VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2022, vol. 93, no. 12, 968–974

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2021.0006

Does platelet aggregation have any importance in fetal growth restriction pregnancies?

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ABSTRACT

Objectives: The aim of the study was to evaluate platelet (PLT) concentration, mean platelet volume (MPV), PLT aggregation and its velocity in pregnancy complicated with fetal growth restriction (FGR) and to analyze the PLT aggregation according to the gestational age and Doppler velocimetry.

Material and methods: The study group included 29 pregnant women diagnosed with FGR. The control group--consisted of 27 females in uncomplicated pregnancy. Then both groups were divided according to the gestational week (< and ≥ 36 weeks) and Doppler velocimetry results. The adenosine diphosphate (ADP)-induced PLT aggregation was performed with the help of the electrical impedance.

Results: There was a significant positive correlation between gestational age and PLT aggregation and between gestational age and velocity of PLT aggregation in FGR. Patients with FGR ≥ 36 weeks of gestation had 73% higher PLT aggregation than control group. Within the FGR group, the PLT aggregation was 135% higher in pregnancies ≥ 36 weeks as compared to < 36 weeks of gestation. In FGR pregnancies ≥ 36 weeks with impaired flow in both uterine arteries (UtA), 2.3-fold higher PLT aggregation was found as compared to FGR patients with normal flow or abnormal flow in one UtA.

Conclusions: The increased PLT aggregation in FGR is related to gestational week and occurs in pregnancies ≥ 36 weeks of gestation. The PLT hyperaggregability in growth-restricted pregnancies is associated with abnormal Doppler velocimetry in both UtA, comparing to patients with altered blood flow in one UtA or normal pulsatility index in both UtA, suggesting the PLT activation due to impaired uteroplacental circulation.

Key words: fetal growth restriction; platelet aggregation; platelet concentration; mean platelet volume; velocity of platelet aggregation; ADP-induced platelet aggregation

Ginekologia Polska 2022; 93, 12: 968–974

INTRODUCTION

Fetal growth restriction occurs in about 6% of pregnancies and is related to higher risk of fetal and neonatal morbidity and mortality [1, 2]. Although it results in peri- and postnatal complications, the etiology of this condition is still unclear. Moreover, there is no proven method of treatment and Doppler monitoring of the fetus remains the only possible course of pregnancy management [3, 4].

One of the potential causes involved in the FGR development are changes in PLT aggregation [5]. Nowadays, we know that physiological pregnancy indicates PLT hyperaggregability and a decrease in PLT concentration throughout the gestation [6, 7]. The relationship between PLT activation and FGR is not well researched, but it is supposed that impaired placentation may cause an increased impedance of uteroplacental blood flow [8]. These abnormalities can lead to endothelium injury and activation of clotting cascade, what results in higher PLT aggregation [9]. Because of that, the role of PLT seems to be crucial in implantation, trophoblast development and placentation, what may result in gestational complications including FGR, preeclampsia (PE), recurrent pregnancy loss and many others [10].

The trial Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based

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Received: 15.12.2021 Accepted: 28.01.2022 Early publication date: 22.03.2022

Preeclampsia Prevention (ASPRE) revealed the decrease of preterm PE incidence by 62% among women, whose estimated risk in the first trimester screening was higher than 1 in 100 and who received appropriate prophylactic treatment — acetylsalicylic acid was introduced (150 mg per day from 11–14 until 36 weeks of gestation) [11]. Moreover, the study showed that acetylsalicylic acid reduces the risk of small for gestational age fetuses (SGA) in about 40 and 70% for infants delivered before 37 and 32 weeks of gestation, accordingly. The prevalence of PE before 37 and 32 weeks of pregnancy was decreased about in 70 and 90%, respectively [12]. Considering the above cited study and the common etiology of FGR and PE, looking for a potential role of changeable PLT aggregation in FGR development seems to be justified.

Objectives

The aim of the study was to evaluate PLT concentration, MPV, PLT aggregation and its velocity in pregnancy complicated with FGR. The objective of the research was to compare the PLT parameters in healthy pregnant patients diagnosed with FGR below and at or over 36 weeks of gestation. Moreover, the PLT aggregation was analyzed in growth-restricted pregnancies according to the Doppler velocimetry.

