Gestational diabetes mellitus is associated with antenatal hypercoagulability and secondary hyperfibrinolysis: a case control study of Chinese women

Yan Liu
Jiangsu Province Academy of Traditional Chinese Medicine
Xiaofang Sun
Yangzhou University Medical Academy
Junxian Tao
Yangzhou University Medical Academy
Bin Song
Yangzhou University Medical Academy
Wei Wu
Yangzhou University Medical Academy
Ying Li
Yangzhou University Medical Academy
Xing Sun
Yangzhou University Medical Academy
Dan Lu
Yangzhou University Medical Academy
Danmo Zhu
Yangzhou University Medical Academy
Chao Liu (liuchao@njucm.edu.cn)
Nanjing University of Chinese Medicine https://orcid.org/0000-0003-0159-2952
Ji Cui
Nanjing Maternity and Child Health Care Hospital

Research article

Keywords: gestational diabetes mellitus, hypercoagulability, secondary hyperfibrinolysis, thromboelastography

Posted Date: September 23rd, 2019

DOI: https://doi.org/10.21203/rs.2.14831/v1

Version of Record: A version of this preprint was published at The Journal of Maternal-Fetal & Neonatal Medicine on September 14th, 2020. See the published version at https://doi.org/10.1080/14767058.2020.1818202.

Abstract

Background : To determine the relationship between gestational diabetes mellitus (GDM) and coagulation/fibrinolysis disorders in antenatal Chinese women . Methods: Case control study. Fifty women had GDM and 132 did not (the NGDM group). Maternal plasma biochemistry and previous medical history were collected from perinatal health records. Antenatal coagulation/fibrinolysis were assessed using thromboelastography and traditional measures, then the relationship between coagulation/fibrinolysis and GDM was analyzed by multiple regression analysis.

Results: GDM was significantly associated with higher activated partial thromboplastin time (odds ratio [OR] 1.5, 95% confidence interval [CI] 0.4–2.6); fibrinogen (OR 0.3, 95% CI 0.1–0.6); and percentage reduction in clot lysis after 30 min (OR 1.2, 95% CI 0.2–2.2), after adjustment for potential confounding factors. Both the intraoperative (238.2±71.0 ml vs . 286.0±102.4 ml, P =0.003) and 24-hour after surgery (270.7±99.8 ml vs . 314.7±131.1 ml, P =0.033) blood loss were lower and the prevalence of cesarean delivery (56.0% vs . 37.9%, P =0.027) was higher in the GDM group. There were no significant differences in the prevalence of maternal thrombotic events or maternal body mass before delivery.

Conclusions: GDM is significantly associated with hypercoagulability and secondary hyperfibrinolysis in these antenatal Chinese women.

Background

Coagulation/fibrinolysis activity (CFA) represents a dynamic balance that is of vital importance to safe childbirth. Coagulability gradually increases from the first to third trimesters [1] in pregnant women, becoming higher than in normal women[2]. Consistent with this, late pregnancy is characterized not only by changes in hormone secretion and liver metabolism, but higher coagulation indices[3]. Moreover, this hypercoagulability during pregnancy is aggravated in the presence of diabetes[4, 5]. Excessive hypercoagulability is associated with adverse pregnancy outcomes, including stroke and deep venous thrombosis (DVT) of the lower extremities[6]. However, neither a nationwide study conducted in Denmark[7], nor another conducted in the Arabian Gulf[8], identified GDM as a risk factor for stroke or DVT. Therefore, we hypothesized that secondary hyperfibrinolysis might coexist with, and gradually worsen, hypercoagulability in GDM.

Many methods have been used to assess CFA. Thromboelastography (TEG) is a relatively new technique that evaluates whole-blood hemostatic properties in real time, and has been shown to be a reliable method of urgently assessing CFA in pregnant women[9]. In addition, fibrinogen (FIB), activated partial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio of prothrombin time (PT-INR), and D-Dimer (DD) are used to assess CFA. In view of the changes in CFA during late pregnancy, we speculated that there would be differences in a number of these parameters between women with GDM and normal pregnant women. However, the results of platelet activation, fibrinolytic activity, and conventional assays of CFA have rarely been compared in women with GDM [10], and there has been no

assessment of the relationship between GDM and CFA, assessed using TEG, in pregnant Chinese women. Therefore, in this study, we aimed to evaluate the relationship between GDM and measures of CFA, after adjustment for potential confounding factors.

1. Methods

1.1 Study design and study population

The study was a case control study. All procedures performed in the study involving the human participants were in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Clinical Medical College, Yangzhou University, China (serial number: 2019KY–067). During the analysis, the data were anonymized, and therefore the requirement for informed consent was waived. To avoid recruitment bias, we collected consecutive data from all pregnant women awaiting delivery, but not yet in labor, in the Obstetrics department of our hospital from 23 October to 23 November 2018. After the exclusion of 18 individuals for the reasons given below, 182 women were included in the analysis, who were classified as having GDM or not having GDM (the GDM group and the NGDM group).

GDM was diagnosed using a one-step strategy[11]: a 75-g 2-hour oral glucose tolerance test (OGTT) was performed in the 24th–28th week of gestation in women who had not previously been diagnosed with overt diabetes. A diagnosis of GDM was made when their fasting plasma glucose was ≥ 5.1 mmol/l, their 1-h plasma glucose was ≥ 10.0 mmol/l, or their 2-h plasma glucose was ≥ 8.5 mmol/l.

The exclusion criteria were: a previous history of diabetes or GDM; a history of smoking; serious liver dysfunction (a prior diagnosis of cirrhosis, hepatitis, and/or known liver function test abnormalities); renal dysfunction (a prior diagnosis of acute kidney injury and/or chronic kidney disease); preeclampsia/eclampsia; endocrine disorders (acromegaly, Cushing's syndrome, or thyroid dysfunction); use of medications with known effects on CFA (such as aspirin, heparin, or enoxaparin); antiphospholipid syndrome; systemic lupus erythematosus or dermatomyositis, which could enhance coagulation; infectious disease (e.g., HIV); eclampsia or preeclampsia before enrollment [12, 13]; insulin or other anti-diabetic drug use.

Two hundred women who had never been smokers were included, 18 of whom were excluded because of severe liver disease (three), diabetes mellitus before pregnancy (eleven), heparin treatment (two), and serious thrombocytopenia (two). Thus, 182 individuals remained for analysis (a flow chart is presented in Figure 1).

