ARC Journal of Gynecology and Obstetrics
Volume 9, Issue 4, 2025, PP 13-20
ISSN 2456-0561 (Online)
DOI: https://doi.org/10.20431/2456-0561.0904003
www.arcjournals.org

Association of Maternal Serum C Reactive Protein with Gestational Diabetes Mellitus

***Dr. Zinia Jafrin Munni[1], Prof. Dr. Syeda Nazia Akhter[2], Dr. Nafisa Jafreen[3], Dr. Masuma Nargish Urmee[4], Dr. Azrina Afrine[5], Dr. Suraiya Siddika[6], Dr. Ireen Akhter[7]**

[1]Assistant Professor, Department of Obstetrics and Gynaecology, Shaheed Suhrawardy Medical College & Hospital, Dhaka, Bangladesh

[2]Professor, Department of Obstetrics and Gynaecology, Institute of Child and Mother Health, Dhaka, Bangladesh

[3]Consultant, Department of Obstetrics and Gynaecology, Shaheed Suhrawardy Medical College & Hospital, Dhaka, Bangladesh

[4]Assistant Professor, Department of Obstetrics and Gynaecology, Manikganj Medical College, Manikganj, Bangladesh

[5]Assistant Professor, Department of Obstetrics and Gynaecology, Mugda Medical College Hospital, Dhaka, Bangladesh

[6]Registrar, Department of Obstetrics and Gynaecology, Shaheed Suhrawardy Medical College & Hospital, Dhaka, Bangladesh

[7]Medical Officer, Department of Obstetrics and Gynaecology, Shaheed Suhrawardy Medical College & Hospital, Dhaka, Bangladesh

Received: 23 October 2025 Accepted: 06 November 2025 Published: 14 November 2025

Corresponding Author:** ***Dr. Zinia Jafrin Munni, *Assistant Professor, Department of Obstetrics and Gynaecology, Shaheed Suhrawardy Medical College & Hospital, Dhaka, Bangladesh*

Abstract

Background: *Gestational diabetes mellitus (GDM) is one of the most common metabolic disorders during pregnancy, sharing several pathophysiological features with type 2 diabetes mellitus, including insulin resistance and chronic low-grade inflammation. C-reactive protein (CRP), a sensitive inflammatory marker, has been suggested to play a role in the development of GDM, but findings have varied across populations.*

Methods: *A cross-sectional observational study was conducted in the Department of Obstetrics and Gynecology, Institute of Child and Mother Health (ICMH), Dhaka, from July 2021 to June 2022. Sixty-two pregnant women aged 18–35 years and between 24–28 weeks of gestation were enrolled and divided into two groups: Group A (GDM) and Group B (non-GDM), each consisting of 31 participants. Serum CRP levels, fasting glucose, and 2-hour post–75 g glucose levels were measured. Data were analyzed using SPSS version 22, and $p < 0.05$ was considered statistically significant.*

Results: *The mean serum CRP level was significantly higher in women with GDM (7.26 ± 3.64 mg/L) compared to those without GDM (3.85 ± 2.22 mg/L) ($p = 0.001$). Elevated CRP levels (≥ 2 mg/L) were found in 80.65% of women with GDM and 41.94% of those without GDM ($p = 0.024$). Both fasting glucose and 2-hour post-glucose values were significantly higher in the GDM group ($p < 0.05$).*

Conclusion: *The study demonstrated a significant association between elevated serum CRP levels and gestational diabetes mellitus, suggesting that increased CRP during pregnancy may serve as an early indicator of GDM risk. Larger multicenter studies are recommended to confirm these findings and explore the potential of CRP as a predictive marker for GDM.*

Keywords: *Gestational diabetes mellitus, C-reactive protein, inflammation, pregnancy, insulin resistance.*

1. INTRODUCTION

Diabetes mellitus is a metabolic ailment that is the most prevalent disorder during pregnancy [1]. Gestational diabetes mellitus (GDM) is a kind of diabetes that is first diagnosed during the later half of pregnancy. Gestational diabetes mellitus (GDM), like type 2 Diabetes mellitus, is characterized by the metabolic defects of β-cell dysfunction and insulin resistance [2]. A potential pathophysiologic relationship between GDM and type 2 diabetes mellitus is further supported by the significantly elevated lifetime risk of type 2 diabetes mellitus in women with a history of previous GDM [3,4]. In the United States, 10 percent of women have gestational diabetes, and 5–10 percent of women with gestational diabetes acquire type 2 diabetes mellitus in the future. In Iran, 4.8 percent of the population was affected by GDM [5]. The following risk factors for gestational diabetes are known: being over the age of 30, having a family history of diabetes in first-degree relatives, being overweight before pregnancy (weighing more than 200 pounds or 91 kg), having had more than four pregnancies, having had a baby with a congenital abnormality or having had a baby with a congenital abnormality in the previous pregnancy, having had a history of pre-pregnancy diabetes, having had recurrent abortions more than three times [6].

