

ORIGINAL ARTICLE

Elevated C-Reactive Protein (CRP) during First-Trimester For Gestational Diabetes Screening

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ABSTRACT

Background: Studies investigating the impact of inflammatory factors on gestational diabetes mellitus (GDM) are extremely sparse. This study aimed to find out the association of inflammation as defined by C-reactive protein (CRP) with gestational diabetes.

Methods: This prospective cohort study, conducted in Patel Hospital Karachi from September 2020 to February 2021, enrolled 172 healthy gravid women at ≤ 10 weeks of pregnancy. A structured proforma was used to record age, education, past medical and obstetric history (parity, number of miscarriages, mode of deliveries, gestational age), blood pressure, height, and weight of all patients. Serum concentration of CRP and levels $>1\text{mg/dl}$ was considered high. Oral glucose tolerance test was performed at 24-28 weeks to diagnose GDM. Data was analysed by using SPSS and Chi-squared test was applied to compare the difference between groups with, and without diabetes and $p\text{-value} \leq 0.05$ was considered significant

Results: Total 93 patients had raised CRP of which 8(4.6%) developed GDM ($p<0.00001$). Advanced age ($p=0.00042$) and weight ($p<0.00001$) were found to be independent risk factors. It was observed that CRP levels rise with increasing weight ($p=0.0095$) however, parity and blood pressure had no effect on GDM development. Women who had diabetes had higher BMI (<0.00001) showing that increasing weight was an independent risk factor. The sensitivity and specificity of CRP in detecting GDM was 100% and 48.17%.

Conclusion: Raised C-reactive protein levels in first trimester can lead to subsequent development of hyperglycaemia of pregnancy and thus can be considered as an easy and simple screening test for GDM.

Keywords: Gestational Diabetes Mellitus; C-Reactive Protein; Inflammation; Oral Glucose Tolerance Test.

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INTRODUCTION

Gestational Diabetes Mellitus (GDM) is defined as hyperglycaemia that is first recognized in the second or third trimester of pregnancy in women with previous normal sugar levels and can lead to numerous adverse outcomes for mother and baby^{1,2}. GDM prevalence varies across the world affecting almost 7-10% of pregnancies worldwide³⁻⁵. The sooner the disease is detected in pregnancy the better would be the outcome. Women who

had a history of hyperglycaemia in pregnancy have an increased chance of getting adult onset diabetes later on in life².

Diabetes of pregnancy is more prevalent in women who are above 30 years, overweight or obese, have diabetes in family, previous history of stillbirth or anomalous baby and have gestational diabetes in the previous pregnancy². GDM screening tests are done after assessing risk factors. There is increase insulin resistance in pregnancy making it a

diabetogenic condition². Insulin resistance is linked with inflammatory conditions and the development of type 2 diabetes. It is shown by several studies that increased inflammation as measured by CRP is an independent risk factor for the development of diabetes⁶.

Although pregnancy itself is an anti-inflammatory condition, there is an increased level of inflammation during the early stage of pregnancy such as during implantation leading to increasing levels of various inflammatory mediators⁷. High maternal CRP is associated with miscarriage, premature labour and rupture of membranes, toxemia of pregnancy, fetal growth restriction and chorioamnionitis^{8,9}. The possible mechanism by which inflammation leading to diabetes could be the increase blood sugar and glycosylated haemoglobin levels (HbA1c) causing the release of CRP¹⁰. In addition, obesity, which is a risk factor for GDM, causes an increase release of pro-inflammatory cytokines from adipocytes⁶. Currently, it is being hypothesized systemic inflammation may be involved in the establishment of GDM¹¹. Early diagnosis and treatment are very crucial to prevent maternal and neonatal adverse outcome. Therefore, this study was performed to define the role of CRP in the screening of gestational diabetes.

METHODS

It was a prospective cohort study conducted from September 2020 until February 2021. A total number of 172 pregnant patients attending antenatal checkups in Department of Obstetrics and Gynaecology of Patel Hospital, Karachi were selected. All pregnant women 18-35 years with single fetus less than 10 weeks of gestation based on their last menstrual period were included in the study after written informed consent. All patients were ensured about the confidentiality of identity and were given free choice of withdrawing from the study at any point. Ethical approval was obtained from the institutional ethic committee (Ref no.102/2020).

A structured proforma was used to record age, education, past medical and obstetric history (parity, number of miscarriages, mode of deliveries,

gestational age), blood pressure, height, and weight of all patients at booking. Patients with previous history of hyperglycaemia in pregnancy, pre-existing or family history of diabetes, random blood sugar (RBS) of more than 140mg/dl, history of macrosomia, stillbirth, recurrent miscarriage, hypertension and polycystic ovarian syndrome were excluded from the study. Patients with chronic hypertension, thyroid disorder, chronic kidney disease, cardiovascular disease, autoimmune and chronic inflammatory disease, current active infection, antibiotic use within two weeks before sampling, seasonal allergy and those taking corticosteroids or non-steroidal anti-inflammatory drugs were also excluded.