Figure 1 Flow chart of patient selection

1.2 Materials and methods

Baseline information, including maternal body mass before pregnancy, mass gain during pregnancy, and previous medical history, were collected from the patient records. Before delivery, the participants underwent a CFA assessment, which comprised the measurement of conventional laboratory parameters (FIB, PT, APTT, PT-INR, and DD) and TEG. Venous blood was collected in the morning, on an empty stomach, and anticoagulated with 0.38% sodium citrate. The blood was then centrifuged at 1500g (2500 rpm) for 20 min to prepare plasma for APTT, PT, TT, FIB, and DD analysis, which was performed using a Stago STAR-R analyzer (Diagnostica STAGO, France). The remaining blood was placed into EDTA tubes for platelet counting using a Huma-Count hematology analyzer (Human GmbH, Germany).

TEG was performed using TEG–5000 Hemostasis analyzers (Haemonetics Corp, Braintree, MA) according to the manufacturer's guidelines [13–15], by two certified laboratory technicians. The TEG–5000 machines underwent quality control assessments every 8 hours. The parameters measured were R (sec) ; K (sec); α-angle; MA (mm) and LY30 (%) (Figure 2). R represents "reaction time", an indicator of clotting time, and is the time to initial fibrin formation (to 2 mm amplitude). K represents "kinetic time", an indicator of clot kinetics, and is the speed at which specific clot strength is reached (period for amplitude to increase from 2 to 20 mm). The α-angle is a measure of clot kinetics, indicative of the rate of fibrin accumulation and cross-linking. MA represents "maximum amplitude", an indicator of clot strength. LY30 is the percentage reduction in amplitude 30 min post-MA, which is a measure of the degree of fibrinolysis.

Figure 2 Typical pattern of TEG with variables measured during coagulation and fibrinolysis

1.3 Statistical analysis

No multiple imputation was performed because < 5% of the data was missing. Continuous variables are expressed as mean ± standard deviation if normally distributed or median (interquartile range) if the distribution was skewed. Categorical variables are expressed as a frequency or a percentage. We used chi-square or Fisher's exact tests, as appropriate, for the comparison of categorical data between the groups. Normally-distributed continuous data were compared using one-way ANOVA, and data with a skewed distribution were compared using nonparametric Kruskal Wallis rank tests. Univariate and multivariate linear regression models were employed to evaluate the relationships between GDM and CFA parameters. Three multivariate linear regression models were constructed: in model 1, no covariates were adjusted for; in model 2, the data were only adjusted for maternal age; and in model 3, the data were adjusted for maternal age, urea nitrogen, ALT, SBP, DBP, and ALP (Table 1).

All the analyses were performed using EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc, Boston, MA). $P < 0.05$ (two-sided) was considered to represent statistical significance.

2. Results

2.1 Baseline characteristics of selected participants

The participants comprised 50 with GDM, accounting for 27% of the study sample. The baseline information of each group are shown in Table 1, which include sociodemographic characteristics, previous medical history, biochemistry, sociodemographic characteristics of the baby, maternal events, and neonatal events. The mean age of the participants was 29.1±4.1 years and their mean body mass index before delivery was 27.2±3.4 kg/m^2. The women with GDM were significantly older than those without GDM (P = 0.012). The body mass of the women with GDM before pregnancy was greater than that of the NGDM group (P = 0.000), whereas the maternal mass gain during pregnancy was less in the GDM than in the NGDM group (P = 0.001). The pregnancies were of shorter duration in the GDM than in the NGDM group (P = 0.013) and the prevalence of caesarean delivery was higher in the GDM group (56.0%) than in the NGDM group (37.9%)(P = 0.027). Hemoglobin concentration and platelet count were similar in the two groups. FIB (4.7±0.8 *vs.* 4.3±0.7 g/l) and APTT (30.9±3.0 *vs.* 29.5±3.3 sec) were significantly higher in the GDM than in the NGDM group. Meanwhile, PT, TT, PT-INR, and DD didn't show the significant difference in the two groups, as were the TEG parameters, including LY30.

2.2 Univariate analysis

The results of the univariate analyses were shown in Table 2. GDM was shown to be positively associated with LY30, FIB, and APTT. Furthermore, ALT, GGT, and fasting glucose positively correlated with FIB. Maternal body mass gain during pregnancy, a previous history of abortion, and a previous history of full-term birth were negatively associated with FIB. Finally, ALT positively correlated with LY30.

2.3 Analysis of the multiple regression equations for the relationships between LY30/FIB and GDM

We constructed three models to analyze the independent effects of GDM on LY30 and FIB, after adjustment for potential confounding factors. The effect values (β) and 95% confidence intervals (CIs) of the three models are shown in Table 3. In the unadjusted model, GDM was positively associated with APTT (odds ratio [OR] 1.4, 95% CI 0.3–2.5), FIB (OR 0.4, 95% CI 0.2–0.6), and LY30 (OR 1.3, 95% CI 0.3–2.2). After adjustment for maternal age, GDM was also independently associated with APTT (OR 1.6, 95% CI 0.5–2.7), FIB (OR 0.4, 95% CI 0.1– 0.6), and LY30 (OR 1.3, 95% CI 0.4–2.3). Finally, after adjustment for maternal age, urea nitrogen, ALT, SBP, DBP, and ALP (Table 1), GDM was still independently associated with APTT (OR 1.5, 95% CI 0.4–2.6), FIB (OR 0.3, 95% CI 0.1–0.6), and LY30 (OR 1.2, 95% CI 0.2–2.2). Thus, using these three models, the positive associations between GDM and APTT, FIB, and LY30 were confirmed to be stable after adjustment for the potential confounding factors presented in Table 1. The P value for the log likelihood ratio test was < 0.05.

3. Discussion

In this case control study, both the conventional CFA measures FIB and APTT, and the newer measure indicator LY30, were found to be strongly associated with GDM, and in the fully-adjusted regression model, these associations remained. In women with GDM, APTT was 1.5 sec longer (OR 1.5, 95% CI 0.4–2.6), FIB was 0.3 g/L higher (OR 0.3, 95% CI 0.1–0.6), and LY30 was 20% higher (OR 1.2, 95% CI 0.2–2.2), which is indicative of both hypercoagulability and secondary hyperfibrinolysis in this group of Chinese women with GDM.

