.58 | 2.14 | 0.03* |
| **Total WBC count (cells/µL)** | 10662.50±2378.25 | 11100.62±2502.91 | 1.38 | 0.16 |
| **Neutrophil (%)** | 71.07±7.81 | 71.26±6.55 | 0.20 | 0.83 |
| **Lymphocyte (%)** | 21.36±6.01 | 21.43±5.59 | 0.09 | 0.92 |
| **Eosinophil (%)** | 2.00±1.52 | 1.99±1.55 | 0.05 | 0.96 |
| **Monocyte (%)** | 3.64±0.83 | 3.89±0.98 | 2.11 | 0.03* |
| **Basophil (%)** | 0.33±0.13 | 0.35±0.17 | 1.01 | 0.30 |
| **ANC (cells/µL)** | 7659.54±2167.38 | 7948.12±2107.11 | 1.03 | 0.29 |
| **ALC (cells/µL)** | 2220.54±577.61 | 2346.44±724.98 | 1.47 | 0.14 |
| **AMC (cells/µL)** | 379.31±84.57 | 428.50±132.25 | 3.41 | <0.001** |
| **Platelets (X $10^4$ cells/µL)** | 2.59±0.63 | 2.76±0.60 | 2.12 | 0.03* |
| **NLR** | 3.24±0.97 | 3.64±1.29 | 2.69 | 0.007** |
| **MLR** | 0.18±0.04 | 0.20±0.07 | 2.70 | 0.007** |
| **PLR** | 0.12±0.01 | 0.13±0.05 | 2.13 | 0.03* |
| **SII** | 904.91±314.60 | 1004.93±412.34 | 2.10 | 0.03* |
| **SIRI** | 1378.84±536.52 | 1571.81±772.22 | 2.23 | 0.02* |

**[Table/Fig-1]:** Comparison of the variables in diabetic and non-diabetic pregnancy. 1-hr OGTT: One-hour oral glucose tolerance test; 2-hr OGTT: Two-hour oral glucose tolerance test; Hb: Haemoglobin; RBC: Red blood cell; MCV: Mean corpuscular volume; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular haemoglobin concentration; WBC: White blood cell; ANC: Absolute neutrophil count; ALC: Absolute lymphocyte count; AMC: Absolute monocyte count; NLR: Neutrophil to lymphocyte ratio; MLR: Monocyte to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; SII: Systemic immune inflammation index; SIRI: Systemic inflammation response index
Data are expressed in mean and standard deviation; the Student's t-test was used. #: Chi-square test and Chi-square value p-value: * statistically significant; ** statistically highly significant

Statistically significant differences were observed between diabetic and non-diabetic pregnant women for glucose (p<0.001), 1-hr OGTT (p<0.001), and 2-hr OGTT (p<0.001). Also, for RBC (p=0.03), MCV (p=0.04), MCH (p=0.01), MCHC (p=0.03), and platelets (p=0.03). Among the WBCs, only monocyte count (%) showed a statistically significant difference (p<0.03) between the groups. All the derived variables showed statistically significant differences between the groups NLR (p=0.007), MLR (p=0.007), PLR (p=0.03), SII (p=0.03), and SIRI (p=0.02) [Table/Fig-1].

Among 118 diabetics, 26 had increased fasting plasma glucose, whereas in non-diabetics only eight had increased levels. Thus, Odds Ratio (OR) was 3.92 [Table/Fig-2].

- Odds Ratio (OR)=ad/bc=3.92
- 95% Confidence Interval (CI)=(1.69-9.07)

| Fasting plasma glucose | Diabetics | Non-diabetics |
|---|---|---|
| Exposed (↑ fasting plasma glucose) | 26 (a) | 8 (b) |
| Non-exposed (normal fasting plasma glucose) | 92 (c) | 111 (d) |

**[Table/Fig-2]:** Odds Ratio (OR) calculated based on fasting plasma glucose.

This means those with elevated fasting plasma glucose had about 3.92 time higher odds of being diabetic, and the result was statistically significant.

Fasting plasma glucose was positively correlated with RBC, PLR, and SII with (r=0.21, p=0.001), (r=0.17, p=0.01), and (r=0.14, p=0.04), respectively. One-hour OGTT was positively correlated with RBC, platelets, PLR and SII with (r=0.20, p=0.003), (r=0.19, p=0.004), (r=0.30, p=0.001), and (r=0.13, p=0.04). Two-hour plasma glucose was correlated with RBC, platelets, PLR and SII with (r=0.17, p=0.007), (r=0.17, p=0.009), (r=0.26, p=0.001), and (r=0.16, p=0.01) [Table/Fig-3].

