European Review for Medical and Pharmacological Sciences 2021; 25: 591-597

Changes of anti-β2 glycoprotein I antibody IgA/G/M, platelet aggregation rate, plasma fibrinogen and d-dimer in guiding venous thrombosis during pregnancy

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Abstract. – OBJECTIVE: This study provides a theoretical basis for the prevention, treatment and diagnosis of venous thrombosis during pregnancy.

PATIENTS AND METHODS: Sixty patients with venous thrombosis in gestation period were treated as the research group, including every 30 people in the middle and late pregnancy groups, and the control group randomly selected 33 healthy pregnant women during the same period. The anti-β2 glycoprotein I antibody IgA/G/M, platelet aggregation rate, plasma fibrinogen, and D-dimer levels were measured in all subjects.

RESULTS: Resistance-β2 glycoprotein I antibody IgA/G/M, platelet aggregation rate, plasma fibrinogen, and compared with the control group, D-dimer levels were significantly increased ($p<0.05$), but for the middle pregnancy group and late pregnancy group, the difference was not statistically significant ($p>0.05$). In the control group of pregnant women anti-β2 glycoprotein I antibody IgA/G/M, platelet aggregation rate, plasma fibrinogen, and D-dimer no obvious correlation ($p>0.05$), Anti-β2 glycoprotein I antibody IgA/G/M, platelet aggregation rate, plasma fibrinogen, D-dimer entry equation are closely related risk factors for venous thrombosis during pregnancy ($p<0.05$), and D-dimer is the most important.

CONCLUSIONS: Vein thrombosis during pregnancy patients anti-β2 glycoprotein I antibody IgA/G/M, platelet aggregation rate, plasma fibrinogen, and D-dimer in pregnant women group increased significantly compared with the control group, suggesting these above indicators are closely related to Venous thrombosis in pregnant women and associated with the severity of the disease. Vascular endothelial injury plays an important role in phlebothrombosis in gestation period.

Key Words:
Phlebothrombosis in gestation period, Platelet aggregation rate, Plasma fibrinogen, Anti-β2 glycoprotein I antibody IgA/G/M, D-dimer, Vascular endothelial injury.

Introduction

Under physiological conditions, the body keeps the blood in a dynamic equilibrium state and maintains an uncoagulated flow state in the role of anticoagulation, coagulation, and fibrinolytic system. During pregnancy, the anticoagulation, coagulation and fibrinolytic system of the pregnant woman will undergo physiological changes, the level of anticoagulant substances will decrease, and the blood will show a state of high coagulation. With the continuous increase of pregnant women's gestational weeks, the accumulation of anticoagulant substances will lead to a state of high coagulation in the blood vessels. Venous thrombosis in pregnancy is the result of venous stasis[1]. At the same time, it can also cause special pathological changes such as vascular injury, which endangers the health of both mothers and infants. It is also an important cause of perinatal adverse outcomes and even death. Its risk is 4-5 times that of non-pregnant women of the same age[2]. The exact pathogenesis is unknown[3]. Hypercoagulability during pregnancy is a protective physiological change of the body. Severe co-

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agulation can cause disseminated intravascular coagulation, can cause maternal coagulation dysfunction during pregnancy or complications related to pregnancy coagulation dysfunction, and severe cases can cause postpartum hemorrhage[4]. Therefore, changes in coagulation function indexes during pregnancy have a great part to play in the genesis and development of venous thrombosis during pregnancy. The coagulation cascade reaction during pregnancy is a gradual aggravation process[5]. Anti-β2 glycoprotein I antibody IgA/G/M, platelet aggregation rate, plasma fibrinogen and D-dimer are markers of vascular coagulation function. Changes in the above indicators can directly lead to vascular endothelial cell damage. Anti-β2 glycoprotein I antibody IgA/G/M is a new marker of oxidative stress[6], activates monocytes, induces vascular inflammation, and severe cases will also damage vascular endothelial cells[7]. Platelet aggregation rate, plasma fibrinogen and D-dimer can lead to the expression of adhesion molecules[8]. But anti-β2 glycoprotein I antibody IgA/G/M in venous thrombosis during pregnancy in the process of the formation and the onset of mechanism is poorly understood. The primary research purpose is through the determination of vein thrombosis during pregnancy and normal pregnant women fight beta 2 glycoprotein I antibody in serum and placenta IgA/G/M, platelet aggregation rate, plasma fibrinogen, expression level of D-dimer, vein thrombosis patients and normal pregnant women during pregnancy in order to understand the above index difference. To discuss the role of anti-β2 glycoprotein I antibody IgA/G/M, platelet aggregation rate, plasma fibrinogen, D-dimer in the occurrence and development of phlebothrombosis in gestation period, and to explore the relationship between the expression of the above indicators and the severity of the disease and provide important theoretical basis for clinical treatment, diagnosis and prevention.