Maintenance of a balance between coagulation and fibrinolysis is of great importance for the perinatal safety of both mothers and infants[16]. A physiologic hypercoagulable state has been demonstrated during pregnancy and the peripartum period[16, 17], which helps to protect women from excessive bleeding during childbirth. Nevertheless, in developed nations, the leading cause of maternal death is thromboembolic disease[18–20]. Thrombotic events during pregnancy, including maternal DVT and pregnancy-related cerebral venous sinus thrombosis, are responsible for increasing levels of maternal mortality worldwide [21, 22]. Previous studies have shown that this hypercoagulability is exacerbated in pregnant women with GDM[4, 23, 24] and that there is a significantly higher frequency of DVT in pregnant women with type 1 diabetes mellitus[25]. However, in a nationwide study conducted in Denmark, an unadjusted model showed a higher risk of thrombosis in patients with GDM, but in a model adjusted for confounding factors this association disappeared[7]. In our study and previous studies[7, 26], no significant differences were identified in the frequency of maternal thrombotic events in GDM group with well control of blood glucose and maternal weight, which seems to be inconsistent with the hypercoagulability identified.

The balance between coagulation and fibrinolysis determines whether hemorrhage, thrombosis, or neither occurs during the perinatal period. FIB is one of the conventional measures of coagulability during the perinatal period, as well as being a biomarker of inflammation, and is a complex glycoprotein synthesized by hepatocytes[27]. FIB increases during normal pregnancies, but also in pregnancy-related complications such as GDM[12, 28], reaching significantly higher values in patients with GDM than those in healthy pregnant women[23, 28]. In the present study, FIB was also higher in GDM patients than that in the NGDM group, confirming a tendency towards hypercoagulability in the former. This helps to explain why, in the present study, the significantly higher prevalence of caesarean delivery in the GDM group was not associated with an increase in blood loss during delivery.

The shortening of APTT in type 2 diabetic patients has been described as indicating a high risk of a hypercoagulable state[29]. It has also been shown that the increase in fibrinogen and the reduction in fibrinolytic activity in GDM are more similar to the changes present in type 2 than in type 1 diabetic patients[30], and it is thought that a shorter APTT is a marker of venous thromboembolism risk[31, 32]. Furthermore, PT and APTT, measured between the 20th and 24th gestational weeks, were significantly lower in patients with GDM than in healthy people[12]. In another study, the mean APTTs of non-diabetic, treated, and untreated type 2 diabetic patients were 32.8 ± 4.12 sec, 34.4 ± 5.3 sec, and 25.4 ±8.5 sec, respectively, which showed that APTT was lower in diabetic patients and that this defect was normalized

by diabetes treatment [29]. This might help to explain the significantly higher APTT in GDM patients identified in the present study. The prenatal maternal fasting plasma glucose (4.8±1.2 mmol/l) and HbA1c (6.5±0.7%) values in the GDM group show that glucose levels were well controlled in the present study. In addition, the significantly lower body mass gain during pregnancy in the GDM group is indicative of good weight control in our recruited subjects. Finally, the characteristic increases in FIB and APTT, indicating hypercoagulability and secondary hyperfibrinolysis, help to explain why there were no significant differences in the prevalence of some adverse maternal events, such as wound infection after caesarean delivery or maternal thrombosis, between these “healthy” GDM women and NGDM women.

Fibrinolytic activity is lower during normal pregnancies and systemic fibrinolysis returns rapidly to normal after delivery, according to previous studies[33, 34]. After delivery, both the coagulatory and fibrinolytic systems of pregnant women are activated for at least 2 weeks[35]. However, few studies have focused on the fibrinolytic activity in GDM. Recently, TEG has been used to monitor the CFA of pregnant women in real time, to study the human CFA process and the sequence of events involved[36]. The TEG parameters measured in the present study have further confirmed the secondary hyperfibrinolysis, and shown that it might develop earlier than hypercoagulability in pre-delivery GDM patients. There were no significant differences in TEG.R, TEG.K, TEG.MA, LY30, or α-angle between the GDM and NGDM groups, which is consistent with the findings of a previous report that showed no significant differences in thromboelastographic parameters between 50 GDM patients and a control group[37]. However, after adjustment for UA, ALT, SBP, DBP, ALP, and maternal age, the correlation between LY30 and GDM remained, which further confirms the existence of secondary hyperfibrinolysis in these pregnant women with GDM. This has not been shown previously. The coexistence of hypercoagulability and secondary hyperfibrinolysis helps to explain why there was no significant increase in the number of thrombotic events in these GDM patients. However, the mechanism involved and its impact on the children of these patients requires further study.

The clinical value of this study is two-fold. Firstly, we have shown robust relationships between GDM even with well controlled and disorders of APTT, LY30, and PT, using both conventional CFA measures and TEG. Secondly, the findings of this study will be helpful in guiding further research regarding biomarkers that could sensitively predict the risk of thrombotic events in GDM patients. Our study was a single-center study, meaning that the study population was more homogeneous. The maternity center is located in a small city in China that has relatively small population mobility, and most of the participants in the study were local residents. These characteristics of the study participants exclude the influence of ethnicity on coagulation that has been previously reported[32]. In addition, we used different methods to assess CFA at the same time point and the results were consistent.

However, this study still had a number of limitations. First, because the data were collected in a single local population, the conclusion should be confirmed by further research and multi-center study. Second, we excluded pregnant women that had undergone heparin treatment and that had a history of other diseases, such as severe liver disease, which might have affected CFA. However, this means that the

conclusions of this study do not apply to pregnant women with these kinds of diseases. Finally, most obstetricians in our hospital do not measure serum lipid concentrations just before delivery; therefore, we could not analyze the influence of serum lipid levels on the CFA function of women with GDM. This deficiency should be considered in future studies' design.

Conclusion

In this case control study, women with GDM demonstrated significant hypercoagulability and secondary hyperfibrinolysis, shown by their significantly higher FIB, APTT, and LY30 values after adjustment for potential confounding factors even in the GDM women with well control of blood glucose and maternal weight. This concomitant hypercoagulability and secondary fibrinolysis in GDM patients may at least in part explain the change in the balance between the incidence of thrombotic events and the severity of postpartum hemorrhage in patients with GDM.

