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The association of maternal serum CRP level with gestational diabetes mellitus

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Article Info

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Abstract

Gestational diabetes mellitus is a common medical condition during pregnancy that has detrimental effects on maternal health and fetal well-being. Many serum markers are known to be associated with gestational diabetes, a subclinical inflammatory state that liberates inflammatory mediators, acute phase proteins like CRP into the maternal circulation. This phenomenon has invited many researchers to study inflammatory mediators and acute phase proteins as markers of gestational diabetes mellitus.This case-control study was conducted in the Department of Obstetrics and Gynecology of Bangabandhu Sheikh Mujib Medical University, Dhaka, between July 2016 and June 2017. The objective of the study was to evaluate the association of serum CRP level with gestational diabetes mellitus. A total of 140 pregnant women who attended the out-patients antenatal clinic at their 2nd and 3rd trimester (13-40 weeks) of pregnancy were enlisted for the study. The case group consisted of 70 pregnant women who were diagnosed with GDM. Similar number of healthy pregnant women were recruited as control. GDM was diagnosed using standard 75 g OGTT. Blood sample was taken from study subjects to estimate the serum CRP level. CRP level up to 5mg/L was taken as normal. Data analysis was done by utilizing SPSS version 16. The mean BMI of the case group women was significantly higher than the mean BMI of the control (p=0.001). The mean CRP level in case was 13.87± 10.19 and the mean for CRP for control group was 4.59± 2.41. There was an association of raised level of CRP with GDM. Pregnant mothers with raised level of CRP (& gt; 5 mg/L) were 6.1 times more likely to have GDM than mothers with normal level of CRP. The study concluded that a significant association was found between the raised level of CRP and gestational diabetes mellitus.

Introduction

Gestational diabetes mellitus (GDM) is a common medical disease during pregnancy. It is defined as any degree of glucose intolerance with onset or first recognition during pregnancy.[1]

Hyperglycaemia first detected at any time during pregnancy is classified as either: Diabetes mellitus in pregnancy(DIP) or gestational diabetes mellitus (GDM). GDM is diagnosed when FBS is 5.1- 6.9mmol/L or 2 hours-plasma glucose is >8.5-11.0 mmol/L following a 75g oral glucose load[2]. Worldwide approximately 7% of pregnancies are associated with GDM, ranging from 1-14%, depending on different population studies and diagnostic criteria employed.[3] Among the diabetic pregnant women, gestational diabetes complicates 87.5% of pregnancies.[4] In Bangladesh, the prevalence of GDM is 9.7%.[5] Certain groups of women are at increased risk of developing GDM. The risk factors are: age above 35 years, BMI more than 30kg/m^2, previous history of GDM, previous history of delivering macrosomic baby (weight >4.0kg), prior history of unexplained still birth, family history of diabetes (in 1st degree) and polycystic ovarian syndrome.[3] GDM has detrimental effects on maternal health and fetal well being. During pregnancy it can cause miscarriage, increased incidence of preeclampsia, polyhydramnios, urinary tract infection, vulvovaginitis, and labour can be complicated by prolonged labour, shoulder dystocia due to macrosomia, birth trauma and increased operative interference. Fetal

and neonatal complications include fetal macrosomia, congenital malformations, IUD, birth injuries, neonatal hypoglycaemia, respiratory distress syndrome, hyperbilirubinaemia, polycythemia and hypocalcemia.[6] Approximately half pregnant women with GDM will ultimately develop type 2 DM later in life.[3] Different guidelines and associations have suggested different screening regimes for GDM. However, in this study, GDM is diagnosed using standard WHO guidelines using a 75g glucose load.[2] The hallmark of GDM is a metabolic defect of β-cell deterioration and insulin resistance. In normal pregnancy, progressive insulin resistance occurs, which is associated with increased insulin release by the β-cells in order to maintain glucose homeostasis. Women with GDM cannot increase insulin production to compensate for the increased insulin resistance resulting in deterioration of β-cells and hyperglycemia.[7] The increased insulin resistance in GDM causes subclinical inflammatory changes in the body, releasing inflammatory mediators like cytokines-IL-6 and TNF-α.[8] CRP is an acute phase protein liberated by the hepatocytes and the production is influenced by the inflammatory cytokines-IL-6 and TNF-α. Therefore, the CRP level rises when there is any inflammatory processes occurring in the body.[8] It has been suggested that GDM may be a state of subclinical inflammation that has not been directly evaluated. Many studies have suggested the use of inflammatory mediators and acute phase proteins (CRP) as the predictor of the development of GDM. However, the results of those studies were conflicting. Most studies have found the raised level of CRP associated with GDM.[9-11] On the contrary, few studies have reported no association with GDM.[12,13] Therefore, this study aimed to find out the association of raised levels of CRP with GDM.