Patients and Methods

Experimental Group

Sixty patients with gestational thrombotic diseases during pregnancy who were prenatal examination in The Fifth Hospital of Wuhan and were hospitalized from 2018-2 to 2019-12 were randomly selected and divided into two groups. There were 30 patients in the middle and late pregnancy groups. Middle pregnancy group (28.0±3.6) years (22-34 years) and average gestational age (28.5±1.0) weeks, late pregnancy group (27.2±3.8 years) (21-34 years), average gestational age (38.8±1.2) week.

This study has been pre-approved by the Ethics Committee of The Fifth Hospital of Wuhan. All subjects have signed the consent forms before recruitment in this study.

Control Group

Pregnant women with an average gestational age (38.8±1.1) week and an average age (27.5±3.7) year (21~34 years) were randomly selected as the control group.

Inclusion and Exclusion Criteria

Inclusion criteria: all subjects had a single first birth, with no obvious difference in health, age or gestational age. Exclusion criteria: atherosclerosis, severe liver and kidney disease, hypertension, coronary heart disease, other endocrine diseases, blood diseases, premature rupture of membranes and other diseases and their complications; bad habits such as smoking and drinking; insulin resistance; recent infection.

Reagents and Equipment

Anti-β2 glycoprotein I antibody IgA/G/M, platelet aggregation rate, plasma fibrinogen and D-dimer enzyme-linked immunosorbent kit (Elabscience, TX, USA), sealing fluid (10% goat serum), anti-mouse biology Secondary antibody (Sizhengbai Biotechnology, Bejing, China) biotinylated goat anti-rabbit secondary antibody working fluid, serum working fluid, endogenous peroxidase sealing fluid, horse radish peroxidase (HRP)-labeled streptavidin (Kangshi, Hong Kong, China), Diaminobenzidine (DAB) substrate buffer, DAB substrate concentrate (20*) (ready-made) (Zhongshan Jinqiao, Beijing, China). Automatic balance centrifuge-70°C low temperature refrigerator 4°C refrigerator, Eppendorf (EP) tube.

General Clinical Data Collection

Record the age, blood pressure, and gestational age of the three groups of subjects. Subjects fasted in the morning. Use a uniform measurement tool to manually measure body mass and height. Calculating BMI (BMI = kg/m^2).

Biochemical Test

Anti-β2 glycoprotein I antibody IgA/G/M, platelet aggregation rate, plasma fibrinogen and

D-dimer, etc. were detected in our hospital's biochemical laboratory.

Specimen Collection

All subjects were centrifuged at 2000 rpm for 10 minutes at room temperature before admission (before any drug treatment) and 6 ml of fasting venous blood was input. Plasma was separated from 3 ml of blood, and stored in an EP tube in a refrigerator at –70°C to measure anti-β2 glycoprotein I antibody IgA/G/M, platelet aggregation rate, plasma fibrinogen, and D-dimer concentrations.