Abbreviations

CFA: Coagulation/fibrinolysis activity; GDM: gestational diabetes mellitus; DVT: deep venous thrombosis; TEG: Thromboelastography; FIB: fibrinogen; APTT: activated partial thromboplastin time; PT: prothrombin time; PT-INR: international normalized ratio of prothrombin time; DD:D-Dimer; OGTT: oral glucose tolerance test; R:reaction time; K:kinetic time; MA: maximum amplitude; LY30: percentage reduction in amplitude 30 min post-MA; ANOVA: analysis of variance; BMI Body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; RBC: blood erythrocytes count; WBC: blood leukocyte Count; NE: neutrophile granulocyte; DBIL: direct bilirubin; STB: serum total bilirubin; IBIL: indirect bilirubin; AST aspartate aminotransferarase; ALT: alanine aminotransferarase; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; γ-GGT: γ-glutamyl transpeptadase; HbA1c: glycated haemoglobin; UA: plasma uric acid; CIs confidence intervals OR odds ratio

Declarations

Ethics approval and consent to participate

All procedures performed in the study involving the human participants were in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Clinical Medical College, Yangzhou University, China (serial number: 2019KY–067). During the analysis, the data were anonymized, and therefore the requirement for informed consent was waived by the local ethics committee with no impact on health outcome.

Consent for publication

During the analysis, the data were anonymized, and therefore the requirement for informed consent was waived by the local ethics committee with no impact on health outcome.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare that they have no competing interests.

Funding

The development of the analytic methods and software used in this work was supported by the Foundation of Jiangsu Subei People's Hospital (fcjs201834). And writing the manuscript was supported in part by the TCM Leading Talents Training Project of Jiangsu Province(SLJ0209)

Authors' contributions

YL, XFS, JXT, CL and JC were responsible for conception, design of the study, acquisition, analysis and interpretation of data. WW, XS were responsible for the test and quality control of CFA assessment. DL and DMZ were responsible for discrimination of obstetric diseases. YL, BS,YL drafted the article and revised contents. All authors have read and approved the final version of the manuscript.

Acknowledgements

The authors thank all the staff members in our institution, and especially Mr. Liu Shunshun, Mr. Sun Guoping, and Miss. Sun Lemeng, the Empower team. We also thank Mrs. Tang Shao Hua, from Yangzhou university and Mark Cleasby, PhD, from Liwen Bianji, Edanz Group China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.

References

[1]Ibeh N, Okocha CE, Aneke CJ, Onah CE, Nwosu AO, Nkwazema KA. Normal pregnancy and coagulation profile: from the first through the third trimester. Nigerian journal of medicine: journal of the National Association of Resident Doctors of Nigeria.2015;24(1): 54–7. PMID: 25807675.

[2]Della Rocca G, Dogareschi T, Cecconet T, Buttera S, Spasiano A, Nadbath P, Angelini M, Galluzzo C, Marchesoni D. Coagulation assessment in normal pregnancy: thrombelastography with citrated non activated samples. Minerva anestesiologica.2012;78(12): 1357–64. PMID: 22858878.

[3]Gong JM, Shen Y, He YX. Reference Intervals of Routine Coagulation Assays During the Pregnancy and Puerperium Period. Journal of clinical laboratory analysis.2016;30(6): 912–7. DOI: 10.1002/jcla.21956.

[4]Teliga-Czajkowska J, Sienko J, Zareba-Szczudlik J, Malinowska-Polubiec A, Romejko-Wolniewicz E, Czajkowski K. Influence of Glycemic Control on Coagulation and Lipid Metabolism in Pregnancies

Complicated by Prege stational and Gestational Diabetes Mellitus. Adv Exp Med Biol. 2019; 1176:81–88. DOI: 10.1007/5584_2019_382.

[5]Liu B, Xu Y, Voss C, Qiu FH, Zhao MZ, Liu YD, Nie J, Wang ZL. Altered protein expression in gestational diabetes mellitus placentas provides insight into insulin resistance and coagulation/fibrinolysis pathways. PloS one. 2012; 7(9): e44701. DOI: 10.1371/journal.pone.0044701. Epub 2012 Sep 7.

[6]Krikun G, Huang ST, Schatz F, Salafia C, Stocco C, Lockwood CJ. Thrombin activation of endometrial endothelial cells: a possible role in intrauterine growth restriction. Thrombosis and haemostasis.2007;97(2): 245–53. PMID: 17264954.

[7]Ovesen PG, Jensen DM, Damm P, Rasmussen S, Kesmodel US. Maternal and neonatal outcomes in pregnancies complicated by gestational diabetes. a nation-wide study. The journal of maternal-fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies.the International Society of Perinatal Obstet.2015; 28(14): 1720–4. DOI: 10.3109/14767058.2014.966677.

[8]Alsayegh F, Al-Jassar W, Wani S, Tahlak M, Albahar A, Al Kharusi L, Al-Tamimi H, El-Taher F, Mahmood N, Al-Zakwani I. Venous Thromboembolism Risk and Adequacy of Prophylaxis in High Risk Pregnancy in the Arabian Gulf. Curr Vasc Pharmacol.2016;14(4): 368–73. PMID: 26517701.

[9]Jarmuzek P, Wielgos M, Bomba-Opon D. Placental pathologic changes in gestational diabetes mellitus. Neuro endocrinology letters.2015;36(2): 101–5. PMID: 26071574.

[10]Liu BY, Jian YL, Zhong M, Yu YH, Wang Q, Zhang J. [Value of coagulation function and fibrinolytic system assessment in patients with gestational diabet es mellitus]. Nan Fang Yi Ke Da Xue Xue Bao.2007;27(1): 35–7. PMID: 17259140.

[11]American Diabetes A. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes–2018. Diabetes care.2018;41 Suppl 1: S13-s27. DOI: 10.2337/dc18-S002.

[12]Gorar S, Alioglu B, Ademoglu E, Uyar S, Bekdemir H, Candan Z, Saglam B, Koc G, Culha C, Aral Y. Is There a Tendency for Thrombosis in Gestational Diabetes Mellitus? Journal of laboratory physicians.2016; 8(2): 101–5. DOI: 10.4103/0974–2727.180790.

[13]Antony KM, Mansouri R, Arndt M, Rocky Hui SK, Jariwala P, Mcmullen VM, Teruya J, Aagaard K. Establishing thromboelastography with platelet-function analyzer reference ranges and other measures in healthy term pregnant women. American journal of perinatology.2015; 32(6): 545–54. DOI: 10.1055/s–0034–1396700.

[14]Zahr Eldeen F, Roll GR, Derosas C, Rao R, Khan MS, Gunson BK, Hodson J, Mergental H, Ferraz-Neto BH, Isaac J, Muiesan P, Mirza DF, Iqbal A, Perera MT. Preoperative Thromboelastography as a Sensitive

Tool Predicting Those at Risk of Developing Early Hep atic Artery Thrombosis After Adult Liver Transplantation. Transplantation. 2016;100(11): 2382–90. DOI: 10.1097/TP.0000000000001395.