MATERIAL AND METHODS

The study and control group

The research was performed in the Department of Perinatology and Gynecology, Poznan University of Medical Sciences. The study group included 29 pregnant women diagnosed with FGR according to the Gratacos criteria [13]. The control group was composed of 27 females in uncomplicated pregnancy. The groups were age matched. All the women signed informed consent form. Subsequently, the patients from both groups were divided according to the gestational age — below and at or over 36 weeks of pregnancy, respectively. Secondly, the women with FGR were assigned according to the Doppler velocimetry. Before enrolling to the study, the obstetric history, chronic diseases, previous treatment, operative procedures and the course of current pregnancy were analyzed. The fetuses from multiple pregnancies or suspected of genetic malformations, congenital infections and metabolic syndrome were excluded from the study. Also, women who declared suffering from thrombocytopenia, hemolysis, elevated liver enzymes and low platelets syndrome (HELLP), hyperthyroidism, diabetes mellitus, systemic lupus erythematosus, antiphospholipid syndrome, cardiovascular or kidney diseases, bronchial asthma, uterine malformation, malnutrition or drug addiction were not included to the study. Chronic treatment with steroids, beta blockers and antiepileptic medicines was also contraindication to include the patients to the study. Moreover, the diagnosis of umbilical cord abnormality such as single umbilical artery, anomalous umbilical position or umbilical vein thrombosis imposed exclusion from the study. The patients had an obstetric and ultrasound examination (GE Voluson E10 BT18) with Doppler imaging. According to the Polish Society of Gynecologists and Obstetricians Recommendations (PSOGO), every pregnant woman underwent an ultrasound examination between $11–13^{+6}$ weeks of gestation with the measurement of the crown-rump length (CRL) and verification of the gestational age [14]. The groups characteristics is presented in Table 1.

The blood collection and impedance aggregometry

About five milliliters of whole blood, except of two millimeters from the first blood stream, were collected into the hirudin-coated tubes. The analyzed parameters includ-

Table 1. The groups characteristics

Characteristics	FGR n = 29	Control group n = 27	p
Age [years] (Mean ± SD)	31 ± 4	31 ± 5	0.943
Gestational age at delivery [weeks] (Mean ± SD)	36 ± 3	38 ± 2	0.007
Mode of delivery [%]			
Spontaneous	37.9	37.0	1.000
Vacuum extractor	3.5	14.8	0.186
Forceps	0.0	0.0	1.000
Cesarean section	58.6	48.2	0.592
Arterial hypertension [%]			
Chronic	0.0	0.0	1.000
Gestational	17.2	0.0	0.052
Preeclampsia	3.5	0.0	1.000
Preeclampsia superimposed on chronic arterial hypertension	0.0	0.0	1.000
Oligohydramnion [%]	31.0	0.0	0.002

FGR — fetal growth restriction; SD — standard deviation

Table 2. Platelet parameters in fetal growth restriction and control group

Parameter	FGR n = 29	Control group n = 27	p
PLT concentration [G/L] (median, min–max)	233 [126–350]	201 [154–331]	0.283
MPV [fL] (mean ± SD)	11.05 ± 1.19	11.38 ± 1.03	0.281
PLT aggregation [U] (median, min–max)	44.3 [3.4–222.0]	46.1 [4.1–185.3]	0.961
Velocity of PLT aggregation [U/min] (median, min–max)	5.3 [1.9–25.6]	6.5 [1.8–19.9]	0.768

PLT — platelet, MPV — mean platelet volume

ed PLT aggregation and velocity of PLT aggregation. Then three milliliters of whole blood were taken to the tubes with ethylenediaminetetraacetic acid (EDTA) to examine the PLT concentration and MPV. The blood aggregation was determined using multiple electrode aggregometry (MEA) on a new-generation impedance aggregometry (Multiplate Analyzer; Dynabyte Medical, Munich, Germany). The system detects the electrical impedance change due to the adhesion and aggregation of PLT on two independent electrode-set surfaces in the test cuvette [15–17]. Hirudin was used as anticoagulant, as recommended by the manufacturer. The degree of ADP-induced PLT aggregation was evaluated after addition of 20 µM ADP solution. A 1:2 dilution of whole blood anticoagulated with hirudin and 0.9% NaCl was stirred for 3 minutes at 37°C in the test cuvettes and then ADP-agonist was added. Conduction changes caused by the adhesion and PLT aggregation were monitored on two independent metal electrodes, continuously. The increase in electrical impedance was recorded for six minutes [18]. The blood was analyzed during the 60–90 minutes after collection. The PLT concentration was expressed in milliard per liter (G/L), MPV in femtoliters (fL), PLT aggregation in aggregation units (U), velocity of PLT aggregation in aggregation units per minute (U/min).