Methods

This case-control study was conducted in the Department of Obstetrics and Gynecology of BSMMU, Dhaka, between July 2016 and June 2017. Ethical clearance for the study was taken from the Institutional Review Board of BSMMU. Permission for the study was taken from the concerned departments where this study was conducted. A total of 140 pregnant women who attended the outdoor antenatal clinic during their 2nd and 3rd trimesters (13-40 weeks) were enrolled for the study. The case group consisted of 70 pregnant women who were diagnosed with GDM. The control group comprised 70 healthy pregnant women. Pregnant mothers with pregestational diabetes, hypertensive disorders, thyroid disorders, chronic renal disease and systemic infections were excluded from this study. The purpose and procedure of the study was discussed with the participants and informed written consent was taken. The study was conducted anonymously and confidentiality of information was assured. An interviewer-administered questionnaire was used for data collection. Comprehensive socio-demographic history, obstetric history, gestational age, family history and medical history were recorded in the predesigned data sheet. Their antenatal records, early ultrasound scans, and medical records of GDM diagnosis were reviewed. Pregnant mothers who had undergone GDM screening and were diagnosed as GDM per the WHO, with FBS 5.1 to 6.9mmol/L and 2 hours after 75g glucose of ≥8.5 to 11.0 mmol/L were enrolled for the study as a case group. Routine physical examination and anthropometric measurements (height, weight) were taken, and obstetric examinations were conducted and recorded.

After selecting cases and controls, with all aseptic measures, 3 ml antecubital venous blood sample was taken from each subject to estimate the serum CRP levels. The blood sample was transferred into a clean, dry test tube and allowed to clot completely before centrifugation. After centrifugation, at least 200µL of cell-free samples were transferred to a storage tube. The tubes were tightly stoppered immediately. Samples were stored in a tightly stoppered tube at room temperature (15-250 C) or no longer than 8 hours. If the assay was not completed within 8 hours, samples were refrigerated at 2-80c. If the assay was not completed within this period, samples were in a freeze at -200c or colder. Samples were thawed only once before the procedure for assay. Serum CRP was measured by immunoturbidimetric method with Automated Analyzer: Beckman Coulter– AU680 at the Department of Biochemistry and Molecular Biology of BSMMU. The reference value of serum CRP was considered normal up to 5 mg/L.

Results

Table - I show demographic data for the study groups. The difference was statistically not significant ($p>0.05$) between two groups. Mean Age ±SD of case is 29.09 ±5 and for control is 27.09 ± 4.64 years.

In the case group, 50% of the subjects were overweight, followed by 22.9% obese, compared to the control group, where 58.6% of pregnant women had normal BMI. The mean BMI of the case was higher than the mean BMI of control (mean BMI is 26.722±3.591 for the case and that of control is 24.362±3.043) which is statistically significant ($p<0.001$) as shown in Table - II.

Majority of the study subjects were multigravida in both the groups with 71.4% and 58.6% for case and control, respectively. The difference was statistically not significant ($p>0.05$) between the two groups. (Table - III)

Table-I

Distribution of patients' profile by demography (n=140)

