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Research Article

# Association of Plasma Fibrinogen and Insulin Resistance in Women with Gestational Diabetes Mellitus

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## Abstract

Gestational diabetes mellitus (GDM) is thought to be developed as a consequence of high insulin resistance (IR). It has been proposed that IR may involve in the pathogenesis of hyperfibrinogenemia in GDM. This study was aimed to evaluate the plasma fibrinogen levels and its association with insulin resistance in GDM. This cross sectional study was performed with 44 GDM women and 44 pregnant women with normal glucose tolerance (NGT) at or after 24 weeks of their gestation. Glucose was measured by glucose oxidase method, fasting insulin was measured by chemiluminescent immunoassay and plasma fibrinogen was measured by STA-fibrinogen kit with an automated coagulation analyzer. GDM women had significantly increased age and higher BMI than pregnant women with NGT ($p=0.008$). Plasma fibrinogen level was significantly higher in GDM ($p<0.001$). Fasting insulin level and Homeostasis Model Assessment of Insulin Resistance [HOMA-IR] were also significantly higher in GDM ($p<0.001$). Fibrinogen showed positive correlation with fasting insulin level ($r=0.470$, $p<0.001$) as well as with HOMA-IR ($r=0.470$, $p<0.001$) in GDM. Using HOMA-IR at cut-off value 2.89, it was observed that a significant number of GDM women had higher

HOMA-IR values than pregnant women with NGT (p=0.002) and GDM women with HOMA-IR values ≥2.89 had significantly higher fibrinogen values (p=0.002). Gestational diabetes mellitus is associated with higher plasma fibrinogen level and increased insulin resistance, indicating a state of hypercoagulability than that of pregnant women with normal glucose tolerance. There is a clear association between hyperfibrinogenemia and insulin resistance.

**Keywords:** Fibrinogen; Gestational Diabetes Mellitus (GDM); Homeostasis Model Assessment of Insulin Resistance [HOMA-IR]; Insulin Resistance (IR); Normal Glucose Tolerance (NGT)

## 1. Introduction

During normal pregnancy, a variety of factors work together to cause insulin resistance (IR) and these include the secretions of cortisone, growth hormone, estrogen, progesterone and the human placental hormones, in addition to increased maternal adipose deposition, decreased exercise and increased calorie intake [1]. This physiological insulin resistance (IR) does not result in dysglycemia because of increased compensatory insulin secretion. Gestational diabetes mellitus (GDM) develops as a consequence of either unusually high IR or because of inadequate β-cell response and concomitant insulin insufficiency [2]. This persistently raised IR increases their susceptibility to future diabetes. That is why GDM is well known to be an antecedent of type 2 diabetes mellitus (T2DM) [3].

Fibrinogen, also called Factor I, is a blood plasma protein produced by the liver that plays an important role in blood coagulation. It is primarily involved in fibrin clot formation, platelet aggregation, wound healing and, its level rises in response to inflammation or tissue injury as an acute phase reactant protein. In a hyperglycemic environment, fibrinogen can become hyperglycosylated, and when this abnormal fibrinogen clots, the resulting fibrin structure is composed of small diameter fibers that are markedly resistant to degradation by plasmin which in turn increases hypercoagulability [4, 5].

Pregnancy induced hypercoagulability appears to be a physiologically adaptive mechanism to decrease bleeding complications in connection with delivery. At that time most coagulation factors increase, including fibrinogen. The coagulation inhibition factors decrease, while fibrinolysis inhibitors increase. Together, changes in hemostasis increase coagulation and decrease fibrinolysis, resulting in a hypercoagulable state indicating decreased risk of bleeding during delivery [6]. However, this physiological mechanism may convert into a pathologic process as there is a potentiation of this hypercoagulable state in a pregnancy complicated by GDM [7, 8]. Several authors reported the higher fibrinogen levels in women with GDM as the indicator of a higher tendency toward the hypercoagulable state in GDM [7-10].

It has been proposed that insulin resistance and hyperinsulinemia stimulate hepatic fibrinogen synthesis [11, 12]. Furthermore, plasma fibrinogen levels rise acutely in response to various stimuli including release of cytokines such as tumor necrosis factor-α (TNF-α) during the inflammation process. Recent studies have shown that TNF-α is implicated in the insulin resistance of human obesity and it is

well known that TNF-α stimulates hepatic fibrinogen synthesis [12]. It is also known that like type 2 diabetes, GDM is associated with IR [13-15] and many markers of systemic inflammation such as C-reactive protein and inflammatory cytokines (i.e. TNF-α, IL-6, IFN-γ) are found to be elevated in women with GDM [16, 17]. So increase IR and inflammatory cytokines like TNF-α may involve in the pathogenesis of hyperfibrinogemia in GDM. Impact of diabetes mellitus on coagulation is known for many years. But there is a scarcity of data about the changes of coagulation function in GDM, so this encouraged us to carry out this study.