The statistics

The statistical analysis was performed in Statistica StatSoft 13.1 and Statistical Package for the Social Sciences (SPSS) 24.0.0 programmes. Normal distribution was checked using Kolmogorow–Smirnov and Lilliefors test. If the evaluated parameters fulfilled the assumptions of Gaussian distribution, the t-Student test was used, if did not the nonparametric Mann–Whitney test was performed. The data in interval scale with normal distribution were described as mean and standard deviation (SD), the rest as median, minimal (Min) and maximal (Max) value. The data in nominal scale were analyzed using the Fisher's exact test and presented in percentages. The correlations were described using Spearman's rank correlation coefficient (r). The significance level was assumed as p-value below 0.05.

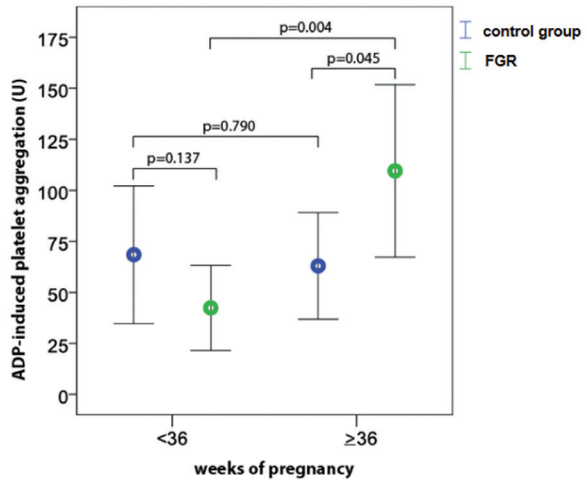

Figure 1. ADP- induced PLT aggregation in fetal growth restriction vs physiological pregnancy according to the gestational week expressed as means and 95% confidence intervals

RESULTS

PLT concentration, MPV and velocity of PLT aggregation in FGR and control patients

Any significant difference in the PLT concentration, MPV and velocity of PLT aggregation was observed between FGR and control group overall (Tab. 2), when assessed < and ≥ 36 weeks of gestation and according to Doppler ultrasound. There was a statistically positive correlation between gestational age and velocity of PLT aggregation in FGR (r = 0.37; p = 0.048).

ADP-induced PLT aggregation in FGR and control patients

ADP-induced PLT aggregation did not differ between FGR and controls groups when assessed in pregnancies < 36 weeks (p = 0,137; Fig. 1). Taking into consideration pregnancies ≥ 36 weeks, there was a remarkable difference between these two groups: patients with FGR had a 73% higher ADP-induced PLT aggregation as controls (p = 0.045; Fig. 1). Accordingly, within the FGR group, the ADP-induced

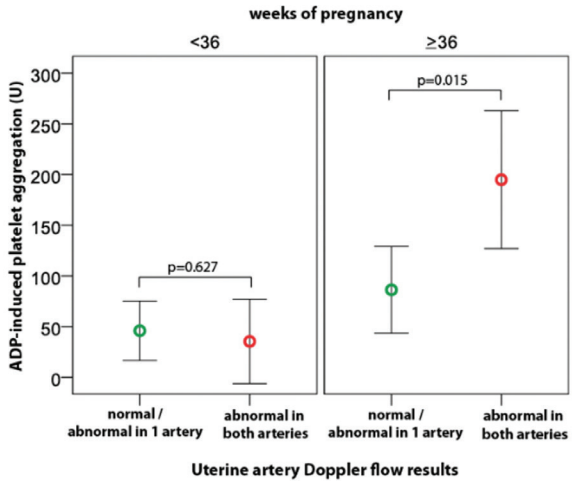

Figure 2. ADP- induced PLT aggregation in fetal growth restriction according to the gestational week and the results of the Doppler flow in the uterine arteries expressed as means and 95% confidence intervals

PLT aggregation increased over time and was 135% higher in pregnancies ≥ 36 weeks as compared to < 36 weeks (p = 0.004; Fig. 1), whereas no differences over time were seen in controls (Fig. 1). The significant positive correlation between PLT aggregation and gestational age in FGR was found (r = 0.40; p = 0.029).