Patient Profile	Case (n=70)	Control (n=70)	P-value
Age (in years)			
≤20	3 (4.3%)	7 (10.0%)	0.34^{ns}
21-30	45 (64.3%)	47 (67.1%)	
31-40	21(30.0%)	16 (22.9%)	
>40	1 (1.4%)	0 (0.0%)	
Occupation			
Housewife	46 (65.7%)	53 (75.7%)	0.254^{ns}
Service holder	20 (28.6%)	16 (22.9%)	
Student	4 (5.7%)	1 (1.4%)	
Education			
Illiterate	4 (5.7 %)	6 (8.6 %)	0.782^{ns}
Primary	9 (12.9 %)	12 (17.1%)	
Secondary	38 (54.3%)	34 (48.6%)	
Higher secondary & above	19 (27.1 %)	18 (25.7%)	
Family Income			
Low Income	13 (18.6%)	9 (12.9%)	0.377^{ns}
Middle Income	37 (52.9%)	45 (64.3%)	
Higher Income	20 (28.6%)	16 (22.9%)	

Table-II

Distribution of study subjects by BMI (n=140)

BMI (kg/m2)	Case	Control	P value
Under weight	5 (7.1%)	6 (8.6%)	0.001^{s*}
Normal	14 (20.0%)	41 (58.6%)	
Over weight	35 (50.0%)	20 (28.6%)	
Obese	16 (22.9%)	3 (4.3%)	
Total	70 (100.0%)	70 (100.0%)	
Mean BMI ±SD	26.722±3.591	24.362±3.043	0.001^{s**}

More than 70% of the were in the range of 29-40 weeks of gestation followed by around 20% in the range of 13-28 weeks in both the groups. The difference was statistically not significant (p>0.05) between two groups. (Table - IV)

Table-III

Distribution of study subjects by gravidity (n=140)

Gravida	Case	Control	P value
Primi	20 (28.6%)	29 (41.4%)	0.111^{ns*}
Multigravida	50 (71.4%)	41 (58.6%)	
Total	70 (100.0%)	70 (100.0%)	
Mean gravida±SD	1.71±.455	1.59±.496	0.122^{ns**}

Table-IV

Distribution of study subjects by gestational age (n=140)

Gestational age (weeks)	Case	Control	P value
13-28	16 (22.9%)	20 (28.6%)	0.425^{ns*}
29-40	54 (77.1%)	50 (71.4%)	
Total	70 (100.0%)	70 (100.0%)	
Mean gestational age ±SD	32.46±5.202	31.74±5.351	0.425^{ns**}

Table-V shows the mean fasting blood sugar of case is significantly higher than the mean fasting blood sugar of control group. The mean FBS of case is 5.61±.609 and for control is 4.54±.403 with the p=0.001. The mean blood sugar level 2 hours after 75g glucos is 8.97±.872 and the mean blood sugar level 2 hours after 75g glucose for control is 6.68±.736. The differences between the case and control is statistically significant (p=0.001).

The mean CRP level of case is significantly higher than the mean CRP level in the control group. The mean of CRP in case is 13.87±10.188 and the mean of CRP for control group is 4.59±2.414 with the p=0.001.

Table - VI shows mothers with GDM had raised level of CRP in 58(82.9%) in comparison to only 31(44.3%) of mothers without GDM had higher level of CRP. The Odds Ratio (OR) of developing GDM in pregnant women with raised level of CRP (>5mg/L) in their 2nd and 3rd trimester (13 – 40 weeks) of pregnancy was found to be 6.1 fold (95% CI: 2.787-13.268) higher than that in women with normal level of CRP (≤ 5mg/L) (p=0.001).

Table-V

Blood sugar levels and CRP levels in study groups (n=140).

Variables	Case		Control		P value*
	n	Mean±SD	n	Mean±SD	
Fasting blood sugar	70	5.61±.609	70	4.54±.403	0.001s
2 hours after 75 g glucose	70	8.97±.872	70	6.68±.736	0.001s
CRP	70	13.87±10.188	70	4.59±2.414	0.001s

Table-VI

Association of CRP level with GDM (n=140)

CRP level (mg/L)	Case (n=70)	Control (n=70)	OR (95% CI)	P value*
>5	58 (82.9%)	31 (44.3%)	6.1 (2.787-13.268)	0.001s
≤5	12 (17.1%)	39 (55.7%)		

Table-VII

Distribution of CRP according to the gestational age in study subjects (n=140):

Gestational age (weeks)	Case (n=70) mean±SD	Control (n=70) mean±SD	p value*
2nd trimester (13-28)	9.92± 7.56	4.21±0.23	0.003s
3rd trimester (29-40)	15.05± 10.62	4.75±2.46	0.001s

Table - VII shows the mean±SD of CRP levels in case group is significantly higher as compared to mean±SD of CRP level in control group ($p<0.05$) in both 2nd (13-28weeks) and 3rd (29-40 weeks) trimester of pregnancy.

