Original Article

Serum C-reactive Protein in GDM Patients in Second Trimester of Pregnancy in a Tertiary Care Hospital of Bangladesh

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Abstract

***Background**: GDM is common, with raising prevalence, and is associated with a variety of adverse maternal and neonatal outcomes and higher morbidity. Many studies have been done recently to establish relationship between C-reactive protein level and GDM. But conflicting conclusions were found among different study populations.* ***Objective**: Aim of this study was to assess the correlation between C-reactive protein level and GDM in Bangladeshi population.* ***Materials and Methods**: This case control study was carried out in BIRDEM General Hospital from July 2019 to June 2020. One hundred subjects were selected. Among them 50 were GDM cases and 50 were healthy pregnant controls in second trimester. Structured questionnaire was used to obtain data. BMI was calculated. OGTT, HbA1c and C-reactive protein level were measured in all study subjects. Independent t-test, Pearson's correlation test and multiple logistic regression analysis were done. Data were analyzed by using SPSS software, version 23.0 for windows.* ***Results**: Mean age of GDM cases were 29.62± 3.96 years and that of controls were 28.54± 4.1 years. No significant difference between GDM and healthy pregnant women was found. Mean BMI of GDM cases was 29.63± 3.45 and of healthy controls was 24.17±2.10 kg/m^2 (significantly higher in GDM cases with p<0.001). FBG, 2 hrPPG and HbA1c levels were significantly higher in GDM cases than in controls. Serum CRP level of GDM cases and controls were 13.63 ±4.20 mg/L and 4.35±2.10 mg/L respectively. CRP was significantly higher (p<0.001) in GDM cases than in healthy controls. Age does not show any significant correlation with any of the glycemic status in GDM cases. BMI correlated significantly with FBG (p<0.05), 2-hr PPG (p<0.05) and HbA1c (p<0.001) in GDM cases. CRP correlated significantly with FBG (p<0.001), 2-hr PPG (p<0.01) and HbA1c (p<0.001) in GDM cases. Multiple logistic regression analysis showed significant association between HbA1c and CRP (p<0.05) in our GDM study subjects.* ***Conclusion :** This study revealed that CRP level is significantly elevated among women with GDM compared with women with normal glucose tolerance, especially during the second trimester.*

***Key words**: C-reactive protein; GDM; OGTT; HbA1c*

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Introduction

Gestational diabetes mellitus (GDM) is one of the most common metabolic disorder found during gestation and is defined as hyperglycemia of variable severity with onset or first recognition during pregnancy that does not proceed by either type 1 and type 2 diabetes.[1] According to 2017 International Diabetes Federation estimates, GDM affects 14% of pregnancies worldwide, representing 18.4 million births annually.[2] In Bangladesh, prevalence of GDM is 9.7% according to the WHO criteria and 12.95% according to ADA criteria.[3]

GDM could lead to adverse maternal and neonatal outcomes, which is largely as a result of high elevated blood glucose levels during 24−28 weeks.[4] Several complications like hypertension, hyperlipidemia, increased need of caesarian delivery, pre-eclampsia, spontaneous abortion, intrauterine fetal demise etc may develop in GDM mother.[5] Uncontrolled GDM mother also leads to neonatal complications like fetal malformations, birth trauma, macrosomia, respiratory distress syndrome, neonatal hypoglycemia and neonatal hyper-bilirubinemia, obesity, diabetes.[6,7] Insulin resistance (IR) and beta cell dysfunction play major role for development of GDM, and so pathophysiology of GDM is similar to type 2 DM.[8]