ADP-induced PLT aggregation in FGR patients according to the results of Doppler ultrasound

There was no dfference in the ADP- induced PLT aggregation according to the Doppler study results in UtA in FGR pregnancies < 36 weeks (Fig. 2). In contrast, in FGR group ≥ 36 weeks, very high ADP-induced PLT aggregation values were found in cases of impaired flow in both UtA: 2.3-fold higher as compared to FGR patients with normal flow or abnormal flow in one of the UtA (p = 0.015; Fig. 2). No difference in ADP-induced PLT aggregation values was found in patients with impaired Doppler flow in one of the UtA comparing to no impaired flow in both UtA (p = 0.587). Accordingly, there were no statistical differences in ADP-induced PLT aggregation values in patients with 1) impaired Doppler flow in the umbilical artery (UA) versus no impaired flow in the UA (p = 0.636) or 2) impaired Doppler flow in the middle cerebral artery (MCA) versus no impaired flow in the MCA (p = 0.636).

DISCUSSION

Although many studies reported increased PLT activity in both physiological and complicated pregnancy, there is only a few data concerning the relationship between FGR and PLT aggregation. Because of the common etiology, of FGR and PE, our study will be partially compared to the studies concerning preeclamptic women. Belo et al. [19] observed no significant differences in PLT count throughout physiological pregnancy as in our study. Additionally, the PLT count did not differ in the third trimester between patients with PE and healthy pregnant controls. Differently to us, Bielecki et al. [20] observed significantly lower PLT count and higher MPV but the researchers compared women diagnosed with PE to healthy pregnant females. Similarly, Kashanian et al. [21] observed the significantly higher MPV value in the first and in the third trimester among preeclamptic patients in comparison to normotensive pregnant women but there was a low predictive value of MPV in PE prognosis. Furthermore, Kanat-Pektas et al. noticed significantly higher MPV in females, who developed PE throughout the second and the third trimester of pregnancy. The MPV value above or equal than 10.5 fl predicted PE with 6.7% sensitivity and 63.8% specificity. The sensitivity and specificity for MPV in prognosis of FGR development scored 82.4% and 60%, respectively [22]. Similarly, Temur et al. observed significantly higher MPV values in PE group comparing to the healthy controls. The cut-off value for MPV in the prediction of PE, with 58,7% sensitivity and 61.7% specificity, was established as 9.15 fl [23]. Otherwise, our study did not confirm the cited results, because any significant difference in PLT concentration and MPV was observed between FGR group and healthy controls. Contrary to above cited results, Ureyen et al. [24] and Koroglu et al. [25], independently, analysed MPV in patients with and without FGR, but there was no significant difference between studied groups, alike in our study.

Burke et al. did not observe the increasing PLT activity from the first to the third trimester of uncomplicated pregnancy in reference to ADP, thrombin receptor activating protein (TRAP) and epinephrine comparing to non-pregnant women. The hyperaggregability was observed only in response to collagen and arachidonic acid [26]. Like the cited paper, we did not notice any significant differences in PLT aggregation using ADP agonist when assessed the pregnancies below 36 weeks, but our study included only women in the second and third trimester of pregnancy.

Pimentel et al. [27] did not find the changes in PLT aggregability between patients with PE and pregnant normotensive women. Similarly, to preeclamptic women, our study did not reveal any significant difference in PLT aggregation, comparing the whole FGR group and healthy controls but when assessed pregnancies at or over 36 weeks, the higher PLT hyperaggregability in FGR was observed comparing to healthy controls and to the FGR group below 36 weeks.

Norris et al. compared the PLT activation between normotensive or hypertensive pregnant women diagnosed

with FGR and healthy primigravida. The authors observed the 30% decrease of PLT count in hypertensive patients in comparison to physiological pregnancy. Moreover, the collagen and ADP-induced PLT aggregation was about 50% lower in patients with coexisted FGR and hypertensive disorders than in uncomplicated gestation. In contrast to the groups with FGR and blood pressure disturbances, the normotensive FGR women showed any significant difference according to PLT level and both ADP and collagen induced PLT aggregation comparing to healthy pregnant controls at 36 weeks [28]. In our study the hypertensive FGR patients accounted for approximately 21% of study group, but we did not analyse the PLT parameters in normotensive and hypertensive patients, separately. Although, our results in reference to PLT count were similar to the observed by Norris et al. [28] in normotensive women with FGR, the ADP-induced PLT aggregation was increased in FGR group at or over 36 weeks comparing to healthy controls and FGR pregnancies below 36 weeks.