Pregnancy is a diabetogenic condition, and one of the signs of this condition is insulin resistance (IR) [6]. Inflammatory response is a metabolic factor associated with an inflammatory state. One study found an association between type 2 diabetes mellitus and inflammation as a central characteristic in the development of type 2 diabetes mellitus [7]. Inflammation has been reported in GDM in different cases [8]. To ensure maternal tolerance to fetal antigens during the middle phase of pregnancy, however, a cessation of inflammation is required during this time. In recent years, there has been an increase in evidence suggesting that dysregulated maternal inflammation during pregnancy may be associatred for a variety of neonatal complications [9,10]. Furthermore, some studies have discovered a link between inflammation and the development of pregnancy-related complications [10,9]. C-reactive protein (CRP) is routinely used in the diagnosis and clinical monitoring of infections, included those occurring in the obstetric field [11,12]. CRP is an acute phase protein released by the liver after the onset of inflammation. Increased serum concentration level of CRP, which indicates chronic metabolic inflammation, can be associated with cardiovascular disease as well as inflammatory reaction among men and women [5,1,6,7].

Multiple studies have shown that chronic inflammation can increase the risk of developing type 2 diabetes [13-16]. Very small variation in the serum levels of CRP, detected by highly sensitive evaluations, may happen in interrelation with metabolic tensions in the lack of acute or chronic inflammatory conditions as they have classically been shown. Substantial bodies of experimental and epidemiologic evidence has established an association between elevated serum levels of acute-phase proteins and several commonly coexisting pathologic conditions, including type 2 diabetes mellitus, obesity, and atherosclerotic cardiovascular disease [10,17,18,9]. Different studies in different countries found that people with high serum level of CRP are at the risk of diabetes, hypertension, and cardiovascular diseases [19]. Moreover, in pregnancy a raise of maternal CRP has been related to pregnancy complications such as early pregnancy loss, preterm labor, pre-eclampsia, intrauterine growth restriction, premature rupture of membranes, and chorioamnionitis [20]. However, results may vary from region to region and community to community. Previous studies suggest that there can be an association between CRP level and GDM during pregnancy. However, to ensure about this concept regional study was required. Therefore, the present study was conducted to investigate the association between CRP level and GDM.

2. METHODOLOGY & MATERIALS

The cross sectional observational study was conducted in the Department of Obstetrics & Gynecology, Institute of Child and Mother Health (ICMH), Dhaka, Bangladesh from July 2021 to June 2022. A total number of 68 pregnant women with GDM and healthy pregnant women of 24-28 weeks of gestation as per inclusion and exclusion criteria, who came to Department of Obstetrics & Gynecology, Institute of Child and Mother Health

(ICMH) in Dhaka. The entire subject was female from 18 to 35 years of age.

The patients were divided into two groups:

- Group A: Pregnant females of 24-28 weeks diagnosed with gestational diabetes mellitus.
- Group B: Normal pregnant females of 24-28 weeks without gestational diabetes mellitus.

2.1. Inclusion criteria for Group A & B

- Singleton pregnancy
- Pregnancy with GDM of 24 th - 28 th weeks
- Age: 18 to 35 (Group A) & Age: 18 to 40 (Group B)
- BMI: 18.5 to 24.9

2.2. Exclusion Criteria for Group A & B

- Any preexisting chronic medical conditions that may affect acute phase markers,
- including hypertension, diabetes mellitus, polycystic ovarian syndrome, collagen vascular
- diseases, inflammatory bowel disease.
- Renal disease
- Recent infections or inflammatory diseases e.g. viral hepatitis, tuberculosis, syphilis.
- Congenital abnormality and Autoimmune diseases.
- Covid 19
- Current use of corticosteroids or use of NSAIDs

2.3. Data Collection Procedure

Different typed of data were collected through interview, clinical examination and laboratory investigation. Detailed medical history of all participants' was recorded in History sheet. Necessary information collected from medical history and clinical examination were noted in a pre-designed Data entry sheet. Data obtained from laboratory reports was also noted in Data sheet carefully.