The blood sample was taken for serum CRP in addition to the standard antenatal tests from all patients in the first trimester. Participants were followed up until 24-28 week of pregnancy and 75g oral glucose tolerance test (OGTT) was carried out at that time. CRP level was measured by latex agglutination semi- quantitative test kit. CRP > 1mg/dl was considered raised. Gestational diabetes was diagnosed by Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) criteria (fasting blood glucose ≥ 92 mg/dl, 1-hour ≥ 180 mg/dl, 2-hour ≥ 153 mg/dl)¹².

Data were analyzed by using SPSS version 22. Mean, standard deviation and frequency table was used for data presentation. Chi-square test was used to compare the difference between groups with and without diabetes. The 2 × 2 contingency table was used for calculating sensitivity, specificity, positive predictive value, negative predictive value and accuracy. The level of significance was kept at p-value ≤ 0.05 .

RESULTS

The average age of patients was 26.5 \pm 5.33 years and mean gestation of pregnancy was 7.5 \pm 1.87 weeks. The majority of participants were multipara (74.41%), educated (72.6%) and working women (76.1%). The average body mass index was 24.03 \pm 3.83 kg/m². The mean random blood sugar was 99.5 \pm 22.7mg/dl. The association of CRP and GDM with baseline characteristics is shown in Table 1.

Table 1: Association of C-reactive protein (CRP) and gestational diabetes (GDM) with age, parity, gestation, BMI, blood pressure and random blood sugar.

Variables	CRP ≤1mg/d	CRP >1mg/dl	p- Value	GDM	p-Value
Age in years					
18-24	20(44.44%)	25 (55.55%)	0.75	01(2.22%)	0.00042
25-30	42(41.17%)	60(58.82%)		02(1.96%)	
31-35	12 (48%)	13(52%)		05(20%)	
Gestational age in weeks					
5-6	21(45.65%)	25(54.34%)	0.98	-	
7-10	58(46.03%)	68(53.96%)		-	
Nullipara	19(43.18%)	25(56.81%)	0.91	2(4.54%)	0.99
Multipara	60(46.87%)	68 (53.12%)		6(4.68%)	
BMI in kg/m²					
18.5-24.9	49(57.64%)	36(42.35%)	0.0095	0	<0.00001
25-29.9	25(34.72)	47(65.27%)		3(4.16%)	
≥30	5(33.33%)	10(66.66%)		5(33.33%)	
Systolic blood pressure in mmHg					
100-120	67(44.66%)	83(55.33%)	0.53	6(4%)	0.10
121-139	12(54.54%)	10(45.45%)		2(9.09%)	
Random blood sugar in mg/dl					
<120	44(46.80%)	50(53.19%)	0.79	0	0.0014
120-139	35(44.87%)	43(55.12%)		8(10.25%)	

BMI: body mass index, GDM: gestational diabetes, BP: Blood pressure.

Out of 172 patients, ninety-three had raised CRP of which 8(8.6%) developed GDM ($p < 0.00001$) showing a significant association between high serum C reactive protein and gestational diabetes

as shown in Figure 1. It is shown in Table 2 that with increasing levels of CRP the risk of GDM also increases.

