

Original Research Article

Elevated first trimester C-reactive protein as a predictor of gestational diabetes

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ABSTRACT

Background: The incidence of type 2 diabetes is increasing at an alarming rate, particularly among young women. GDM is a unique prediabetes state that shares common risk factors with type 2 diabetes, and similar alterations in carbohydrate metabolism. Objectives of this study the elevation of C-reactive protein in the first trimester of pregnancy as a predictor of gestational diabetes.

Methods: This hospital-based study comprised of patients (Primigravida) visiting the obstetric OPD or admitted in Obstetric wards. Detailed history and clinical examination of the patient was recorded on a Proforma. Blood samples of patients were taken for: (i) C-reactive protein in first trimester of pregnancy; and (ii) Blood sugar (fasting & post-prandial) during their first antenatal visit and patients were followed up in subsequent visits in second and third trimester for development of gestational diabetes.

Results: There were seven women who developed gestational diabetes and had elevated first trimester C-reactive protein levels as compared to other group in which only two women developed gestational diabetes mellitus but did not have elevated C-reactive protein in their first trimester. However, there were two women, who had elevated C-reactive protein, but did not subsequently develop gestational diabetes mellitus and women with C-reactive protein in normal range who did not develop gestational diabetes mellitus were 56.

Conclusion: An association between first trimester inflammation marked by increased CRP levels, and subsequent risk of development of GDM has been identified.

Keywords: C-Reactive Protein, First Trimester, Gestational Diabetes, Predictor

INTRODUCTION

The emphasis in classifying diabetes mellitus has shifted more etiology.¹ Type 1 diabetics often express particular HLA haplotypes and have anti-islet cell antibodies contributing to their insulin dependence and risk of ketoacidosis.^{1,2} Type 2 diabetics have minimal to no risk of ketoacidosis even though they may require insulin to control their blood glucose levels.^{1,3} Debate continues over whether gestational diabetics are women whose glucose intolerance is solely a function of their pregnant

compared with their non-pregnant state. Alternatively, pregnancy may merely serve to unmask an underlying propensity for glucose intolerance, which will be evident even in the nonpregnant state at some time in future if not in the immediate postpartum period.⁴

Gestational diabetes mellitus (GDM), defined as the new onset or new diagnosis of glucose intolerance during pregnancy, com of pregnancies.⁵ This estimate will likely increase in the future, given the alarming increase in rates of obesity and type 2 diabetes among young Women Like

type 2 diabetes, GDM results from a combination of increased insulin resistance and impaired pancreatic insulin resistance and impaired pancreatic insulin secretion, and women with a history of GDM are at significantly increased risk of developing type 2 diabetes in the future.⁵ Pregnancy is associated with increased tissue resistance to insulin, resulting in increased levels of blood insulin as well as glucose and triglycerides.⁶ These changes are due to placental lactogen and elevated circulating estrogens and progesterone. Although pregnancy does not appear to alter the long term consequences of diabetes, retinopathy and nephropathy may first appear or become worse during pregnancy.⁶

The insulin resistance of pregnancy appears to be a post receptor phenomenon.⁷ Because, delivery of the fuels, required for the growth and oxidative needs of the fetus is a function of the maternal fuel concentration & placental blood flow, resistance to insulin action in the maternal circulation raises the mean levels of glucose and other nutrients in the maternal circulation, thereby shunting a larger amount of glucose and aminoacids from the mother to the fetus in the last half of pregnancy, the time of maximal fetal growth.⁷ Fasting and pre-prandial glucose values are lower during pregnancy in both diabetic and nondiabetic women.⁸ Euglycemia is considered to be 60-80 mg/dl while fasting and 30-45 minutes before meals and <120mg/dl 2 hours after meals. Gestational diabetes is present when two or more of the following venous plasma concentrations are equaled or exceeded: fasting, 105mg/dl, and after a 100 gm of oral glucose load, plasma glucose values of 190mg/dL at 1 hr, and 165 mg/dL at 2 hr, and 145 mg/dL at 3 hr.⁹

While perinatal problems for mother and baby are decreased by fastidious diabetic control, the incidence of hydramnios, preeclampsia, eclampsia, infections and prematurity are increased even in carefully managed diabetic pregnancies.¹⁰ There is no doubt that impressive strides have been made with regard to diabetes in pregnancy, so that at present time the expectation of the diabetic mother regarding pregnancy performance and fetal outcome can be fairly similar to that of a nondiabetic patient. There seems to be needed to give an insight into magnitude of the problem of diabetes and pregnancy and to search for early predictors of gestational diabetes.