## 2. Material and Methods

This cross-sectional study was conducted at Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from March 2017 to September 2018. The study was conducted after obtaining approval of the institutional review board (IRB) of the University (BSMMU). Informed written consent was taken from all the study subjects prior to the enrollment.

### 2.1 Subjects

We recruited 44 pregnant women with gestational diabetes mellitus [GDM (age: 28.52±3.77 years, BMI: 27.22±3.99 kg/m$^2$)] and equal number of pregnant women with normal glucose tolerance [NGT (age: 26.30±5.02 years, BMI: 25.15±3.11 kg/m$^2$)] diagnosed on basis of WHO criterion-2013 [18] at or after 24 weeks of their gestation to see the fibrinogen and fasting insulin levels. Patients with overt diabetes, history of taking oral antidiabetic agents or insulin, diabetes mellitus in pregnancy (DIP), co-morbid diseases (like- hepatic, renal or thyroid disorders, preeclampsia/eclampsia), coagulation or bleeding disorder and patients using medication that could affect coagulation-fibrinolytic system (e.g., anticoagulant, antiplatelet agents) were excluded from the study.

### 2.2 Procedure

Demographic and anthropometric measures as well as other relevant information of all study subjects were recorded in a data collection sheet. Their oral glucose tolerance test (OGTT) was performed after an overnight fasting. Depending on the results of OGTT, study subjects were leveled as GDM (fulfilling the WHO 2013 diagnostic criteria for GDM, which requires at least one of the following on the OGTT: fasting plasma glucose 5.1-6.9 mmol/L, 1-hour glucose ≥ 10.0 mmol/L, 2-hour glucose 8.5- 11.0 mmol/L) [18]. Healthy pregnant women with normal OGTT served as control subjects. Fasting venous blood samples for insulin (2 ml) and fibrinogen (2ml) were collected from each subject during OGTT. Samples were transported to the laboratory in pre-labeled test tubes, where plasma glucose and plasma fibrinogen were assayed immediately. For insulin, serum was separated by centrifugation (around 8000 rpm) in room temperature (22˚C - 24˚C) and preserved at -80˚C until further analysis.

### 2.3 Laboratory analysis

Quantitative determination of serum insulin levels was done by chemiluminescent immunoassay method using Access Immunoassay System (REF- 33410), Beckman Coulter, Inc., USA that uses simultaneous one-step immunoenzymatic ("sandwich") assay. Plasma glucose was measured by glucose oxidase method using dimension EXL 200 Integrated

Chemistry System (Siemens, Germany). The STA-fibrinogen kit (Diagnostica Stago, STA compact max, France) was used with STA-R analyzers for the quantitative determination of fibrinogen levels in plasma using the clotting method of Clauss. Normal values of fibrinogen levels ranges from 200-400 mg/dl [19].

### 2.4 Measurement of insulin resistance

Insulin resistance index were calculated by Homeostasis Model Assessment of insulin resistance (HOMA-IR) index as described by Matthews *et al*. [20]; [HOMA-IR=Fasting insulin (μIU/ml) × Fasting glucose (mmol/L)/22.5]. A cut-off of HOMA-IR ≥2.89 was used to define high IR according to previous study [21].

### 2.5 Statistical analysis

All data were processed by using the Statistical Package for the Social Sciences (SPSS) program (version 23.0). Data were expressed as frequencies/percentages for qualitative values and mean (±SD) for quantitative values within normal distribution. The subgroups were compared by Chi-square test ($\chi^2$-test), Fishers Exact test and unpaired t-test as applicable. The correlation between two variables was studied with the Pearson's correlation coefficient test. A p-value <0.05 was considered as statistically significant.

## 3. Results

This study was intended to evaluate the plasma fibrinogen levels and its association with insulin resistance in GDM. A total of 44 GDM women (age: 28.52±3.77 years, BMI: 27.22±3.99 kg/m$^2$) were included and compared with equal number of women with normal glucose tolerance (NGT) [Control group (age: 26.30±5.02 years, BMI: 25.15±3.11 kg/m$^2$)].