For a successful pregnancy inflammation may play a major role.[9] Inflammatory process is associated with implantation and decasualization during early periods of gestation, yet additionally in the uterine activation during delivery.[10] Nonetheless, during the mid-gestation a quiescence of inflammation is needed to ensure maternal tolerances for fetal antigen.[11] Inflammatory biomarkers with low cost is able to predict high risk pregnancy and thus allow a better screening during gestation. Most common inflammatory biomarker is C reactive protein which is an acute phase protein produced by hepatocytes in response to tissue injury, infection and inflammation.[12] CRP is significantly associated with several cardiovascular risk factors such as obesity, DM, smoking and hypertension. GDM is also associated with increased incidence of cardiovascular diseases and type 2 diabetes in future. GDM is an inflammatory state characterized by elevated levels of cytokines such as high sensitivity of CRP.[13] These inflammatory agents are insulin antagonists which increase resistance to insulin and stimulate acute phase of inflammatory response (CRP). In pregnancy an increase in maternal CRP has been associated with a variety of pregnancy complications including early pregnancy loss, preterm delivery, pre-eclampsia, fetal growth restriction, premature rupture of membranes and chorioamnionitis. [14]

Studies suggest that woman with elevated CRP levels had significantly increased risk of diabetes, independent adiposity and other risk factors.[15] Prevalence of GDM is 20% higher in Asian people.[16] Thus aim of this study was to assess the correlation between CRP level and GDM in Bangladeshi population.

Materials and Methods

This case-control study was carried out in Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) General Hospital from July 2019 to June 2020. A total of 100 subjects were selected for study from outpatient department of Gynecology and Obstetrics, BIRDEM-2 General Hospital. Among them, 50 were GDM cases and 50 were healthy pregnant women as controls.

Diagnosed GDM subjects in second trimester as cases and healthy pregnant women in second trimester as controls were included in this study. First and third trimester GDM subjects, healthy pregnant women, subjects with previous history of diabetes mellitus, pre-eclampsia and eclampsia, acute and chronic complications like hypertension, cardiac, renal and liver diseases, any recent acute infection such as fever, active infectious diseases such as viral hepatitis, tuberculosis, syphilis etc were excluded. Subjects with history of taking folic acid, vitamin B12, anti-inflammatory drugs such as NSAIDs were also excluded.

Purpose of this study was explained in details and informed written consent was taken from all study subjects. A structured questionnaire was used to obtain personal, medical, family, socioeconomic, drugs and obstetrical history. BMI was calculated from the anthropometric data.

A 75 gm OGTT was performed on all study subjects. GDM cases were diagnosed according to ADA criteria.[17] Blood glucose was measured by Beckman Coulter Au-680 auto analyzer using hexokinase method. HbA1c was measured by HPLC method by Bio-Rad variant™ II Turbo. CRP was measured in immunonephelometry on BN Prospec system. Descriptive statistics were presented as mean ± SD. Differences between groups were compared by independent t-test. Pearson's correlation coefficient test was done to explore correlation between plasma CRP level and glycemic status. Multiple logistic regression analysis was used to determine association between plasma CRP and HbA1c. $p<0.05$ was accepted as statistically significant. Statistical analysis was performed by using SPSS software, version 23.0 for windows.

Results

Table I shows 90% of GDM cases were above 25 years of age in comparison to 86% in controls. Among the GDM cases 72% were multipara in comparison to 68% of controls. Of the GDM cases 80% had family history of DM in comparison to 18% of controls. Among the GDM cases 82% had no previous history of GDM in comparison to 100% of controls.

Table II shows the mean age, BMI, FBG (fasting blood glucose), 2 hrs PPG (postprandial glucose), HbA1c and CRP level both in GDM cases and healthy controls. It shows the comparison of different parameters between GDM cases and healthy controls. Independent t-test was done to see the comparison. Mean age of GDM subjects and healthy controls were 29.62 ± 3.96 and 28.54 ±4.10 years respectively. No significant difference was found between the two groups regarding age. Mean BMI of GDM subjects and healthy controls were 29.63±3.45 and 24.17±2.10 kg/m^2. Significant difference was found between the two groups regarding BMI. Mean FBG of GDM subjects and healthy controls were 8.17±2.82 and 4.61±0.41 mmol/L. Significant difference was found between the two groups regarding FBG. Mean 2 hr PPG of GDM subjects and healthy controls were 11.58±2.54 and 6.9 ± 1.00 mmol/L. Significant difference was found between the two groups regarding 2-hour PPG. Mean HbA1c of GDM subjects and healthy controls were 10.95 ± 4.82% and 5.10 ±0.58%. Significant differences was found ($p<0.01$). Mean CRP of GDM subjects and healthy controls were 13.63± 4.20 and 4.35±2.10 mg/L. Here also significant difference was found between the two groups regarding.