Inflammation, marked by increased serum levels of C – reactive protein (CRP), is an important independent risk factor for cardiovascular disease.¹¹ Inflammation is also associated with insulin resistance, and studies indicate that increase inflammation at base line is an independent of type 2 diabetes.¹² The molecular basis for the link between inflammation and diabetes likely relates to the actions of cytokines such as interleukins (IL-6) and tumor necrosis factor, (TNF) which induce insulin resistance and stimulate the acute phase inflammatory response.¹³ Whether inflammation is similarly associated with the development of GDM is unknown.

This prospective study is designed to study the elevation of C-reactive protein measured by ELISA technique in the first trimester of pregnancy as a predictor of gestational diabetes.

METHODS

This hospital-based study of the Elevated first trimester C-reactive protein as a predictor of gestational diabetes. Comprised of patients (Primigravida) visiting the obstetric OPD or admitted in Obstetric wards of SMGS Hospital - and associated hospital of Govt. Medical College, Jammu from June 2013 to May 2014. Study was approved by Institutional Ethics Committee. Written informed consent was obtained from the study participants before enrolling them into the study. Detailed history and clinical examination of the patient was recorded on a Proforma.

Blood samples of patients were taken for

- C-reactive protein in first trimester of pregnancy.
- Blood sugar (fasting & post-prandial) during their first antenatal visit and patients were followed up in subsequent visits in second and third trimester for development of gestational diabetes.

C-Reactive protein measurements

Standard CRP methods routinely available in the clinical laboratory have limits of detection of three to five mg/l. However, these methods are unsuitable for detecting CRP as risk factor for coronary heart disease since the serum CRP concentration could be much lower than the cutoff levels in the standard CRP tests. Therefore, only high sensitivity or ultrasensitive test for C-reactive proteins were used for this purpose. High sensitivity assays now commercially available, typically have a detection limit of about 0.015 mg/dl. These high sensitivity methods usually use enzyme linked immunosorbent assay (ELISA), nephelometric or turbidimetric methods. Quantitative assay of C-reactive protein was done by ELISA method. Blood Samples were drawn within 24 hours (maximum 72 hours) of hospital admission and at discharge. Control blood samples (Total No. 25) were obtained from age/sex matched control population without history of diabetes, drawn from attendants of patients admitted in obstetric wards.

Blood sugar (fasting and post-prandial) measurement

All women in this prospective study without a history of antenatal type 1 or type 2 diabetes underwent routine GDM screening with the 50 gm oral glucose loading test (GLT) in the first trimester. In the non-fasting state, subjects consumed 50 gm of oral glucose and glucose levels were assayed using glucose oxidase-peroxidase method in 1-hr post loading plasma samples. Women with 1 hr post-loading plasma glucose level >140mg/dl were considered to be at increased risk for gestational

diabetes mellitus (GDM) and underwent a diagnostic, fasting, 100gm - 3 hr oral glucose tolerance test (GTT) within a week following GLT. Women were diagnosed with GDM if two or more of the following venous plasma concentrations were equaled or exceeded: fasting, 105 mg/dl, 190 mg/dL at 1 hr, and 165 mg/dL at 2 hr, and 145 mg/dL at 3 hr.

RESULTS

In this study, a total of 67 primigravida women were enrolled from June 2013 to May 2014. Given the association of hypertension, multiparity and antenatal history of diabetes mellitus with increased C-Reactive protein levels, only primigravida with no antenatal history of diabetes were included. Demographic and anthropometric characteristics of these women are shown in Table 1.

Table 1: Demographic and anthropometric characteristics of pregnant women.

Variables	Mean±S.D.	Range
Age (years)	26.01±2.55	20-33
Height (m)	4.11-5.55±5.16	4.11-5.50
Weight (kg)	56.41±4.43	45-72
CRP (mg/dL)	5.32±4.00	2-18

All these women in this prospective study underwent routine GDM screening with 50 gm. of oral glucose loading test (GLT) in the first trimester (between 8-12 weeks). In a non-fasting random state, subjects consumed 50 gm of oral glucose and glucose levels were assayed after 1 hr. Women with 1-hr postloading plasma glucose level > 140 mg/dl (in our study 9 women) were considered to be at increased risk for development of GDM and underwent a diagnostic 3 hr. oral glucose tolerance test (GTT) with 100 gm of glucose. Women were diagnosed with GDM if two or more of the following venous plasma concentrations were equaled or exceeded: fasting, 105 mg/dl, 190 mg/dL at 1 hr, and 165 mg/dL at 2 hr, and 145 mg/dL at 3 hr.