There is a positive correlation of CRP levels with 2 hours after 75g glucose level in pregnant mothers with GDM with r=0.317 and p=0.007 as compared to no correlation in mothers without GDM (r=.011, p=.925). (Figure-1)

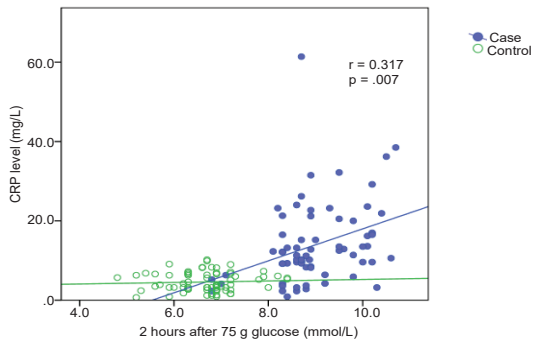

Figure -1: "Scatter plot" showing the correlation of CRP levels with 2hours after 75g glucose level

There was a positive correlation between CRP level and gestational age in mothers with GDM with r=0.260 (p=0.030). However, there was a negative correlation between CRP levels and gestational age in control group with r= -0.128 (p=0.286) as shown in figure - 2.

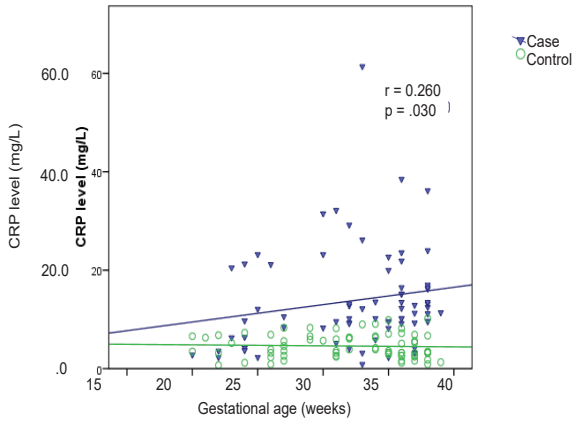

Figure - 2: "Scatter plot" showing the correlation of CRP level with gestational age

Discussion

The aim of this case-control study was to demonstrate the association between raised level of CRP and gestational diabetes mellitus. Several studies showed the association of inflammatory mediators with diabetes.

The link between the raised level of inflammatory mediators in the maternal circulation and the development of gestational diabetes is suggested to be due to the release of inflammatory substances in response to subclinical inflammation caused by raised insulin resistance present in the diabetic patients.[8-10]

In this study, a total of 140 pregnant women were evaluated and among them 4.3% participants of case group and 10% of control group were below 20 years; 64.3% of case and 67.1% of control were between 21 to 30 years of age; 30% of case and 22.9% of control were between 31-40 years of age; and more than 40 years of age were 1.4% cases. The age range of patients was between 18 and 44 years with the mean age was 29.09±1.9 for case and 27.09 ± 4.64 for control.

Majority of them were between 21 to 30 years of age in both groups.

In current study, maximum patients were housewives 46 (65.7%) of case, 53 (75.7 %) of control and, 20 (28.6%) of case and 16 (22.9 %) of control were service holders. Whereas 4 (5.7 %) of case and 1 (1.4%) of control were students. Majority belonged to lower- and middle-class family.

Some studies have related pre-pregnancy BMI with the development of gestational diabetes.[14,15] In this study, 50% of the mothers with gestational diabetes were overweight and 23% of them were obese. The mean BMI of case was significantly higher than that of control (mean BMI of case is 26.722±3.591 and control is 24.362±3.043 with p=0.001). From this finding, high BMI could be regarded a as risk factor for gestational diabetes.