Determination of Plasma Anti-β2 Glycoprotein I Antibody IgA/G/M and D-dimer Concentration

The enzyme-linked immunosorbent kit was performed by a sandwich enzyme-linked immunosorbent assay (ELISA). Samples, standards, and add horseradish peroxidase (HRP)-labeled antibodies to the coated microwells of pre-coated antibodies and incubate and wash thoroughly for 3 min. Tetramethylbenzidine (TMB) expands the substrate. Under the catalysis of horseradish peroxidase, TMB is converted to blue, and it is converted to final yellow under the action of acid. Optical density (OD) value was detected at 450 nm. The OD values were positively correlated with the concentration of anti-β2 glycoprotein I antibody IgA/G/M, platelet aggregation rate, plasma fibrinogen and D-dimer concentration in the sample. The standard curve is used to calculate the concentration.

Statistical Analysis

SPSS 23.0 statistical software (IBM Corp., Armonk, NY, USA) was used for data analysis. Percent is showed as %. The measurement data are showed as average value ± standard deviation. First, the homogeneity of variance of the data is tested, and the average of multiple samples is compared by analysis of variance (ANOVA). The *t*-test was compared to the average of each two samples. If the variance is not a *t*-test, compare the sampling rate with the χ^2-test. Thrombosis during pregnancy as the dependent variable, anti-β2 glycoprotein I antibody IgA/G/M, platelet aggregation rate, plasma fibrinogen, and D-dimer factors as independent variables, multivariate logistic regression analysis with significant difference $p< 0.05$.

Results

To Compare Plasma D-dimer Levels

The level of plasma D-dimer in the control group was 45.98-78.97 ng/ml, with an average of 63.97±8.9 ng/ml. The plasma D-dimer level in the middle pregnancy group was 84.89-126.77 ng/ml, with an average of 105.92±11.6 ng/ml. The horizontal range is 87.42-131.98 ng/ml, and the average value is 109.68±12.2 ng/ml. The statistical results showed that the plasma D-dimer levels in the control group were significantly lower than those in the middle and late pregnancy groups (both $p<0.05$) with significant difference. The plasma D-dimer level in the late pregnancy group was slightly higher than that in the middle pregnancy group with no significant difference ($p>0.05$), as shown in Table I.

Note: making a comparison with the control group, it is $^{a}p<0.05$, making a comparison with the middle pregnancy group, it is $^{b}p<0.05$.

To Compare Plasma Fibrinogen Concentration in Each Group

The plasma fibrinogen concentration in the control group was 18.45-39.19 ng/ml, with an average of 26.90±4.7 ng/ml. The plasma fibrinogen concentration in the medium pregnancy group was 30.94-90.58 ng/ml, with an average of 61.95±15.3 ng/ml. The average concentration was 64.82±17.1 ng/ml, 34.18-96.14 ng/ml. Statistical consequences indicated that in the control group the plasma plasma fibrinogen level was significantly lower than that in the middle and late pregnancy groups (both $p<0.05$) with significant difference. At the same time, plasma fibrinogen levels in the middle pregnancy group were slightly lower than in the late pregnancy group

Table I. To compare of plasma D-dimer levels.

Group	Concentration range	Average
Control group	45.98~78.97 ng/ml	63.97 ± 8.9 ng/ml[b]
Middle pregnancy group	87.42~131.98 ng/ml	105.92 ± 11.6 ng/ml[a]
Late pregnancy group	87.42~131.98 ng/ml	109.68 ± 12.2 ng/ml[a]

Table II. To compare of plasma plasma fibrinogen concentrations.

Group	Concentration range	Average
Control group	18.45~39.19 ng/ml	26.90 ± 4.7 ng/ml[b]
Middle pregnancy group	30.94~90.58 ng/ml	61.95 ± 15.3 ng/ml[a]
Late pregnancy group	34.18-96.14 ng/ml	64.82 ± 17.1 ng/ml[a]

(p>0.05) with no significant difference, as shown in Table II.

Note: making a comparison with the control group, it is [a]p<0.05, making a comparison with the middle pregnancy group, it is [b]p<0.05.

