Elevated maternal serum sP-selectin levels in preeclamptic pregnancies with and without intrauterine fetal growth restriction, but not in normotensive pregnancies complicated by isolated IUGR

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The aim of this study was to show differences of maternal serum sP-selectin levels in pregnancies complicated by intrauterine fetal growth restriction (IUGR) in the course of preeclampsia and to compare the results with normotensive pregnant women with isolated IUGR. These studies were also conducted on preeclamptic pregnancies with appropriate-for-gestational-age weight infants and on the control normotensive pregnant women.

Material/Methods: The study was carried out on 55 patients with pregnancy complicated by fetal growth restriction in the course of preeclampsia, 70 normotensive patients with pregnancies complicated by isolated IUGR, 39 preeclamptic patients with appropriate-for-gestational-age weight fetuses and 54 healthy normotensive pregnant patients with normal fetal growth. Maternal serum levels of sP-selectin were determined using the enzyme-linked immunosorbent assay.

Results: Levels of sP-selectin were higher in women with pregnancy complicated by preeclampsia with and without IUGR; whereas, in the group of normotensive pregnant women with isolated fetal growth restriction, serum sP-selectin levels tended to be lower than in the control subjects, but this difference was not statistically significant. The mean values were 192.05±70.96 ng/mL in the IUGR group, 293.18±222.92 ng/mL in the PI group, 379.78±353.13 ng/mL in the P group and 227.96±134.04 ng/mL in the healthy controls (p<0.001*).

Conclusions: Our findings may suggest that the elevated level of the soluble P-selectin is associated with preeclampsia, and that it may confirm the presence of platelet and endothelial activation, the presence of the hypercoagulant state and may be due to the systemic inflammatory response in this serious pregnancy disorder.

Key words: intrauterine fetal growth restriction (IUGR) • preeclampsia • sP-selectin

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Background

Preeclampsia is a serious hypertensive disease specific to human pregnancy, with a worldwide incidence of 2–10% [1]. There is growing evidence that shallow implantation, reduced placental blood and impaired placental function result in preeclampsia, chronic fetal hypoxia, or intrauterine fetal growth restriction (IUGR) [2,3]. Although preeclampsia is one of the main causes of intrauterine fetal growth restriction, in many cases of pregnancies complicated by IUGR, an idiopathic placental failure with abnormal placental development, suboptimal fetal nutrition, and oxygenation without maternal hypertension or preeclampsia can occur [4–7]. Intrauterine fetal growth restriction is also an important clinical problem associated with increased perinatal mortality and morbidity, and it impacts health in later life.

Reduced uteroplacental perfusion in preeclamptic pregnancies is associated with endothelial dysfunction, which is one of the causes leading to the failures of trophoblast invasion and spiral artery transformation, and which results in an impaired placentation [8]. In preeclamptic pregnancies there are no inadequate physiologic changes of spiral arteries remodeling. Impaired trophoblast invasion into the placental bed in pregnancies complicated by preeclampsia and intrauterine growth restriction is limited by increased apoptosis, resulting in narrower spiral arteries [9,10]. Abnormal spiral arteries adaptation results in an increase of their sensitivity to vasoactive agents and limits placental blood flow in pregnancies complicated by preeclampsia and fetal growth restriction [10]. Recent observations support the hypothesis that altered expression of placental anti-angiogenic factors is responsible for the clinical manifestations of the disease [6].

Furthermore, Kaufmann et al. [11], Hogg et al. [12], and Onalan et al. [13] have observed reduced endovascular trophoblast invasion and the absence of pregnancy-specific changes in uteroplacental arteries in pregnancies complicated by preeclampsia and IUGR. Similar spiral artery abnormalities have been reported in the placental bed of normotensive pregnant women with isolated fetal growth restriction by Lyall et al. [3] and Sheppard et al. [14].

It was suggested that an important factor for proper trophoblast invasion and vascular remodelling is the expression and activity of adhesion molecules [8,15,16].