The current study showed that among 70 mothers with gestational diabetes, majority 43 (61.4%) were multiparous as compared to only 27 (38.6%) are nulliparous. The finding is in line with the study[15] where they have studied on the risk factors for gestational diabetes mellitus. It was a retrospective study. The study reported that multiparous women were more likely to develop gestational diabetes than nulliparous with OR=1.93 (1.24–3.02) and p=0.004.

In the present study 54 (77.1%) of the mothers were diagnosed to have gestational diabetes at 29-40 weeks of gestation as compared to only 16 (22.9%) diagnosed at 13-28 weeks of gestation. The possible reason could be, most of the mothers made first antenatal visit (booking visit) late. The other reason could be that mothers do not come in a fasting state to the hospital. So, OGTT test cannot be done at the booking visit. However, they were screened later in the pregnancy and most of them were diagnosed late in their pregnancy. One study shows fasting blood glucose level was found to decrease gradually from pre-conceptional period to conception.[16]

The fasting blood glucose level further decreases through second and third trimester of the pregnancy and returns back to pre-conceptional level during the postpartum period. Therefore, although the diagnosis of gestational diabetes was made late in the gestational period, there is less chance of miss diagnosing the case in this current study.

The current study showed there is a positive correlation between CRP level and gestational age in mothers with gestational diabetes (r=0.260) as compared to mothers without gestational diabetes where there is a negative correlation (r= -0.128). The possible explanation could be that with increasing in gestational age, the level of insulin resistance also rises depending on the control of sugar level. Ultimately increased level of CRP is released into maternal circulation. The present study showed there is an association between raised level of CRP (>6.310 mg/dl) with gestational diabetes mellitus. Among 70 pregnant mothers with gestational diabetes, 55 (78.6%) had raised level of CRP as compared to only 19 (27.1%) out of 70 had raised level of CRP in pregnant mothers without gestational diabetes. Mean CRP level of the cases was significantly higher than that of the control group (mean CRP of case is 13.87±10.188 and mean CRP of control is 4.59±2.414 with p=0.001). The findings are consistent with the previous study which showed the median CRP level was significantly higher in GDM (5.5 mg/liter) as compared to IGT (4.4 mg/liter) and lean NGT (4.4 mg/ liter) (overall p=0.0297).[11] The same study had measured fasting insulin levels as well. The GDM patients had higher fasting insulin levels as compared to normal NGT (overall p=0.0007). However, the present study finding could not comment on the fasting insulin level as the fasting insulin level was not checked. Another study compared the CRP level between two groups of women; one group who had a history of gestational diabetes and another group who had no history of gestational diabetes.[17] The CRP level was found significantly higher in the group who had a history of gestational diabetes as compared to the group who did not have the history of gestational diabetes. This shows CRP level can be used for the marker of gestational diabetes.

In the present study the correlation between CRP level and the blood glucose level 2 hours after 75g glucose load showed positive correlation. A similar type of study reported significant correlation between CRP level and fasting blood sugar level.[18] However, they have not done correlation with 2 hours after 75g glucose load.

The present study demonstrated that there was an association with raised level of CRP with GDM. Mothers with GDM had raised level of CRP in 58 (82.9%) as compared to only 31 (44.3%) of mothers without GDM who had raised level of CRP. The Odds Ratio (OR) of developing GDM in pregnant women with raised level of CRP (>5mg/L) in their 2nd and 3rd trimester (13 – 40 weeks) of pregnancy was found to be 6.1 fold (95% CI: 2.787-13.268) higher than that in women with normal level of CRP (≤5mg/L) (p=0.001). This finding is in line with other similar type of study.[10]

Conclusion

This study attempted to investigate maternal serum CRP and its association with GDM. It concluded that serum CRP level is found to be significantly elevated in pregnant women with gestational diabetes mellitus when compared with non GDM pregnant women. Thus, high serum CRP may be considered as a risk factor for the development of GDM. Therefore, it can be considered as a reliable screening test for pregnant women with GDM risk factors.

Limitations

The study was carried out within a short period. The study population was selected from one selected hospital, so that the results of the study may not express the exact picture of the country. Small sample size with purposive sampling was also a limitation of the present study.

Recommendations

Our study suggests maternal serum CRP is significantly associated with GDM. Further study with larger sample size in multiple centers with long duration may strengthen the outcome of this study result.

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