To Compare Platelet Aggregation Rate

The platelet aggregation rate in the control group was 45.98-78.97%, with an average of 63.97±8.9%. The platelet aggregation rate in the medium pregnancy group was 84.89-96.77%, with an average of 90.92±11.6%. The platelet aggregation rate in the late pregnancy group was 87.42-97.98%, with an average value of 94.68±12.2%. The statistical results showed that the platelet aggregation rate is significantly higher in the pregnant group and the late pregnancy group than in the control group (both p<0.05) with significant difference. The platelet aggregation rate in the late pregnancy group was slightly higher than that in the middle pregnancy group with no significant difference. (p>0.05), as shown in Table III.

Note: making a comparison with the control group, it is [a]p<0.05, making a comparison with the middle pregnancy group, it is [b]p<0.05.

To Compare Plasma Anti-β2 Glycoprotein I Antibody Ig/G/M Concentration

The concentration of anti-β2 glycoprotein I antibody Ig/G/M in the control group was 18.45-39.19 ng/ml, with an average of 26.90±4.7 ng/ml, and the concentration of the middle pregnancy group was 30.94-90.58 ng/ml, with an average of 61.95 ± 15.3 ng/ml, the concentration in the late pregnancy group was 34.18-96.14 ng/ml, with an average of 64.82 ± 17.1 ng/ml. The statistical consequences indicated that the concentration of the middle and late pregnancy groups was significantly higher than that of the control group with significant difference (both p<0.05). At the same time, the concentration of annexin A5 in the late pregnancy group was slightly higher than that in the middle pregnancy group with no significant difference (p>0.05), as shown in Table IV.

Note: making a comparison with the control group, it is [a]p<0.05, making a comparison the middle pregnancy group, it is [b]p<0.05.

Analysis of Multiple Risk Factors of Venous Thrombosis During Pregnancy

According to the above indicators, relevant risk factors were analyzed. Anti-β2 glycoprotein I antibody Ig/G/M, platelet aggregation rate, plasma fibrinogen, D-dimer were used as independent variables, and the presence or absence of venous thrombosis was used as the dependent variable. Logistic regression analysis showed that anti-β2 glycoprotein I antibody Ig/G/M, platelet aggregation rate, plasma fibrinogen, and D-dimer entered the equation, which was closely related risk factors for venous thrombosis during pregnancy (p<0.05) and D-dimer is the most important (OR=6.58, 95% CI: 2.71-19.35, p=0.001; Table V).

Discussion

The number of platelets during pregnancy is higher than that during non-pregnancy, and fibrin production is increased, which is one of the reasons for the increasing morbidity and mortality of pregnant women and premature babies. The decrease of fibrinolytic activity leads to the oc-

Table III. To compare of platelet aggregation rate.

Group	Concentration range	Average
Control group	45.98~78.97%	26.90 ± 4.7%[b]
Middle pregnancy group	84.89~96.77%	90.92 ± 11.6%[a]
Late pregnancy group	87.42~97.98 %	94.68 ± 12.2 %[a]

Table IV. To compare of plasma anti-β2 glycoprotein I antibody Ig/G/M concentrations.

Group	Concentration range	Average
Control group	18.45~39.19 ng/ml	26.90 ± 4.7 ng/ml[b]
Middle pregnancy group	30.94~90.58 ng/ml	61.95 ± 15.3 ng/ml[a]
Late pregnancy group	34.18~96.14 ng/ml	64.82 ± 17.1 ng/ml[a]

currence of hypercoagulability and the increase of coagulation factors, which is closely related to adverse pregnancy outcomes[9]. At the same time, it can cause diseases related to vascular dysfunction, such as metabolic syndrome, type 2 diabetes, and cardiovascular risk. Its incidence is reported to be approximately 1.3/1000 pregnancies[10]. If the venous thrombus falls off and is embedded in the blood vessels of the lungs next week, it can cause pulmonary embolism and increase the risk of pulmonary embolism death[11]. Therefore, it is very important to diagnose and treat deep vein thrombosis of lower limbs in time. However, the research mechanism of gestational thrombosis has not been clearly studied. Therefore, actively exploring the mechanism of thrombosis, pathogenesis and development during pregnancy is helpful to the prevention and control of the disease and has a positive effect on improving pregnancy outcomes. Current research has shown that genetic defects are important in the risk factors for venous thrombosis[12]. Studies on coagulation function indicators of women during normal pregnancy have been reported abroad. Protein C deficiency, protein S deficiency, protein Z deficiency, and factor V mutations can cause changes in coagulation function. The current research is to investigate the diagnosis of a certain pregnancy during pregnancy[13], and there are few domestic research reports. Therefore, to explore and study the markers of venous thrombosis during pregnancy is of great significance to guide the prevention and treatment of diseases.

