

Prothrombin time and activated partial thromboplastin time in women with gestational diabetes mellitus

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Abstract

Impact of gestational diabetes mellitus (GDM) on the coagulation system still remains unclear and there is limited data available regarding haemostatic changes in GDM in Bangladesh. This study was aimed at determining plasmaprothrombin time (PT), activated partial thromboplastin time (APTT) in women with GDM. This cross sectional study encompassed 44 GDM (age: 28.5 ± 3.8 years, BMI: 27.2 ± 4.0 kg/m²; mean \pm SD) and equal number of pregnant women with normal glucose tolerance (NGT) diagnosed on the basis of WHO criterion 2013 at or after 24 weeks of gestation to see PT and APTT. Plasma glucose was measured by glucose oxidase method, PT and APTT by automated coagulation analyzer. There was no statistically significant difference between the GDM and NGT groups for PT (12.3 ± 0.5 vs. 12.2 ± 0.4 sec, mean \pm SD; $P=0.40$) or APTT (30.53 ± 1.01 vs. 30.9 ± 4.5 sec, mean \pm SD; $P=0.56$). In conclusion, PT and APTT do not differ between women with or without GDM.

Keywords: Gestational diabetes mellitus, prothrombin time, activated partial thromboplastin time.

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Introduction

Gestational diabetes mellitus (GDM) is the commonest diabetes related complication that occurs during pregnancy. It is related to insulin resistance (IR) and inadequate insulin secretion resulting in hyperglycemia during their second and third trimester.¹ The main pathophysiological defect that occurs in GDM are the same as those observed with type 2 diabetes (T2DM), marked IR. That is why in GDM there is susceptibility of development of diabetes in future.²

Hyperglycemia in T2DM and GDM are referred to as a hypercoagulable state.³

Hypercoagulable states can have dire consequences, especially when these conditions are not properly identified and treated. People with hypercoagulable states have an increased risk for thrombus formation in the arteries and veins leading to increased risk for stroke, heart attack, peripheral arterial disease, or even amputation. The stability of the hemostatic system is maintained via an excellent balance between production and activation of prothrombotic and fibrinolytic factors and under normal circumstances this is rigorously well controlled. However, under certain physiological and pathological

condition as in pregnancy and diabetes mellitus (DM) this balance is shifted toward a prothrombotic state.³

Prothrombin time (PT) is a laboratory screening test used to detect disorders involving the activity of the factors I, II, V, VII, and X of the extrinsic and common pathways. Activated partial thromboplastin time (APTT) measures the activities of factors I, II, V, VIII, IX, XI, and XII of the intrinsic and common pathways.⁴⁻⁵ Numerous factor deficiencies are known to prolong these screening test results and can be related to bleeding. Shortened PT, APTT could therefore be the expression of a hypercoagulable state. Shortened APTT may result from an accumulation of circulating activated coagulation factors in plasma caused by enhanced coagulation in vivo and increased risk for thromboembolism.^{4,6} Earlier studies have found some evidence that APTT is related to a higher incidence of thromboembolic disorders and adverse cardiovascular events.⁵⁻⁷ Patients with short APTTs have increased thrombin generation and are at increased risk for thromboembolism, mainly venous thrombosis.^{5,8} Recent studies have shown that diabetes mellitus is a prothrombotic state and T2DM patients had shorter APTT-PT which favors increased risk of hypercoagulability.^{6,9-10}

Pregnancy induced hypercoagulability is a physiologically adaptive mechanism that decrease bleeding complications during delivery. It is reported that during pregnancy thrombin generation is increased, APTT is slightly decreased and PT is shortened.¹¹ During pregnancy most coagulation factors increase. The coagulation inhibition factors decrease and fibrinolysis inhibitors increase. So increased coagulation and decreased fibrinolysis, resulting in a hypercoagulable state in pregnancy which decrease the risk of bleeding during delivery.¹² However, this physiological mechanism may convert into a pathologic process in GDM. There is a potentiation of this hypercoagulable state in GDM.^{3,13} Some authors found significantly lower PT and APTT in GDM patients.¹ Although this might indicate further worsening of the hypercoagulable state of normal pregnancy, another group reported that both parameters were unchanged in women with GDM.³ Some other investigators reported this

hypercoagulable state of GDM as a risk factor for venous thromboembolism; while another found no significant association between GDM and venous thromboembolism.¹⁴⁻¹⁵

Impact of diabetes mellitus on coagulation is known for many years. But there is scarcity of data about the changes in coagulation function in GDM in our country. So this encouraged us to carry out this study. The aim of this study is to compare the PT and APTT between women with or without GDM.