In contrast to our study, Müllers et al. noticed a decreased PLT reactivity regarding all agonists (arachidonic acid, ADP, collagen, thrombin receptor-activating peptide, epinephrine) in FGR comparing to healthy pregnant women. Moreover, they observed significantly higher reduction in PLT activity in women with FGR, who developed PE or gestational hypertension in comparison to FGR group without hypertensive disorders [29].

One of the first studies, concerning the PLT function and Doppler velocimetry in pregnant women, did not show any significant correlation between ADP-induced PLT aggregation and UA flow but the researchers analyzed blood obtained during cordocentesis and the study group was composed only of 10 patients [30]. Only a few studies analyzed the relationship between PLT aggregation or other PLT parameters and Doppler velocimetry in FGR patients. Even though our study was not performed on a large group of patients, the other study, supported by the Fetal Medicine Foundation, performed by Missfelder-Lobos et al. [8], analyzed PLT aggregation in four cases of isolated FGR and 8 patients who developed PE with subsequently FGR in 50% of cases. The researchers observed no significant disparity according to PLT count and collagen-induced aggregability between pregnant patients both with normal and disturbed uterine arteries pulsatility index (UtA PI) and nonpregnant healthy women. Moreover, the researchers reported significant differences in MPV between pregnant women with normal and abnormal UtA blood flow and significantly higher ADP1-induced PLT aggregation, comparing pregnant women both with and without disturbed blood flow in UtA to healthy controls [8]. Our study also showed the increased PLT aggregation but only within FGR group when assessed at or over 36 weeks with abnormal blood flow in both UtA comparing to disturbed blood flow in one UtA or normal Doppler screening. Although the results of PLT count were compatible with the cited paper, we did not observe any significant difference in MPV.

In contrast to our and the above cited study, Everett et al. observed any correlation between Doppler velocimetry in UtA and PLT aggragation in response to ADP. The authors found a relationship between mean UtA PI and collagen induced PLT aggregation [31].

In the literature there are only three above cited studies referring to relationship between ADP-induced PLT aggregation and Doppler screening, but the results of them are contradictory. A few researchers concentrated on association between MPV and abnormalities in Doppler ultrasound. Ureyen et al. [32] analyzed MPV in patients with and without FGR in reference to Doppler velocimetry, but there was no significant difference between studied groups as in our study. Moreover, there was no correlation between MPV and Doppler parameters. Contrary to our results, Piazze et al. [33] found significantly higher MPV in patients with abnormal UtA Doppler screening in comparison to females without alterations in Doppler velocimetry. Additionally, they noticed higher MPV in pregnancies with abnormal Doppler profile and PE than in FGR. Moreover, the researchers observed significant relationship between uterine arteries resistance index (UtA RI) and MPV both in PE and FGR women. Otherwise, Gioia et al. [34] noticed the significantly higher MPV in patients with PE and FGR with coexisted abnormal Doppler in comparison to normotensive pregnant women without Doppler disturbances.

Although, there are many publications related to PLT activity in pregnancy, only few of them concern on PLT aggregation in patients diagnosed with FGR. Moreover, the results are contradictory and do not allow to draw unambiguous conclusions. Our study did not reveal significant changes in PLT aggregation among women with FGR in comparison to physiological pregnancy, so lack of statistical significance imposes to plan further research with the use of other reagents to evaluate PLT aggregation. Moreover, because of small amount of data concerning relationship between PLT aggregation and Doppler velocimetry in FGR and ambiguous results there is a need for further studies including more numerous groups. Furthermore, the serial measurement of PLT activity in each trimester of pregnancy could give the valuable information about altered PLT function.

CONCLUSIONS

The increased PLT aggregation in FGR is related to gestational week and occurs in pregnancies at or over 36 weeks. Moreover, the PLT hyperaggregability in

growth-restricted pregnancies is associated with abnormal Doppler velocimetry in both uterine arteries, comparing to patients with altered blood flow in one uterine artery or normal pulsatility index in both uterine arteries, suggesting the PLT activation due to impaired uteroplacental circulation.

Because there are only a few data concerning the PLT aggregation in pregnancies complicated with FGR and the results are contradictory, it is necessary to use other PLT agonists to evaluate induced PLT aggregation. Further studies, recruiting more patients diagnosed with FGR and formation of more homogenous group according to abnormalities in Doppler imaging and hypertensive disorders, are needed. Moreover, it seems reasonable to collect blood repeatedly in each trimester of pregnancy to observe real changes in PLT parameters over time.

Conflict of interest

All authors declare no conflict of interest.

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