P-selectin (CD62P), which is a 140kD protein found in the alpha granules of platelets and the Weibel-Palade bodies of endothelial cells, is a member of the selectin family of adhesion molecules, which play a crucial role in the reproduction and hemostasis [17–19]. During pregnancy, maternal endothelial E- and P-selectin expression occurs exclusively at the implantation

site and may provide a mechanism for maternal and fetal cell interaction to enable the trophoblast to implant itself within the uteroplacental vessel lumen [20]. P-selectin is released from the cell surface and circulates as a soluble molecule in the plasma [21]. Both the membrane form and the soluble form of P-selectin are agonists of the processes of thrombosis and inflammation [22]. Furthermore, CD62 could support platelet-platelet interactions and play a critical role in the early stages of inflammation, thrombosis and atherosclerosis by mediating plaque formation and progression [22].

The changes observed in pregnancy complicated by fetal growth restriction may be related to the disturbances in P-selectin activity. These observations were the inspiration for our study.

The aim of this study was to evaluate the levels of soluble P-selectin in maternal serum in pregnancies complicated by severe preeclampsia with and without intrauterine fetal growth restriction, and in normotensive pregnancies complicated by isolated IUGR, in comparison with healthy normotensive pregnant women with normal fetal growth.

The study was accepted by the local Ethics Committee.

Material and Methods

The study was carried out on 70 normotensive pregnant patients in the third trimester of pregnancy complicated by fetal growth restriction (the IUGR group), 55 patients with pregnancy complicated by IUGR in the course of severe preeclampsia (the PI group), and 39 preeclamptic women with appropriate-for-gestational-age fetuses (the P group). The control group consisted of 54 healthy normotensive pregnant patients with uncomplicated singleton pregnancies, without any renal, cardiac and vascular diseases, with normal laboratory test results, and with proper fetal growth and development (the C group).

Intrauterine fetal growth restriction (IUGR) was defined according to ultrasonographic measurement when the weight of the fetus was lower than expected in relation to gestational age as determined by the standard curves characteristic of the Polish population, when the fetus was below the 10th percentile for gestational age. Additionally, IUGR pregnancies were characterized by at least 1 of the disturbed placental functions and by an abnormal ultrasonographic examination (elevated pulsatility index [PI] in the uterine arteries and/or early diastolic notches, elevated PI in umbilical arteries, and elevated head/abdomen ratio, reduced AFI) according to Stepan et al. [23]. The diagnosis was confirmed by the infant's weight at birth.

The exclusion criteria for women whose pregnancies were complicated by IUGR were the presence of a congenital

malformation or chromosomal abnormality in the fetus, recent cytomegalovirus infection, or drug or alcohol abuse during pregnancy. Pregnant women with multiple pregnancies were also excluded from this study.

Preeclampsia was diagnosed by the increased blood pressure of >140 mmHg systolic and >90 mmHg diastolic in women who were normotensive before 20 weeks of gestation accompanied by proteinuria, defined as the urinary excretion of >0.3 g protein in a 24-hr specimen.

Severe preeclampsia was defined as blood pressure >160/110 mmHg on at least 2 occasions 6 hours apart in women who were normotensive before 20 weeks of gestation with proteinuria >5 g in a 24-hour urinary protein excretion, and when hypertension and proteinuria were associated with 1 or more of the following clinical manifestations: renal abnormalities, hematologic abnormalities (thrombocytopenia, microangiopathic hemolysis) or HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count, right-upper quadrant pain), or neurologic symptoms (headache, visual disturbances, seizures). Preeclamptic patients were admitted to the Department of Obstetrics and Perinatology at the Medical University Hospital in Lublin because of the symptoms of the disease and without any signs of labor. None of the pregnant patients with preeclampsia were affected by chronic hypertension, renal disorders and/or proteinuria before pregnancy and all were normotensive before the 20th week of pregnancy. All preeclamptic women were normotensive 3 months after delivery.