| Variables | r-value/p-value | FPG | 1-hr OGTT | 2-hr OGTT |
|---|---|---|---|---|
| WBC | r-value | -0.06 | -0.03 | 0.02 |
| | p-value | 0.36 | 0.55 | 0.76 |
| RBC | r-value | 0.21 | 0.20 | 0.17 |
| | p-value | 0.001** | 0.003** | 0.007** |
| Platelets | r-value | 0.11 | 0.19 | 0.17 |
| | p-value | 0.10 | 0.004** | 0.009** |
| ANC | r-value | -0.04 | -0.04 | 0.03 |
| | p-value | 0.50 | 0.53 | 0.61 |
| ALC | r-value | -0.01 | 0.02 | -0.01 |
| | p-value | 0.83 | 0.75 | 0.95 |
| AMC | r-value | -0.09 | -0.02 | 0.01 |
| | p-value | 0.14 | 0.75 | 0.84 |
| NLR | r-value | 0.09 | 0.09 | 0.12 |
| | p-value | 0.18 | 0.17 | 0.07 |
| MLR | r-value | -0.03 | 0.03 | 0.05 |
| | p-value | 0.68 | 0.70 | 0.49 |
| PLR | r-value | 0.17 | 0.30 | 0.26 |
| | p-value | 0.01* | 0.001** | 0.001** |
| SII | r-value | 0.14 | 0.13 | 0.16 |
| | p-value | 0.04* | 0.04* | 0.01* |
| SIRI | r-value | -0.01 | 0.01 | 0.07 |
| | p-value | 0.83 | 0.83 | 0.27 |

**[Table/Fig-3]:** Correlation of plasma glucose with CBC and derived variables such as NLR, PLR, MLR, SII and SIRI.
Correlation analysis among the variables.
FPG: Fasting plasma glucose; 1-hr OGTT: One-hour oral glucose tolerance test; 2-hr OGTT: Two-hour oral glucose tolerance test; WBC: White blood cell; RBC: Red blood cell; ANC: Absolute neutrophil count; ALC: Absolute lymphocyte count; AMC: Absolute monocyte count; NLR: Neutrophil to lymphocyte ratio; MLR: Monocyte to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; SII: Systemic immune inflammation index; SIRI: Systemic inflammation response index
R and p-values are shown; p-value: * statistically significant; **statistically highly significant

## DISCUSSION

The GDM is a condition where it affects both the mother and the foetus, resulting in dreadful complications [14]. Placental hormones secreted in the later part of the first-trimester as well as in the second trimester of pregnancy cause insulin resistance, leading to GDM [15]. Recently, it has been studied that inflammation is highly associated with insulin resistance and beta-cell dysfunction [16]. Inflammation can impair insulin sensitivity and lead to complications such as preeclampsia and preterm birth [17]. Altered haematological parameters as seen in pregnancy reflect the maternal immune response and the blood viscosity, which could form the primary pathophysiology of GDM [18].

An OGTT is performed to diagnose GDM. However, OGTT has certain limitations. Patients with even a single abnormal value on a 3-hour OGTT will likely exhibit some glucose intolerance. Left untreated, these patients are at higher risk for foetal macrosomia and neonatal morbidity. If the abnormal value on the OGTT was obtained before 26 weeks gestation, a repeat OGTT needs to be performed approximately four weeks later [19]. GDM screening is done during the second trimester because the chances of insulin resistance are high in this gestation period. The metabolic alterations in the mother and the foetus could have started much earlier than the rise in plasma glucose levels [7]. Other tests, such as Glycated Haemoglobin (HbA1c) or fructosamine, are not recommended because of low sensitivity [20]. Hence, it is better to identify a good marker with adequate sensitivity and specificity to diagnose GDM early during pregnancy.

The present study included 118 gestational diabetic women and 119 non-diabetic pregnant women. GDM patients had higher plasma glucose values than non-diabetics, irrespective of fasting plasma glucose or 1-hr or 2-hr glucose OGTT [Table/Fig-1]. Beta cell dysfunction and insulin resistance usually develop during the second trimester of pregnancy. In later days, the beta cell function will deteriorate due to excessive insulin production in response to excess energy consumption, exhausting the cell turnover time [21].

Haemoglobin value was slightly higher in diabetic pregnant than in non-diabetic pregnant women, though it was not statistically significant. Benny BM et al., in their study, gave a cut-off for Hb and stated that if the value of Hb is more than 12.6 g/dL, women are at risk of developing GDM. Increased oxidative stress and Reactive Oxygen Species (ROS) associated with hyperglycaemia decrease insulin sensitivity and production [22]. High levels of RBC and Hb are found in GDM women, possibly due to higher blood viscosity. Although iron is important for many metabolic processes, through the Fenton reaction, excess iron can produce ROS, which may cause oxidative stress and beta cell dysfunction, leading to insulin resistance [22].

In diabetic pregnant women, WBCs, RBCs, and platelets are continuously exposed to a high-glucose environment. This leads to an influx of glucose through the GLUT1 transporter and results in non-enzymatic glycation and formation of advanced glycated end products. ROS seen in hyperglycaemia interferes with integrity of RBC membranes, and decreased RBC lifespan results in haematological diseases [23]. The present study findings are similar to the study by Benny BM et al., [22]. The current study showed higher RBC values in diabetic pregnant women, which showed statistical significance (p=0.002).