[15]Brill JB, Badiee J, Zander AL, Wallace JD, Lewis PR, Sise MJ, Bansal V, Shackford SR. The rate of deep vein thrombosis doubles in trauma patients with hypercoagulable thromboelastography. J Trauma Acute Care Surg. 2017; 83(3): 413–9. DOI: 10.1097/TA.0000000000001618.

[16]Sousa Gomes M, Guimaraes M, Montenegro N. Thrombolysis in pregnancy: a literature review. The journal of maternal-fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2019; 32(14): 2418–28. DOI: 10.1080/14767058.2018.1434141.

[17]Chandra S, Tripathi AK, Mishra S, Amzarul M, Vaish AK. Physiological changes in hematological parameters during pregnancy. Indian journal of hematology & blood transfusion: an official journal of Indian Society of Hematology and Blood Transfusion. 2012; 28(3): 144–6. DOI: 10.1007/s12288–012–0175–6.

[18]Marik PE, Plante LA. Venous thromboembolic disease and pregnancy. N Engl J Med. 2008; 359(19): 2025–33. DOI: 10.1056/NEJMra0707993.

[19]Edlow JA, Caplan LR, O'brien K, Tibbles CD. Diagnosis of acute neurological emergencies in pregnant and post-partum women. Lancet Neurol. 2013; 12(2): 175–85. DOI: 10.1016/S1474–4422(12)70306-X.

[20]Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med.2005;143(10): 697–706. DOI: 10.7326/0003–4819–143–10–200511150–00006.

[21]Liang ZW, Gao WL, Feng LM. Clinical characteristics and prognosis of cerebral venous thrombosis in Chinese women during pregnancy and puerperium. Scientific reports. 2017;7:43866. DOI: 10.1038/srep43866.

[22]Devis P, Knuttinen MG. Deep venous thrombosis in pregnancy: incidence, pathogenesis and endovascular management. Cardiovasc Diagn Ther.2017;7 Suppl 3: S309-s19. DOI: 10.21037/cdt.2017.10.08.

[23]Abdel Gader AG, Khashoggi TY, Habib F, Awadallah SB. Haemostatic and cytokine changes in gestational diabetes mellitus. Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology.2011;27(5): 356–60. DOI: 10.3109/09513590.2010.495241.

[24]Gumus, Ii, Kargili A, Karakurt F, Kasapoglu B, Derbent A, Kaygusuz I, Koca C, Sevgili S. Levels of thrombin activatable fibrinolysis inhibitor in gestational diabetes mellitus. Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology.2013; 29(4): 327–30. DOI: 10.3109/09513590.2010.501884.

[25]Bleau N, Patenaude V, Abenhaim HA. Risk of Venous Thromboembolic Events in Pregnant Patients With Autoimmune Diseases: A Population-Based Study. Clin Appl Thromb Hemost. 2016; 22(3): 285–91. DOI: 10.1177/1076029614553023.

[26]Yang YY, Fang YH, Wang X, Zhang Y, Liu XJ, Yin ZZ. A retrospective cohort study of risk factors and pregnancy outcomes in 14,014 Chinese pregnant women. Medicine (Baltimore). 2018; 97(33): e11748. DOI: 10.1097/MD.0000000000011748.

[27]Ko GT, Yeung VT, Chan JC, Chow CC, Li JK, So WY, Tsang LW, Cockram CS. Plasma fibrinogen concentration in a Chinese population. Atherosclerosis. 1997; 131(2): 211–7. DOI: 10.1016/s0021–9150(97)06109–1.

[28]Bellart J, Gilabert R, Fontcuberta J, Carreras E, Miralles RM, Cabero L. Coagulation and fibrinolysis parameters in normal pregnancy and in gestational diabetes. American journal of perinatology.1998;15(8): 479–86. DOI: 10.1055/s–2007–994069.

[29]Ambelu YA, Shiferaw MB, Abebe M, Enawgaw B. Prothrombin time, activated partial thromboplastin time and platelet counts of type II diabetes melli tus: a comparative study. J Diabetes Metab Disord. 2018;17(2): 117–21. DOI: 10.1007/s40200–018–0347–5.

[30]Kvasnicka J, Bendl J, Zivn J, Umlaufov¨ç A, Maslowsk¨ç H. [Changes in hemostasis and fibrinolysis in gestational diabetes]. Cas Lek Cesk.1996; 135(4): 106–10. PMID: 8625379.

[31]Aboud MR, Ma DD. Increased incidence of venous thrombosis in patients with shortened activated partial thromboplastin times and low ratios for activated protein C resistance. Clin Lab Haematol. 2001;23(6): 411–6. PMID: 11843891.

[32]Weng LC, Cushman M, Pankow JS, Basu S, Boerwinkle E, Folsom AR, Tang W. A genetic association study of activated partial thromboplastin time in European Americans and African Americans: the ARIC Study. Hum Mol Genet. 2015; 24(8): 2401–8. DOI: 10.1093/hmg/ddu732.

[33]Djelmis J, Ivanisevic M, Kurjak A, Mayer D. Hemostatic problems before, during and after delivery. J Perinat Med. 2001; 29(3): 241–6. DOI: 10.1515/JPM.2001.034.

[34]Wright JG, Cooper P, Astedt B, Lecander I, Wilde JT, Preston FE, Greaves M. Fibrinolysis during normal human pregnancy: complex inter-relationships between plasma levels of tissue plasminogen activator and inhibitors and the euglobulin clot lysis time. Br J Haematol.1988; 69(2): 253–8. DOI: 10.1111/j.1365–2141.1988.tb07630.x.

[35]Pelage JP, Fohlen A, Le Pennec V. [Role of arterial embolization in the management of postpartum hemorrhage]. J Gynecol Obstet Biol Reprod (Paris). 2014;43(10): 1063–82. DOI: 10.1016/j.jgyn.2014.10.002.

[36]Meier J. A new application for thrombelastography in pregnant women at term. Minerva anestesiologica.2012; 78(12): 1319–20. PMID: 23044742.

[37]Wang W, Wang AM, Huang XQ, Jiang W, Jia XN. Thromboelastography in women with pathological pregnancies: a preliminary study. Chin Med Sci J. 2014;29(1): 63–4. PMID: 24698684.