It was observed that, women in the NGT group were younger than those with GDM (GDM versus NGT: 28.52±3.77 years versus 26.30±5.02 years, p=0.021) and women with GDM showed significantly higher body mass index (BMI) than NGT women (27.22±3.99 kg/m$^2$ versus 25.15±3.11 kg/m$^2$, p=0.008). However, none of the clinical parameters like gestational weeks (GDM versus NGT: 29.84±3.55 weeks and 28.55±4.00 weeks, p=0.112) systolic blood pressure (GDM versus NGT: 106.25±11.42 mm Hg and 107.23±13.87 mm Hg, p=0.719) and diastolic blood pressure (GDM versus NGT: 69.32±8.80 mm Hg and 67.05±10.25 mm Hg, p=0.267), bad obstetric history (p=0.784), family history of diabetes mellitus (DM) in 1$^{st}$ degree relatives (GDM versus NGT: 47.7% versus 29.5%, p=0.080) or previous history of GDM (GDM versus NGT: 6.8% versus 3.3%, p=0.616) were statistically different between the two groups (Table 1).

| **Variables** | **GDM** (n= 44) | **NGT** (n= 44) | **P** |
|---|---|---|---|
| **Age** (years, mean±SD) | 28.52±3.77 | 26.30±5.02 | 0.021 |
| **Occupation** | | | |
| Housewife | 25(56.8) | 30(68.2) | 0.027 |
| Service | 19(43.2) | 10(22.7) | |
| Others | 0 | 4(9.1) | |
| **BMI** (kg/m$^2$, mean±SD) | 27.22±3.99 | 25.15±3.11 | 0.008 |
| **Gestational weeks** (mean±SD) | 29.84±3.55 | 28.55±4.00 | 0.112 |
| **SBP** (mm Hg, mean±SD) | 106.25±11.42 | 107.23±13.87 | 0.719 |
| **DBP** (mm Hg, mean±SD) | 69.32±8.80 | 67.05±10.25 | 0.267 |
| **Bad obstetric history** | | | 0.784 |
| None | 31(70.5) | 29(65.9) | |
| Macrosomia | 2(4.5) | 1(2.3) | |
| Abortion | 10(22.7) | 11(25) | |
| IUD | 0 | 1(2.3) | |
| Stillbirth | 0 | 1(2.3) | |
| Abortion +IUD | 1(2.3) | 1(2.3) | |
| **Family history of DM** | 21(47.7) | 13(29.5) | 0.080 |
| **Previous history of GDM** | 3(6.8) | 1(3.3) | 0.616 |

Data were expressed as frequency, percentage, mean±SD; Values within the parenthesis denote corresponding percentage; Comparison between the groups done by Student's t-test and $\chi$2-test/Fishers Exact test**;** GDM: Gestational Diabetes Mellitus; NGT: Normal Glucose Tolerance; BMI: Body Mass Index; DM: Diabetes Mellitus; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; IUD= Intra Uterine Death; GDM= Gestational Diabetes Mellitus; NGT= Normal Glucose Tolerance

**Table 1:** Characteristics of the study subjects (N= 88).

| **Variables** | **GDM (n=44)** | **NGT (n=44)** | **P** |
|---|---|---|---|
| Fibrinogen (mg/dl) | 416.27±34.01 | 356.29±49.74 | <0.001 |

Data were expressed as mean±SD; Comparison between groups done by Student's t test; GDM: Gestational Diabetes Mellitus; NGT: Normal Glucose Tolerance

**Table 2:** Fibrinogen level in study groups.

Among the study groups plasma fibrinogen level was found significantly higher in GDM women than that of NGT women (416.27±34.01 mg/dl versus 356.29±49.74 mg/dl, p<0.001) (Table 2).

In this study fasting insulin level (GDM versus NGT: 10.32±4.75 µIU/ml versus 7.33±2.71 µIU/ml, p<0.001) and Homeostasis Model Assessment of Insulin Resistance [HOMA-IR (GDM versus NGT: 2.60±1.14 versus 1.49±0.55, p<0.001) were found significantly higher in GDM than NGT group (Table 3).

| **Variables** | **GDM (n=44)** | **NGT (n=44)** | **P** |
|---|---|---|---|
| Fasting insulin (µIU/ml) | 11.32±4.75 | 7.33±2.71 | <0.001 |
| HOMA-IR | 2.60±1.14 | 1.49±0.55 | <0.001 |

Data were expressed as mean±SD; Comparison between groups done by Student's t test; GDM: Gestational Diabetes Mellitus; NGT: Normal Glucose Tolerance; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance

**Table 3:** Indices of insulin resistance among study groups.

On correlation analysis, fibrinogen showed positive correlation with fasting insulin (r=0.470, p<0.001) as well as with Homeostasis Model Assessment of Insulin Resistance [HOMA-IR (r=0.470, p<0.001)] in GDM group, whereas no such significant correlation was found in NGT group (Table 4).

| **Determinants of 'r'** | **GDM (n=44)** | | **NGT (n=44)** | |
|---|---|---|---|---|
| | **r** | **p** | **r** | **p** |
| Fibrinogen versus fasting insulin | 0.470 | 0.001 | 0.093 | 0.550 |
| Fibrinogen versus HOMA-IR | 0.470 | 0.001 | 0.100 | 0.517 |

Pearson's correlation coefficient test was performed; GDM: Gestational Diabetes Mellitus; NGT: Normal Glucose Tolerance; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance

**Table 4:** Correlations of fibrinogen with fasting insulin and HOMA-IR.

While, fibrinogen showed no correlation with clinical variables like systolic blood pressure [SBP (r=-0.007, p =0.96)] and diastolic blood pressure [DBP (r=0.026, p=0.866)], body mass index [BMI (r=0.122, p=0.429)], gestational age (r=0.153, p=0.322) in GDM group. However, in NGT group positive correlation was observed between fibrinogen and gestational age (r=0.316, p=0.037) (Table 5).

| **Determinants of 'r'** | **GDM (n=44)** | | **NGT (n=44)** | |
|---|---|---|---|---|
| | **r** | **p** | **r** | **P** |
| Fibrinogen versus SBP | -0.007 | 0.965 | 0.228 | 0.137 |
| Fibrinogen versus DBP | 0.026 | 0.866 | 0.144 | 0.352 |
| Fibrinogen versus BMI | 0.122 | 0.429 | 0.224 | 0.144 |
| Fibrinogen versus Gestational age | 0.153 | 0.322 | 0.316 | 0.037 |

Pearson's correlation coefficient test was done; GDM: Gestational Diabetes Mellitus; NGT: Normal Glucose Tolerance; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BMI: Body Mass Index

**Table 5:** Correlations of Fibrinogen with different clinical variables.

Using the cut-off for HOMA-IR at the level of 2.89, it was observed that statistically significant number of GDM women had higher HOMA-IR values in comparison to NGT women (GDM versus NGT; 29.5% versus 4.5%, p=0.002) (Table 6).

| **HOMA-IR cut-off value** | **Groups** | | **P** |
|---|---|---|---|
| | **GDM (n=44)** | **NGT (n=44)** | |
| <2.89 | 31 (70.5) | 42 (95.5) | 0.002 |
| ≥2.89* | 13 (29.5) | 2 (4.5) | |

Significance values obtained from $\chi 2$-test; GDM: Gestational Diabetes Mellitus; NGT: Normal Glucose Tolerance HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; * Cut-off value of HOMA-IR 2.89 [21]

**Table 6:** Frequencies of women under HOMA-IR cut-off at 2.89*.

Data analysis revealed that, GDM women with HOMA-IR values ≥2.89 had significantly higher fibrinogen level (HOMA-IR <2.89 versus ≥2.89: 406.48±30.01 mg/d versus 439.61±32.51 mg/dl, p=0.002). However, none of the clinical variables like- maternal age (p=0.679), gestational age (p=0.355), body mass index (p=0.152), family history of DM (p=0.064), previous history of GDM (p=0.544), bad obstetric history (p=0.713) were statistically different between the groups (Table 7).

| **Variables** | **Groups** | | **P** |
|---|---|---|---|
| | **HOMA-IR <2.89 (n=31)** | **HOMA-IR ≥2.89 (n=13)** | |
| **Age** (years) | 28.68±4.16 | 28.315±2.73 | 0.679 |
| **Gestational age** (weeks) | 29.52±3.58 | 30.62±3.50 | 0.355 |
| **BMI** (kg/m$^2$) | 26.66±4.39 | 28.56±2.49 | 0.152 |
| **Family history of DM** | 2(38.7%) | 9(69.2%) | 0.064 |
| **Previous history of GDM** | 3(9.7%) | 0 | 0.544 |
| **Bad obstetric history** | | | |
| None | 21(67.7%) | 10(76.9%) | |
| Macrosomia | 2(6.5%) | 0 | 0.713 |
| Abortion | 7(22.6%) | 3(23.1%) | |
| Abortion +IUD | 1(3.2%) | 0 | |
| **Fibrinogen** (mg/dl) | 406.48±30.01 | 439.61±32.51 | 0.002 |