All arterial blood pressure measurements in the control group and in the group of patients with isolated IUGR were normal and did not exceed 135/85 mmHg. None of the patients from these groups suffered from proteinuria. All patients in the study were non-smokers. Informed consent was obtained from all studied patients for peripheral blood sampling.

Five milliliters of blood were collected by venipuncture from each preeclamptic patient, from each patient with pregnancy complicated by isolated IUGR, and from each woman in the control group, placed in sterile tubes and centrifuged for 15 min at 500 × g. The level of maternal serum soluble P-selectin was determined using a sandwich ELISA assay according to the manufacturer's instructions (human sP-selectin sandwich ELISA kit, Bender MedSystems, Vienna, Austria).

In the statistical analysis, results were expressed as mean ±SD or SEM or as median values and were statistically analyzed with the computer program "Statistica" using the Shapiro-Wilk test for the normally distributed data, and equality of variance by Levene test and, subsequently two-tailed t tests, or (in unequal variance) the Cochran-Cox test.

The ANOVA and Kruskal-Wallis tests were used to test for differences among 4 independent groups. A statistically significant effect in ANOVA was followed up with follow-up post-hoc Tukey's test in order to assess which group is different from which other groups. A *p*-value of less than 0.05 was considered to be significant.

Results

There were no statistically significant differences in gravidity, parity, maternal age and maternal height in patient profiles between groups. Creatinine and urea levels were normal in all patients and did not exceed 1.1 mg% for creatinine and 40 mg% for urea in all the women studied.

Among preeclamptic patients there were 3 patients with HELLP syndrome (1 in the P group and 2 in the PI group) and 2 patients with eclampsia (1 in the P group and 1 in the PI group).

Maternal weight and BMI were lower in the group of patients with pregnancy complicated by isolated IUGR than in the control group, and also in comparison with both groups of preeclamptic patients. Systolic and diastolic blood pressures were higher in the preeclamptic women than in the control group and in the pregnant patients with isolated IUGR (p<0.001*).

Lower gestational age and lower birth weight of infants were found in both preeclamptic groups and in the group of normotensive women with isolated IUGR. The birth weight of infants was lowest in the PI group. There were no statistically significant differences in the birth weight of infants between normotensive patients with isolated IUGR and preeclamptic women with and without IUGR (the P and PI groups), despite the significantly higher age of pregnancy in the IUGR group (Table 1).

Both groups of preeclamptic patients with appropriate-for-gestational-age fetuses and with fetal growth restriction in the course of preeclampsia had increased serum levels of sP-selectin. These differences were statistically significant (p<0.001* from the ANOVA analysis).

The pregnant patients with isolated IUGR had lower levels of sP-selectin in the maternal serum than in the healthy controls and in the women with pregnancies complicated by severe preeclampsia with and without fetal growth restriction, but these differences were statistically significant only in comparison with both preeclamptic groups of pregnant women studied (p<0.001* for the P group, p<0.043* for the PI group and p=0.792 for the control group respectively). The mean values were 192.05±70.96 ng/mL in the IUGR group, 293.18±222.92 ng/mL in preeclamptic patients with IUGR, 379.78±353.13 ng/mL in preeclamptic patients with appropriate intrauterine

Table 1. Analysis of maternal and fetal characteristics in studied groups of pregnant women.