2.4. Data Analysis

Data were processed and analyzed by SPSS 22 (Statistical program for Social Sciences). Chi-square test and independent sample t-test were used to analyze the statistical significant difference between the two groups. A P-value less than 0.05 was considered statistically significant. The summarized data was presented as percentages on table, graph and diagram.

3. RESULTS

Table I. *Demographics and obstetric outcomes*

Variable	Group A	Group B	p value
Age (Mean)	26.94	24.82	0.121
Age range (Min–Max)	18 – 35	19 – 35	
Gravidity Median (Min–Max)	2 (1–3)	2 (1–4)	0.149
Parity (Mean ± SD) (Min–Max)	1 (0–3)	1 (0–3)	0.11
BMI (Mean)	24.86	22.75	0.248

*p-value was determined by Independent sample t test. P < 0.05 was considered significant.

The demographic characteristics and obstetric outcomes of the patients are shown in Table 1 There was no statistically significant difference between Group A and Group B in terms of age, gravidity, parity and BMI (p > 0.05).In Group A, mean age is 26.94 (±11.06) years and in Group B, mean age is 24.82 (±12.71) years. Minimum age in Group A is 18 years and in Group B is 19years; whereas maximum age in both group is 36 years.

Table II. *Comparison of CRP level between the two groups*

CRP Level					
Group	**n**	**Min (mg/L)**	**Max (mg/L)**	**Mean ± SD**	**p value**
Group A	31	1.5	14	7.26 ± 3.64	0.001
Group B	31	0.9	8	3.85 ± 2.22	

*p-value was determined by Independent sample t test. P < 0.05 was considered significant.

Serum level of CRP was done in all patients. Mean value of CRP in Group A and Group B were compared. Minimum CRP level observed in group A is 1.50 mg/l and maximum 14.0 mg/l. In group

B minimum CRP level observed is 0.90 mg/l and maximum 8.0 mg/l. The mean of serum CRP level in women with gestational diabetes is 7.26 (±3.64) mg/l, and women without gestational diabetes is 3.85 (±2.22) mg/l. Table 2 shows a significantly difference (p=0.001) of Serum CRP level between Group A and Group B.

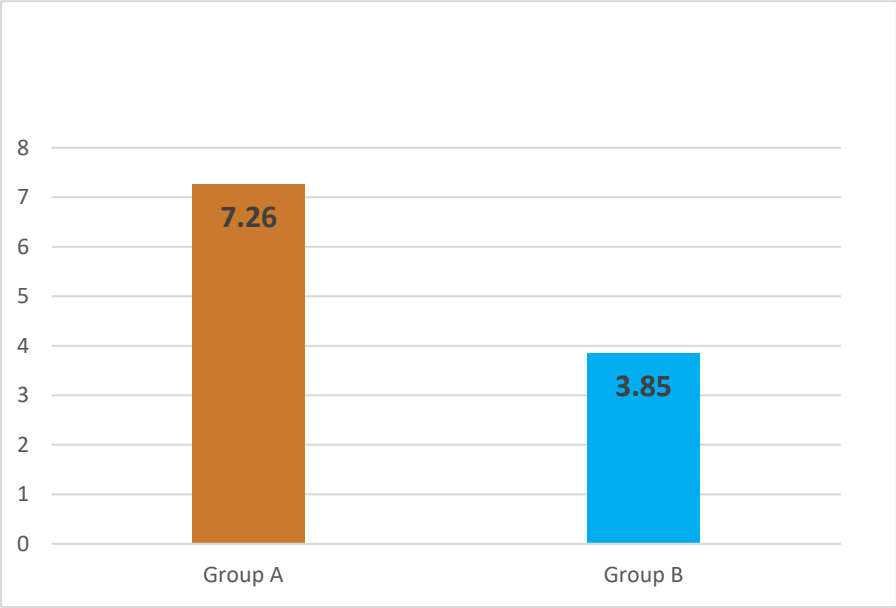

Figure 1. *Comparison of mean CRP level between two groups*

Table III. *Comparison CRP level between the two groups*

CRP < 2 mg/dL		**CRP ≥ 2 mg/dL**	
Group	**n (%)**	**n (%)**	**p**
Group A	6 (19.35)	25 (80.65)	0.024
Group B	18 (58.06)	13 (41.94)	

Chi square test was used to analyze the data. Data was expressed in frequency and percentage

*p < 0.05 was considered significant.