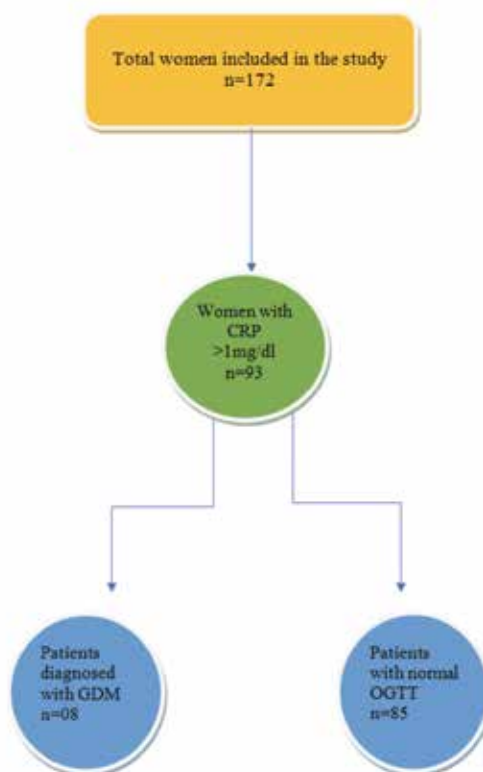


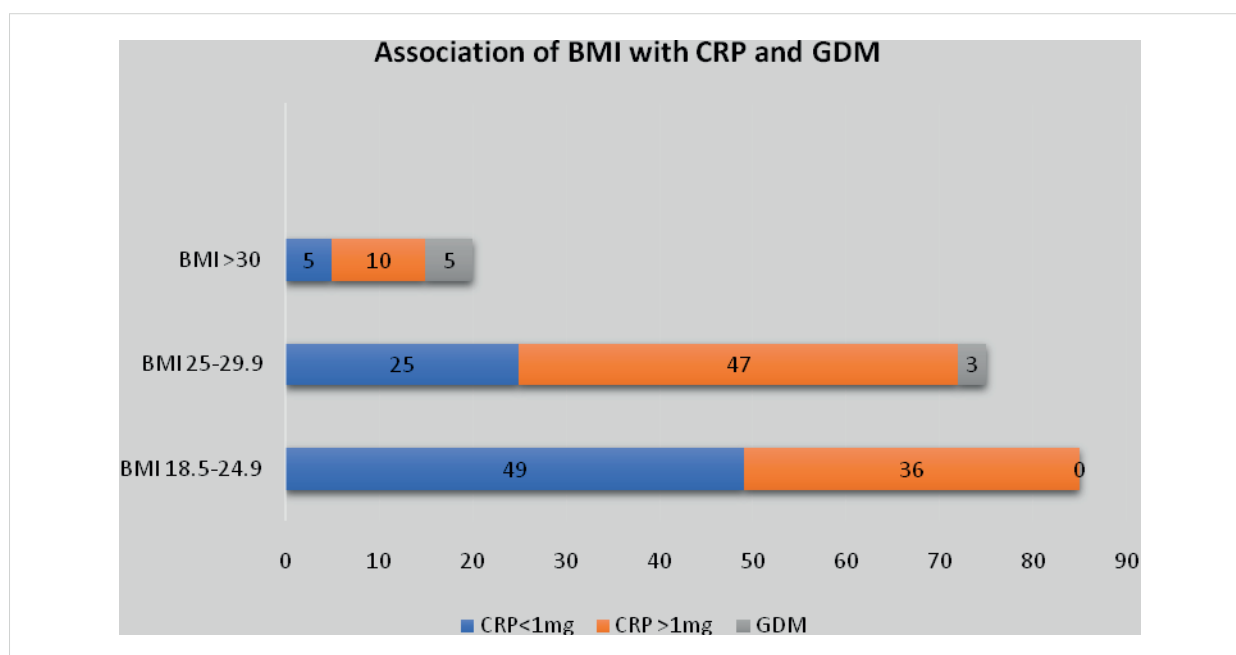
Figure 1: Flow chart showing results of the study.

Table 2: Comparison of C-reactive protein (CRP) levels and gestational diabetes (GDM).

Quantitative CRP mg/dl	GDM	Without GDM	p-Value
≤1	00	79 (100%)	<0.00001
2-4	00	67 (100%)	
5-10	02 (11.11%)	16 (88.88%)	
>10	06 (75%)	02 (25%)	
C-reactive protein	GDM	Without GDM	Total
Positive CRP	08 (TP)	85 (FP)	93 (54.06%)
Negative CRP	0 (FN)	79 (TN)	79 (45.9%)
Total	08 (4.65%)	164 (95.345)	

It was found that CRP levels rise with increasing weight ($p=0.0095$) indicating that CRP level is independently related to BMI which can be seen in Figure 2. The risk of GDM increased with advance maternal age ($p=0.00042$). However, parity and blood pressure had

no effect on GDM development. It was also found in our study that women who had diabetes were of higher Body mass index (BMI) (<0.00001) Table 1. Thus, it was showing that increasing weight was an independent risk factor for GDM as shown in Figure 2.



X-axis: Number of patients, Y-axis: Body mass index (BMI kg/m²).

Figure 2: Association of body mass index (BMI) with C-reactive protein (CRP) levels and gestational diabetes (GDM).

The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of CRP in

detecting GDM was 100%, 48.17%, 8.6%, 100% and 50.58% respectively as shown in Table 3.

Table 3: Accuracy of C-reactive protein (CRP) as a screening test for gestational diabetes (GDM).

Statistic	Value	95% CI
Sensitivity	100%	63.06 - 100
Specificity	48.17%	40.31 - 56.10
PPV	8.60%	7.51- 9.84
NPV	100%	-
Accuracy	50.58%	42.87-58.28
Positive likelihood ratio	1.93	1.66 -2.24
Negative likelihood ratio	0.00	-

PPV: Positive Predictive Value, NPV: Negative Predictive Value, CI: Confidence Interval.