Data	The control group (C) (n=54)	The iugr group Normotensive women with IUGR (n=70)	The PI group Preeclamptic women with IUGR (n=55)	The P group Preeclamptic women with normal fetal growth (n=39)	ANOVA analysis p value	Post-hoc test * statistical significance
Maternal age (years)	30.29±1.98	28.91±4.81	30.49±4.98	30.06±6.28	p=0.416	
Maternal height (cm)	164.25±6.52	164.77±6.38	164.00±5.62	165.67±7.23	p=0.885	
Maternal weight (kg)	78.42±11.24	67.72±9.46	84.23±13.82	91.22±16.13	p<0.001*	C/P*, iugr/PI*, iugr/P*
Maternal BMI (kg/m²)	29.06±3.83	25.04±3.71	31.13±4.81	32.94±4.74	p<0.001*	iugr/P*, iugr/PI*, C/P*
Systolic blood pressure (mmHg)	114.64±9.46	111.91±19.15	163.31±17.58	166.00±14.65	p<0.001*	C/P*, C/PI*, iugr/P*, iugr/PI*
Diastolic blood pressure (mmHg)	74.36±8.07	72.15±10.06	107.71±8.59	103.28±21.95	p<0.001*	C/P*, C/PI*, iugr/P*, iugr/PI*
Age of pregnancy (weeks)	38.22±1.98	36.41±2.43	33.36±3.38	32.31±4.978	p<0.001*	C/PI*, C/P*, iugr/PI*, iugr/P*
Birth weight (g)	3200.38±570.18	2008.18±563.70	1666.51±587.81	1936.35±1024.02	p<0.001*	C/P*, C/iugr*, C/PI
Maternal serum sP-selectin (ng/mL)	227.96±134.04	192.05±70.96	293.18±222.92	379.78±353.13	p<0.001*	C/P*, C/PI*, iugr/P*, iugr/PI*
Percentile newborn's weight Mean ±SD Median	48.20±27.03 41.00	4.84±6.03 3.00	8.27±6.65 6.00	34.31±21.29 31.00	p<0.001	C/PI*, C/iugr*, P/PI*, P/iugr*

Data presented as a mean ±SD. * statistical significance (p<0.05).
Groups of studied pregnant women: C – the control group – healthy normotensive pregnant women with appropriate fetal growth; iugr – normotensive women with pregnancy complicated by isolated intrauterine fetal growth restriction; PI – women with IUGR in the course of preeclampsia; P – preeclamptic women with proper fetal growth.

fetal growth, and 227.96±134.04 ng/mL in the control group (p<0.001*) (Figure 1).

In all groups of pregnant patients studied there were no significant correlations between maternal serum sP-selectin and BMI (correlation coefficient R=−0.140415, R=−0.064238, R=0.072527, R=−0.095759 and p=0.484823, p=0.667938, p=0.805376 and p=0.641691, respectively for the C, IUGR, P and PI groups).

A significant inverse correlation between maternal serum sP-selectin levels and fetal weight percentile was observed in normotensive women with pregnancies complicated by isolated fetal growth restriction (correlation coefficient R=−0.307123 and p=0.013567* for the IUGR group), but this correlation was not significant in other groups of studied women (correlation coefficient R=−0.108798, R=−0.298924, R=−0.101190 and p value p=0.509704, p=0.138795 and p=0.551229, respectively for the C, P and PI groups).

Discussion

Our study was focussed on the problem of whether the abnormal expression of adhesion molecules contribute to the placental pathologies found in pregnancies complicated by isolated intrauterine fetal growth restriction or due to preeclampsia. This study is one of a small number presenting the changes in the levels of sP-selectin concentrations in normotensive pregnancies complicated by isolated fetal growth restriction.