Tables

Table 1 Baseline characteristics of the participants

	GDM group N=50	NGDM group N=132	*P*-value
Sociodemographic characteristics of gravidas			
Prenatal maternal age (years, mean ± sd)	30.3±4.4	28.6±3.9	0.012
Prenatal maternal BMI (kg/m2, mean ± sd)	27.9±3.5	26.9±3.3	0.091
Prenatal maternal weight (kg, mean ± sd)	73.5±10.1	70.1±9.0	0.053
Maternal weight before pregnancy (kg, mean ± sd)	61.79±9.48	55.96±8.31	0.000
Maternal weight gain during pregnancy (kg/m2, mean ± sd)	11.66±4.68	14.19±4.17	0.001
SBP (mmHg, mean ± sd)	121.0±10.3	122.5±11.1	0.405
DBP(mmHg, mean ± sd)	80.4 ±8.2	79.4+9.0	0.693
Actual days of pregnancy (days, mean ± sd)	271.3±8.3	274.7±11.0	0.013
Previous maternal history			
Thyroid disorder during pregnancy (persons, %)	7(14%)	21(15.9 %)	0.931
Preecalmpsia and clampsia (persons, %)	1(2 %)	2(1.5%)	0.677
Previous history of full-term births times	26 (52.0%)	58 (43.9%)	0.330
Previous history of premature delivery	0 (0.0%)	3 (2.3%)	0.563
Previous history of abortion	23 (46.0%)	54 (40.9%)	0.535
Maternal biochemical indexes			
RBC($\times10^9$/L, mean ± sd)	4.1±0.6	4.0±0.4	0.115
Hemoglobin (g/L, mean ± sd)	124.7±12.3	120.5±13.4	0.052
WBC($\times10^9$/L, mean ± sd)	8.3 ±2.6	9.1±2.3	0.068
NE($\times10^9$/L, mean ± sd)	6.3±2.3	6.8±2.1	0.183
Platelet($\times10^9$/L, mean ± sd)	180.5±42.8	194.3±50.3	0.207
ALB(g/L, mean ± sd)	35.5±3.3	36.0±3.6	0.362
Plasma total protein(g/L, mean ± sd)	61.9±5.0	63.1±5.9	0.220
Plasma globulin(g/L, mean ± sd)	26.4±3.7	27.0±4.6	0.567
DBIL(umol/L，mean ± sd)	2.7 (2.0-3.4)	2.2 (1.7-3.2)	0.093
STB(umol/L，mean ± sd)	8.4±5.2	6.8±3.6	0.012
IBIL(umol/L，mean ± sd)	4.9±3.1	4.3±3.0	0.113
AST(U/L, mean ± sd)	22.9±16.9	20.6±8.1	0.209
ALT(U/L, Median (Q1-Q3))	15.0 (10.0-25.5)	12.5 (9.0-20.2)	0.168
LDH(U/L, Median (Q1-Q3))	192.0 (161.5-236.8)	194.0 (171.0-220.2)	0.799
ALP(U/L, mean ± sd)	175.8±50.2	158.2±46.7	0.028
GGT(U/L, mean ± sd)	11.0 (8.0-22.0)	11.5 (8.0-18.0)	0.610
FPG (mmol/L, mean ± sd)	4.8±1.2	4.2±0.7	0.001
HbA1c(%，mean ± sd)	6.5±0.7	NA	
UA (umol/L, mean ± sd)	300.8±71.2	303.9±73.2	0.796
Plasma urea nitrogen(mmol/L, mean ± sd)	3.1±0.9	3.4±0.8	0.094
Plasma creatinine（umol/L, mean ± sd）	53.8±11.8	54.6±9.3	0.623
Plasma total bile acid(umol/L, Median (Q1-Q3))	3.2 (2.1-4.6)	3.7 (2.5-5.0)	0.095
R (seconds, mean ± sd)	7.1±1.3	6.8±1.2	0.089
K (seconds, mean ± sd)	1.3±0.4	1.2±0.3	0.071
α-angle (degrees, mean ± sd)	75.8±3.1	76.4±2.8	0.175
MA (millimeters, mean ± sd)	66.8±6.7	66.2±5.7	0.524
LY30 (%,Median (Q1-Q3))	0.1 (0.1-3.7)	0.1 (0.1-0.6)	0.363
FIB(g/L, mean ± sd)	4.7±0.8	4.3±0.7	0.001
PT(second, mean ± sd)	11.5±0.8	11.3±0.6	0.063
TT(second, mean ± sd)	16.0±1.5	15.8±1.1	0.287
APTT(second, mean ± sd)	30.9±3.0	29.5±3.3	0.010
PT-INR(INR, Median (Q1-Q3))	1.0 (0.1)	1.0 (0.1)	0.191
DD (ug/ml, Median (Q1-Q3))	1.6 (1.2-2.2)	1.6 (1.2-2.2)	0.955
Sociodemographic characteristics of baby			
Neonatal weight (g, mean ± sd)	3354.1±569.66	3320.64±449.13	0.678
Maternal events			
Intrapartum bleeding volume (ml, mean ± sd)	238.2±71.0	286.0±102.4	0.003

Postpartum 24-hour bleeding volume (ml, mean ± sd)	270.7±99.8	314.7±131.1	0.033
Cesarean delivery (persons,%)	28 (56.0%)	50 (37.9%)	0.027
Wound infection after Caesarean delivery (persons,%)	2(4.0%)	3(2.3%)	0.906
Thrombotic event (persons,%)	1(2.0%)	2(1.5%)	0.677
Neonatal events			
Neonatal malformation (persons,%)	4(8.0%)	2(1.5%)	0.084
Intrauterine growth retardation or fetal distress (persons,%)	4(8. 0%)	2(1.5%)	0.084
Perinatal death (persons,%)	0(0)	0(0)	
Still birth≥24 weeks (persons,%)	0(0)	0(0)	
Preterm birth (persons,%)	11(22%)	47(35.6%)	0.114
Very Preterm birth (persons,%)	0(0)	9(6.8)	0.132
Macrosomia (persons,%)	6(12%)	10(7.6%)	0.521

Data are mean±SD if normally distributed, and median (interquartile range) or N (%) if not.