Platelet aggregation rate, plasma fibrinogen, and D-dimer are important markers that cause thrombosis and endothelial function destruction. As various white blood cells aggregate to the site of inflammation, they can lead to activation and adhesion of endothelial cells[14]. When leukocytes adhere to the surface of endothelial cells, plasma fibrinogen and D-dimer increase, and the platelet aggregation rate increases. That is, when the body produces a large number of oxidative intermediates that cause insufficient oxidants, the oxidized intermediate shell can bind to lipid proteins, leading to peroxidation, which destroys the function of endothelial cells and causes increased protein oxidative damage. Lipid oxidation can cause increased DNA damage[15]. The main clinical manifestation of lipid oxidative damage is dyslipidemia. But little is known about oxidative damage to proteins. However, the role of oxidative damage cannot be ignored. Anti-β2 glycoprotein I antibody IgA/G/M is a molecular marker of oxidative stress and is the final product of oxidative stress caused by oxidative stress. The increased production of anti-β2 glycoprotein I antibody IgA/G/M can cause the body's monocytes and neutrophils to suddenly increase, can induce monocytes to produce more reactive oxygen species, and the oxidative stress response is continuously strengthened, thereby making vascular endothelial cells produce active oxygen, reduce the fluidity of the cell membrane, lipid peroxidation will increase the permeability between cells, thereby inducing calcium overload, thereby damaging vascular endothelial cells, inducing oxidative stress, and the vicious cycle will cause blood vessels endothelial injury and promotes increased annexin expression. Other studies have

Table V. Multivariate logistic regression analysis of venous thrombosis during pregnancy.

Risk factor	β	*p*	OR	95% CI
D-dimer	1.792	0.001*	6.581	2.713~19.355
Platelet aggregation rate	1.124	0.045*	2.673	1.053~7.423
Anti-β2 glycoprotein I antibody IgA/G/M	1.445	0.002*	4.285	1.453~13.084
Plasma fibrinogen	1.563	0.013*	4.935	1.379~16.493
Constant	-3.275	0.000	0.043	

confirmed that vascular endothelial damage occurs in maternal tissues of thrombosis patients in gestation period and occurs in fetus[16]. It has also been confirmed that vascular diseases and metabolic system diseases are based on endothelial cell damage, but the specific mechanism of endothelial cell damage in pregnancy thrombosis remains to be studied. Therefore, it is valuable to study vascular endothelial damage in the pathogenesis of thrombosis during pregnancy.