One of the significant findings in our present study is a different pattern of sP-selectin in normotensive pregnancies complicated by isolated IUGR and in pregnancies complicated by fetal growth restriction in the course of severe preeclampsia. Our study reveals higher levels of sP-selectin in preeclamptic pregnancies complicated by IUGR and in preeclamptic pregnancies with appropriate-for-gestational-age fetuses. The levels of sP-selectin in the maternal serum of normotensive patients
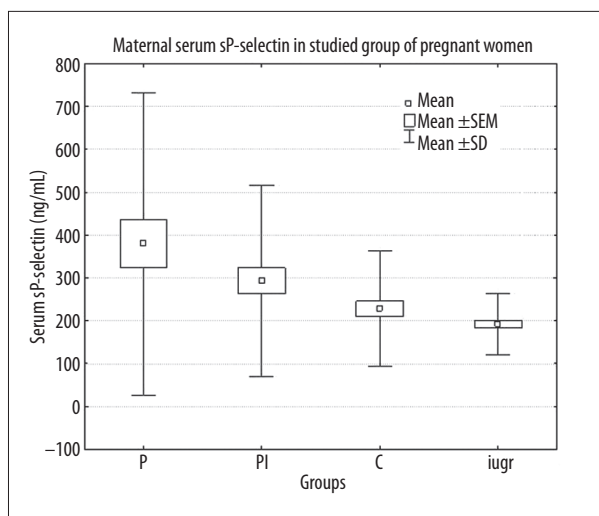
Figure 1. Analysis of sP-selectin in studied groups of pregnant women with pregnancy complicated by IUGR with and without preeclampsia, in preeclamptic patients appropriate-for-gestational age fetuses and in healthy controls.

with pregnancies complicated by IUGR alone tended to be lower, but these differences were not statistically significant in comparison with the control group. However, maternal serum sP-selectin levels in normotensive pregnant women with isolated fetal growth restriction were significantly lower in comparison with both groups of preeclamptic women with normal fetal growth and in preeclampsia with IUGR.

Our findings suggest that platelets are particularly activated in preeclampsia but not in normotensive women with IUGR alone. Elevated sP-selectin levels in both groups of preeclamptic women may also reflect a systemic inflammatory process in pregnancies complicated by preeclampsia, but not in normotensive pregnancies complicated by isolated IUGR.

sP-selectin acts as a marker for platelet and endothelial activation and as an inducer of the procoagulant condition, as well as playing a crucial role in atherosclerosis. Our findings of elevated sP-selectin in preeclampsia seem to confirm that these processes occur in preeclamptic pregnancies. Higher levels of soluble P-selectin in preeclamptic pregnancies suggest that the excess circulating sP-selectin contributes to the pathogenesis of this pregnancy-specific disorder.

Levels of soluble P-selectin tended to be lower in normotensive pregnancies with IUGR, but this difference was not significant in comparison with the healthy controls. Our results may suggest that there was no excessive platelet or endothelial activation or inflammatory state, and that this pathway is not responsible for fetal growth restriction in normotensive pregnancies complicated by isolated idiopathic IUGR alone.

Possibly, different mechanisms lead to the development of intrauterine fetal growth restriction due to preeclampsia and isolated IUGR in normotensive pregnancies.

We observed the highest levels in pregnancies complicated by preeclampsia with proper intrauterine fetal growth. The soluble form of P-selectin is an agonist of thrombotic and inflammatory processes, and is thought of as a marker for platelet and endothelium activation and as an inducer of the procoagulant state. Soluble P-selectin plays a crucial role in atherosclerosis and atherosclerotic plaque formation. These results suggest that sP-selectin may be at least partly responsible for the etiopathogenesis of the maternal preeclampsia syndrome, but that it is not associated with the pathophysiological processes underlying the fetal syndrome of fetal growth restriction, and it may be a marker of preeclampsia but not of IUGR.

Holmes et al. [24] reported a significantly higher concentration of sP-selectin in the second and third trimester of pregnancy than in non-pregnant control women. On the basis of their studies, these authors concluded that human pregnancy is associated with higher levels of soluble P-selectin, which are a direct inducer of the hypercoagulant condition, as well as being a marker of increased platelet activation.

Yoneyama et al. [25] presented a significantly higher expression of P-selectin in preeclampsia than in normal healthy pregnancies. Similar results of increased levels of sP-selectin in preeclamptic pregnancies were presented by Halim et al. [26] and Chaiworapongsa et al. [27]. Preeclampsia may be associated with a significant increase in the concentration of sP-selectin and in the activation of platelets, leukocytes and endothelial cells [27].