Methods

Subjects

This cross-sectional study was undertaken at gestational diabetes mellitus (GDM) clinic of the department of endocrinology, BSMMU from March 2017 to September 2018. Forty four GDM (age: 28.5±3.8 years, BMI: 27.2±4.0 kg/m²; mean±SD) and equal number of pregnant women with normal glucose tolerance (NGT; age: 26.3±5.0 years, BMI: 25.2±3.1 kg/m²; mean±SD) were recruited. They were diagnosed on the basis of WHO Criterion-2013¹⁶ at or after 24 weeks of their gestation to see PT, APTT. Patients with overt diabetes, history of taking oral antidiabetic agents or insulin, diabetes mellitus in pregnancy (DIP), comorbid diseases (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. The study was conducted according to the guidelines provided by the institutional review board (IRB) of the University (No. BSMMU/2017/3433). Written informed consent was obtained from and signed by all the patients.

Data collection methods

Demographic and anthropometric measures as well as other information of all study subjects were recorded in data collection sheet. Following overnight fast (at least 8 hours), venous blood (7ml) was drawn for fasting plasma glucose (2 ml) and PT, APTT (3ml) respectively. After that, the participants were asked to drink the standard 75 gm glucose solution and a second and third sample of 2 ml blood was obtained 1 hour and 2 hours

later for plasma glucose measurements. Samples were transported to the laboratory in pre-labeled test tubes, where plasma glucose and hematological parameters were assayed immediately.

Laboratory analysis

Plasma glucose was measured by glucose oxidase method in department of Biochemistry, BSMMU and hematological parameters were measured in department of hematology, BSMMU. The STA-neoplastine CI plus kit (Diagnosticastago, STA compact max, France) was used with STA-R analyzers for the determination of PT. Normal values ranges from 12-16 seconds.¹⁶ The STA - C.K. Prest 5 kit (Diagnosticastago) was used for the determination of the kaolin-activated partial thromboplastin time (APTT) in plasma on STA-R and STA Compact. Normal time ranges from 26-40 seconds.¹⁷

Statistical analysis

Data were expressed as frequencies or percentages for qualitative values (bad obstetric history, previous history of GDM, family history of DM among the 1st degree relatives) and mean (\pm SD) for quantitative values (Gestational age, BMI, maternal age, PT, APTT) with normal distribution. In subgroups made on the basis of biochemical findings were compared by Chi-square test for qualitative values and unpaired t-test for quantitative values as applicable. The correlation between two variables was studied with the Pearson's correlation coefficient test. P-value \leq 0.05 was considered as statistically significant. All data were processed by using the Statistical Package for the Social Sciences (SPSS) program (version 23.0).

Results

In an attempt to assess the PT, APTT levels, 88 pregnant mothers (age: 27.41 \pm 4.56 years, BMI: 26.19 \pm 3.71 kg/m²; mean \pm SD) were included in this study. 44 GDM (age: 28.52 \pm 3.77 years, BMI: 27.22 \pm 3.99 kg/m²; mean \pm SD) and equal number of pregnant women with normal glucose tolerance (NGT) were diagnosed on basis of WHO criterion-2013. Among all participants, the NGT

group were younger than those with GDM (GDM vs. NGT: 28.52 \pm 3.77 vs. 26.30 \pm 5.02 years, mean \pm SD; $P=0.021$). Women with GDM showed significantly higher BMI (27.22 \pm 3.99 vs. 25.15 \pm 3.11 kg/m², mean \pm SD; $P=0.008$) than NGT. However, other clinical parameters like gestational weeks (GDM vs. NGT: 29.84 \pm 3.55 vs. 28.55 \pm 4.00 weeks, mean \pm SD; $P=0.112$), bad obstetric history ($p=0.784$), family history of DM in 1st degree relatives (GDM vs. NGT: 47.7% vs. 29.5%, $P=0.080$) or previous history of GDM (GDM vs. NGT: 6.8% vs. 3.3%, $P=0.616$) were not significantly different between the two groups.¹⁸