Data were expressed as frequency, percentage, mean±SD; Values within the parenthesis denote corresponding percentage; Comparison between groups done by Student's t test and $\chi$2-test/Fisher's Exact test; BMI: Body Mass Index; DM: Diabetes Mellitus; GDM: Gestational Diabetes Mellitus; IUD: Intra Uterine Death; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance

**Table 7:** Characters in GDM under HOMA-IR cut-off 2.89**.**

## 4. Discussion

In this present study, we intended to relate plasma fibrinogen level with magnitude of insulin resistance (IR) [as measured by HOMA-IR] in women with gestational diabetes mellitus (GDM). It was observed that levels of plasma fibrinogen and HOMA-IR were significantly higher in GDM women in comparison to women with normal glucose tolerance (NGT). The present findings match with the observation of other investigators [8-10]. The stability of the hemostatic system is maintained via an excellent balance between production and activation of prothrombotic and fibrinolytic factors. However, under certain physiological and pathological conditions as in pregnancy and diabetes mellitus (DM) this balance is shifted toward a prothrombotic state [22]. Several researchers have observed that hemostatic changes associated with pregnancy are more pronounced after mid-pregnancy [22]. On the other hand, progressive increase in IR begins near mid pregnancy and progresses through the third trimester to levels that approximate the IR seen in individuals with type 2 diabetes mellitus (T2DM ) [23].

Therefore, the present study which included subjects of pregnant women at or after 24 weeks of gestation for the study was seemingly appropriate.

As shown in the medical literature, fibrinogen increases not only in a normal pregnancy but also in pregnancy related complications such as GDM, and preeclampsia [8-10]. It was reported that fibrinogen levels in GDM patients were higher compared to pregnant subjects without GDM [8-10]. Similarly, we also found that fibrinogen levels were higher in GDM patients compared to healthy pregnant controls in this study. Thus, this higher level of fibrinogen put these women at higher risk of hypercoagulability. But relevance to the overall impact of hypercoagulability in GDM is still yet to be explored.

Like type 2 diabetes mellitus (T2DM), GDM is most commonly associated with insulin resistance (IR). It is known that IR rises during pregnancy, and the rise of IR in GDM is more than in non-GDM pregnancies [15]. This study assessed fasting insulin and HOMA-IR values and found those values to be significantly higher in GDM group than that of NGT group. At present, there is no universal cut-off value to differentiate IR in GDM. In a previous study, HOMA-IR values ≥2.89 at diagnosis of GDM was found to have strong correlation with early initiation of insulin therapy and daily insulin requirement [21]. In this study, about 29.5% GDM patients were found to have HOMA-IR values ≥2.89, which was significantly higher than NGT group ($p<0.002$). We also found that GDM women with HOMA-IR values ≥2.89 had significantly higher fibrinogen values than pregnant women with NGT ($p<0.002$). It has been proposed that IR and hyperinsulinemia stimulate hepatic fibrinogen synthesis [11-12]. Such mechanism, i.e. hyperfibrinogenemia in association with IR could well apply to our GDM patients and explain higher plasma fibrinogen than in normal pregnancy. In this respect, we found positive correlation between fibrinogen and fasting insulin, as well as HOMA-IR in GDM groups.

The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index is regarded as an inexpensive and reliable measure of IR [24]. So insulin resistance (IR) was assessed in the current study by the homeostasis model assessment (HOMA) model, which is widely used in research arena because of its simplicity in comparison to euglycemic clamp. This study did not evaluate the thrombotic events of the participants in prospective manner and hence increase in fibrinogen level cannot be directly related to the adverse pregnancy outcome observed in GDM. Significantly high fibrinogen level in GDM, especially in those with relatively higher IR may stimulate further studies to illuminate these aspects. Measurements of other hemostatic factors (thrombin generation, D-dimer, t-PA, PAI-1, PAI-2, protein C) might provide additional informative data about the relationship between GDM and hemostatic system.

## 5. Conclusion

Gestational diabetes mellitus (GDM) is associated with higher plasma fibrinogen level in addition to increased insulin resistance (IR) and this state might play a role in the pathogenesis of a thrombotic tendency similar to diabetes mellitus (DM). There is a clear association between hyperfibrinogenemia and insulin resistance.

## Limitations of the Study

It was a single center study with a relatively small sample size.

## Recommendation

Further studies at larger scales are needed to explore the issue more precisely.

## Conflict of Interest

The authors declare no conflicts of interest regarding the publication of this article.

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