This study found that the anti-β2 glycoprotein I antibody IgA/G/M, platelet aggregation rate, plasma fibrinogen, and D-dimer in plasma of patients with thrombosis during pregnancy were prominently higher than those in the control group ($p<0.05$), suggesting that the above indicators are closely related to the incidence of thrombosis in gestation period, indicating that the thrombosis and endothelial damage mechanism have a vital role in thrombosis development during pregnancy. Since studies have indicated that platelet aggregation rate, plasma fibrinogen, and D-dimer are not only a new marker of oxidative stress, but also a new inflammatory mediator that mediates angiogenesis, we have studied its positive significance to study its role in thrombosis during pregnancy. Our research also found that the risk factors for venous thrombosis during pregnancy can be as follows: (1) *D-dimer*. Multi-factor Logistic analysis also confirmed that increased D-dimer expression is a dangerous element for phlebothrombosis in gestation period, an OR index is 6.58 higher than other factors, suggesting that increased D-dimer expression is the most important dangerous for phlebothrombosis during pregnancy; results are consistent with those reported in literature[17]. (2) *Platelet aggregation rate*. Multiple factor Logistic analysis also confirmed that platelet aggregation rate was a risk factor for venous thrombosis in pregnancy. The study reported that the incidence of platelet aggregation in patients with gestational thrombosis was 2.67 times higher than that in healthy control group (OR=2.67). The consequence is similar to those reported in literature[18]. (3) *Anti-β2 glycoprotein I antibody IgA/G/M*. In recent years the research thinks that the mechanism of increased anti-β2 glycoprotein I antibody IgA/G/M on pregnancy thrombosis is complex. The expression of high anti-β2 glycoprotein I antibody IgA/G/M will produce a large number of acidic metabolites in the thrombus site, produces toxic to cells, damage the vascular endothelium and dilate local blood vessels, leading to rupture of capillaries and bleeding[19]. Logistic analysis confirmed that anti-β2 glycoprotein I antibody IgA/G/M is a dangerous element for venous thrombosis in gestation period, which is similar to the results reported in the literature. (4) *Plasma fibrinogen*. Increased plasma fibrinogen can trigger downstream cascades, leading to free-radical chain reactions, resulting in overexpression of adhesion molecules[20], eventually leading to abnormal protein structure and function of endothelial cells, accelerating vascular disease, thereby damaging vascular endothelium and thrombosis, the above factors are the central links of the pathophysiology of thrombosis during pregnancy.

At present, little is known about the changes of anti-β2 glycoprotein I antibody IgA/G/M, platelet aggregation rate, plasma fibrinogen, and D-dimer in patients with phlebothrombosis in gestation period at home and abroad. In this study, the plasma anti-β2 glycoprotein I antibody IgA/G/M, platelet aggregation rate, plasma fibrinogen, and D-dimer levels in patients with thrombus during pregnancy and pregnancy thrombosis patients were prominently higher than that in the control group, as well as these indicators of late pregnancy is significantly higher than the middle pregnancy. At present, although there are many studies on thrombotic oxidative stress during pregnancy, studies on anti-β2 glycoprotein I antibody IgA/G/M during pregnancy have not been reported.