Table 3 showed that serum CRP levels in the Group A were higher than those in the Group B. Group A shows 80.65% women have a high CRP level, ≥ 2 mg/dL and 19.35% women have CRP level < 2 mg/dL; whereas Group B shows 41.94% women have CRP level, ≥ 2 mg/dL and 58.06% women have CRP level < 2 mg/dL. The association of elevated CRP (≥2 mg/L) between groups was observed and found significantly significant (p = 0.024).

Table IV. *Correlation of maternal CRP with OGTT between two groups)*

Parameter	**Group A (n =31)**	**Group B (n =31)**	**p value**
	Mean ± SD		
Fasting Glucose (mg/dL)	98.79 ± 7.84	85.79 ± 8.17	0.001
2 hr After 75 gm Glucose (mg/dL)	176.06 ± 29.24	121.33 ± 35.92	0.01
CRP Level (mg/dL)	7.26 ± 3.64	3.85 ± 2.22	0.001

*p-value was determined by Independent sample t test. P < 0.05 was considered significant.

Table 4 shows the Correlation of maternal CRP with OGTT between two groups. The CRP of the two studied groups showed statistically significant differences with a mean of 7.26 ± 3.64 mg /dl and 3.85 ± 2.22 mg/dl in Group A and Group B respectively. Glycemic parameters of fasting and 2 hours after 75 gm glucose, showed higher blood glucose value in Group A where all are diagnosed as GDM. Table 4 shows mean fasting glucose in Group A is 98.79 mg/dL (± 7.84) and mean fasting

glucose in Group B is 85.79 mg/dL (± 8.17), which showed statistically significant differences (p=0.001). Mean value of 2 hours after 75 gm glucose in Group A is 176.06 mg/dL (±29.24) and in Group B is 121.33 mg/dL (±35.92), which showed statistically significant differences (p=0.01). CRP was also significantly correlated with Glycemic parameters of the study groups. These data indicated that elevated CRP levels were associated with GDM.

4. Discussion

American Diabetes Association (ADA) defined GDM as follows: "diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation"[2]. C-reactive protein (CRP), the predominant and sensitive marker in acute phase response, elevates obviously during acute inflammation, trauma and other diseases [21]. Increasing evidences support that there are distinct degrees of subclinical inflammation in women with GDM and inflammation effect, which plays an important role in the process from insulin resistance to gestational diabetes mellitus [22]. There is some evidence to support the theory that chronic inflammation might be a risk factor for type 2 diabetes [23]. Gestational diabetes is a biochemical and epidemiological condition similar to type 2 diabetes [24], so pro-inflammatory cytokines such as CRP may be associated with GDM. Some studies have measured CRP at various gestational ages in pregnant women and found inconsistent results regarding the association between inflammatory markers and the incidence of GDM and the interdependence with the degree of adiposity [9].

The aim of the present study was to identify the association between C-reactive protein level and the gestational diabetes mellitus. The study included sixty-two pregnant women in Institute of Child and Mother Health (ICMH), Dhaka. Patients were classified into two groups- Group A: 31 women with gestational diabetes and Group B: 31 normal pregnant females. In the present study patients were subjected to 75 gm oral glucose tolerance test to confirm diagnosis of GDM and serum C reactive protein level were measured. The results of the present study showed that, there were no statistically significant differences between the two groups concerning age, gravidity, parity, gestational age and BMI.

The result of the study showed that serum CRP levels in the GDM group were higher than those in the normal group. The CRP of the two studied groups showed statistically significant differences with a mean of 7.26 ± 3.64 mg /dl and 3.85 ± 2.22 mg/dl in GDM and normal groups respectively. These data indicated that elevated CRP levels were associated with GDM. The association of elevated CRP (≥2 mg/dL) in Group A with OGTT test was observed and it was found that OGTT level also showed a statistically significant differences and significantly associated with the level of CRP (≥2 mg/dL) in comparison with Group B.

Present study was in accordance with the findings of Li et al., Liu et al., and Rota et al., [25-27] . In their study they found that serum CRP level was higher in the women with GDM as compared to normal pregnant women. Qiu et al., and Wolf M et al., also found that CRP was higher in patients of GDM compared to normal pregnant women [28,29]. In the patients of GDM, there is increased expression of genes for chronic stress and inflammatory pathways. This leads to increase in production of CRP. In a prospective study directed by Qiu et al. to analyze the relationship among CRP and GDM risk [28]. Their study exhibited that raised CRP was related with GDM risk. After adjustment of maternal pre-pregnancy BMI, family history of diabetes and nulliparity women with CRP in the most elevated tertile encountered a 3.5-fold increased risk of GDM (95% CI 1.2-9.8) as contrasted with those in the least tertile.