Note: SBP: systolic blood pressure; DBP: diastolic blood pressure; RBC: blood erythrocytes count; WBC: blood leukocyte Count; NE: neutrophile granulocyte; DBIL: Direct Bilirubin; STB: Serum total bilirubin; IBIL: Indirect bilirubin; AST□aspartate aminotransferarase; ALT: alanine aminotransferarase; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; γ-GGT:γ-glutamyl transpeptadase; HbA1c: glycated haemoglobin; UA: plasma Uric Acid; R: reaction time; K: kinetic time; α-angle: a measure of clot kinetics; MA: maximum amplitude; LY30: the percentage reduction in amplitude 30 min post-MA; FIB: fibrinogen; PT□prothrombin time; TT□thrombin time; APTT□activated partial thromboplastin time; PT-INR□ international normalized ratio of prothrombin time; DD: D-Dimer.

Table 2 Univariate analysis of the relationships between CFA and other parameters

	Statistics	LY30	*P* value	FIB	*P* value	APTT	*P* value
GDM (YES)	50 (27.50%)	1.30 (0.4, 2.24)	0.008	0.39 (0.2, 0.6)	0.001	1.40 (0.3, 2.5)	0.010
Maternal age (years, mean ± sd)	29.08 ± 4.11	0.01 (-0.1, 0.11)	0.865	0.01 (-0.02, 0.04)	0.392	-0.08 (-0.20, 0.04)	0.202
Maternal BMI (kg/m2, mean ± sd)	27.15 ± 3.38	0.04 (-0.09, 0.17)	0.549	0.00 (-0.03, 0.03)	0.951	-0.04 (-0.17, 0.10)	0.546
Maternal weight gain during pregnancy (kg/m2, mean ± sd)	13.49 ± 4.45	0.01 (-0.09, 0.11)	0.834	-0.04(-0.06, -0.02)	0.002	-0.05 (-0.15, 0.06)	0.408
SBP (mmHg, mean ± sd)	122.06 ± 10.85	0.00 (-0.03, 0.05)	0.728	-0.00 (-0.01, 0.01)	0.884	-0.01 (-0.05, 0.04)	0.671
DBP (mmHg, mean ± sd)	79.71 ± 8.74	0.00 (-0.05, 0.05)	0.946	0.00 (-0.01, 0.02)	0.590	0.00 (-0.05, 0.06)	0.909
platelet (*10 9/L, mean ± sd)	190.48 ± 48.64	-0.00 (-0.01, 0.01)	0.360	0.00 (0.00, 0.01)	0.034	-0.01 (-0.02, 0.00)	0.061
ALT (IU/L, median (interquartile))	18.07 ± 18.29	0.03 (0.01, 0.06)	0.004	0.01 (0.00, 0.01)	0.013	0.01 (-0.02, 0.03)	0.688
AST	21.22 ± 11.22	0.02 (-0.02, 0.06)	0.245	0.01 (-0.00, 0.02)	0.208	-0.02 (-0.06, 0.02)	0.334
ALP (IU/L, median (interquartile))	163.000 ± 48.205	0.01 (-0.00, 0.02)	0.073	0.00 (0.00, 0.01)	0.040	0.00 (-0.01, 0.01)	0.581
GGT (IU/L, median (interquartile))	17.24 ± 18.15	0.02 (-0.01, 0.04)	0.176	0.01 (0.00, 0.01)	0.041	-0.01 (-0.04, 0.02)	0.549
Fasting glucose (mmol/L, mean ± sd)	4.34 ± 0.91	0.02 (-0.45, 0.50)	0.928	0.17 (0.06, 0.29)	0.004	-0.01 (-0.54, 0.53)	0.982
urea nitrogen (mmol/L, mean ± sd)	3.31 ± 0.84	0.34 (-0.17, 0.85)	0.191	0.04 (-0.09, 0.17)	0.509	-0.36 (-0.93, 0.21)	0.219
serum creatinine (umol/L, mean ± sd)	54.40± 10.03	0.01 (-0.03, 0.06)	0.560	-0.00 (-0.02, 0.01)	0.501	-0.02 (-0.07, 0.03)	0.427
UA (umol/L, mean ± sd)	303.04 ± 72.48	0.00 (-0.01, 0.01)	0.782	-0.00 (-0.00, 0.00)	0.283	-0.01 (-0.01, 0.00)	0.093
Plasma total bile acid(μmol/l, Median (Q1-Q3))	4.21± 4.37	-0.03 (-0.13, 0.07)	0.504	0.01 (-0.02, 0.03)	0.523	-0.09 (-0.20, 0.02)	0.125
Actual days of pregnancy (days, mean ± sd)	273.76 ± 10.43	-0.01 (-0.05, 0.03)	0.664	-0.01 (-0.02, 0.00)	0.243	-0.02 (-0.07, 0.02)	0.337
Previous history of abortion	77 (42.31%)	0.30 (-0.57, 1.17)	0.499	-0.34 (-0.56, -0.13)	0.002	0.05 (-0.93, 1.02)	0.922
Previous history of full-term births times	84 (46.15%)	-0.06 (-0.93, 0.80)	0.887	-0.25 (-0.46, -0.03)	0.027	-0.33 (-1.30, 0.64)	0.506
Previous history of premature delivery	3 (1.65%)	-1.36 (-4.74, 2.02)	0.432	-0.32(-1.18, 0.54)	0.468	0.29 (-3.50, 4.07)	0.882

Data are β (95% confidence interval [CI]) and *P* value, or odds ratio (95% CI) and *P* value.

Table 3 Multiple regression models for the relationships between LY30, FIB, APTT, and GDM

indicators	Model 1		Model 2		Model 3	
	Adjusted OR, 95%CI	*P*	Adjusted OR, 95%CI	*P*	Adjusted OR, 95%CI	*P*
APTT	1.4 (0.3, 2.5)	0.010	1.6 (0.5, 2.7)	0.004	1.5 (0.4, 2.6)	0.011
FIB	0.4 (0.2, 0.6)	0.001	0.4 (0.1, 0.6)	0.002	0.3 (0.1, 0.6)	0.011
LY30	1.3 (0.3, 2.2)	0.008	1.3 (0.4, 2.3)	0.008	1.2 (0.2, 2.2)	0.019

Data are β (95% CI) and *P* value, or (95% CI) and *P* value.

Model 1 was unadjusted. Model 2 was adjusted for maternal age (years, mean ± sd). Model 3 was adjusted for urea nitrogen (mmol/L, mean ± sd), ALT (IU/L, median [interquartile range]), SBP (mmHg, mean ± sd), DBP (mmHg, mean ± sd), ALP (IU/L, median [interquartile range]), and maternal age (years, mean ± sd).