Table I: Distribution of study subjects according to characteristics (n=100)

Parameters		Cases (GDM) (n=50)		Controls (n=50)	
		Number	Percentage	Number	Percentage
Age	<25 years	5	10	7	14
	>25 years	45	90	43	86
Gravida	Primipara	14	28	16	32
	Multipara	36	72	34	68
Family history of DM	Yes	40	80	9	18
	No	10	20	41	82
History of GDM	Yes	9	18	0	0
	No	41	82	50	100

Table II: Anthropometric and biochemical measures of study subjects (n=100)

Variables	Cases (GDM) (n=50) Mean ± SD	Controls (n=50) Mean ± SD	p values
Age (years)	29.62 ± 3.96	28.54 ± 4.1	0.188
BMI (kg/m^2)	29.63 ± 3.45	24.17 ±2.10	<0.001
FBG (mmol/L)	8.17 ± 2.82	4.61 ± 0.41	<0.001
2 hrs PPG (mmol/L)	11.58 ± 2.54	6.9 ± 1.00	<0.001
HbA1c (%)	10.95 ± 4.82	5.10 ±0.58	<0.01
CRP (mg/L)	13.63± 4.20	4.35±2.10	<0.001

Table III shows correlation of FBG with age, BMI, blood glucose 2-hour after 75 gm glucose, HbA1c and CRP. Significant positive correlation was found with BMI ($p<0.05$), 2-hr PPG ($p<0.001$), HbA1c ($p<0.001$) and CRP ($p<0.001$). Table IV shows correlation of 2-hr PPG with age, BMI, FBG, HbA1c and CRP. Significant positive correlation was found with BMI ($p<0.05$), FBG ($p<0.001$), HbA1c ($p<0.01$) and CRP ($p<0.01$).

Table III: Correlation of FBG with different variables in GDM cases (n=50)

	Correlated variables	r values	p values
Fasting blood glucose	Age	0.163	0.104
	BMI	0.581	<0.05
	2-hr PPG	0.710	<0.001
	HbA1c	0.663	<0.001
	CRP (mg/L)	0.586	<0.001

Pearson's correlation test done

Table IV: Correlation of 2-hr PPG with different variables in GDM cases (n=50)

	Correlated variables	r values	p values
2-hr PPG (after 75 gm glucose)	Age	0.115	0.253
	BMI	0.491	<0.05
	FBG	0.710	<0.001
	HbA1c	0.618	<0.01
	CRP	0.592	<0.01

Pearson's correlation test done

Table V shows correlation of HbA1c with age, BMI, FBG, 2hr PPG and CRP. Significant positive correlation was found with BMI ($p<0.001$), FBG ($p<0.01$), 2hr PPG ($p<0.001$) and CRP ($p<0.001$). Age had no significant correlation ($p=0.998$) with HbA1c. Multiple logistic regression analysis showed significant association between HbA1c and CRP. (Table VI)

Table V: Correlation of HbA1c with different variables in GDM cases (n=50)

	Correlated variables	r values	p values
HbA1c	Age	0.130	0.998
	BMI	0.496	<0.001
	FBG	0.610	<0.01
	2hr PPG	0.618	<0.001
	CRP (mg/L)	0.605	<0.001

Pearson's correlation test done

Table VI: Association of HbA1c with CRP in GDM cases (n=50)

Variables	Beta	p value
HbA1c	0.324	<0.05*
CRP (mg/L)		

Multiple logistic regression analysis done. Beta for standardized regression coefficient

Discussion

GDM is increasing day by day in Bangladesh. It is associated with an increased risk of type 2 diabetes, hypertension and cardiovascular diseases. Inflammation is marked by increased serum level of C-reactive protein, one of the markers of cardiovascular risk.[18] The aim of this study was to assess the relationship between plasma CRP level and GDM in Bangladeshi population. For this purpose 50 GDM cases and 50 non-GDM healthy pregnant women were studied in a tertiary level hospital of Bangladesh.