Among these 67 women gestational diabetes mellitus was diagnosed in nine. The average gestational age at the time of first antenatal visit when serum was sampled for CRP was between 8-12 weeks. Women who subsequently developed gestational diabetes mellitus were heavier as shown in Table 2.

Table 2: Body Mass Index and development of GDM.

Body Mass Index (kg/m ²)	No. of women who developed GDM	No. of women who did not develop GDM
<25	4	58
25-30	5	0

Table 2 shows distribution of women who participated in

study depending upon the body mass index. As evident from Table No 2, women who developed GDM having BMI less than 25 were four in number as compared to women with BMI between 25-30 who were five in number. Two women who had elevated C-reactive protein in first trimester did not develop gestational diabetes mellitus (Table 3). On statistical analysis (Fisher Exact Test) P value was found as 0.00001. Women with GDM delivered by LSCS and most delivered babies were of higher birth weight.

Table 3: C-reactive protein levels and development of GDM.

C-Reactive Protein Levels	No. of women who developed GDM	No of women who did not develop GDM
Elevated	7	2
Not elevated	2	56

Table 3 shows distribution of women CRP level wise. There were seven women who developed gestational diabetes and had elevated first trimester C- reactive protein levels as compared to other group in which only two women developed gestational diabetes mellitus but did not have elevated C-reactive protein in their first trimester. However, there were two women, who had elevated C-reactive protein, but did not subsequently develop gestational diabetes mellitus and women with C-reactive protein in normal range who did not develop gestational diabetes mellitus were 56. On statistical analysis P value was found to be significant (P: 0.000001).

Table 4: Family history of Diabetes Mellitus and development of GDM.

Family history of diabetes mellitus	No. of women who developed GDM	No. of women who did not develop GDM
Present	6	3
Not Present	3	55

Table 4 shows distribution of women depending upon the family history of diabetes mellitus. As clear from the table no. 6, women who developed gestational diabetes mellitus had a family history of diabetes mellitus and three women who did not have family history of diabetes mellitus developed gestational diabetes mellitus. On statistical analysis P value was found to be 0.00006.

Table 5 shows lipid profile wise distribution of women who developed gestational diabetes mellitus. As evident from the Table no. 5, women who developed gestational diabetes mellitus had deranged lipid profile in the form of elevated total cholesterol and TGL levels, whereas in rest of them no lipid profile abnormality was seen.

Table 5: Lipid profile and development of GDM.

Lipid Profile	No. of women who developed GDM	No. of women who did not develop GDM
Deranged	9	0
Not deranged	0	58

Using proportion hazard model, the risk factors for development of gestational diabetes mellitus were assessed by using C-reactive protein, body mass index, height, weight as independent variables (Table 6). It was found that the strongest predictor of gestational diabetes mellitus was C-reactive protein (X^2 24.12 $p < 0.00009$) followed by weight and height (X^2 17.22 $p < 0.0003$) and (X^2 4.33 $p < 0.03$) respectively. Other factors did not have predictive ability. Logistic regression analysis shows C-reactive protein as a strong risk marker for development of gestational diabetes mellitus. Other variables like weight and height were also found to be significantly predicting the risk of development of gestational diabetes mellitus.

Table 6: Proportion hazard model for assessment of the risk factors for development of gestational diabetes mellitus.

Variable	X^2	P value
CRP	24.12	0.00009
BMI	2.50	0.11
Wt	17.22	0.0003
Ht	4.33	0.03

CRP:C – reactive protein, BMI: Body Mass Index, Wt.: Weight, Ht: Height.

DISCUSSION

In this prospective study we tried to identify an association between first trimester inflammation, marked by increased CRP levels, and subsequent risk of development of GDM. This effect was independent of established risk factors for GDM such as age, multiparity, smoking, antenatal history of diabetes mellitus. This association of elevated first-trimester CRP and subsequent development of GDM faces a challenge by the results in four cases of study wherein two cases which showed elevated first-trimester CRP but never developed GDM and the other two cases where women developed GDM but never displayed elevation of CRP in first-trimester. Subjects who developed gestational diabetes mellitus were divided into two groups depending upon their BMI i.e. BMI <25 and BMI between 25-30. Five women out of nine with BMI in range of 25-30 developed GDM whereas women with GDM with BMI <25 were four in number.