Conclusions

Anti-β2 glycoprotein I antibody IgA/G/M, platelet aggregation rate, plasma fibrinogen, and D-dimer are a reliable method for measuring thrombosis during pregnancy, which can assess the effect of thrombosis and treatment. Therefore, The monitoring of anti-β2 glycoprotein I antibody IgA/G/M, platelet aggregation rate, plasma fibrinogen and D-dimer in pregnancy thrombosis is a warning sign for early detection and thrombosis, and it can also through the drug intervention to improve disease progression, can help early diagnosis of pregnancy thrombosis, but further multicenter large sample studies are needed.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Kim C. Gestational diabetes mellitus in korean women: similarities and differences from other racial/ethnic groups. Diabetes Metab J 2014; 38: 1-12.
2) Magon N, Seshiah V. Gestational diabetes mellitus: insulinic management. J Obstet Gynaecol India 2014; 64: 82-90.
3) Sun YH, Cui L, Chen J, Wang M, Liu JJ, Liu XX, Huang XE. Analysis of relationships between prethrombotic states and cervical cancer. Asian Pac J Cancer Prev 2015; 16: 6163-6166.
4) Ndrepepa G, Braun S, King L, Fusaro M, Keta D, Cassese S, Tada T, Schömig A, Kastrati A. Relation of fibrinogen level with cardiovascular events in patients with coronary artery disease. Am J Cardiol 2013; 111: 804-810.
5) Kornblith LZ, Howard B, Kunitake R, Redick B, Nelson M, Cohen MJ, Callcut R. Obesity and clotting: Body mass index independently contributes to hypercoagulability after injury. J Trauma Acute Care Surg 2015; 78: 30-36.
6) Zhao D, Shen L, Wei Y, Xie J, Chen S, Liang Y, Chen Y, Wu H. Identification of candidate biomarkers for the prediction of gestational diabetes mellitus in the early stages of pregnancy using iTRAQ quantitative proteomics. Proteomics Clin Appl 2017; 11: 7-8.
7) Fogerty AE. Challenges of anticoagulation therapy in pregnancy. Curr Treat Options Cardiovasc Med 2017; 19: 76.
8) Dłuski D, Mierzyński R, Poniedziałek-Czajkowska E, Leszczyńska-Gorzelak B. Adverse pregnancy outcomes and inherited thrombophilia. J Perinat Med 2018; 46: 411-417.
9) Lucas G, Burdet P, Cantoni M, Hébert C. Multivariate statistical analysis as a tool for the segmentation of 3D spectral data. Micron 2013; 53: 49-56.
10) Walton BL, Getz TM, Bergmeier W, Lin FC, Uitte de Willige S, Wolberg AS. The fibrinogen γA/γ' isoform does not promote acute arterial thrombosis in mice. J Thromb Haemost 2014; 12: 680-689.
11) Kleinwechter H, Schäfer-Graf U, Bührer C, Hoesli I, Kainer F, Kautzky-Willer A, Pawlowski B, Schunck K, Somville T, Sorger M; German Diabetes Association; German Association for Gynaecology and Obstetrics. Gestational diabetes mellitus (GDM) diagnosis, therapy and follow-up care: Practice Guideline of the German Diabetes Association (DDG) and the German Association for Gynaecologyand Obstetrics (DGGG). Exp Clin Endocrinol Diabetes 2014; 122: 395-405.
12) Blumer I, Hadar E, Hadden DR, Jovanovič L, Mestman JH, Murad MH, Yogev Y. Diabetes and pregnancy: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2013; 98: 4227-4249.
13) Moreira Alves RD, Boroni Moreira AP, Macedo VS, Bressan J, de Cássia Gonçalves Alfenas R, Mattes R, Brunoro Costa NM. High-oleic peanuts: new perspective to attenuate glucose homeostasis disruption and inflammation related obesity. Obesity (Silver Spring) 2014; 22: 1981-1988.
14) Afandi BO, Hassanein MM, Majd LM, Nagelkerke NJD. Impact of Ramadan fasting on glucose levels in women with gestational diabetes mellitus treated with diet alone or diet plus metformin: a continuous glucose monitoring study. BMJ Open Diabetes Res Care 2017; 5: e000470.
15) Abbasalizadeh F, Saleh P, Dousti R, Piri R, Naghavi-Behzad M, Abbasalizadeh S. Effects of atorvastatin on proteinuria of type 2 diabetic nephropathy in patients with history of gestational diabetes mellitus: A clinical study. Niger Med J 2017; 58: 63-67.
16) Ducarme G, Desroys Du Roure F, Le Thuaut A, Grange J, Dimet J, Crepin-Delcourt I. Efficacy of maternal and biological parameters at the time of diagnosis of gestational diabetes mellitus in predicting neonatal morbidity. Eur J Obstet Gynecol Reprod Biol 2018; 221: 113-118.
17) Kumari R, Singh H. The prevalence of elevated high-sensitivity C-reactive protein in normal pregnancy and gestational diabetes mellitus. J Family Med Prim Care 2017; 6: 259-264.
18) Nwose EU, Richards RS, Bwititi PT. Cardiovascular risks in prediabetes: preliminary data on "vasculopathy triad". N Am J Med Sci 2014; 6: 328-332.
19) Gante I, Ferreira AC, Pestana G, Pires D, Amaral N, Dores J, do Céu Almeida M, Sandoval JL. Maternal educational level and the risk of persistent post-partum glucose metabolism disorders in women with gestational diabetes mellitus. Acta Diabetol 2018; 55: 243-251.
20) Palareti G, Legnani C, Cosmi B, Antonucci E, Erba N, Poli D, Testa S, Tosetto A; DULCIS (D-dimer-ULtrasonography in Combination Italian Study) Investigators (See Appendix); DULCIS (D-dimer-ULtrasonography in Combination Italian Study) Investigators. Comparison between different D-Dimer cutoff values to assess the individual risk of recurrent venous thromboembolism: analysis of results obtained in the DULCIS study. Int J Lab Hematol 2016; 38: 42-49.