DISCUSSION

In a current study out of ninety-three patients with raised CRP, 8(8.6%) developed GDM ($p < 0.00001$) showing that high C-reactive protein can result in GDM. This is inconsistency with previous research studies^{13,14}. Increased levels of CRP in the blood can lead to hyperglycaemia by influencing insulin resistance¹⁵. It has been shown in others studies that elevated CRP levels in blood have a notable relation with subsequent development of hyperglycaemia of pregnancy¹⁶. Patients with gestational diabetes tend to have higher CRP levels as compared to normal pregnant women¹⁶. Hence, quantitative C-reactive protein level is an acceptable test in predicting diabetes in pregnancy¹⁷. In contrast to the above, the studies by Corcoran and Korkmazer showed no association between CRP and GDM^{18,19}.

Despite many researches, there is no general agreement on screening of gestational diabetes and the diagnostic threshold for glucose challenge test (GCT) varies. Furthermore, the tests used for screening diabetes in the first trimester involve drinking glucose solution that can cause nausea, sweaty or light-headedness¹. A research study by Cunningham et al. showed that the sensitivity and specificity of GCT in GDM screening varies with glucose thresholds such as 80% and 82-86% with 140mg/dl while 90% and 75-80% when kept at 130mg/dl²⁰. Whereas Farghaly et al. reported that CRP has a sensitivity and specificity of 86.49% and 98.47% respectively in detecting GDM¹³. The current study showed 100% sensitivity and 48.17% specificity of CRP in detecting GDM thus making it a good screening test for GDM owing to the very high sensitivity and simplicity of the test.

Gestational diabetes resolves spontaneously after delivery but is linked to complications in both mother and the newborn²¹. It has been proven that intrauterine exposure to maternal GDM can lead to glucose intolerance, obesity and type 2 diabetes in offspring²². Recently, there has been an increased interest to disclose the role of inflammation in GDM development. In a previous study, increased levels of CRP and IL-6 were observed in pregnant women with glucose intolerance and GDM. Thus, suggesting that these may have a role in the pathophysiology of glucose intolerance and can serve as potential serum markers for the early screening of glucose intolerance²³. Furthermore, there is an elevated inflammatory response with increasing age and BMI and has a significant association with GDM and inflammatory response is observed with increases in both age and BMI²⁴. Studies have suggested that there is strong correlation between body fat mass and serum CRP levels²⁴. Obesity has been identified as a predictor of elevated CRP, which is a risk factor for cardiovascular and coronary heart disease²⁵. Furthermore, C-reactive protein was highly correlated with body mass index in some previous

research studies⁶. In the current study it was observed that patients with high BMI tend to have increased CRP levels ($p = < 0.0095$) and there was a remarkable correlation between GDM and obesity ($p = < 0.00001$).

Seeing that it is known that inflammation can cause diabetes in pregnancy by causing insulin resistance⁶. The increase in blood sugar levels accelerates the synthesis of glycosylated haemoglobin and the expression of macrophages thus causing the release of inflammatory markers like CRP¹⁰. CRP is a commonly available laboratory test and if combined with maternal risk factors as assessed by history and demographic features, can be predictive of GDM¹¹. Thus, it helps in identification of those patients who are at higher risk of developing hyperglycaemia of pregnancy as early as in the first trimester. Recognizing these patients earlier can help in better maternal and neonatal outcomes by intervening through treatment and lifestyle modification.

However, a single measurement of serum CRP level does not provide a measure of maternal inflammation status. Besides, C reactive protein levels rise during normal pregnancy¹⁵. Further comprehensive studies are needed to assess diagnostic accuracy of serum CRP in GDM screening. In addition, inflammatory cytokine levels fluctuate throughout pregnancy. Therefore, the levels should be monitored multiple times for finding a specific correlation between inflammation and GDM or glucose intolerance.

CONCLUSION

Women with hyperglycaemia of pregnancy have increased inflammatory reactions during the first trimester. C reactive protein measurement could be a useful screening test in the first-trimester for the prediction of GDM. CRP test can be a new, fast and reliable screening test for GDM screening. However, further research studies are needed to strengthen these findings. It is easy to measure and can predict the risk of other pregnancy complications as well such as preeclampsia, preterm labour, intrauterine growth restriction etc. allowing better surveillance during gestation.

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CONFLICT OF INTEREST

There is no conflict of interest.

ETHICS APPROVAL

The ethical board of Patel Hospital (Ref no.102/2020) approved the following study.

PATIENTS CONSENT

Verbal and written informed consents were obtained from all patients.

AUTHORS' CONTRIBUTION

SY was involved in randomization of patients, data collection and analysis, literature review, discussion, results and reference writing and authored the manuscript.

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