Figures

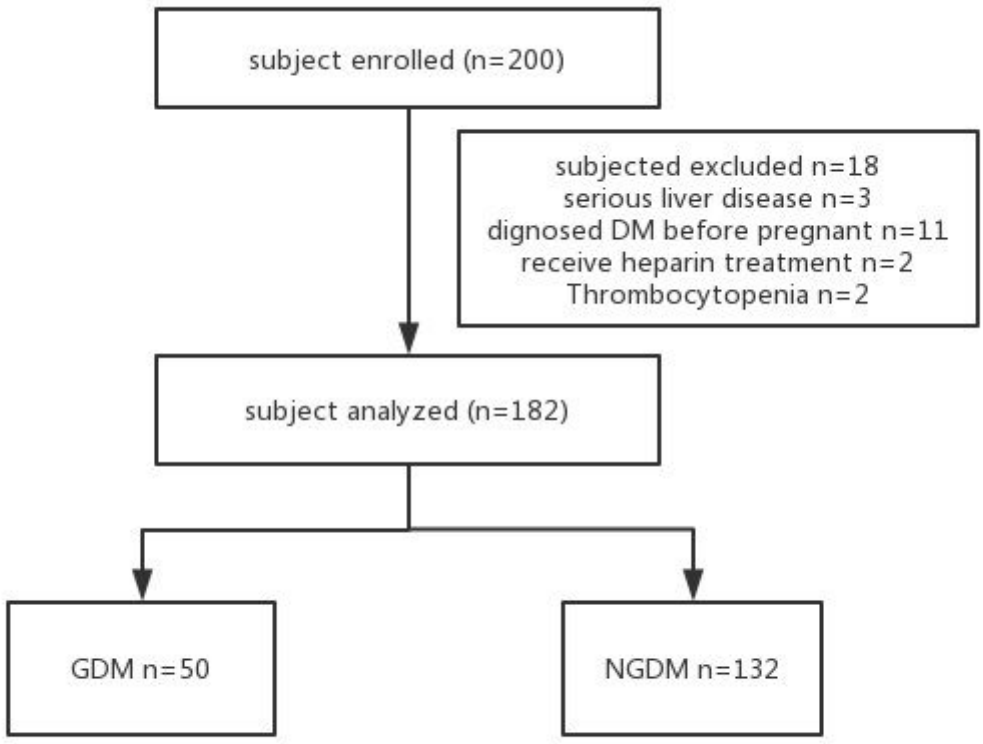

Figure 1

Flow chart of patient selection

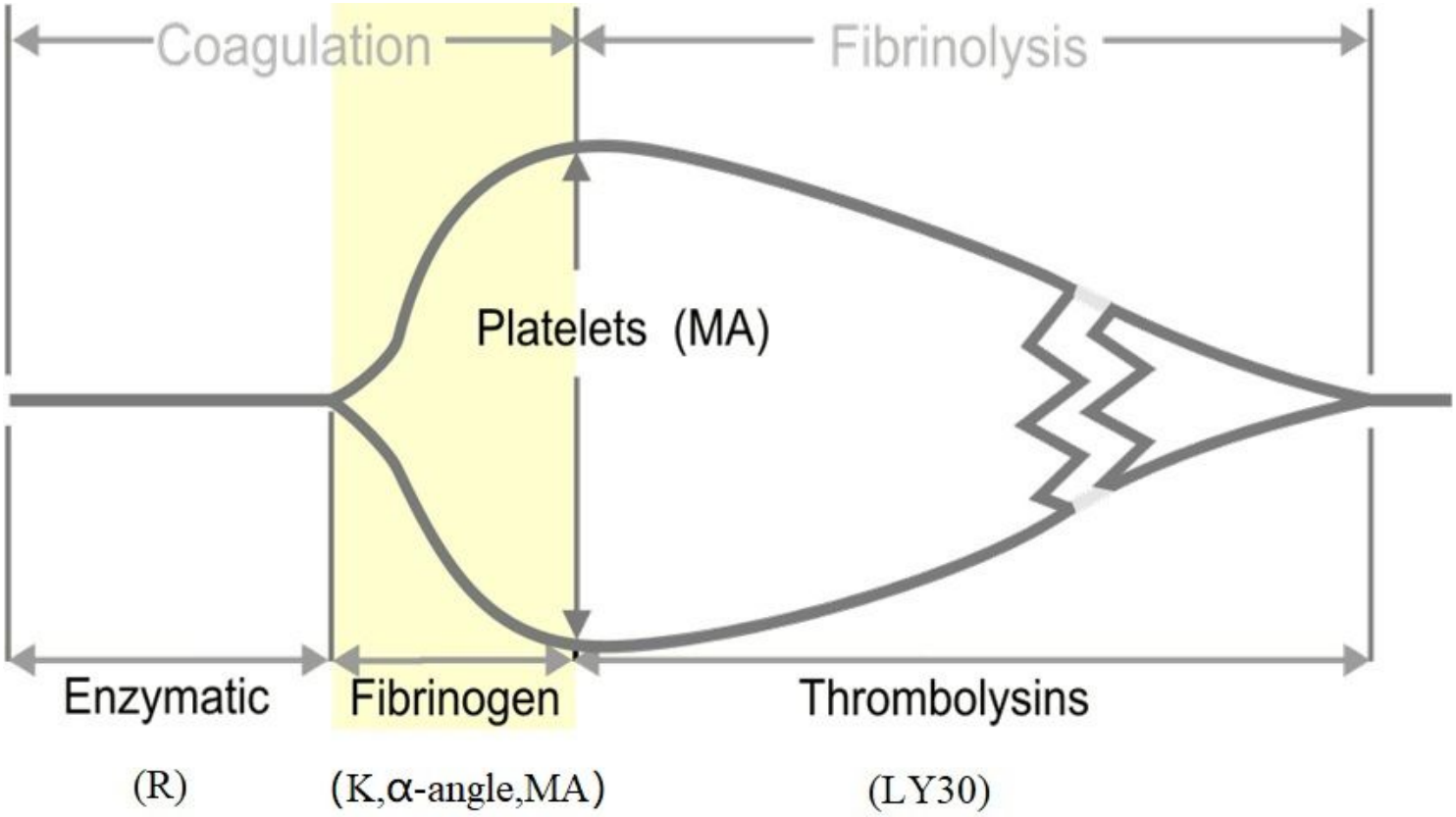

Figure 2

Typical pattern of TEG with variables measured during coagulation and fibrinolysis