Several studies have firmly established the strong association between obesity and elevated inflammatory markers, leading to the recognition of obesity as a state of chronic low-grade inflammation.¹⁴⁻¹⁷ Circulating levels of

CRP correlate highly with BMI.¹⁸ Given the demonstrated value of CRP in predicting incident type 2 DM and cardiovascular disease, chronic sub clinical inflammation has been proposed as a pathophysiologic mechanism linking adiposity with an increased risk of metabolic and atherosclerotic disease.¹⁹ This hypothesis is consistent with the observation from several studies that the inclusion of measures of adiposity in multivariate models partially attenuates the relationship between baseline CRP and incident diabetes.²⁰⁻²³

Demonstrated microvascular endothelial dysfunction, metabolic perturbation (including fasting hyperinsulinemia), and low grade inflammation, as manifested by elevated CRP and IL-6, in normoglycemic obese pregnant women, compared with lean pregnant controls.[24] The findings of the present study further support an independent association between maternal obesity and CRP while extending the relationship over different strator of glycemic tolerance.²⁴

On the other hand, knowledge of pre-pregnancy BMI and insulin levels would have further added to this study for strengthening above mentioned hypothesis but lack of regular follow-up of patients remains one of biggest setbacks in studies in our region.

Maternal obesity has been associated with the up-regulation of inflammatory markers in the first trimester prior to any observed glucose dysregulation.²⁴ Findings of present study suggest that the subsequent development of glucose intolerance later in pregnancy is not independently related to maternal CRP level. Furthermore, it is important to recognize that an overwhelming effect of maternal obesity on inflammatory markers is not obscuring an underlying relationship between CRP and GDM. Women who had BMI <25 in this study, CRP was not totally predictive of glucose intolerance. These findings are in contrast to the association between CRP and incident diabetes observed in nonpregnant individuals.²⁵ Many factors may be responsible to this difference. First of all, the current study involves young, healthy women, in whom the effect of unrecognized intercurrent condition that up-regulate inflammatory markers should be minimal. A second possibility is that hormonal and metabolic factors specific to pregnancy may affect the relationship between inflammation and diabetogenesis.

Although in this study, seven out of nine women who developed GDM had elevation of CRP which shows a strong correlation, absence of elevation of CRP in two cases puts a challenge to the correlation. Furthermore, elevation of CRP in two cases that never developed GDM puts a question mark to this correlation. Nevertheless, this observation demands further study.

The classic paradigm that insulin resistance in pregnancy is due to placental hormones such as estrogen, progesterone, and human placental lactogen has recently

been challenged. Kirwan et al. demonstrated that TNF was the strongest independent predictor of insulin resistance throughout pregnancy, whereas the placental reproductive hormones did not correlate with insulin sensitivity in late pregnancy.²⁶ Previously implicated as a factor in obesity-related insulin resistance, TNF induces expression of IL-6, the principal determinant of hepatic CRP expression.²⁶ As such, the role of TNF signalling in the association between CRP and insulin resistance in pregnancy warrants further study.

In the present study, the association identified between increased CRP levels and subsequent GDM was attenuated when BMI, family history of diabetes, lipid profile abnormalities were added to the model. There are several potential interpretations for this observation. First, one could argue that there is no association between CRP and GDM- rather; CRP confounds the true association between obesity and GDM. This is unlikely, however, given the strong independent association between CRP and type 2 diabetes and the similar pathogenesis of GDM and type 2 diabetes. A second interpretation is that rather than confounding the association, BMI and CRP might share a causal diabetogenic pathway; therefore, including BMI in the model would represent an over adjustment that could potentially obscure an important association that truly exists.

This study has strength factors as well. To limit potential confounding by prevalent diabetes, we excluded women in whom GDM was diagnosed before GLT and GTT screening, and thus might have been present when serum was sampled for CRP, based on the known association between prevalent diabetes and increased inflammation, one would expect women with early GDM to have increased CRP levels. Therefore, by excluding these women we were more likely to underestimate the true difference in CRP levels among cases of GDM, as defined by ADA criteria, and control subjects.

CONCLUSION

In this prospective study, an association between first trimester inflammation marked by increased CRP levels, and subsequent risk of development of GDM has been identified. The present study is one of a very few studies investigating the relationship between CRP, maternal obesity and glucose intolerance in pregnancy. The small number of cases in this study limits its generalized applicability. Further prospective studies are indicated. Until then, early pregnancy CRP testing remains a research tool.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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