In the study conducted by Liu and colleagues, there was a significant difference between both case and control groups in terms of quantitative CRP [26]. Wang and co-workers, Heidari and colleagues also achieved similar results. Increasing serum CRP levels by affecting IR can lead to gestational diabetes, which has resulted in this study [30,31]. Savvidou and others also reported that there was a significant association between increased serum CRP level and the risk of gestational diabetes in the first trimester of gestation and [32].

In this present study, the increase in blood sugar of women correlates with gestational diabetes and consequently increases of CRP. This hypothesis suggests that gestational diabetes may be the cause of increase in inflammatory factor such as CRP.

Result of this present study is partially opposing the report of Rentankaran et al., likewise which exhibited that maternal serum levels of CRP are not

related to GDM at the time of oral glucose tolerance testing in late second or early third trimester [9]. They conduct oral glucose tolerance test on 180 healthy pregnant women in the late second or early third trimester. Median CRP level was most elevated in overweight NGT subjects (8.8 mg/liter), followed by GDM (5.5 mg/liter), impaired glucose tolerance (4.4 mg/liter), and lean NGT (4.4 mg/liter) (overall P _ 0.0297). They showed CRP was significantly associated with pre-pregnancy BMI (P < 0.0001), followed by fasting insulin (P = 0.0002) and fasting blood glucose (P = 0.016). In multivariate direct relapse examination, prepregnancy. Their data propose a model in which obesity mediates a systemic inflammatory response, with possible downstream metabolic sequelae, including insulin resistance and glucose dysregulation.

Contrary to the results of this research and the mentioned studies, Corcoran and co-workers did not observe any association between serum CRP levels and the probability of GDM [33]. Furthermore, in a study conducted by Korkmazer and colleagues, despite a significant association between serum CRP levels and insulin, there was no association between CRP and the risk of gestational diabetes [34]. In their study, serum CRP levels were significantly associated with pre-pregnancy obesity, which may indicate that adipose tissue acts as an independent released agent of mediators that stimulates clinical systemic inflammatory response and thus causes an increase in the serum levels of inflammatory factors such as CRP, resulting in a sequence of metabolic disorders including Insulin Resistance and Glucose Distribution Disorder.

Mojibian et al., showed that CRP serum level was not correlated with GDM in pregnant women, and CRP serum level in pregnant women could not predict the probability of women's IGT or GDM [35]. In the present study, the body mass index (BMI) was identical in both groups with and without gestational diabetes. So, as obesity could not affect serum CRP levels in our study, our results can show more strongly that an independent agent like GDM may increases inflammatory factors and caused increased CRP level.

Based on the results of this present study, there is a significant association between CRP and GDM at 24 th - 28 th weeks of pregnancy in women who had no significant difference in BMI.

5. Limitations of the Study

This study was a single-center study. This study took a small sample size due to the short study period, which may limit the generalizability of the findings. The cross-sectional study was done by non sampling method.

6. Conclusion and Recommendations

Gestational Diabetes Mellitus is the most common disorder during pregnancy in 8-14% of pregnancies. Due to maternal and neonatal morbidity and mortality, early diagnosis and appropriate treatment of GDM is very important. This study was conducted to find out the association of CRP with GDM during 24 th - 28 th weeks of pregnancy. Result of this present study showed that, increasing serum CRP levels during 24th - 28th weeks of pregnancy can be a risk factor for GDM and early diagnosis of GDM could be predicted or possible with the result of the CRP.

Diagnostic tests for GDM are highly recommended to be done for all pregnant women with high serum C reactive protein level.C reactive protein is suggested to be done as routine investigation. Furthermore studies on large number of patients to confirm the association between high CRP level and the development of gestational diabetes mellitus.

Funding: No funding sources

Conflict of Interest: None declared

Ethical Approval: This study was ethically approved

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Citation: *Dr. Zinia Jafrin Munni et al. Association of Maternal Serum C Reactive Protein with Gestational Diabetes Mellitus. ARC Journal of Gynecology and Obstetrics. 2025; 9(4):13-20. DOI: https://doi.org/10.20431/2456-0561.0904003.*

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