PT and APTT in GDM

Table- I shows PT, APTT in GDM and NGT. There was no statistically significant difference between the GDM and NGT groups for PT (12.31 \pm 0.44 vs. 12.24 \pm 0.37sec, mean \pm SD; $P=0.404$) or APTT (30.53 \pm 1.01 vs. 30.93 \pm 4.51sec, mean \pm SD; $P=0.561$).

Discussion

In the present study, we intended to assess the possible contribution of hypercoagulability in the etiopathogenesis of GDM. For this purpose, we measured PT, APTT in women with GDM and pregnant women with normal glucose tolerance (NGT). It demonstrated that PT, APTT values do not differ between two groups.

DM is a hypercoagulable states.^{10,19} Plasma levels of clotting factors such as fibrinogen; factors (F) VII, VIII, XI, and XII and von Willebrand factor increase while fibrinolysis is inhibited due to the compact structure and innate resistance of the fibrin molecule to lysis in DM.^{1,19,20}

TABLE 1 Patient prothombin time and activated partial thromboplastin time

Variables	Gestational diabetes mellitus (n=44)	Normal glucose tolerance (n=44)	P
Prothrombin time (sec)	12.3 \pm 0.5	12.2 \pm 0.4	0.404
Activated partial thromboplastin time (sec)	30.5 \pm 1.0	30.9 \pm 4.5	0.561

Data were expressed as mean \pm SD
Comparison between groups done by Student's t test

On the other hand, normal pregnancy is associated with changes in the coagulation and fibrinolytic systems that are considered to represent physiologic and adaptive mechanisms for the hemostatic challenges of delivery. Most coagulation factors increase during pregnancy and this physiological hypercoagulable state that characterizes normal pregnancy, prepares pregnant women to hemostatic challenge of childbirth and placental separation.^{12,21}

Subjects in the present study were recruited at or after 24 weeks of pregnancy. Activation of the coagulation system in both diabetes and normal pregnancy has aroused interest in coagulation irregularities in GDM. Several researchers have observed that hemostatic changes associated with pregnancy are more pronounced after mid-pregnancy.²¹ On the other hand, glucose intolerance detected early in the pregnancy probably represents preexistence of type-2 DM.²² Moreover, physiological changes that occur in pregnancy is characterized by progressive IR that begins near mid pregnancy and progresses through the third trimester to levels that approximate the IR seen in individuals with type 2 diabetes.²³ Therefore, the present study which included subjects of pregnant mothers at or after 24 weeks of gestation for the study was seemingly appropriate.

Important measures in assessing the coagulation cascade are PT and APTT. There are studies showing that decreased PT and APTT support hypercoagulability status in both normal pregnancy and GDM.^{1,24} It was determined that APTT and platelet counts were significantly lower in the 3rd trimester of normal pregnancy.²⁴ However, another group reported that both parameters were unchanged in women with GDM and normal pregnancy.³ In our findings, PT and APTT were not significantly different in pregnant women with normal glucose tolerance than with GDM. But both parameters were in the lower limit of reference range in both groups and it is presumed that this data support hypercoagulable state in GDM.

Conclusion

In conclusion, PT and APTT do not differ between women with GDM and NGT groups. Further clinical studies at larger scales are needed to further delineate the relationship between GDM and NGT groups.

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Author Contribution

SM conceptualized, guided data analysis, interpreted results, wrote the manuscript; SS revised the manuscript critically. MM reviewed the literature; all approved the final version.

Conflict of Interest

We don't have any conflict of interest.

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