Furthermore, Bosio et al. [28] found higher levels of sP-selectin in preeclampsia but levels of soluble P-selectin were not significantly increased in women with gestational hypertension without proteinuria. They concluded that plasma P-selectin is a significant marker of preeclampsia in women in the first trimester of pregnancy. Bosio et al. [28] also suggest that their findings support an inflammatory model for preeclampsia, while the endothelial cell activation may be secondary to a primary inflammatory response.

However, Karalis [29] observed significantly increased levels of both P-selectin and its soluble form in women with pregnancy-induced hypertension (PIH) in comparison with normotensive pregnancies, and concluded that normal pregnancy is associated with increased platelet activation followed by further alteration in these parameters in pregnancies complicated by PIH.

Halim et al. [26] showed elevated plasma P-selectin in the first trimester in pregnant women who subsequently developed

preeclampsia. However, different results were presented by Heyl et al. [30], who found levels of P-selectin in hypertensive patients similar to those found in healthy controls. Burger and Wagner [31] showed that P-selectin is crucial for the growth of atherosclerotic lesions and may stimulate the deposit of fibrin and enhanced procoagulant activity. On the basis of their studies, they suggest that healthy women with elevated levels of sP-selectin are at increased risk of future cardiovascular disorders [31].

Salazar-Exaire et al. [32] suggest that P-selectin is a marker not only for platelet activation, but also for endothelium activation in patients with severe preeclampsia. According to Chen and Geng [33], P-selectin plays a role in hemostasis and thrombosis by mediating the heterotypic aggregation of platelets on stimulated endothelial cells and adherent leukocytes.

In our study the average gestational age at delivery was earlier in both groups of women with preeclampsia compared to the other study groups. The age of pregnancy was also lower in patients with isolated IUGR in comparison with the control group, and higher than in both preeclamptic groups. However, Holmes et al. showed [24] that gestational time has no significant effect on sP-selectin levels in pregnant women, and that soluble P-selectin levels remain stable throughout normal pregnancy. Furthermore, Bosio et al. [28] observed stable plasma P-selectin levels throughout normal pregnancy, with only a slight, non-significant increase at 28–32 weeks of gestation and a plateau to term thereafter. These authors [28] also showed that pregnant patients with gestational hypertension and normotensive population exhibited remarkably similar sP-selectin concentrations throughout pregnancy. On the other hand, they demonstrated significantly increased concentrations of plasma P-selectin in preeclamptic women throughout

pregnancy when compared with both the normotensive and gestational hypertensive populations [28].

Conclusions

In summary, our results support the role of increased levels of sP-selectin in maternal serum in the pathophysiology of preeclampsia and intrauterine fetal growth restriction due to preeclampsia, but not in normotensive pregnancies with isolated IUGR. Increases in sP-selectin concentrations in preeclamptic pregnancies with and without growth-restricted fetuses prove the endothelial and platelet activation and the hypercoagulant state, and may also reflect the inflammatory process in preeclampsia. The levels of soluble P-selectin tended to be lower in normotensive women with pregnancies complicated by isolated IUGR than in healthy controls with proper fetal growth, but this difference was not significant. However, levels of soluble P-selectin were significantly lower in normotensive pregnancies with IUGR than in both groups of preeclamptic patients. Because fetal growth restriction in normotensive women is not associated with higher maternal serum sP-selectin levels, it seems that endothelial or platelet activation, hypercoagulant state, and higher inflammatory response may not play crucial roles in the pathophysiology of isolated IUGR in women without preeclampsia. We cannot exclude the possibility that fetal growth restriction in the course of preeclampsia differs from isolated IUGR in normotensive pregnancies. Lower levels of sP-selectin in maternal serum in normotensive pregnancies complicated by fetal growth restriction alone may be associated with insufficient endovascular remodelling and changes specific for normal pregnancy that contribute to the placental pathologies and result in IUGR without preeclampsia. Further studies are needed to clarify these aspects.

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