Mean age of our GDM cases were 29.62±3.96 years and that of controls were 28.54±4.1 years. There was no significant difference of age between GDM and healthy pregnant women with a p value of 0.188.

Zheng et al[19] also found similar results. But older age is accepted as an independent risk factor of GDM. As maternal age increases, incidence of GDM increases from 2.2% in women age under 25 years to 14.7% in women over 35 years.[20] Some studies reported that plasma CRP levels increased with age.[21] But whether age influenced rise of associated GDM still needs further study.

In our study, we observed that mean BMI of GDM cases was higher when compared to that of healthy controls and it was significantly higher in GDM cases ($p<0.001$). It represents that overweight women or women with BMI$\geq$25kg/m^2 had more chance to develop GDM. This finding is similar to the finding of Kumari & Singh[22] and also Makgoba et al[23].

Genetic background plays a vital role in the occurrence of GDM. Family history of T2DM was also reported as an independent risk factor of GDM in many studies.[24] Our study also showed 80% of GDM cases had family history of DM in comparison to 18% in controls. Most studies found higher odds ratio of family history of T2DM in first-degree relatives for developing GDM.[25] In our study18% of the GDM cases had history of GDM in previous pregnancies.

In our study, FBG, 2-hr PPG and HbA1c levels were significantly higher in GDM cases than in controls. Other studies showed that worsening glycemic status has predominant role in developing GDM.[26,27]

Many of the research articles showed a strong association between obesity and elevated inflammatory markers that recognize obesity as a state of chronic low grade inflammation. Maternal obesity has been associated with upregulation of inflammatory marker.[28,29]

The aim of our study was to find out the correlation and association of C-reactive protein with development of gestational diabetes. Pearson correlation test was done to assess correlation between different glycemic status of GDM cases with age, BMI and CRP level. Age does not show any significant correlation with glycemic status, contrary to the findings of Kumari & Singh[22]. BMI correlated significantly with FBG ($p<0.05$), 2-hr PPG ($p<0.05$) and HbA1c ($p<0.001$). CRP correlated significantly with FBG ($p<0.001$), 2-hr PPG ($p<0.01$) and HbA1c ($p<0.001$).

In our study mean serum CRP in GDM cases was significantly higher than in healthy pregnant women. It is similar to Mostafa et al[30]. Our study also showed that maternal CRP had significant positive correlation with GDM ($p<0.001$) which is similar to the findings of Kumari & Singh[22]. Another study done by Mojibian et al[31] showed no significant relationship between high serum CRP and GDM.

In multivariate analysis with GDM, CRP had significant positive association with GDM ($p=0.021$). Study done by Zhu et al[21] also showed association of CRP with GDM.

This study revealed that CRP level is significantly elevated among women with GDM compared with women with normal glucose tolerance, especially during the second trimester. Thus this study supports the hypothesis that inflammation contributes to the development of glucose intolerance. Here it suggests that subsequent development of glucose intolerance in second trimester is related to maternal high CRP. Furthermore, it also recognizes an overwhelming effect of maternal obesity on inflammatory marker to establish the relationship between high CRP with GDM.[32] As CRP seems to have an impact on GDM women, so much attention should be paid to CRP for assessing the risk of maternal and fetal adverse outcome.

This study indicates that in Bangladeshi population, pregnant women with higher plasma CRP level might have a higher GDM risk. So, early detection of CRP during pregnancy will help in prevention and management of many adverse pregnancy outcomes.

Limitations

Several limitations of this study are worth mentioning. Our sample size was small. The confounding factors such as dietary and exercise status could not be eliminated completely. Since this study was not prospective, causes of sequential rise of CRP and GDM risk could not be determined.

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