The WBC was slightly higher in diabetic pregnant women than in non-diabetic women. According to Pattanathaiyanon P et al., chronic subclinical inflammation results in insulin resistance. In-vitro and in-vivo experiments explain that a few inflammatory markers, like Tumour Necrosis Factor-alpha (TNF-α) and Interleukin (IL)-6, interfere with the insulin receptor signaling pathway. Leptin is shown to cause beta-cell apoptosis. These inflammatory markers are responsible for WBC differentiation, thus increasing the WBC value in GDM compared to non-diabetic women [24].

The present study showed slightly higher platelet counts in GDM than in non-diabetic pregnant women, though it was not statistically significant. Yang H et al., study has proven that activated platelets release chemokines and express an array of membrane receptors responsible for inflammation [16]. As per Fashami MA et al., platelets also play a role in intercellular communications and immunisation [25]. In GDM, plateletcrit has higher sensitivity and specificity than platelet count and mean platelet volume [26].

All the derived variables -NLR, MLR, PLR, SII, and SIRI showed significantly higher values in GDM individuals than in non-diabetic pregnant women [Table/Fig-1]. The increase in inflammatory markers indicates underlying inflammation, probably due to hyperglycaemia [27]. During pregnancy, innate immunity is activated

more than adaptive immunity, which reduces foetal rejection. During pregnancy, the T helper cell 1 converts to T helper cell 2, an anti-inflammatory important for foetal protection. This also explains the haematological changes in pregnancy [13].

In the present study, among the WBCs, only monocyte count (%) showed a statistically significant difference (p<0.03) between the groups [Table/Fig-1]. Based on the fasting plasma glucose, OR was found to be 3.92 [Table/Fig-2]. Fasting plasma glucose was positively correlated with RBC, PLR, and SII with (p=0.001), (p=0.01), and (p=0.04), respectively. One-hour OGTT was positively correlated with RBC, platelets, PLR and SII with (p=0.003), (p=0.004), (p=0.001), and (p=0.04). Two-hour plasma glucose was correlated with RBC, platelets, PLR and SII with (p=0.007), (p=0.009), (p=0.001), and (p=0.01) [Table/Fig-3]. The study correlation findings were similar to the study by Bai YY et al., [28].

Changes in peripheral blood of pregnant women indicate that normal pregnancy is associated with generalised inflammatory response which is shown by increased WBC count, especially neutrophils whereas lymphocytes are decreased. This response during healthy pregnancy is needed to prevent allo-rejection of the foetus [28]. The neutrophil phenomenon for GDM is explained by Hashemipour S et al., Neutrophils produce Neutrophil Extracellular Traps (NETs) by extrusion of DNA into extracellular space and trap invalid antigens. NETs are increased in diabetic pregnant women than in normal pregnancy, which further increases with sepsis and preeclampsia [29]. PLR is positively correlated with SII and SIRI. A recent meta-analysis explains that PLR is associated with GDM [30]. It is attributed to systemic inflammatory response and is significantly associated with atherosclerosis and other metabolic disturbances [31].

Study by Yıldırım SB et al., showed that an increase in circulating monocytes leads to activation of Monocyte Chemoattractant Protein 1 (MCP-1) [32]. Placental cellular products increase circulating monocytes, with increased expression of surface markers like CD54 and CD64. Also, there is increased expression of IL-12 and IL-β, which is responsible for innate immunity that helps in pregnancy [21]. According to Bai YY et al., there is positive correlation between SII and SIRI, which could be due to increased sex hormones like oestrogen and progesterone. These sex hormones cause aggregation of monocytes and the formation of platelet precursors [28]. During pregnancy, OGTT, glycated haemoglobin, and fructosamine have their limitations with reduced sensitivity and specificity. Hence, derived markers such as NLR, PLR, MLR, SII, and SIRI seem to be potential biomarkers in diagnosing GDM.

### Limitation(s)

The study could have been done as a prospective cohort study, in which the pregnant individuals could have been followed from the first trimester until the second trimester, and an OGTT performed to show whether they had diabetes or not. A few risk factors, such as obesity, family history of diabetes mellitus, nutritional and economic status, stress-related factors, and physical activity, could have been included to remove the effect of confounders such as diet intake, physical activity, BMI, family history, other endocrine disorders which can cause hyperglycaemia, etc. Stratification could have been done based on the age of the individuals.

## CONCLUSION(S)

The GDM patients had higher plasma glucose values compared to non-diabetic pregnant women. All the derived variables -NLR, MLR, PLR, SII, and SIRI showed higher values in GDM individuals than in non-diabetic pregnant women. The systemic immune inflammation index and the platelet-to-lymphocyte ratio showed good correlations with fasting glucose and the 1-hr and 2-hr OGTTs. Hence, inflammatory markers could serve as potential diagnostic markers for GDM. The systemic immune inflammation index could be the best marker since the levels correlate with glucose. The inflammatory markers could serve as earlier markers than glucose in GDM. Larger sample studies would clarify and enhance the results obtained.

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